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Vienna University of Technology

DIPLOMARBEIT

CHIRAL CYCLOOCTADIENE LIGANDS FOR RHODIUM CATALYSIS

ausgeführt am
Institut für Angewandte Synthesechemie,
TU Wien

unter der Leitung von
Associate Prof. Dipl.-Ing. Dr.techn. Michael Schnürch

von
Charlie Lim
Josef-Baumann Gasse 8A/340, 1220 – Wien
Österreich

Jenen gewidmet,
die mich stets begleitet und unterstützt haben.

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The course of study was quite an interesting adventure I would not want to miss! The paths in this adventure would often diverge in many ways and I always tried my best to walk the path that was less traveled by. I believe that this has sometimes made all the difference.

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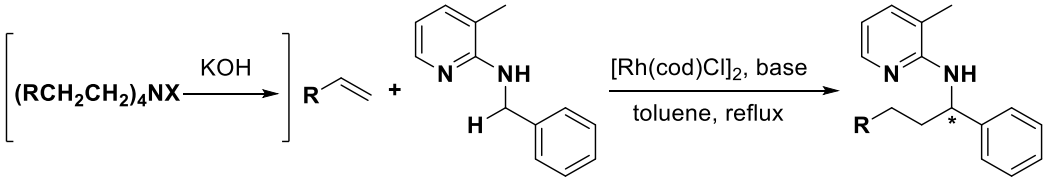
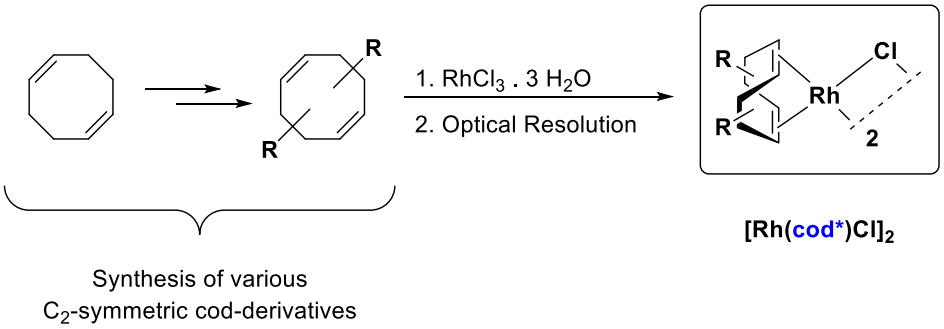
Abstract

Site-selective C-H functionalization has been under intensive research within the last decades and today, many strategies are employed to achieve site-selectivity. Our group has previously reported the direct alkylation of benzylic amines *via* C-H functionalization by utilizing olefins as alkylating agents. In particular, an intrinsic pyridine-moiety was exploited as a directing group to target a benzylic C-H bond. With optimized conditions in hand for the direct C(sp^3)-H activation with alkenes and quaternary ammonium salts as solid-olefin-surrogates, the focus was appointed towards enantioselectivity.



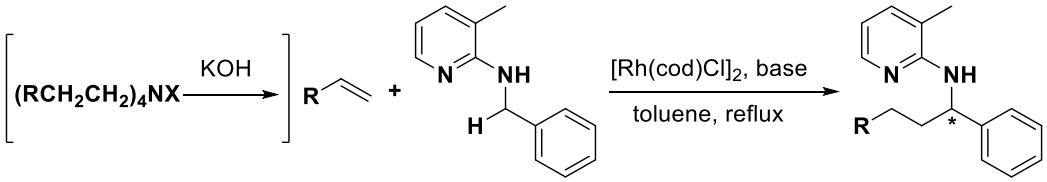
To date, enantioselective C-H functionalization occupies a rather small quantity of the reported methodologies. The lack of attention is quite striking as enantioselective C-H protocols are potential methodologies for late-stage-modifications in pharmaceuticals and related topics. This leaves room for further investigation and within this project, we are investigating the stereochemical induction of the model reaction. To elucidate the feasibility, we were focusing on ligand modification of the rhodium catalyst used in the alkylation reaction.



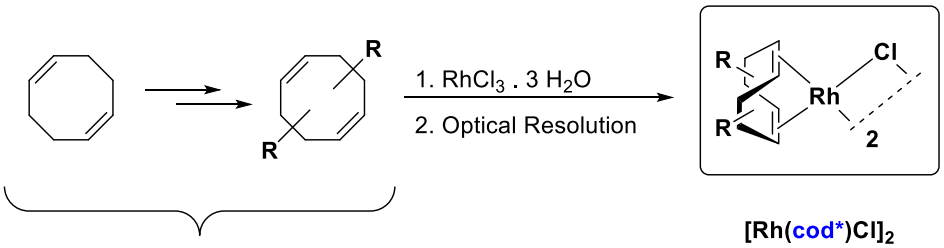
Our catalyst is a rhodium(I) dimer bearing 1,5-cyclooctadiene (cod) as ligand. This cod-ligand is very common in catalytic systems and the application of such systems spans over a broad variety of reaction types. Cycloocta-1,5-diene can be considered a standard ligand employed in many systems, but chiral cod-ligands are not commonly applied.

Deutsche Kurzfassung

Die Regioselektivität war und ist einer der Forschungsschwerpunkte innerhalb der C-H Aktivierung und mittlerweile sind eine Vielzahl an etablierten und zuverlässigen Strategien vorhanden. In diesem Zusammenhang hat unsere Forschungsgruppe die direkte Alkylierung von benzylischen Aminen *via* C-H Aktivierungsmethoden veröffentlicht. Dabei wurden Olefine bzw. Olefin-Substitute im Fall von gasförmigen Alkenen als Alkylierungsreagenzien eingesetzt. Die Regioselektivität wurde durch die Ausnutzung der sogenannten „directing-group-strategy" erreicht, indem eine intrinsische Pyridin-Funktionalität als dirigierende Gruppe benutzt wurde. Dadurch konnte die benzylische Position direkt alkyliert werden. Die Reaktionsbedingungen für diese C(sp^3)-H Aktivierung wurden in vorangegangen Arbeiten optimiert und der nächste logische Schritt war die Steuerung der Enantioselektivität.



Enantioselektive C-H Aktivierung stellt bis heute eine Herausforderung dar und nur ein kleiner Bruchteil der veröffentlichten Arbeiten adressiert die Stereochemie innerhalb von C-H Funktionalisierungen. Daher stellt die, relativ junge, enantioselektive C-H Aktivierung eine interessante Herausforderung dar und der Fokus dieser Diplomarbeit liegt auf der potentiell möglichen enantioselektiven Induktion der Alkylierungsreaktion von benzylischen Aminen. Der Schwerpunkt wurde hierbei auf die Liganden-Modifizierung des Rhodium-Katalysators gelegt.



Der Katalysator ist ein Rhodium(I)-Dimer mit einem 1,5-Cyclooktadien-Liganden (cod). Dieser cod-Ligand wird in vielen katalytischen Systemen eingesetzt und die Applikation dieser Komplexe umfasst viele unterschiedliche Reaktionstypen. Cyclookta-1,5-dien ist einer von vielen Standardliganden, aber chiral-modifizierte cod-Liganden stellen eine Seltenheit in der Literatur dar.

Key

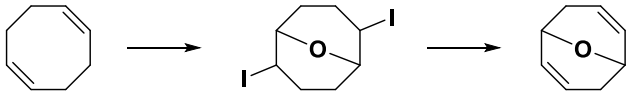
All compounds synthesized in this thesis are labeled with bold Arabic numbers. Intermediates are indicated with bold Roman numerals. Byproducts generated in some reactions or compounds that are intended to be grouped together are labeled with bold Arabic numbers followed by bold Latin alphabetic characters.

Literature citations are indicated by superscript Arabic numbers. Footnotes in tables, figures or schemes are indicated with superscript Latin characters and are found directly below the respective table, figure or scheme.

Content

1. General schemes

1.1 Synthesis of cyclooctadiene derivatives



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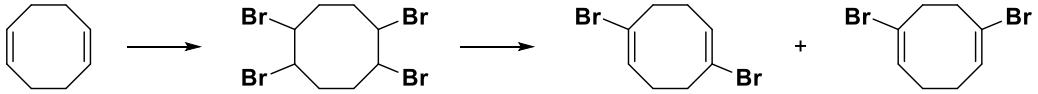

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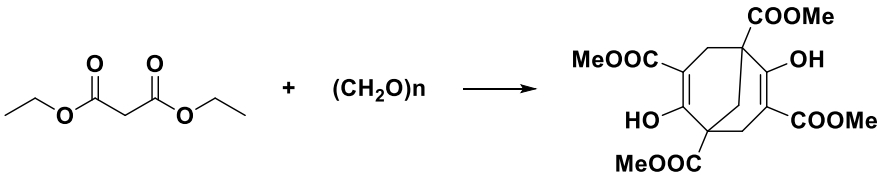

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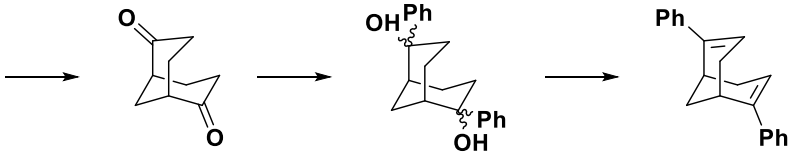

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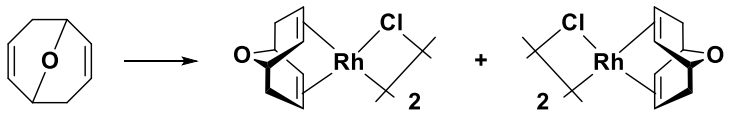
1.2 Synthesis of rhodium complexes



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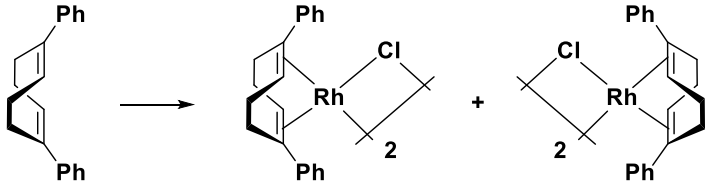

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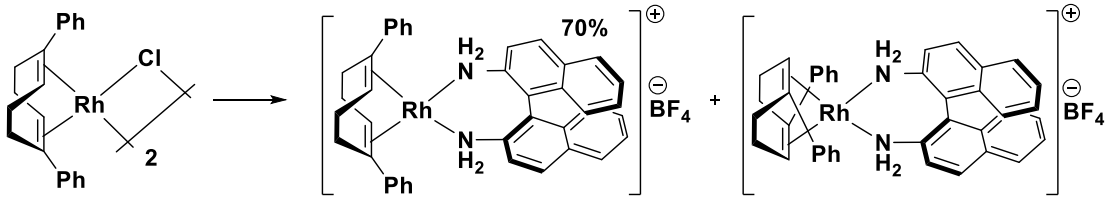
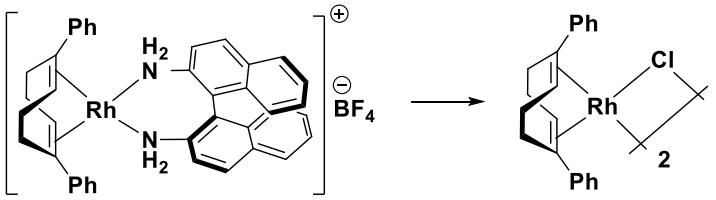
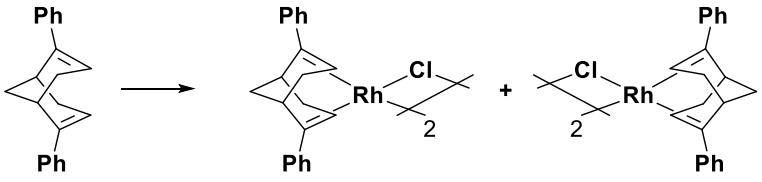


dl-7 (*R*,*R*)-8



(*R*,*R*)-8 *(R)*-7



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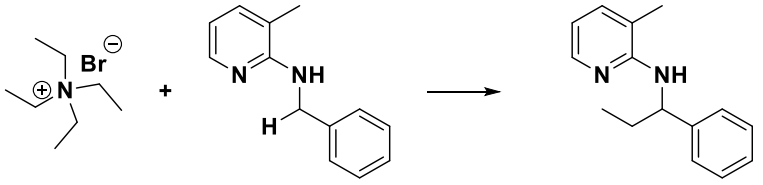
1.3 Alkylation of benzylic amines



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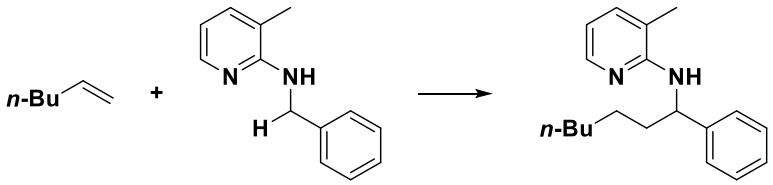


14

2. Abbreviations

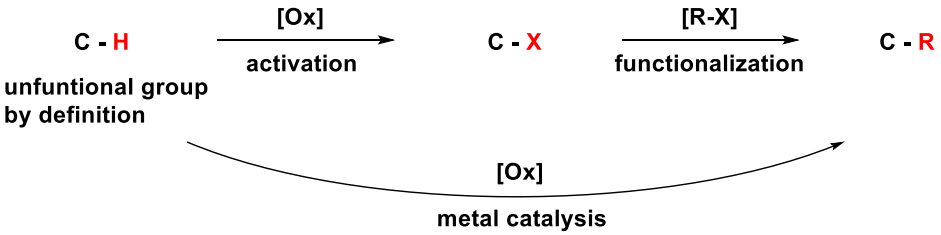
(*R*)-(+)-DABN	*(R)*-1,1´-binaphthyl-2,2´-diamine
AcOH	acetic acid
cat.	catalytic
cod	1,5-cyclooctadiene
d	doublet
eq.	equivalent
Et_2O	diethyl ether
EtOAc	Ethyl acetate
LP	light petroleum
m	multiplet
mp	melting point
n-Bu	n-butyl
n-Hex	n-hexyl
q	quartet
rac.	racemic
sat. aqu.	saturated aqueous
t	triplet

3. Introduction

The framework of organic molecules is dominated by the presence of carbon-hydrogen (C-H) and carbon-carbon (C-C) bonds, accompanied by the incorporation of a few heteroatoms. Considering this dominance of carbon atoms, it is only natural that C-C bond forming transformations are of fundamental interest for organic chemists. Among numerous approaches, transition metal-catalyzed cross-coupling reactions have overwhelmingly contributed to this subject and the foundations date back to the 1970s with innovative publications from Beletskaya, Corriu, Kumada, Kochi, Murahashi, Sonogashira, Stille, Trost Tsuji and many more.[1] Today, cross-coupling reactions are unquestionable highly useful C-C bond forming transformations and the scope of substrates and functional group tolerance has undergone substantial growth since the last decade.[2] These methodologies have strongly influenced on how chemists set up strategies and the awarding of the 2010 Nobel Prize in Chemistry to Richard Heck, Ei-chi Negishi and Akira Suzuki for their contribution in palladium-catalyzed cross-coupling reactions has clearly highlighted the importance of such transformations.[3–7] Besides palladium, a variety of other transition metals are known to be catalytically-active including nickel, copper, platinum, iron and cobalt. Despite this diverse availability of cheap or cheaper transition metals, palladium-based catalysts are still preferably used due to their stability under various conditions and high functional group tolerance.

3.1 C-H functionalization

The major drawback with transition metal catalyzed cross-coupling reactions is the need for pre-functionalized coupling partners. This is where C-H functionalization proves to be superior. The selective C-H functionalization, a very promising field within the plethora of C-C bond forming transformations, allows the direct coupling of non-pre-functionalized substrates and results in a more atom- and step-efficient synthesis. [8]

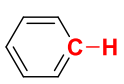
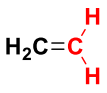
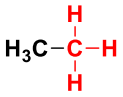
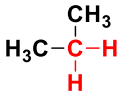
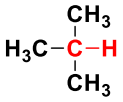
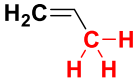


Scheme 1: C-H activation as a shortcut to direct functionalization

A carbon-hydrogen bond is the unfunctional group by "definition" [8] and an organic molecule has several types of C-H bonds incorporated that can serve as potential functional groups. The p*K*a values (Table *1*) of these non-acidic bonds decrease tremendously along the series $C(sp^3)$-H → $C(sp^2)$-H ~ allylic $C(sp^3)$-H → C(sp)-H and respectively, the acidity shows the opposite trend.[9–11] The significant gap in reactivity between $C(sp^2)$-H and $C(sp^3)$-H bonds is

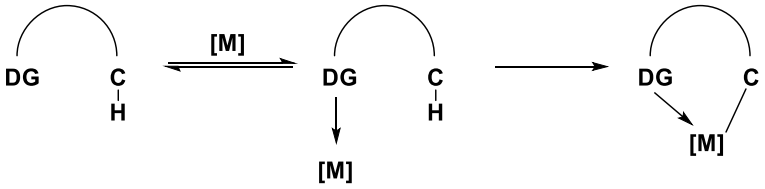
also in compliance with the current literature, as the majority of examples are still focusing on C(sp^2)-H functionalization. [12,13]

Table 1: p*Ka* values of selected carbon-hydrogen bonds

	C(sp^2)-H_{arom}	C(sp^2)-H_{vinyl}	C(sp^3)-$H_{1°}$	C(sp^3)-$H_{2°}$	C(sp^3)-$H_{3°}$	C(sp^3)-$H_{allylic}$
						
p*Ka*	~43	~44	~50	~50	~50	~43

3.2 Directed C-H functionalization

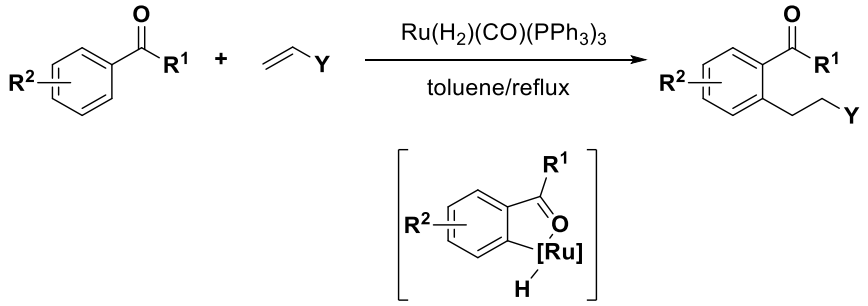
In order to achieve widespread application of C-H activation methodologies, control of selectivity is one of the utmost requirements. To expand on the selectivity, it has been traditionally difficult to control chemo-, site- and enantioselectivity owing to the presence of multiple C-H bonds of comparable bond strength and steric environments.[14] One way to address the challenge of site-selectivity is the assistance of a directing group (DG). These DGs consist of a coordinating moiety that directs the metal catalyst into proximity of the target C-H bond to form a typically five- or six-membered metallacycle intermediate (Scheme 2).[15] The coordination of the metal catalyst with the directing group is usually considered the fundamental step in C-H activation processes. [16]



Scheme 2: Utilizing directing groups as an approach to overcome site-selectivity issues

This strategy would also allow to overrule innate functionalization[17] in (hetero)arenes, as heteroatoms in aromatic systems usually appoint the site-selectivity due to their influence on the electron density within heterocycles. [18–22]

To date, the directing group strategy has been the most successful approach in directed C-H functionalization, established through the pioneering contributions of Murai (Scheme 3) and Chatani in the late 1990s. [23,24] About a quarter of the recent C-H functionalization publications in *The Journal of the American Chemical Society*, *The Journal of Organic Chemistry* and *Organic Letters* are exploiting an intrinsic functionality as directing group and this emphasizes the broad applicability of this strategy. [25]

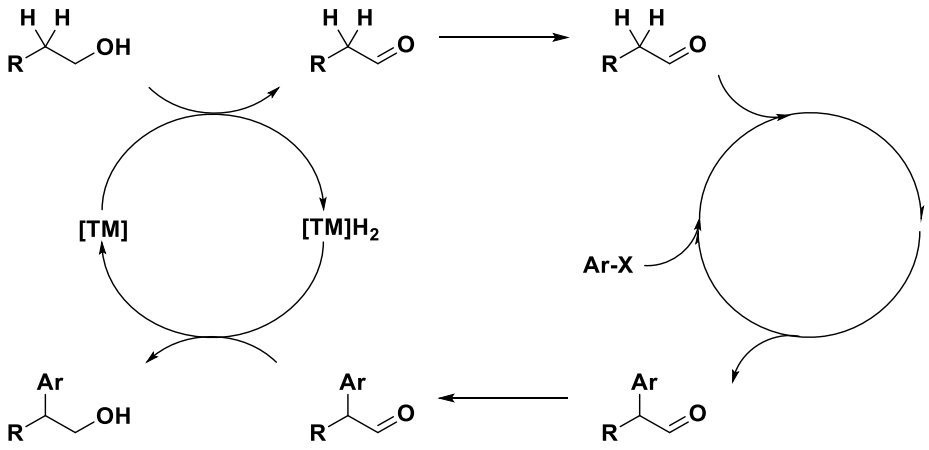


Scheme 3: Ru-catalyzed olefination of aromatic ketones as pioneering work in the directing group strategy

The Ruthenium-catalyzed alkylation of aromatic ketones (Scheme 3), discovered by the group of Murai. [24], was among the first examples of C(sp^2)-H functionalization to proceed *via* the directing group strategy. The absence of any substitution on the aromatic system predominantly yielded mono-alkylation within reasonable time, accompanied by di-alkylation as side product. The ratio shifted in favor for the di-alkylation with prolonged reaction time in case of triethoxyvinylsilane as alkylating agent. The undesired side product was successfully suppressed *via ortho*-substitution or introduction of steric bulk on the non-aromatic side.

Within the last three decades, the scope of applicable directing groups has undergone substantial growth. The scope that can now be accessed includes a variety of carbonyl-based moieties like aldehydes[26], carboxylic acids[27], esters[28], carbamates[29] and many more. Heterocycles have also been utilized as DG; especially pyridine has frequently been reported as an effective DG due to its simplicity and ease of installation. [30,31] For a comprehensive overview, Sambiaggio *et al.*[15] is suggested.

Recently, transient directing groups have emerged as new advances in this area of research. In this approach, the *in-situ* installment and removal of the DG provides a shortcut to C-H functionalization, making a covalent bonded motif dispensable. [32] For instance, aldehyde and ketone derivatives such as imines, oximes and hydrazones, are frequently used as transient coordinating moiety. [24]

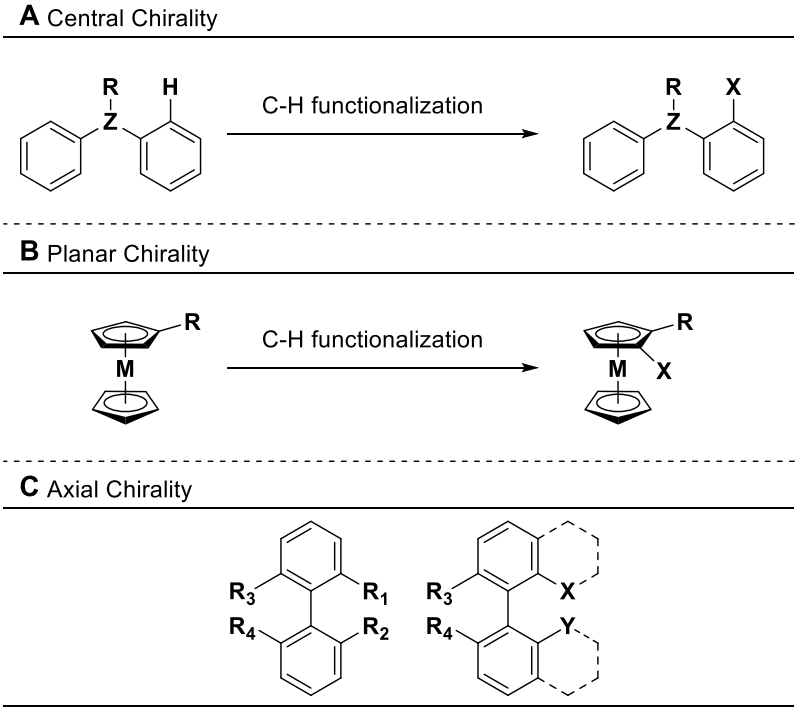


Scheme 4: C-H functionalization using a transient DG through dual-catalytic transition metal catalysis

Recently, the group of Pawel[33] used a dual-catalytic transition metal system for the functionalization of alcohols in a cascade sequences of reactions. (Scheme 4) The two catalytic cycles are independent of each other and utilize different transition metal complexes for the dynamic covalent bonding of the DG and the actual C-H functionalization. Initially, the alcohol reacts reversibly with a Ruthenium complex to form the aldehyde intermediate *via* a "hydrogen-borrowing" mechanism in cycle I. The aldehyde then enables the Pd-catalyzed C-H functionalization in the second cycle II. Hydrogenation of the functionalized intermediate completes the first catalytic cycle and affords the β-functionalized alcohol. This dual-catalytic system allows the functionalization on sites that are in general directly inaccessible and the applicability was demonstrated with a broad scope of 81 examples.

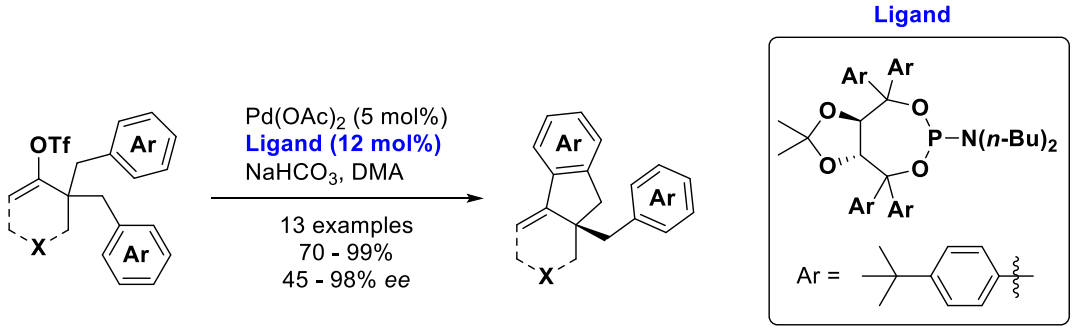
3.3 Enantioselective C-H functionalization

With recent advances made in site-selectivity by exploiting innate or directing effects, stereochemistry generating C-H activation methodologies are currently under intensive research. Enantioselective C-H functionalization, a promising field yet to mature, was first demonstrated on sp^2-hybridized carbons due to their greater steric accessibility and acidity than their sp^3-hybridized counterparts. In general, enantioselective C(sp^2)-H activation proceeds through desymmetrization of a prochiral starting material *via* the selective C-H functionalization of an enantiotopic aryl C-H bond, followed by inter- or intramolecular functionalization to generate central, planar or axial chirality (Scheme 5A-C). [34]



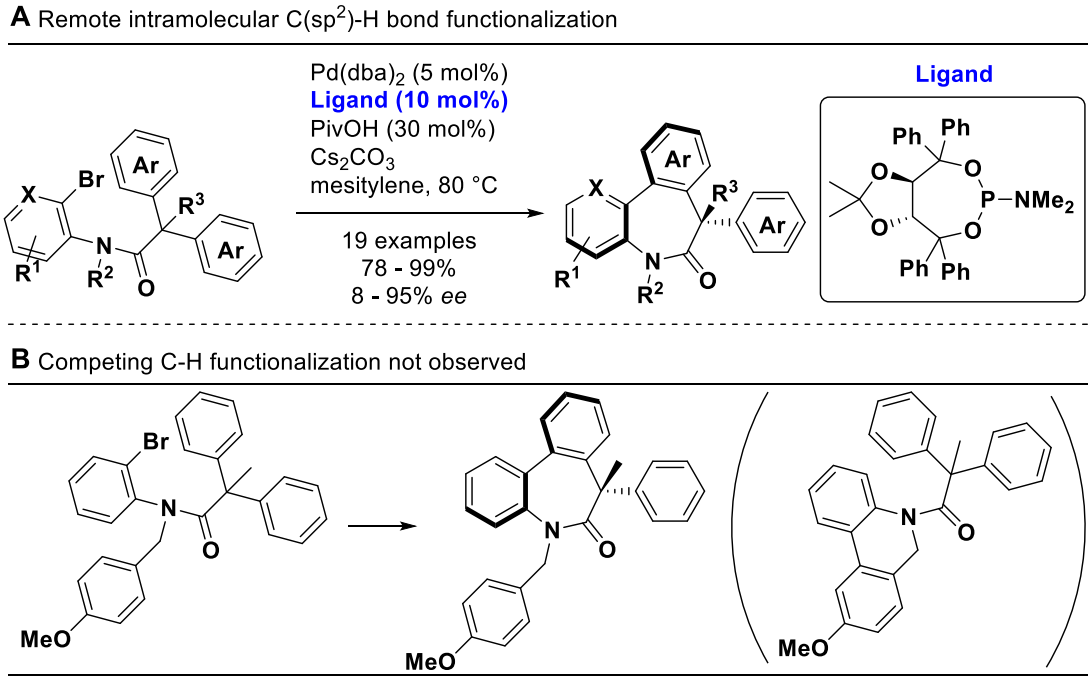
Scheme 5: General nature of chirality in asymmetric C(sp^2)-H activation

In 2009, the group of Cramer[35] reported the first enantioselective C(sp^2)-H functionalization. In particular, the intramolecular arylation of vinyl triflates yielded chiral indanes utilizing a Pd(0)/Pd(II) catalytic cycle. The origin of the enantioselectivity was derived from a monodentate TADDOL-phosphoramidite and in case of *p*-^{t}Bu-phenyl substitution high enantiocontrol at room temperature was achieved.



Scheme 6: First example of enantioselective C-H functionalization

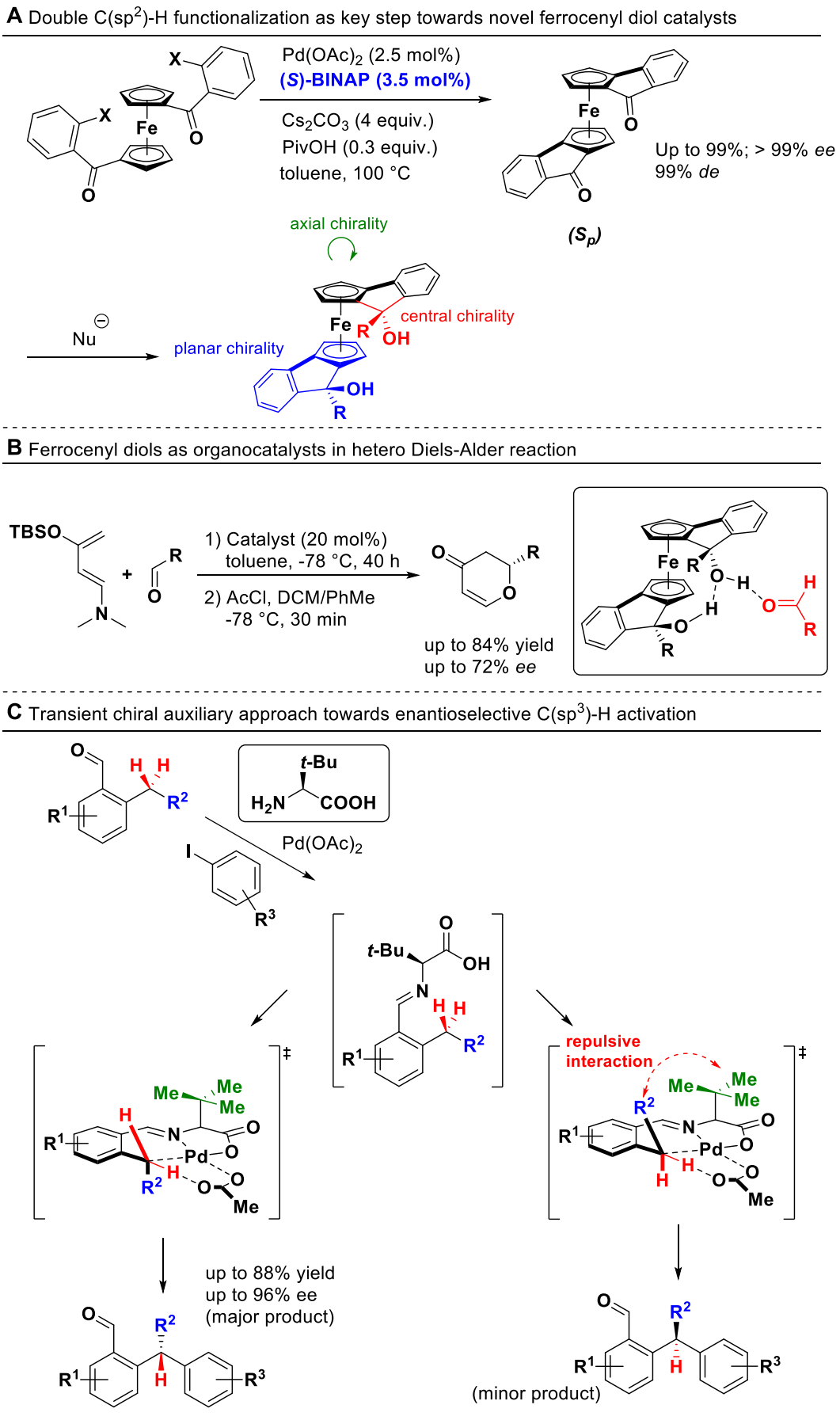
This methodology was also applied to the intramolecular arylation of amides to yield chiral dibenzazepinones *via* remote C-H bond functionalization (Scheme 7A). [36] Protection of the amide was essential for the reactivity and the reaction proceeded with high enantiocontrol, except for X = N. The mechanism includes an unusual eight-membered cyclometalation intermediate and in case of *p*-methoxybenzyl-protection, no competing reaction to the dihydrophenanthridine *via* seven-membered cyclometalation intermediate was observed (Scheme 7B).



Scheme 7: Dibenzazepinones *via* intramolecular arylation of *N*-substituted amides

Recently, the synthesis towards a novel ferrocenyl diol organocatalyst family was reported that facilitates a double C(sp^2)-H cyclization as a key step to provide the dione intermediates with high diastereomeric and enantiomeric control (Scheme 8A). Further modification *via* nucleophilic addition yielded the diols with high stereocontrol. The ferrocenyl diols have been applied as hydrogen-bond donor catalysts to asymmetric hetero Diels-Alder reactions. (Scheme 8B) The scaffold features a unique combination of planar, axial and central chirality and these chiral diols are additionally valuable synthons for diamines, phosphines, phosphoramidites and more. [37–39]

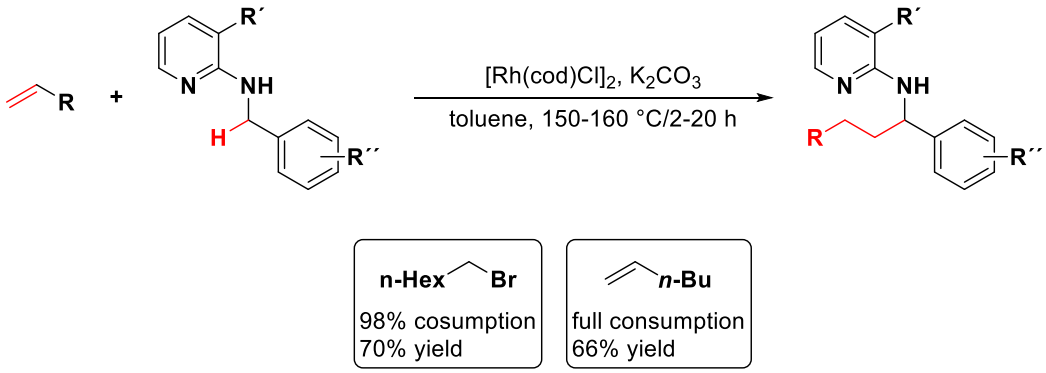
The group of Yu developed an elegant transient chiral auxiliary approach for enantioselective C(sp^3)-H desymmetrization. The approach relies on the *in-situ* formation of an imine intermediate between the amine moiety of the amino acid ligand and the aldehyde motif of the substrate. Upon coordination with Pd(II), the transition state with less steric repulsion leads to the major product, following the principle of diastereoselection. [14,40]



Scheme 8: Enantioselective C(sp^2)-H and C(sp^3)-H functionalization approaches

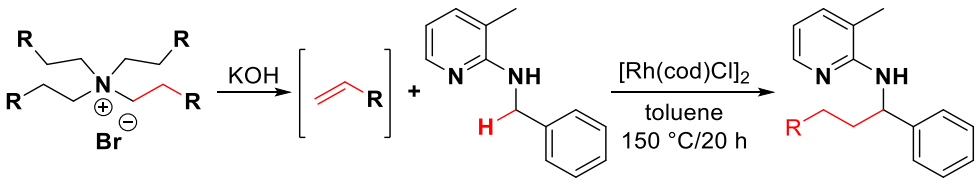
3.4 Alkylation of benzylic amines via C-H functionalization

Our group has previously reported a Rh(I)-catalyzed direct alkylation of benzylic amines by utilizing alkyl bromides and olefins as alkylating agents (Scheme 9). [41,42]



Scheme 9: Direct alkylation of benzylic amines *via* C-H activation pathway

The applicability was demonstrated with a variety of alkyl bromides including linear chains (C_2 to C_{22}), branched and functional group-containing (e.g. ester) systems. Substitution (*para*, *ortho*, *meta*) on the benzylic amine was also tolerable. In initial experiments with 1-bromobutane and 2-bromobutane, the same alkylation product at the terminal carbon was obtained. The alkylation reaction using alkenes proceeded considerably faster and thus the temperature could be reduced from 160 °C to 150 °C. In case of short-chain olefins, the low boiling point of the substrates is inconvenient for the procedure and results in the need of high-pressure equipment. To target this drawback, our group has disclosed the *in-situ* formation of gaseous olefins by utilizing quaternary ammonium salts as alkylating agents. [43] The approach is based on the very fundamental Hofmann-elimination and provides an easy-to-handle alternative.

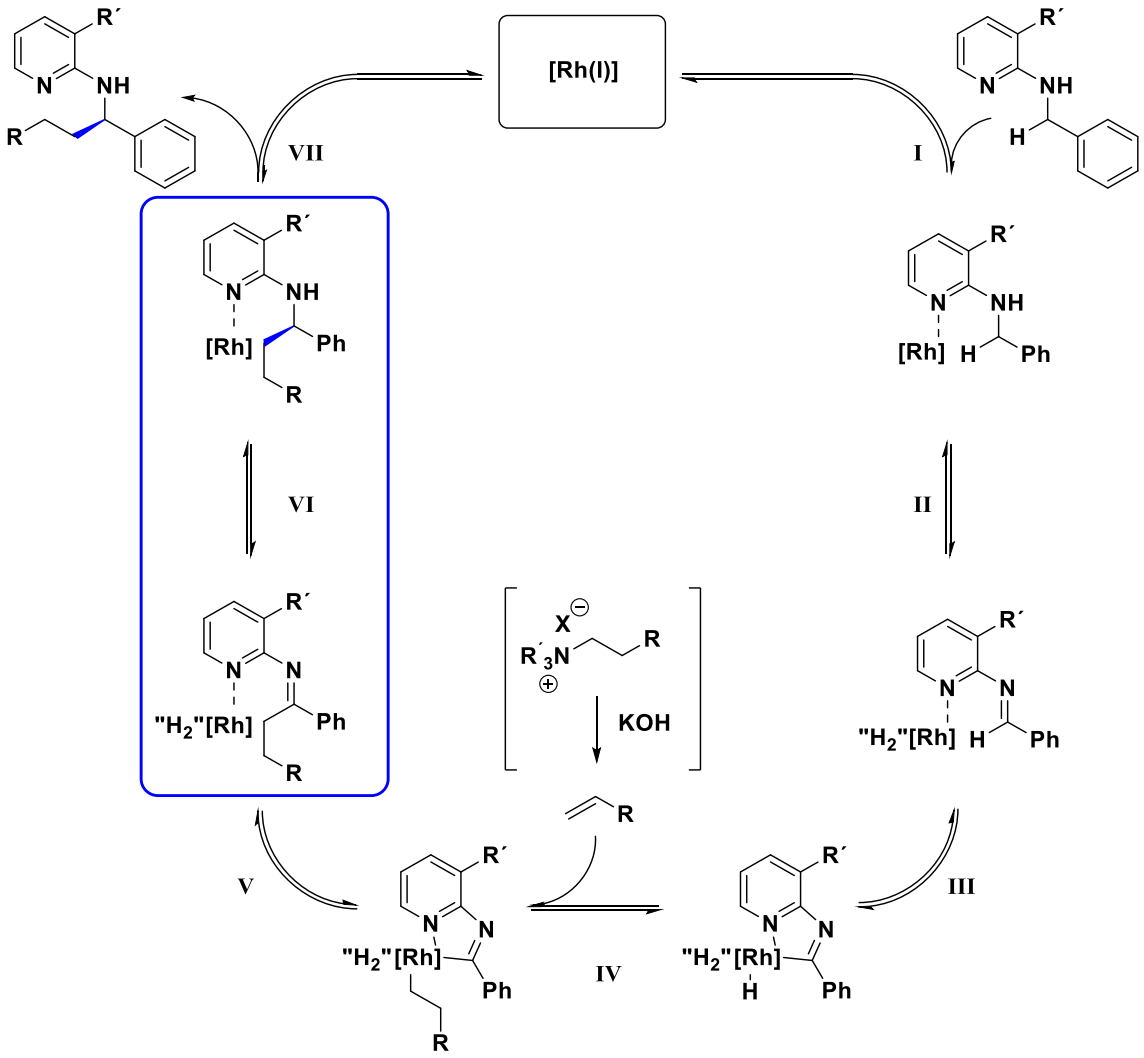


Carbons	Yield
1	12%
2	68%
3	62%
4	60%
5	58%
6	61%
8	40%

Scheme 10: Direct alkylation utilizing solid-olefin-surrogates as alkyl source

The latter methodology stemmed from optimizing the alkene protocol. Among several modifications, it was observed that the addition of triethylamine most widely avoided the formation of side products (not depicted here). In addition, the ethylated product was obtained and thus indicating the presence of ethene. Alkylation of triethylamine to the corresponding quaternary ammonium salt and subsequent Hofmann-elimination was implicated to precede

the actual C-H functionalization. This finding has led to the successful application of quaternary ammonium salts as solid-olefin-surrogates in our initial alkylation reaction (Scheme 10).

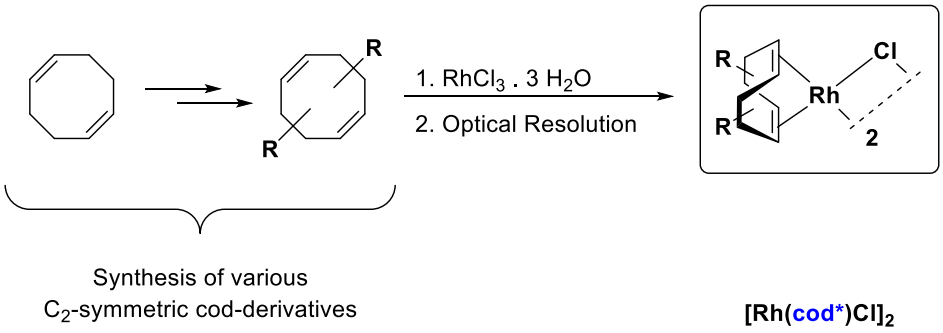


Scheme 11: Proposed mechanism for the Rhodium-catalyzed alkylation of benzylic amines

Mechanistic studies[44] of the formally C(sp^3)-H functionalization are suggesting an intermediate C(sp^2)-H activation pathway for the direct alkylation. The proposed catalytic cycle (Scheme 11) is initiated by the coordination of the pyridine-directing group onto the rhodium(I) species. The substrate-rhodium complex is then reversibly dehydrogenated to the corresponding imine (II). The reduction may occur *via* transfer hydrogenation onto a ligand or oxidative addition into the rhodium species. Transfer hydrogenation in association with coordinated ligands is very common. [45–53] The oxidative addition to the dihydride complex would yield an uncommon Rh(V) system but has been reported on different systems employing rhodium catalysis. [54–60] The actual alkylation within steps (IV) and (V) leads to the elongation of the intermediate. Hydrogenation of the imine (VI) and release of the product (VII) closes the proposed catalytic cycle.

3.5 Motivation for this thesis

With optimized conditions in hand for the alkylation with alkenes and quaternary ammonium salts as solid-olefin-surrogates, the focus was appointed towards enantioselectivity. The catalytic cycle (Scheme 11) proposes an interconversion from an imine to an amine in step (VI), representing a change in hybridization from sp^2 to sp^3. This crucial step leaves potential room for the stereochemical induction within this proposed mechanism. To elucidate the feasibility, we are focusing on ligand modification of the rhodium catalyst used in the alkylation reaction (Scheme 12).



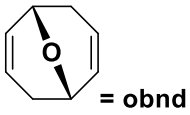
Scheme 12: Our approach towards enantioselective induction

Our catalyst is a rhodium(I) dimer bearing 1,5-cyclooctadiene (cod) as ligand. This cod-ligand is very common in catalytic systems and the application of cod-ligated complexes spans over a broad variety of reaction types, including direct C-H arylation of BINOLs towards 3,3´-diaryl BINOLs[61], hydrogenation of arenes[62], to name only a few examples. Cycloocta-1,5-diene can be considered a standard ligand employed in many systems, but chiral cod-ligands are not commonly applied. The lack of attention is quite striking, given the frequent use as ligand.

4. Results and discussion

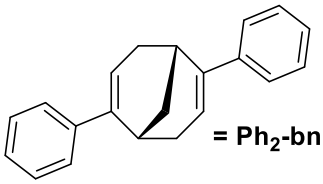
4.1 Derivatives of cycloocta-1,5-diene known in the literature

A 9-Oxabicyclo[3.3.1]nona-2,6-diene



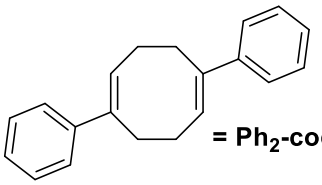
= obnd

C 2,6-Diphenylbicyclo[3.3.1]nona-2,6-diene



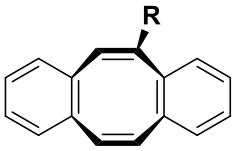
= Ph_2-bnd

B 1,5-Diphenyl-cycloocta-1,5-diene



= Ph_2-cod

D Dibenzo[a,e]cyclooctenes

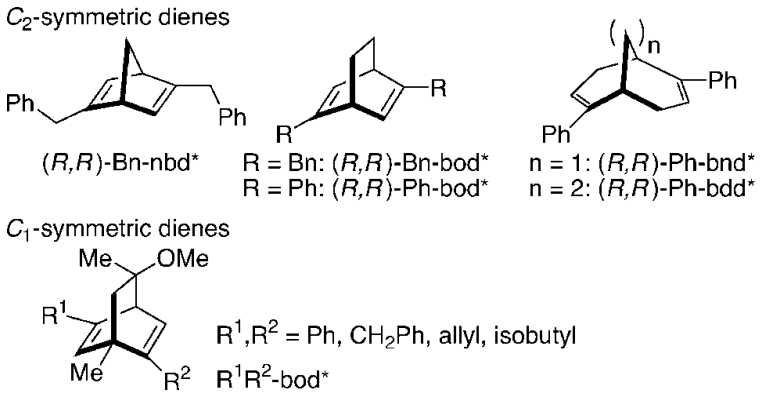


= Ph_2-dbcot

Scheme 13: Known chiral cod-derivatives

The scope of synthetically accessible cod-derivatives (Scheme 13)[63–66] in the literature was surprisingly negligible as various bicyclic chiral dienes have already been employed in asymmetric catalysis (Scheme *14*). [65,67–74] The pro-chiral Ph_2-dbcot (Scheme 13D) was of less interest for the intended purpose, due to the C_1-symmetric nature of the scaffold that is in general less beneficial for the enantioselective induction.

To proof the general applicability of modified cod-ligands in the target alkylation reaction, 9-oxabicyclo[3.3.1]nona-2,6-diene (obnd) and 1,5-diphenyl-1,5-cyclooctadiene (Ph_2-cod) were initially short-listed as target ligands due to their fast access towards the racemic form. (Scheme 13A-B) Hence, it can be quickly tested whether the catalyst modification is tolerated by our test reaction.

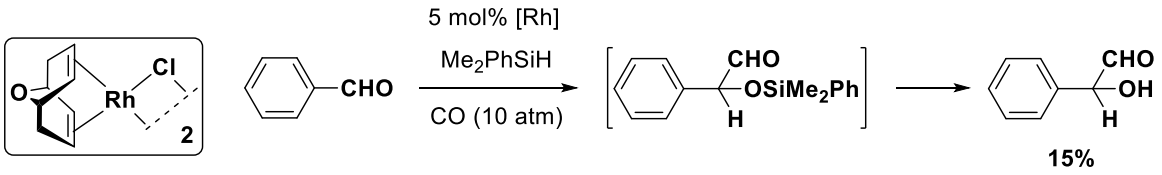


Scheme 14: Various chiral bicyclic dienes employed in asymmetric catalysis[a]

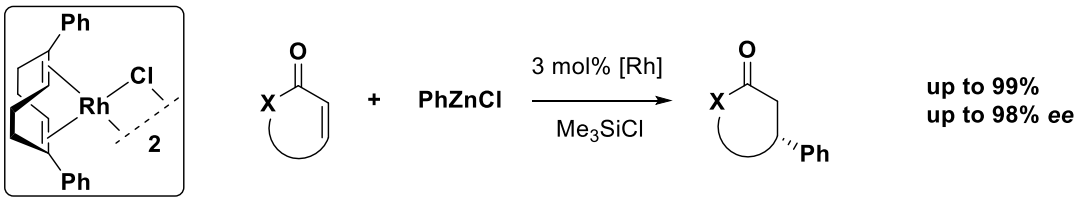
The three C_2-symmetric ligands obnd, Ph_2-cod and Ph_2-bnd were already applied in (asymmetric) rhodium-catalysis reactions (Scheme 15). In a preliminary study, [Rh((*R*,*R*)-obnd)Cl]$_2$ was used in the silylformylation of benzaldehyde that did not lead to satisfactory results.; the reaction afforded a hydroxyaldehyde in only 15% yield (Scheme 15A). [66] An enantiomeric excess was not reported. Surprisingly, this catalyst has since not been applied to any other reaction. The compound [Rh((*R*)-Ph_2-cod)Cl]$_2$ showed high catalytic activity and enantioselectivity in the asymmetric 1,4-addition of phenylzinc chloride to various enones; mediated by chlorotrimethylsilane (Scheme 15B). [63] The complex [Rh((*R*)-Ph_2-cod)Cl]$_2$ was applied in asymmetric arylation of *N*-(4-nitrobenzenesulfonyl)arylimines with arylboroxines and high yields and enantioselectivities were obtained (Scheme 15C). [65]

[a] Kina, A.; Ueyama, K.; Hayashi, T. Enantiomerically Pure Rhodium Complexes Bearing 1,5-Diphenyl-1,5- Cyclooctadiene as a Chiral Diene Ligand. Their Use as Catalysts for Asymmetric 1,4-Addition of Phenylzinc Chloride. *Org. Lett.*, **2005**, 7 (26), 5889–5892

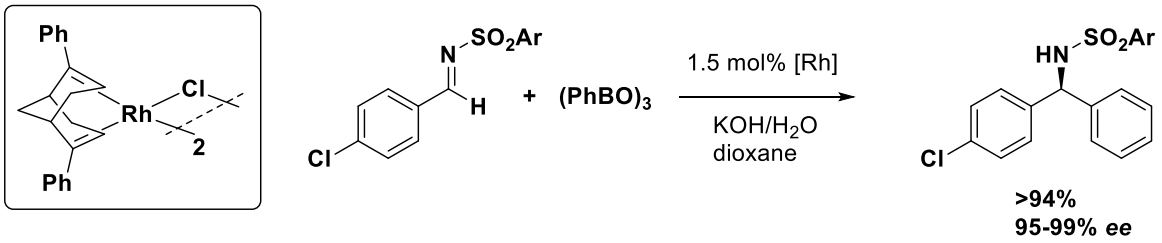
A Silylformylation of benzaldehyde



B Asymmetric 1,4-addition to cyclic ketones and esters



C Asymmetric arylation of *N*-(4-nitrobenzenesulfonyl)arylimines with arylboroxines

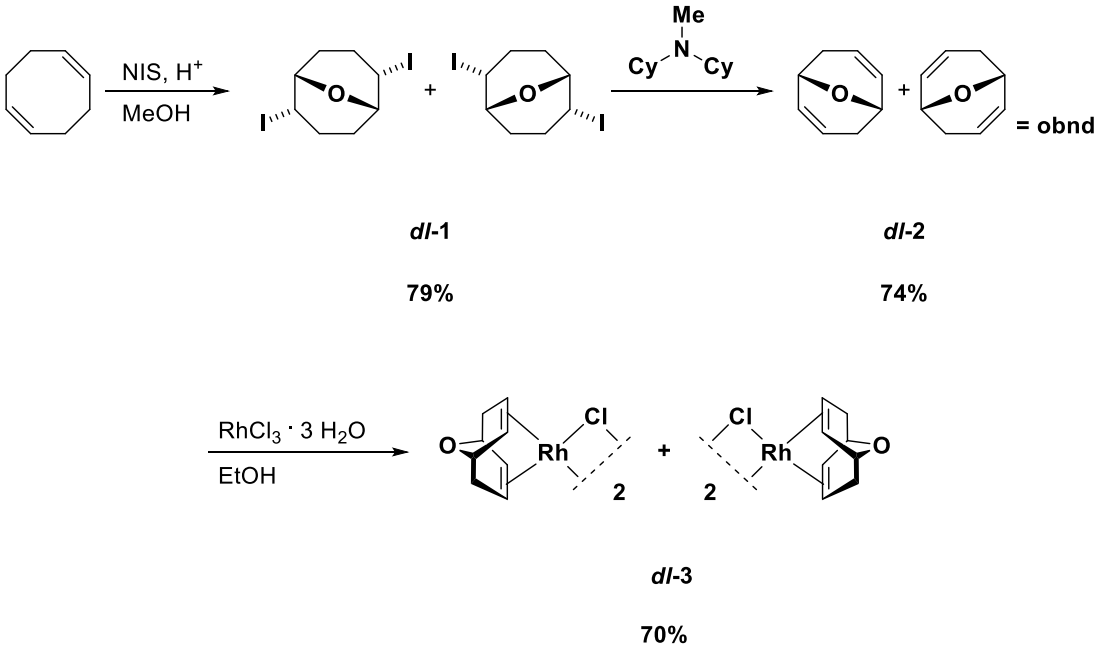


Scheme 15: Application of target Rhodium-complexes in asymmetric catalysis

4.2 Synthesis towards racemic $[Rh(obnd)Cl]_2$ and $[Rh(Ph_2\text{-}cod)Cl]_2$

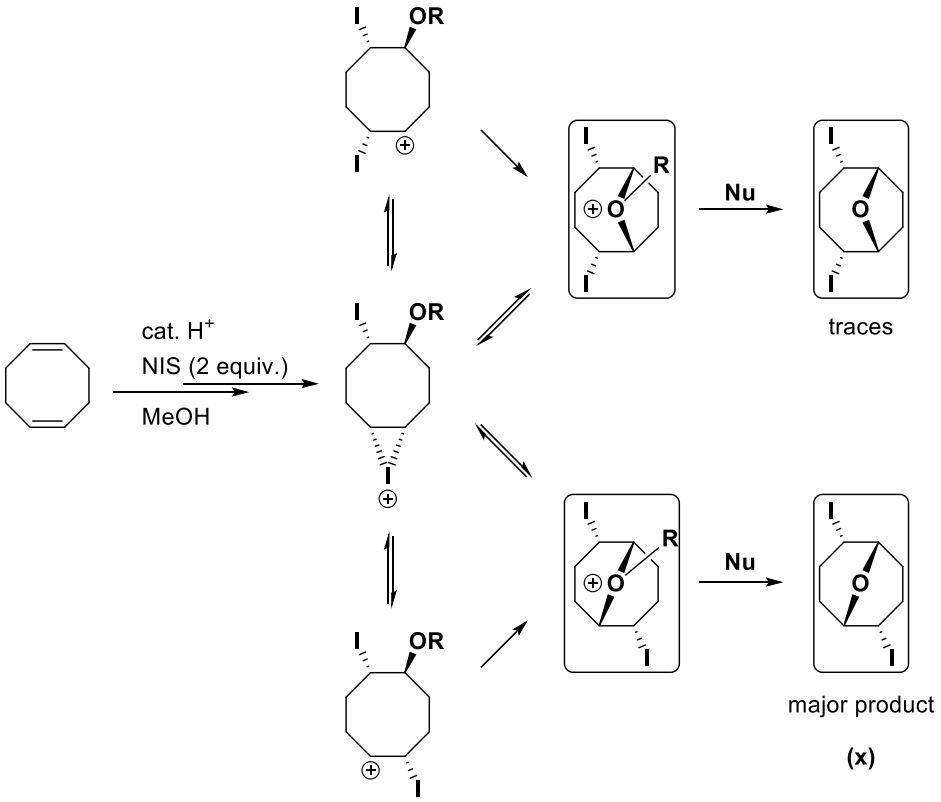
4.2.1 9-Oxabicyclo[3.3.1]nona-2,6-diene

The racemic form of 9-oxabicyclo[3.3.1]nona-2,6-diene (obnd) was accessible in a three-step approach (Scheme *16*) [75]. The treatment of cod with *N*-iodosuccinimide in MeOH with cat. amount of acid afforded 2,6-diiodobicyclo[3.3.1]nonane ***dl*-1**.



Scheme 16: Approach towards racemic $[Rh(obnd)Cl]_2$

The mechanism[76] includes the formation of an iodonium ion on both alkenes, followed by alkoxy halogenation on one of these ions. The ether-functionality can then undergo an intramolecular attack and ring opening leads to the two intermediates I and II. In case of R being a bad leaving group (e.g. Me, Et), the intermediate II is isomerized to the thermodynamically more stable intermediate I from which the desired product is formed. The possible side product was only observed in traces (<1% in NMR). The last step is most likely a substitution reaction, in which the attack of any present nucleophile (MeOH, residual succinimide) leads to demethylation and the cyclic ether acts as a leaving group. The demethylation *via* methyl iodide-formation is less likely, as only 2 equivalents of NIS are present.



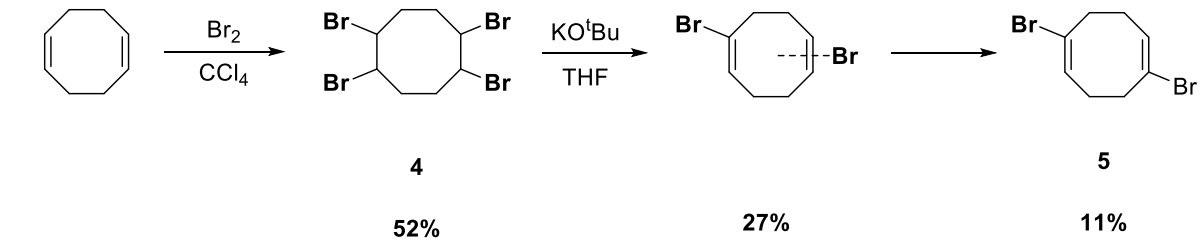
Scheme 17: Proposed mechanism for the formation of the cyclic ether

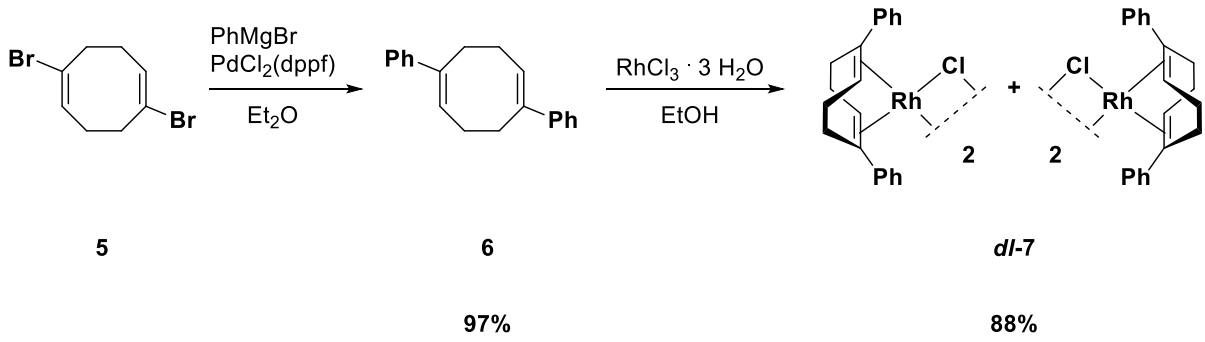
The best conditions for the dehydrohalogenation of 2,6-diiodobicyclo[3.3.1]nonane ***dl*-1** to 9-oxabicyclo[3.3.1]nona-2,6-diene ***dl*-2** were obtained with dicyclohexylmethylamine (neat) at 200 °C within 2 hours. [77] Other protocols, including DBU/DMF, KOH/Ag_2O/MeOH and KOH/MeOH[75] under various conditions led to prolonged reaction times, lower yields and the formation of side products. The following redox reaction of $RhCl_3 \cdot 3\ H_2O$ and EtOH as reducing agent afforded the desired racemic mixture of $[Rh(obnd)Cl]_2$ ***dl*-3**. [78]

4.2.2 1,5-Diphenylcycloocta-1,5-diene

The key intermediate 1,5-dibromocycloocta-1,5-diene **5** for the synthesis towards 1,5-diphenylcycloocta-1,5-diene **6** (Ph_2-cod) was obtained *via* bromination of cod to yield **4** as a mix of diastereomers (Scheme 18). Purification *via* recrystallization from *n*-hexane afforded 52% of 1,2,5,6-tetrabromocyclooctane with high purity, compensating the low yield. In addition, the separation of the diastereomers was applicable *via* column chromatography in small quantities. The dehydrobromination of 1,2,5,6-tetrabromocyclooctane **4** with potassium *tert*-butoxide afforded a mixture of constitutional isomers of 1,5- and 1,6-dibromocycloocta-1,5-diene[79,80] and separation of these two isomers *via* column chromatography was not applicable. Repeated fractional crystallization from *n*-heptane at 40 °C gave desired 1,5-dibromocycloocta-1,5-diene **5** as colorless precipitate by slowly cooling to room temperature.

The Palladium-catalyzed cross-coupling of 1,5-dibromocycloocta-1,5-diene **5** with phenylmagnesium bromide afforded the pro-chiral 1,5-diphenylcycloocta-1,5-diene **6**. [63]



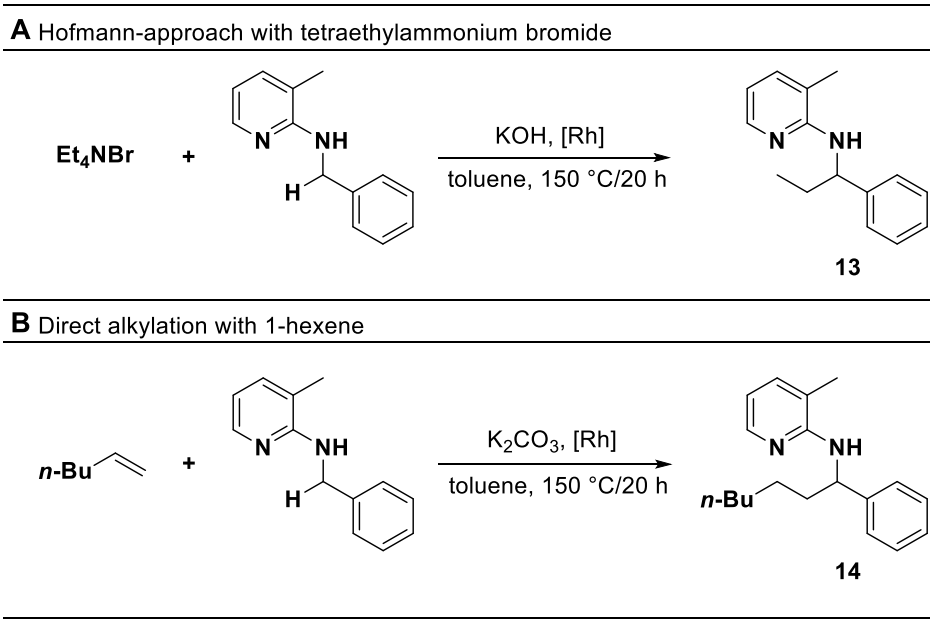


Scheme 18: Synthesis towards racemic $[Rh(Ph_2\text{-cod})Cl]_2$

The diene **6** was coordinated *via* redox reaction from $RhCl_3 \cdot 3\ H_2O$ and EtOH to afford racemic $[Rh(Ph_2\text{-cod})Cl]_2$ ***dl*-7** as red crystals. The pro-chiral diene generates planar chirality upon coordination with the alkene-moiety. [81]

4.3 Alkylation reaction with racemic $[Rh(obnd)Cl]_2$ and $[Rh(Ph_2\text{-}cod)Cl]_2$

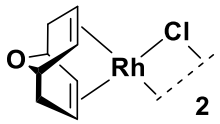
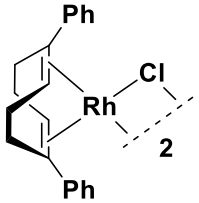
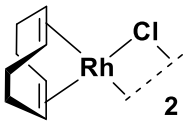
Two model reactions were chosen for the testing of the racemic catalysts. One protocol for the direct alkylation with 1-hexene, and one protocol for the Hofmann-approach with tetraethylammonium bromide. (Scheme *19*)



Scheme 19: Model reactions for the testing of the catalysts

Both racemic complexes ***dl*-3** and ***dl*-7** showed catalytic activity, but the general yield was less compared to the standard catalyst $[Rh(cod)Cl]_2$. (Table 2) At this point, no further reaction optimization was done as the synthesis towards an enantiomerically pure form of one of these complexes was of fundamental interest. In case of model reaction A, ***dl*-7** showed a higher catalytic activity.

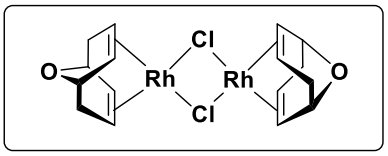
Table 2: Results of the catalysts in both model reactions

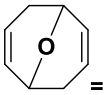
			
	***dl*-3**	***dl*-7**	**Standard**
A	44%	51%	71%
B	44%	42%	64%

4.4 Synthesis towards enantiomerically pure [Rh((*R*)-Ph$_2$-cod)Cl]$_2$

The total synthesis towards an enantiomerically pure form of ***dl*-3** within twelve steps, including highly toxic HMPA as reagent and an overall yield of roughly 3%, was quite elaborate and less attractive (Scheme 21). [66,82]

9-Oxabicyclo[3.3.1]nona-2,6-diene

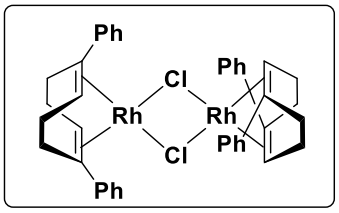


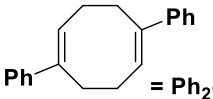


= obnd

***) access to enantiomerically pure form more elaborately**

1,5-Diphenylcycloocta-1,5-diene





= Ph$_2$-cod

***) route to chiral pure form more accessible**

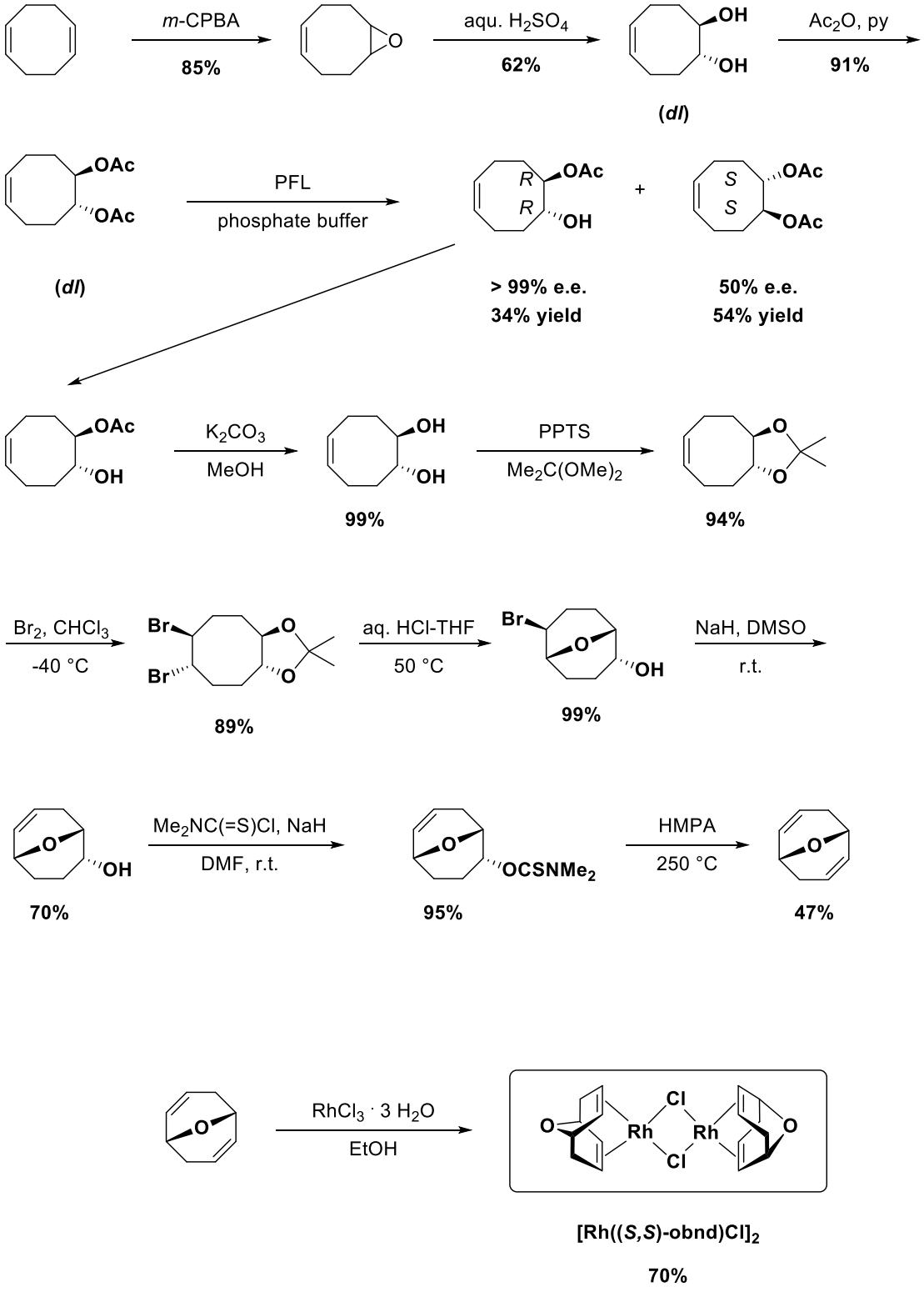
***) optical resolution directly from racemic mixture**

***) induces more steric bulk in close proximity to [Rh]**

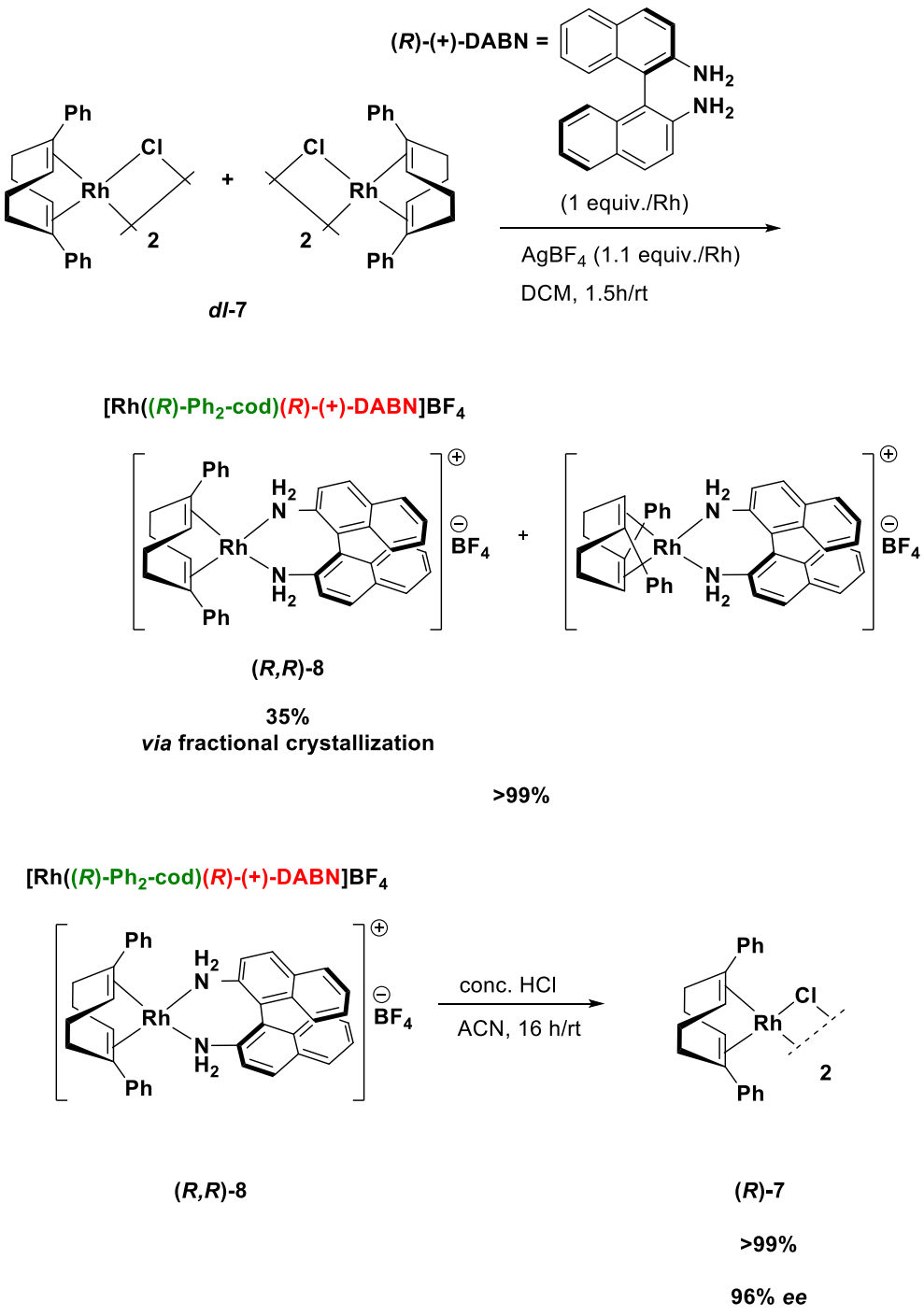
Scheme 20: Comparison of the two target complexes

In case of the synthesis towards the enantiomerically pure [Rh((*R*)-Ph$_2$-cod)Cl]$_2$ **(*R*)-7**, the route to the chiral pure form was more accessible. In particular, the optical resolution could be done directly from the racemic mixture and thus provided a more attractive synthetic pathway with less steps and higher yields (Scheme *22*). In addition, the target complex already showed high catalytic activity and enantioselectivity in asymmetric Michael addition to various enones (Scheme 15). [63]

The optical resolution of the racemic complex was conducted according to the Grützmacher method. [64] The racemic mixture [Rh(Ph$_2$-cod)Cl]$_2$ ***dl*-7** was treated with (*R*)-1,1´-binaphthyl-2,2´-diamine and AgBF$_4$ as counter anion to give a mix of diastereomers in equimolar ratio. The desired isomer [Rh((*R*)-Ph$_2$-cod)(*R*)-(+)-DABN)]BF$_4$ **(*R,R*)-8** was isolated *via* fractional crystallization from THF by stirring at 40-50 °C and slowly cooling to room temperature in THF. Precipitation of **(*R,R*)-8** was then facilitated at -20 °C to give a red, gummy solid. Additional washing with *n*-pentane afforded **(*R,R*)-8** as orange crystals. Hydrolysis of the optical resolution agent, (*R*)-1,1´-binaphthyl-2,2´-diamine, *via* treatment with concentrated HCl in acetonitrile gave enantiomerically pure [Rh((*R*)-Ph$_2$-cod)Cl]$_2$ **(*R*)-7** as orange powder.



Scheme 21: Total synthesis towards rhodium dimer with (*S,S*)-obnd ligand



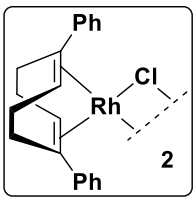
Scheme 22: Optical resolution *via* Grützmacher method

The enantiomeric excess of [Rh((*R*)-Ph$_2$-cod)Cl]$_2$ **(*R*)-7** was determined by evaluating the diastereomeric excess of **(*R,R*)-8** from the ^{1}H-NMR spectra.

4.5 Alkylation reaction with enantiomerically pure [Rh((*R*)-Ph$_2$-cod)Cl]$_2$

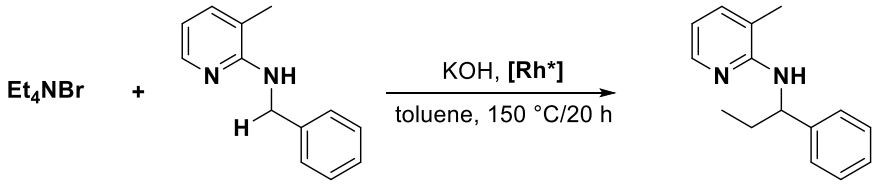
The enantiomerically pure catalyst **(*R*)-7** was then examined for its stereochemical induction in the alkylation reaction using the Hofmann-approach. Unfortunately, the reaction did not afford a satisfactory result as no enantiomeric excess of **13** was obtained.

A Enantiomerically pure rhodium catalyst



[Rh((*R*)-Ph$_2$-cod)Cl]$_2$

B Alkylation via Hofmann-approach using chiral catalyst



13 (56%)

no *ee*

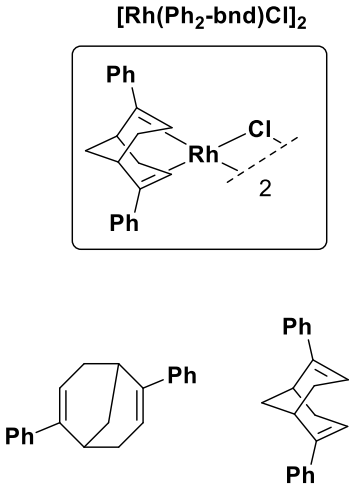
Scheme 23: Attempt of chiral catalysis

This result may originate from the racemization of the catalyst by dissociation of the ligand from the rhodium complex. The free ligand can then undergo a change in conformation and re-coordinate on the other face.

As a result, a further molecular design towards incorporation of a bridge-moiety was deemed necessary.

4.6 Synthesis towards racemic $[Rh(Ph_2\text{-bnd})Cl]_2$

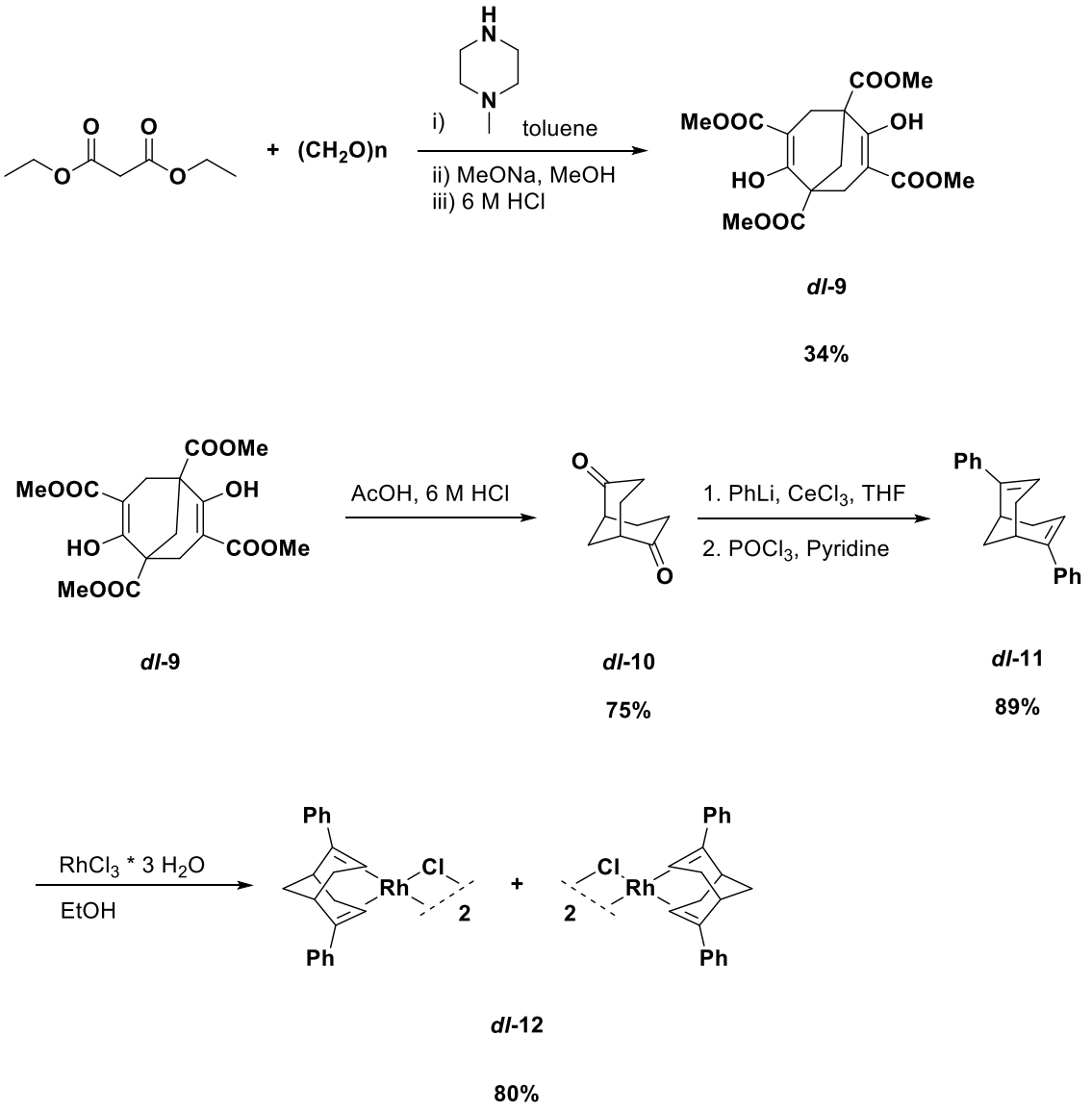
Hayashi *et al.*[65] also reported the synthesis of 2,6-diphenylbicyclo[3.3.1]nona-2,6-diene (Ph_2-bnd) that features a similar scaffold as Ph_2-cod, but has a methylene-bridge incorporated in its scaffold.



Scheme 24: Ph_2-bnd as next target ligand

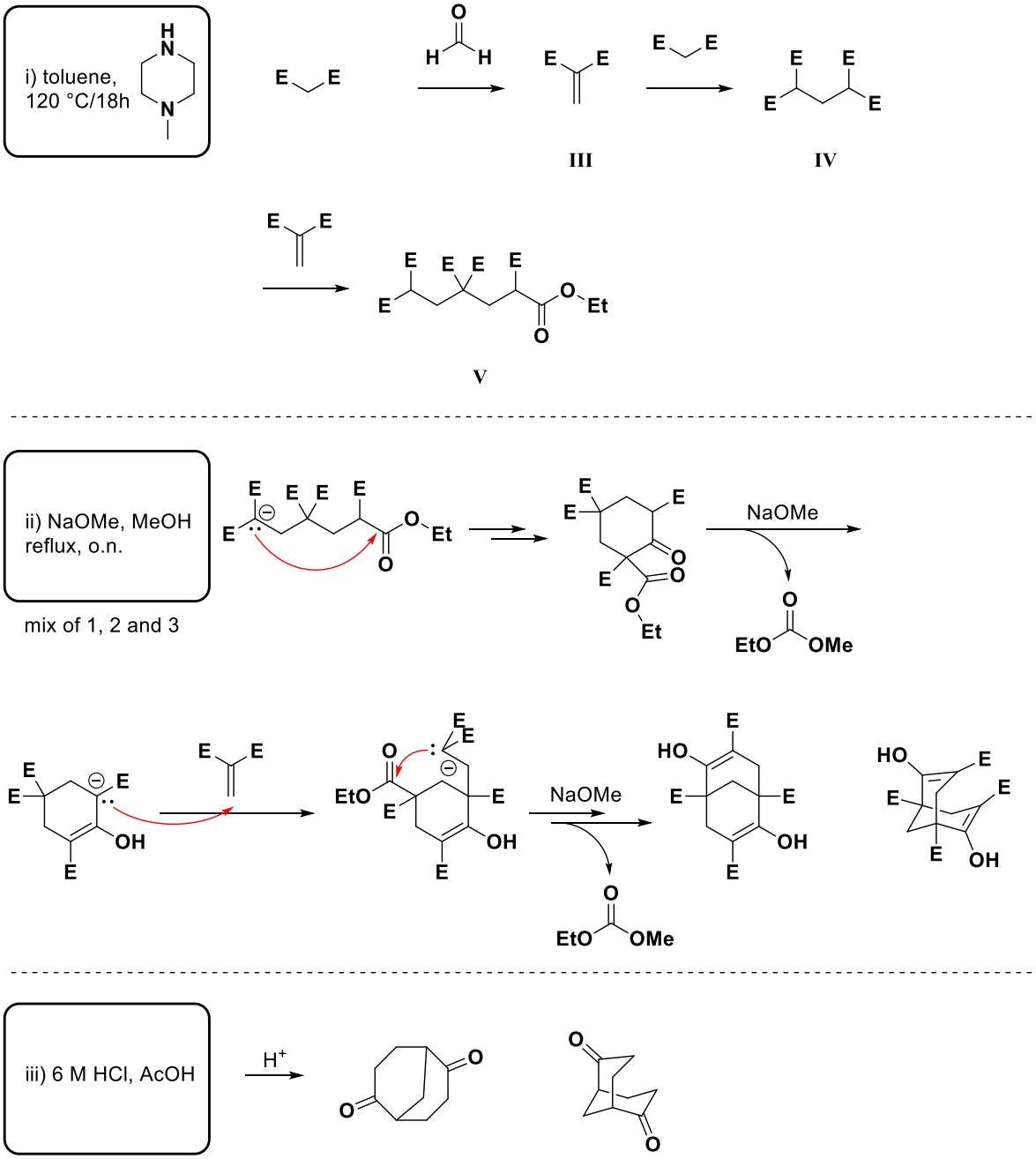
This bridge-moiety would potentially trap the conformation leading to a rigid scaffold and may prevent the proposed racemization.

In a continues Knoevenagel reaction and Michael addition between diethyl malonate and formaldehyde[83–85], yielded the Meerwein ester ***dl*-9** in 34% as reported in the literature under optimized conditions. The conditions also afforded an additional transesterification to the methyl ester. The decarboxylation of Meerwein ester ***dl*-9** afforded the key intermediate bicyclo[3.3.1]nona-2,6-dione ***dl*-10**. [86] In a nucleophilic addition reaction with phenylcerium reagent generated from phenyllithium and ceriumtrichloride in THF, followed by elimination reaction with phosphorus oxychloride, the target 2,6-diphenylbicyclo[3.3.1]nona-2,6-diene ***dl*-11** was obtained (Scheme 25). The racemic $[Rh(Ph_2\text{-bnd})Cl]_2$ ***dl*-12** was obtained in 80% by a redox reaction between $RhCl_3 \cdot 3\ H_2O$ and ***dl*-11** in EtOH.



Scheme 25: Synthesis towards racemic $[Rh(Ph_2\text{-bnd})Cl]_2$

The proposed mechanism of the Meerwein ester formation (Scheme 26)[87] includes in the first step the synthesis of intermediates III, IV and V *via* continues Knoevenagel reaction and Michael addition with 1-methylpiperazine in toluene. The second step is a twofold Dieckmann condensation with sodium methoxide in methanol to yield the Meerwein ester. Hydrolysis of the Meerwein ester then affords the key intermediate Bicyclo[3.3.1]nona-2,6-dione ***dl*-10**.

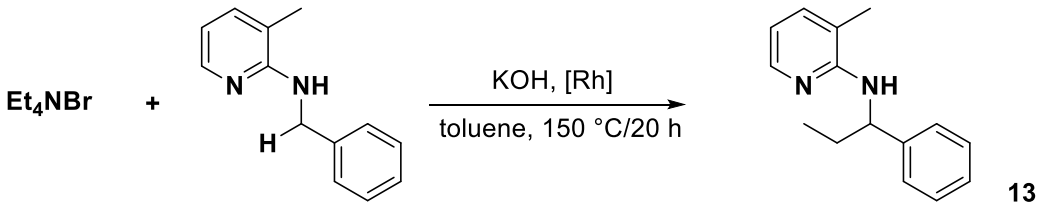


Scheme 26: Proposed mechanism for the Meerwein ester formation (E = ester group)

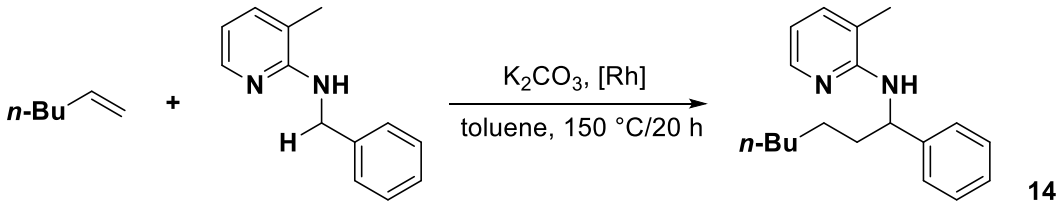
4.7 Alkylation reaction with racemic $[Rh(Ph_2\text{-bnd})Cl]_2$

The new catalyst was then applied to the two model reactions for the alkylation. In case of the ethylation *via* the Hofmann-approach (Scheme *27*), similar yields compared to the standard catalyst were obtained. The C_6-alkylation was surprisingly low yielding, but this may be attributed to the one-off experiment. As the general catalytic activity of this new catalyst was shown, the focus was set on the optical resolution.

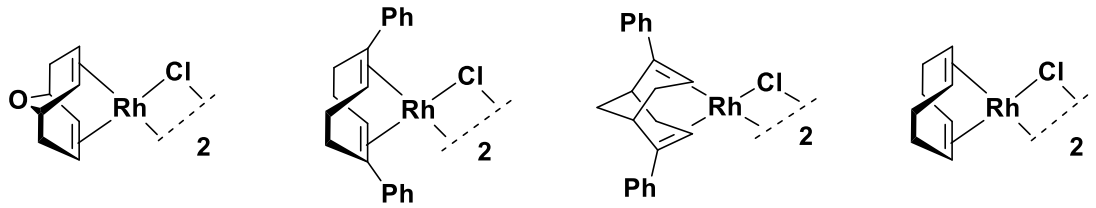
A Hofmann-approach with tetraethylammonium bromide



B Direct alkylation with 1-hexene



C Overview of all catalysts



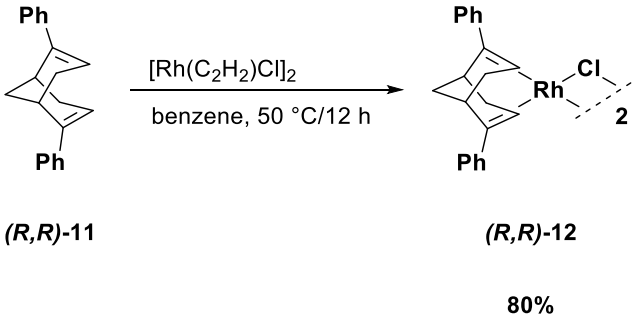
	dl-3	*(R)-7*	*dl-12*	**Standard**
A	44%	56%	64%	71%
B	44%	42%	21%	64%

Scheme 27: Comparison of catalysts used in the alkylation

4.8 Attempted optical resolution of $[Rh(Ph_2\text{-bnd})Cl]_2$

The group of Hayashi[65] used a chiral stationary phase column (Chiralcel OJ) for the optical resolution of racemic Ph_2-bnd and then afforded directly the enantiomerically pure catalyst *via* ligand exchange by treatment with $[Rh(C_2H_2)Cl]_2$ in benzene.

As such chiral stationary phase columns were not available in the equipment, the Grützmacher method was applied for the attempted optical resolution.



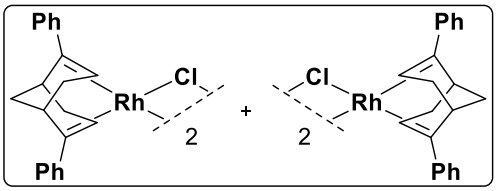
***(R,R)*-11** ***(R,R)*-12**

80%

Scheme 28: Direct synthesis of chiral pure **(*R,R*)-12** by Hayashi *et al.*

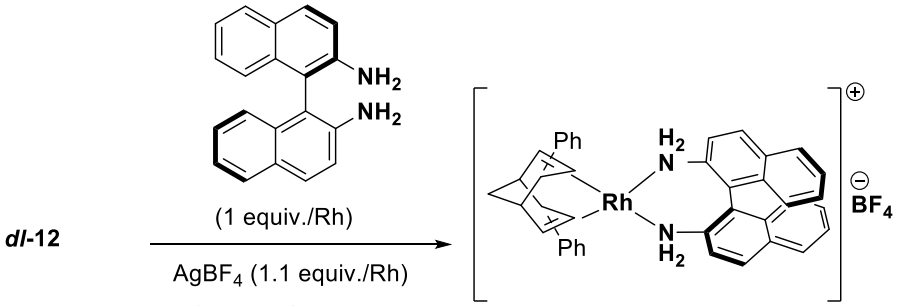
The Grützmacher method surprisingly proofed to be quite convenient in the optical resolution of diastereomers [Rh((*R*)-Ph_2-cod)(*R*)-(+)-DABN]BF_4 and [Rh((*S*)-Ph_2-cod)(*R*)-(+)-DABN]BF_4 *via* fractional crystallization from THF and expectation were that by prudent solvent choice this methodology may also be applicable for the optical resolution of ***dl*-12**.

At the beginning, the standard conditions were applied using (*R*)-1,1´-binaphthyl-2,2´-diamine as optical resolving agent and $AgBF_4$ as counter anion. The corresponding diastereomers were obtained quantitatively as red/orange powder by stirring in dry DCM for approximately 1.5 hours (Scheme 29). The fractional crystallization from several solvents and solvent mixtures, respectively, did not facilitate the precipitation of a single diastereomer and in most cases resulted in an oily residue. Crystallization experiments, conducted in benzene, toluene, toluene/*n*-pentane, *n*-pentane/THF, toluene/THF, were not feasible under various conditions in terms of temperature and concentrations. The diastereomers showed no solubility in aliphatic solvents like *n*-pentane, as it was observed in case of [Rh((*R/S*)-Ph_2-cod)(R)-(+)-DABN]BF_4. Aliphatic solvents were predestined washing solvents for these polar complexes and were used as such. The careful addition of THF to *n*-pentane at room temperature until complete dissolution and slow evaporation of the solvent mixture at room temperature and then at -20 °C did not facilitate the distinct precipitation of a single diastereomer. These experiments were also conducted in the reverse direction by means of dissolution in THF and then addition of *n*-pentane, but no satisfactory results were obtained.



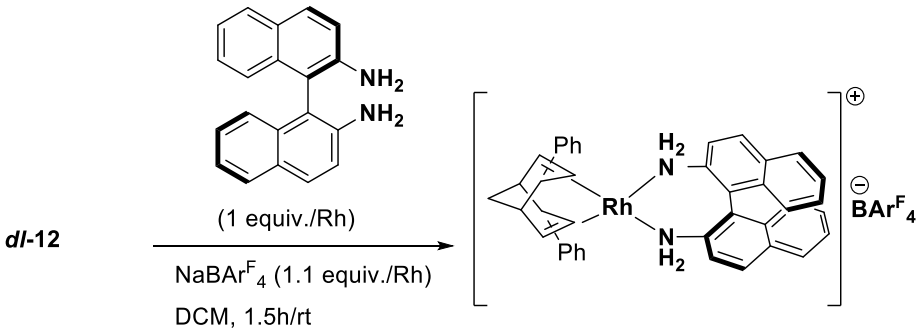
***dl*-12**

A Standard conditions according to Grützmacher



>99%

B Steric more demanding counter anion containing more fluorine



>99%

Scheme 29: Grützmacher method applied on racemic [Rh(Ph_2-bnd)Cl]$_2$

Experiments on TLC (aluminum coated with silica gel 60 F254) using a mixture of DCM/MeOH 20:1 indicated two distinct spots, but column chromatography using silica gel, applying a gradient of MeOH in DCM from 0% to 1%, resulted in decomposition (Figure 1).

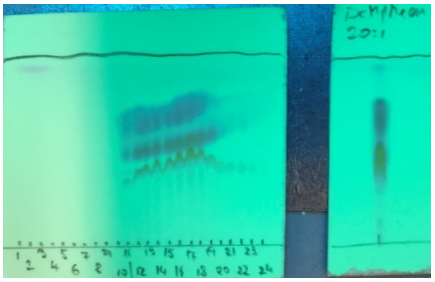


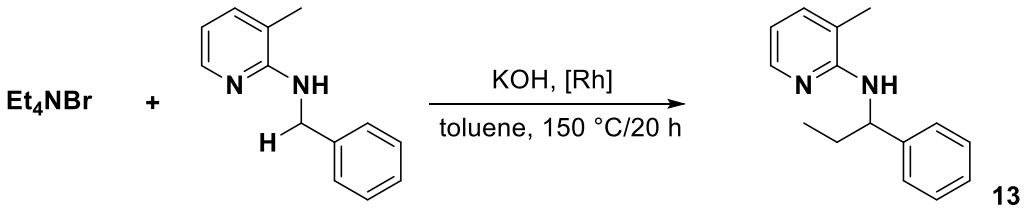
Figure 1: (left) after column chromatography (right) before

As no more strategies seemed applicable, the counter anion in the crystallization approach was changed to the sterically more demanding tetrakis(3,5-bis(trifluoromethyl)phenyl)borate ($NaBAr^F_4$). This species additionally features a higher fluorine-substitution than $AgBF_4$ and may facilitate the fractional crystallization. The treatment of ***dl*-12** with (*R*)-1,1´-binaphthyl-2,2´-diamine and $NaBAr^F_4$ in dry DCM quantitively afforded the diastereomers [Rh((*R/S*)-Ph_2-cod)(R)-(+)-DABN]BAr^F_4 as a yellow foam. The measurement *via* (+) linear LDI-TOF-MS confirmed the anticipated complex containing the new anion. Fractional crystallization of the diastereomers was not applicable at all, as even aliphatic solvents like *n*-pentane did not facilitate the precipitation of the polar diastereomeric mixture but rather gave an oily residue. Further experiments showed full dissolution and no solid material could be isolated.

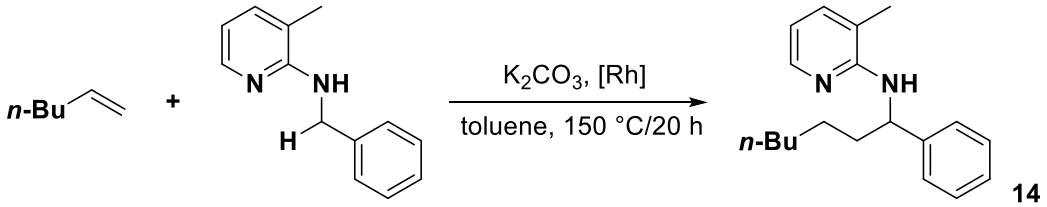
4.9 Conclusion

The catalyst [Rh((*R*)-Ph_2-cod)Cl]$_2$ **(*R*)-7**, bearing a 1,5-diphenyl-substituted cod-ligand, showed no enantiomeric excess due to possible racemization *via* ligand dissociation of Ph_2-cod from the rhodium species and re-coordination of the ligand on the other face. To elucidate the proposed racemization, the focus was set on ligands that feature an incorporated bridge-moiety in their backbone. In this context, the catalysts ***dl*-3** and ***dl*-12** with the desired motif in the scaffold were synthesized in a racemic approach and both complexes showed catalytic activity. The optical resolution of ***dl*-12** using the Grützmacher method was not applicable as no conditions were found to facilitate the precipitation of one single diastereomer. The optical resolution of the third catalyst ***dl*-3** is of special interest for further investigation. The total synthesis towards an enantiomerically pure form of complex **3** includes 12 steps with an overall yield of roughly 3%, whereas the racemic synthesis approach followed by the optical resolution *via* the Grützmacher method would be a drastic cut-down to roughly 5 steps with presumably greater overall yield. Additionally, this catalyst has not been applied to any asymmetric catalysis yet.

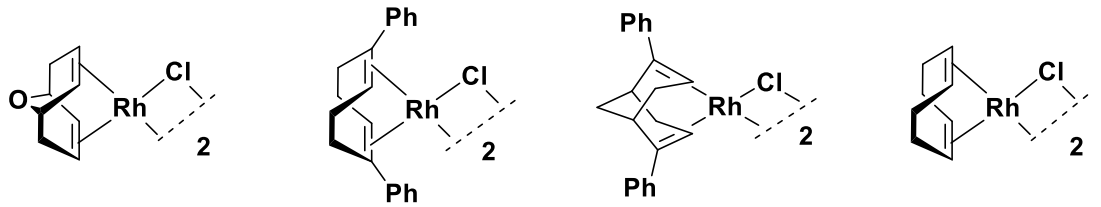
A Hofmann-approach with tetraethylammonium bromide



B Direct alkylation with 1-hexene



C Overview of all catalysts



	dl-3	*(R)*-7	*dl*-12	Standard
A	44%	56%	64%	71%
B	44%	42%	21%	64%

5. Experimental part

5.1 General methods

Chemicals were purchased from commercial suppliers and used without further purification, unless noted otherwise. Dry and degassed toluene was stored over molecular sieves in the glovebox under argon.

NMR spectra were recorded at 297 K in the solvent indicated, with a Bruker Advance 400 MHz instrument employing standard software provided by the manufacturer. ^{1}H-NMR and ^{13}C-NMR spectra were referenced to tetramethylsilane (TMS, δ = 0) by calibration with the residual organic solvent signals. [88]

GC-MS was performed on a Thermo Trace 1300 GC/ MS ISQ LT (quadrupole, EI+) with a TR5 capillary column (7m x 0.32 mm, 0.25µm film, achiral). Temperature program: Start at 100 °C (hold 2 min), 35 °C/min, 300 °C (hold 4 min).

TLCs were performed on aluminum coated with silica gel 60 F254. The spots were visualized with UV-light or standard stains.

Column chromatography was performed on a Büchi Sepacore Flash System (2 x Büchi Pump Module C-605, Büchi Pump Manager C-615, Büchi UV Photometer C635, Büchi Fraction Collector C-660) using silica gel 60 (230-400 mesh, Merck).

Melting points were determined on an automated melting point system (Büchi Melting Point B-545) and are uncorrected.

Optical rotation was determined from solution of the indicated solvent and measured on an Anton Paar MCP 300 circlepolarimeter. The used cuvette was a 100 mm-cell with serial number: 16037274.

Enantiomeric excess was determined *via* normal phase HPLC with an OD column (250 mm x 4.6 mm ID) on a Thermo Scientific/Dionex Ulitmate 3000 HPLC, using a mixture of *n*-hexane and ^{i}PrOH (99.9 to 0.1).

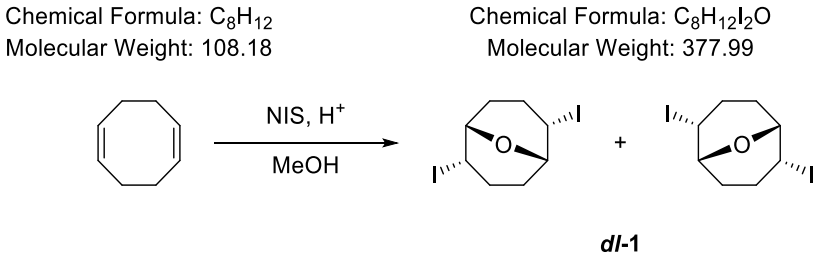
MALDI measurements were performed on a Shimadzu Kratos Axima TOF^{2} MALDI reflectron time-of-flight mass spectrometer (Shimadzu Kratos, Manchester, UK) fitted with a nitrogen laser (Lamda = 337 nm) and a repetition rate of 20 Hz. Mass calibration for positive-ion linear as well as reflectron mass spectrometry was done with the $[M+Na]^{+}$ adduct ion of the major component of castor bean oil (m/z 955.76) and several low mass ions of the MALDI matrix 2,4,6-trihydroxy-acetophenone (purity > 99.5 %, Fluka, Buchs, Switzerland). All measurements of the analytes were conducted without any matrix in the laser desorption/ionisation (LDI) mode and up to 1000 individual laser shots were acquired for the final mass spectra.

5.2 Synthetic procedures

5.2.1 Synthesis of ligands

5.2.1.1 Synthesis of 9-oxabicyclo[3.3.1]nona-2,6-diene ***dl*-2**

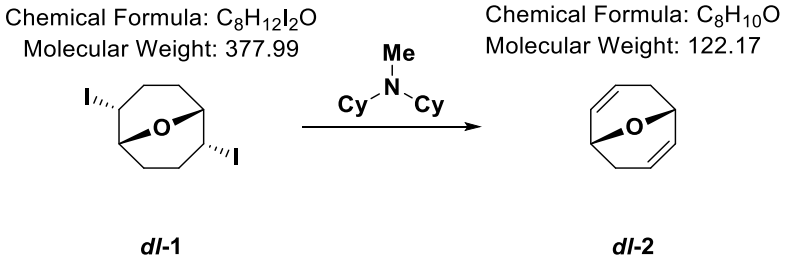
5.2.1.1.1 2,6-Diiodo-9-oxabicyclo[3.3.1]nonane ***dl*-1**



To a solution of *N*-iodosuccinimide (4.16 g, 18.5 mmol, 2.00 equiv.) in MeOH (20 ml) was added 1,5-cyclooctadiene (1.14 ml, 9.24 mmol, 1.00 equiv.) and sulfuric acid (conc., 100 µl) at 0 °C. The mixture was slowly warmed to room temperature overnight and the formation of a colorless precipitate was observed. Monitoring *via* GC-MS indicated full consumption of the starting material and the reaction was quenched by addition of sat. aqu. Na_2SO_3. The aqueous phase was extracted with EtOAc and the combined organic layers were washed with sat. aqu. $NaHCO_3$, water and brine. Drying over $MgSO_4$ and removal of the solvent in *vacuo* afforded 98% (3.34 g) of crude ***dl*-1** as white solid. Purification *via* recrystallization from MeOH afforded 79% (2.75 g) of ***dl*-1** as colorless solid.
The analytical data is in accordance to the literature. [76]

2,6-Diiodo-9-oxabicyclo[3.3.1]nonane (*dl*-1): colorless solid (79%, 2.75 g)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.83 – 4.50 (m, 2H, H2, H6), 4.05 (t, *J* = 5.5 Hz, 2H, H1, H5), 2.83 – 2.43 (m, 4H, H3a, H3b, H7a, H7b), 2.36 – 1.96 (m, 4H, H4a, H4b, H8a, H8b) ppm
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 70.6 (CH, C1 & C5), 33.2 (CH_2, C3 & C7), 29.8 (CH, C2 & C6), 28.9 (CH_2, C4 & C5) ppm
mp = 120.6 – 120.8 °C (MeOH)

5.2.1.1.2 9-Oxabicyclo[3.3.1]nona-2,6-diene ***dl*-2**



***dl*-1** ***dl*-2**

A solution of 2,6-diiodo-9-oxabicyclo[3.3.1]nonane ***dl*-1** (1.50 g, 3.96 mmol, 1.00 equiv.) and dicyclohexylmethylamine (1.87 ml, 8.72 mmol, 2.20 equiv.) was stirred at 200 °C for 2 hours. Full consumption of starting material was indicated *via* TLC monitoring (LP/EtOAc 10:1). To the crude solid material was added 2 N HCl and Et_2O. The layers were separated and the aqueous phase was re-extracted with Et_2O. The combined organic layers were subsequently treated with sat. aqu. $NaHCO_3$, water and brine. Drying over $MgSO_4$ and removal of the solvent in *vacuo* afforded 118% (573 mg) of crude ***dl*-2** as a dark liquid. Purification *via* column chromatography using silica gel, applying a gradient of EtOAc in LP from 0% to 10%, afforded 74% (359 mg) of ***dl*-2** as a yellowish liquid.
The analytical data is in accordance to the literature. [77]

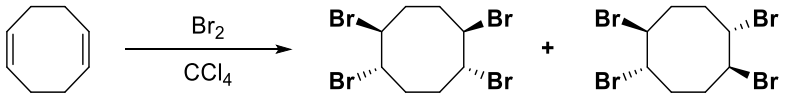
9-Oxabicyclo[3.3.1]nona-2,6-diene (*dl*-3): yellowish liquid (74%, 359 mg)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.23 – 5.36 (m, 4H, H2, H3, H6, H7), 4.47 (s, 2H, H1, H5), 2.53 (dd, *J* = 17.7, 6.0 Hz, 2H, H4a, H8a), 1.78 (dd, *J* = 17.4, 5.0 Hz, 2H, H4b, H8b) ppm
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 129.8 (CH, C2 & C6), 122.8 (CH, C3 & C7), 66.6 (CH, C1 & C5), 28.4 (CH_2, C4, C8) ppm
R_f = 0.45 in LP/EtOAc 10:1

5.2.1.2 Synthesis of 1,5-diphenylcycloocta-1,5-diene **6**

5.2.1.2.1 1,2,5,6-Tetrabromocyclooctane **4**

Chemical Formula: C_8H_{12}
Molecular Weight: 108.18

Chemical Formula: $C_8H_{12}Br_4$
Molecular Weight: 427.80



4a **4b**

To a solution of 1,5-cyclooctadiene (11.4 ml, 92.4 mmol, 1.00 equiv.) in CCl_4 (50 ml) was added bromine (10.3 ml, 201 mmol, 2.2 equiv.) at 0 °C. The solution was slowly warmed to room temperature overnight. TLC (LP/EtOAc 50:1) indicated full consumption after 12 hours. The reaction was quenched by addition of sat. aqu. Na_2SO_3 and the aqueous phase was extracted with DCM. The combined organic layers were subsequently treated with sat. aqu. Na_2SO_3, sat. aqu. $NaHCO_3$, water and brine. Drying over Na_2SO_4 and removal of the solvent in *vacuo* afforded crude **4** as a brownish oil with 92% yield (36.4 g). Purification *via* recrystallization from *n*-hexane afforded colorless to beige crystals of 1,2,5,6-tetrabromocyclooctane **4** as a mix of diastereomers with 52% yield (20.7 g). Column chromatography using silica gel, applying a gradient of EtOAc in LP from 0% to 10%, afforded the separation of the two diastereomers **4a** and **4b** in quantitative yields for analytical purposes. The analytical data is in accordance to the literature. [80]

1,2,5,6-Tetrabromocyclooctane (4a & 4b): colorless to beige crystals (52%, 20.7 g)

(1*R*,5*S*,6*S*)-1,2,5,6-Tetrabromocyclooctane (4a):

- **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 4.57 (m, 4H, H1, H2, H5, H6), 2.55 (m 4H, H3a, H4a, H7a, H8a), 2.41 (m 4H, H3b, H4b, H7b, H8b) ppm
- **^{13}C-NMR** (101 MHz, $CDCl_3$): δ = 58.5 (CH, C1 & C2 & C5 & C6), 31.6 (CH_2, C3 & C4 & C7 & C8) ppm
- **R_f** = 0.3 in LP/EtOAc 50:1
- **mp** = 133.2 – 133.5 °C (*n*-hexane)

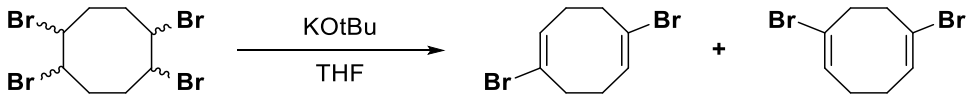
(1*S*,2*S*,5*S*,6*S*)-1,2,5,6-Tetrabromocyclooctane (4b):

- **^{1}H-NMR (400 MHz, $CDCl_3$):** δ = 4.76 (m, 4H, H1, H2, H5, H6), 2.81 (m 4H, H3a, H4a, H7a, H8a), 2.11 (m 4H, H3b, H4b, H7b, H8b) ppm
- **^{13}C-NMR (101 MHz, $CDCl_3$):** δ = 57.4 (CH, C1 & C2 & C5 & C6), 26.8 (CH_2, C3 & C4 & C7 & C8) ppm
- **R_f** = 0.4 in LP/EtOAc 50:1
- **mp** = 133.9 – 134.0 °C (*n*-hexane)

5.2.1.2.2 1,5-Dibromocycloocta-1,5-diene **5**

Chemical Formula: $C_8H_{12}Br_4$
Molecular Weight: 427.80

Chemical Formula: $C_8H_{10}Br_2$
Molecular Weight: 265.98

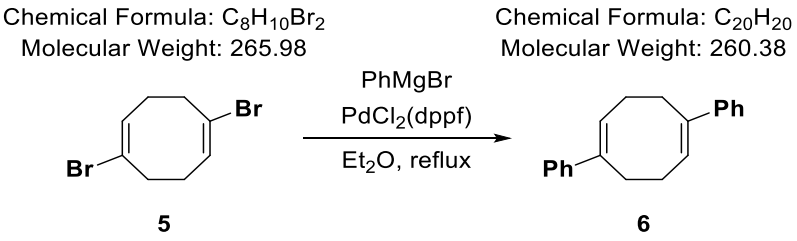


4 **5**

To a solution of 1,2,5,6-tetrabromocyclooctane **4** (9.76 g, 22.8 mmol, 1.00 equiv.) in THF (abs., 55 ml) was added $KO^tBu_{(s)}$ (12.5 g, 112 mmol, 4.90 equiv.) in THF (abs., 40 ml) at -80 °C. The reaction was slowly warmed up and full consumption of starting material was indicated after 2 hours *via* GC-MS. The reaction was quenched by addition of sat. aqu. NH_4Cl and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with sat. aqu. $NaHCO_3$, water and brine. Drying over Na_2SO_4 and removal of the solvent in *vacuo* afforded 67% (4.09 g) of a crude mixture of constitutional isomers as a brownish oil. Column chromatography, using silica gel and LP as eluent, afforded the separation of undesired impurities from the mixture. The desired isomer 1,5-dibromocycloocta-1,5-diene **5** was yielded with 11% (671 mg) as a colorless solid *via* fractional crystallization from *n*-heptane. The analytical data is in accordance to the literature. [80]

1,5-Dibromocycloocta-1,5-diene (5): colorless solid (11%, 671 mg)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.09 (t, *J* = 7.1 Hz, 2H, H2, H6), 3.05 – 2.68 (m, 4H, H4, H8), 2.41 (m, 4H, H3, H7) ppm
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 129.7 (CH, C2 & C6), 124.6 (CBr, C1 & C5), 38.4 (CH_2, C4 & C8), 27. 6 (CH_2, C3 & C7) ppm
mp = 67 – 68 °C

5.2.1.2.3 1,5-Diphenylcycloocta-1,5-diene **6**



To a suspension of 1,5-dibromo-1,5-cyclooctadiene **5** (362 mg, 1.36 mmol, 1.00 equiv.) and $PdCl_2$(dppf) (20 mg, 0.03 mmol, 0.02 equiv.) in Et_2O (abs., 9 ml) was added phenylmagnesium bromide (1.0 M in THF, 5.44 ml, 5.44 mmol, 4.00 equiv.) at room temperature. The reaction was refluxed overnight. TLC monitoring (LP/EtOAc 50:1) indicated full consumption of the starting material after 18 hours. The reaction was quenched by addition of sat. aqu. NH_4Cl. The layers were separated, and the aqueous phase was re-extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and removal of the solvent in *vacuo* afforded 157% (557 mg) of a brownish liquid. Purification *via* column chromatography, using silica gel and LP as eluent, afforded 1,5-diphenylcycloocta-1,5-diene **6** in >99% yield as colorless solid.
The analytical data is in accordance to the literature. [63]

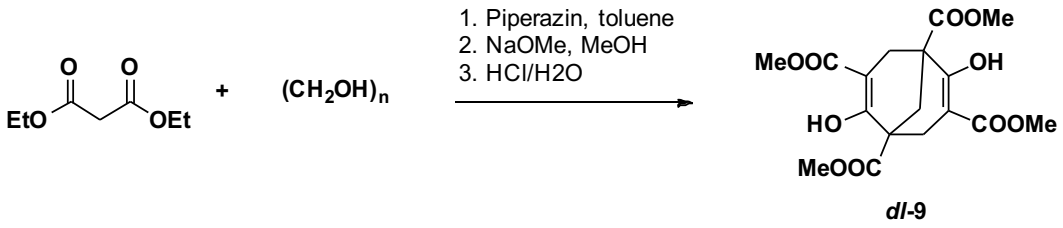
1,5-Diphenylcycloocta-1,5-diene (6): colorless solid (>99%, 354 mg)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.24 (m, 8H, Ar-H2, Ar-H3, Ar-H5, Ar-H6), 7.24 – 7.18 (m, 2H, Ar-H4), 5.90 (t, *J* = 6.6 Hz, 2H, H2, H6), 2.89 (t, *J* = 7.1 Hz, 4H, H4, H8), 2.61 (q, *J* = 6.9 Hz, 4H, H3, H7) ppm
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 144.9 (Ar-C1), 140.6 (Ar-*C*=CH, C1 & C5), 128.3 (CH, Ar-C3 & Ar-C5), 127.0 (Ar-C=*C*H, C2 & C6), 126.6 (CH, Ar-C4), 126.2 (CH, Ar-C2, Ar-C6), 31.2 (CH_2, C4 & C8), 27. 8 (CH_2, C3 & C7) ppm
R_f = 0.3 in LP/EtOAc 50:1
mp = 45 – 46 °C

5.2.1.3 Synthesis of 2,6-diphenylbicyclo[3.3.1]nona-2,6-diene ***dl*-11**

5.2.1.3.1 Meerwein Ester ***dl*-9**

Chemical Formula: $C_7H_{12}O_4$
Molecular Weight: 160.17

Chemical Formula: $C_{17}H_{20}O_{10}$
Molecular Weight: 384.34



***dl*-9**

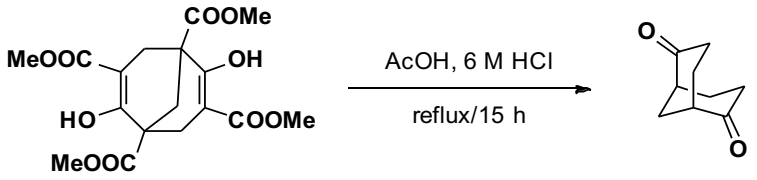
A suspension of diethyl malonate (10.0 g, 76 mmol, 1.20 equiv.), paraformaldehyde (1.89 g, 63 mmol, 1.00 equiv.) and 1-methylpiperazine (0.21 ml, 2 mmol, 0.03 equiv.) in toluene (abs., 35 ml) was stirred under gentle heat supply in a Dean-Stark apparatus until a homogeneous solution was obtained. The mixture was then refluxed for 18 hours at 120 °C. Water accumulation in the water trap was observed and removal of the solvent in *vacuo* afforded a yellow oily residue that was re-dissolved in MeOH (abs., 10 ml). The solution was added to a freshly made solution of NaOMe (1.4 g Na, 59 mmol, 0.94 equiv.) in MeOH (abs., 22 ml) and the mixture was refluxed for 24 hours until a pale-yellow precipitate was observed. The precipitate was isolated *via* filtration and was washed with MeOH and Et_2O. The white residue was re-dissolved in water (100 ml) and dropwise treatment with HCl (6 M) gave ***dl*-9** as a white precipitate. The precipitate was collected by filtration and was washed with water. The crude material was re-dissolved in EtOAc, washed with brine and dried over $MgSO_4$. Removal of the solvent in *vacuo* afforded 38% (2.6 g) of the Meerwein Ester ***dl*-9** as a colorless foam.
The analytical data is in accordance to the literature. [83,89]

Meerwein Ester (*dl*-9): colorless foam (38%, 2.6 g)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 12.16 (s, 2H, OH), 3.77 (s, 6H, CH_3), 3.76 (s, 6H, CH_3), 2.87 (s, 4H, H4, H8), 2.32 (s, 2H, H9) ppm
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 172.6 (C=O), 172.1 (C=O), 168.3 (C-OH, C2 & C6), 97.1 (HO-C-*C(sp^3)*, C1 & C5), 52.9 (CH_3), 52.1 (CH_3), 47.8 (HO-C-*C(sp^2)*, C3 & C7), 35.4 (CH_2, C9), 29.9 (CH_2, C4 & C8) ppm
mp = 148 – 149 °C

5.2.1.3.2 Bicyclo[3.3.1]nona-2,6-dione ***dl*-10**

Chemical Formula: $C_{17}H_{20}O_{10}$
Molecular Weight: 384.34

Chemical Formula: $C_9H_{12}O_2$
Molecular Weight: 152.19

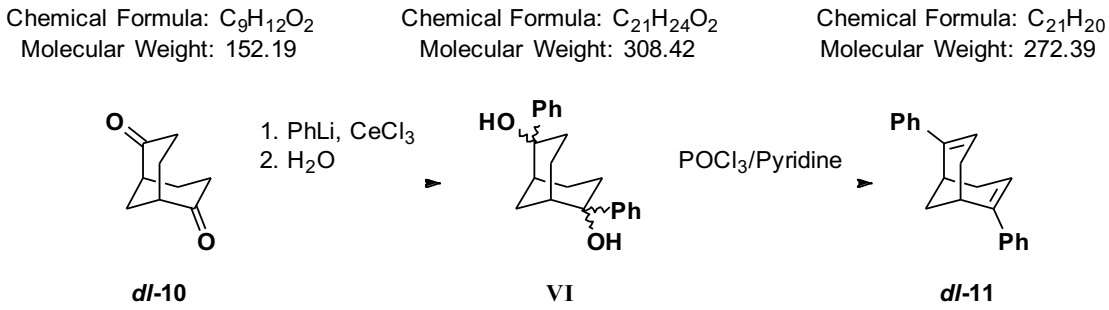


***dl*-9** ***dl*-10**

A solution of Meerwein ester ***dl*-9** (1.00 g, 2.3 mmol, 1.00 equiv.) and aqueous HCl (6 M, 1.70 ml, 10.2 mmol, 4.50 equiv.) in glacial acetic acid (2.5 ml) was refluxed overnight. TLC (LP/EtOAc 5:1) and GC-MS (12 min method) indicated full consumption of the starting material after 15 hours. The mixture was neutralized with sat. aqu. $NaHCO_3$ and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent in *vacuo* afforded 92% (352 mg) of a slightly yellowish solid. Purification *via* column chromatography using silica gel, applying a gradient of EtOAc in LP from 0% to 40%, afforded 75% (286 mg) of bicyclo[3.3.1]nona-2,6-dione ***dl*-10** as colorless solid.
The analytical data is in accordance to the literature. [83,86]

Bicyclo[3.3.1]nona-2,6-dione (*dl*-10): colorless solid (75%, 286 mg)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.73 (s, 2H, H1, H5), 2.64 – 2.50 (m, 2H, H3a, H7a), 2.39 (dt, *J* = 17.3, 9.0 Hz, 2H, H3b, H7b), 2.20 (s, 2H, H9), 2.15 – 1.94 (m, 4H, H4, H8) ppm
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 212.8 (C=O, C2 & C6), 43.7 (*C*H(C=O), C1 & C5), 37.2 (CH_2, C3 & C7), 31.6 (CH_2, C9), 26.8 (CH_2, C4 & C8) ppm
R_f = 0.09 in LP/EtOAc 5:1
mp = 138 – 139 °C

5.2.1.3.3 2,6-Diphenylbicyclo[3.3.1]nona-2,6-diene ***dl*-11**



$CeCl_3 * 7\ H_2O$ (1010 mg, 2.7 mmol, 2.75 equiv.) was stirred in *vacuo* at 130 °C for 2.5 hours. THF (abs., 10 ml) was added at 0 °C and the suspension was stirred for 2.5 hours at room temperature under argon. A solution of phenyllithium (1.97 M in dibutylether, 1.38 ml, 2.7 mmol, 2.75 equiv.) was added at -78 °C. The reaction was continued to stir for 1 hour at this temperature and then bicyclo[3.3.1]nonane-2,6-dione ***dl*-10** (150 mg, 1.0 mmol, 1.00 equiv.) in THF (abs. 3.5 ml) was added. TLC (LP/EtOAc 1:1) indicated full consumption of starting material after 4 hours at -78 °C. The reaction was quenched by addition of sat. aqu. NH_4Cl. The aqueous phase was extracted with Et_2O and the combined organic layers were subsequently treated with water and brine. Drying over Na_2SO_4 and removal of the solvent in *vacuo* afforded 123% (375 mg) of the crude diol as a white solid.

A solution of the crude diol and $POCl_3$ (0.18 ml, 2.02 mmol, 6.00 equiv.) in pyridine (abs., 0.6 ml) was refluxed for 18 hours. Full consumption of the diol was indicated *via* TLC (LP/EtOAc 5:1, LP/EtOAc 10:1). The reaction mixture was quenched by addition of water and the aqueous phase was extracted with Et_2O. The combined organic layers were subsequently treated with 2 N NaOH and brine. Drying over Na_2SO_4 and removal of the solvent in *vacuo* afforded 99% (91 mg) of crude ***dl*-11** as a yellowish oil. Purification *via* column chromatography using silica gel, applying a gradient of EtOAc in LP from 0% to 5%, afforded 89% (240 mg) of ***dl*-11** as a colorless solid.

The analytical data is in accordance to the literature. [65]

2,6-Diphenylbicyclo[3.3.1]nona-2,6-diene (*dl*-11): colorless solid (89%, 240 mg)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.48 – 7.39 (m, 4H, Ar), 7.36 – 7.28 (m, 4H, Ar), 7.26 – 7.19 (m, 2H, Ar), 5.98 (dd, *J* = 5.1, 2.4 Hz, 2H, H3, H7), 3.17 – 3.07 (m, 2H, H1, H5), 2.56 – 2.38 (m, 2H, H4a, H8a), 2.09 (dd, *J* = 18.3, 5.1 Hz, 2H, H4b, H8b), 2.00 (t, *J* = 3.1 Hz, 2H, H9) ppm

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 141.6 (Ar-C1), 140.3 (Ar-*C*=C, C2 & C6), 128.4 (CH, Ar-C3 & Ar-C5), 126.8 (CH, Ar-C4), 126.0 (CH, Ar-C2 & Ar-C6), 122.8 (C=*C*H, C3 & C7), 31.8 (CH_2, C4 & C8), 29.9 (CH_2, C9), 29.4 (CH, C1 & C5) ppm

R_f = 0.65 in LP/EtOAc 10:1

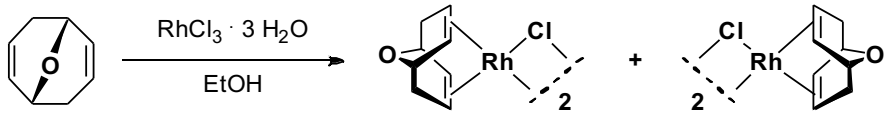
mp = 86 – 87 °C

5.2.2 Synthesis of rhodium complexes

5.2.2.1 Synthesis of *dl*-[Rh(obnd)Cl]$_2$ ***dl*-3**

Chemical Formula: $C_8H_{10}O$
Molecular Weight: 122.17

Chemical Formula: $C_{16}H_{20}Cl_2O_2Rh_2$
Molecular Weight: 521.05



***dl*-2** ***dl*-3**

A suspension of 9-oxabicyclonona-2,6-diene ***dl*-2** (464 mg, 3.80 mmol, 5.00 equiv.) and $RhCl_3 \cdot 3\ H_2O$ (200 mg, 0.76 mmol, 1.00 equiv.) in EtOH (2 ml) was stirred at 80 °C for 20 hours. The solvent was removed in *vacuo* to afford ***dl*-3** as an orange/reddish gum. The residue was washed in *n*-hexane and removal of the solvent in *vacuo* afforded ***dl*-3** as a brown powder with 87% (172 mg).
The analytical data is in accordance to the literature. [66]

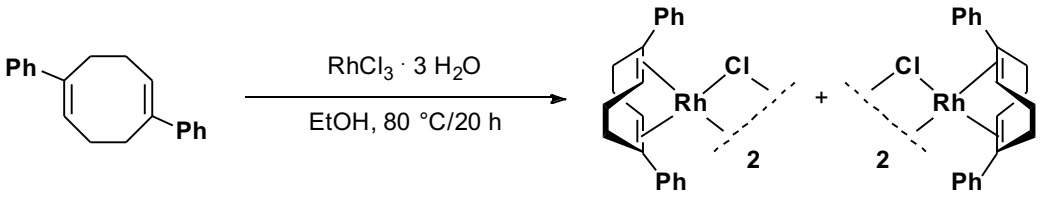
[Rh(obnd)Cl]$_2$ (*dl*-3): brown powder (87%, 172 mg)
^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 4.89 (s, 2H, H2, H6), 4.14 (s, 2H, H3, H7), 4.09 (s, 2H, H1, H5), 2.61 (d, *J* = 15.0 Hz, 2H, H4a, H8a), 2.34 (d, *J* = 15.1 Hz, 2H, H4b, H8b) ppm
^{13}C-NMR (101 MHz, CD_2Cl_2): δ = 77.7 (d, $J_{C\text{-}Rh}$ = 8.8 Hz, CH, C2 & C6), 73.1 (d, $J_{C\text{-}Rh}$ = 13.2 Hz, CH, C3 & C7), 68.7 (CH, C1 & C5), 38.7 (CH_2, C4 & C8) ppm

5.2.2.2 Synthesis of [Rh((*R*)-Ph_2-cod)Cl]$_2$ ***(R)-7***

5.2.2.2.1 [Rh(Ph_2-cod)Cl]$_2$ ***dl-7***

Chemical Formula: $C_{20}H_{20}$
Molecular Weight: 260.38

Chemical Formula: $C_{40}H_{40}Cl_2Rh_2$
Molecular Weight: 797.47



6 ***dl-7***

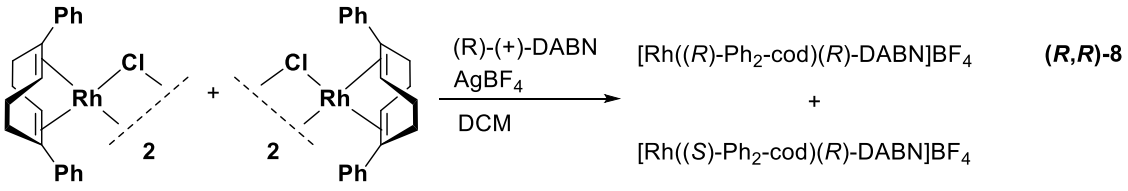
A solution of 1,5-diphenylcycloocta-1,5-diene **6** (330 mg, 1.27 mmol, 2.90 equiv.) and $RhCl_3 * 3\ H_2O$ (115 mg, 0.44 mmol, 1.00 equiv.) in EtOH (2.4 ml) was stirred at 80 °C for 20 hours. The solvent was removed in *vacuo* to afford an orange/reddish gum. The residue was washed with *n*-hexane and removal of the solvent in *vacuo* afforded >99% (185 mg) of [Rh(Ph_2-cod)Cl]$_2$ ***dl-7*** as an orange powder.
The analytical data is in accordance to the literature. [63]

[Rh(Ph_2-cod)Cl]$_2$ (*dl*-7): orange powder (>99%, 185 mg)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 – 7.36 (m, 4H, Ar-H2, Ar-H6), 7.36 – 7.17 (m, 6H, Ar-H3, Ar-H4, Ar-H5), 4.35 (d, J = 6.3 Hz, 2H, H2, H6), 3.26 – 3.00 (m, 2H, H3, H7), 2.30 (dd, J = 13.9, 10.6 Hz, 2H, H4, H8), 2.20 (dd, J = 15.0, 8.1 Hz, 2H, H3, H7), 1.81 – 1.66 (m, 2H, H4, H8) ppm
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 148.0 (Ar-C1), 127.6 (CH, Ar), 126.8 (CH, Ar), 126.4 (CH, Ar), 91.7 (d, $J_{C\text{-}Rh}$ = 14.7 Hz, Ar-*C*=C, C1 & C5), 72.2 (d, $J_{C\text{-}Rh}$ = 12.7 Hz, C=*C*H, C2 & C6), 36.4 (CH_2, C4 & C8), 34.5 (CH_2, C3 & C7) ppm

5.2.2.2.2 [Rh((*R*)-Ph_2-cod)((*R*)-1,1'-binaphthyl-2,2'-diamine)]BF_4 **(*R*,*R*)-8**

Chemical Formula: $C_{40}H_{40}Cl_2Rh_2$
Molecular Weight: 797.47

Chemical Formula: $C_{40}H_{36}BF_4N_2Rh$
Molecular Weight: 734.45



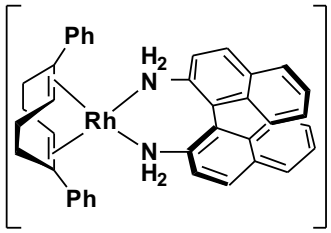
***dl*-7**

A suspension of [Rh(Ph_2-cod)Cl]$_2$ ***dl*-7** (174 mg, 0.22 mmol, 1.00 equiv.), (*R*)-1,1'- binaphthyl-2,2'-diamine (124 mg, 0.44 mmol, 2.00 equiv.) and $AgBF_4$ (93 mg, 0.48 mmol, 2.20 equiv.) in dichloromethane (dry, 1.5 ml) was stirred at room temperature for 1.5 hours. The solid material was separated *via* filtration over Celite® and removal of the solvent in *vacuo* afforded >99% (322 mg) of a diastereomeric mixture. Recrystallization from THF and benzene afforded 35% (112 mg) of the diastereomer [Rh((*R*)-Ph_2-cod)(*R*)-1,1'- binaphthyl-2,2'-diamine]BF_4 **(*R*,*R*)-8** as orange powder (96% de, determined by ^{1}H-NMR).
The analytical data is in accordance to the literature. [63]

[Rh((*R*)-Ph_2-cod)(*R*)-DABN]BF_4 ((*R*,*R*)-8): red powder (35%, 112 mg)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.8 Hz, 2H), 8.08 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.2 Hz, 2H), 7.50 (s, 4H), 7.44 (t, J = 7.6 Hz, 2H), 7.15 (t, J = 7.7 Hz, 2H), 6.80 – 6.58 (m, 8H, F), 4.83 (s, 2H), 4.32 – 4.16 (m, 2H), 3.34 – 3.02 (m, 2H), 2.98 – 2.76 (m, 2H), 2.31 – 2.13 (m, 2H), 1.89 (m, 2H), 1.33 (s, 2H) ppm
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 143.8 (C), 137.5 (C), 132.2 (C), 132.0 (C), 131.4 (CH), 128.7 (C), 128.5 (CH), 128.2 (CH), 127.7 (CH), 126.0 (CH), 124.8 (CH), 120.2 (CH), 119.1 (C), 100.2 (d, $J_{C\text{-}Rh}$ = 13.8 Hz, Ar-*C*=C), 71.9 (d, $J_{C\text{-}Rh}$ = 12.6 Hz, C=*C*H), 39.8 (CH_2), 29.9 (CH_2) ppm

5.2.2.2.3 [Rh((*R*)-Ph_2-cod)Cl]$_2$ **(*R*)-7**

Chemical Formula: $C_{40}H_{40}Cl_2Rh_2$
Molecular Weight: 797.47



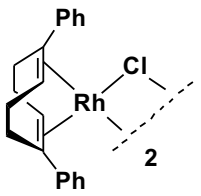
(*R*,*R*)-8

BF_4

conc. HCl

ACN, 10h/rt

Chemical Formula: $C_{40}H_{40}Cl_2Rh_2$
Molecular Weight: 797.47



(*R*)-7

A solution of [Rh((*R*)-Ph_2-cod)(*R*)-1,1'- binaphthyl-2,2'-diamine]BF_4 **(*R*,*R*)-8** (112 mg, 0.15 mmol) and hydrochloric acid (conc., 0.6 ml) in acetonitrile (3.1 ml) was stirred at room temperature for 16 hours. The crude mixture was extracted with toluene (3x) and the combined organic layers were dried over $MgSO_4$. The organic phase was treated with sat. aqu. $NaHCO_3$ and removal of the solvent in *vacuo* afforded >99% (61 mg) of [Rh((*R*)-Ph_2-cod)Cl]$_2$ **(*R*)-7** as an orange powder.

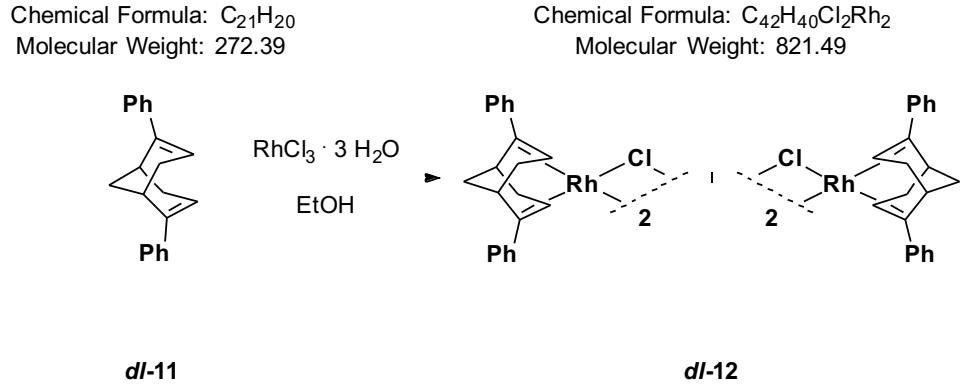
[Rh((*R*)-Ph_2-cod)Cl]$_2$ ((*R*)-7): orange powder (>99%, 61 mg)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62 – 7.36 (m, 4H, Ar-H2, Ar-H6), 7.36 – 7.17 (m, 6H, Ar-H3, Ar-H4, Ar-H5), 4.35 (d, J = 6.3 Hz, 2H, H2, H6), 3.26 – 3.00 (m, 2H, H3, H7), 2.30 (dd, J = 13.9, 10.6 Hz, 2H, H4, H8), 2.20 (dd, J = 15.0, 8.1 Hz, 2H, H3, H7), 1.81 – 1.66 (m, 2H, H4, H8) ppm

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 148.0 (Ar-C1), 127.6 (CH, Ar), 126.8 (CH, Ar), 126.4 (CH, Ar), 91.7 (d, $J_{C\text{-}Rh}$ = 14.7 Hz, Ar-*C*=C, C1 & C5), 72.2 (d, $J_{C\text{-}Rh}$ = 12.7 Hz, C=*C*H, C2 & C6), 36.4 (CH_2, C4 & C8), 34.5 (CH_2, C3 & C7) ppm

$[\alpha]^{20}_D$ = -274 (*c* 1.00, $CHCl_3$)

5.2.2.3 Synthesis of [Rh(Ph$_2$-bnd)Cl]$_2$ ***dl*-12**

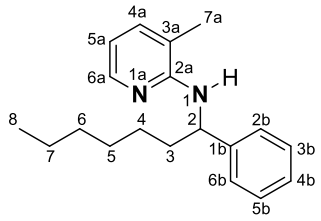


A solution of 2,6-diphenylbicyclo[3.3.1]nona-2,6-diene ***dl*-11** (52 mg, 0.19 mmol, 2.50 equiv.) and $RhCl_3 * 3\ H_2O$ (20 mg, 0.08 mmol, 1.00 equiv.) in EtOH (1 ml) was stirred at 80 °C for 20 hours. The solvent was removed in *vacuo* and the residue was dissolved in DCM. The insoluble impurities were separated *via* filtration over Celite® and the solvent was evaporated in *vacuo*. The residue was washed with *n*-pentane and removal of the solvent afforded 83% (26 mg) of [Rh(Ph$_2$-bnd)Cl]$_2$ ***dl*-12** as an orange powder.
The analytical data is in accordance to the literature. [65]

[Rh(Ph$_2$-bnd)Cl]$_2$ (*dl*-12): orange powder (83%, 26 mg)
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.58 – 7.41 (m, 8H, CH, Ar), 7.30 – 7.07 (m, 12H, CH, Ar), 4.70 (s, 4H, H3, H7), 3.78 – 3.08 (m, 4H, H4a, H8a), 2.30 (d, *J* = 15.4 Hz, 4H, H4a, H8a), 2.25 (s, 4H, H1, H5), 1.29 (s, 4H, H9) ppm
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 144.9 (Ar-C1), 127.9 (Ar-C2 & Ar-C6), 126.8 (Ar-C4), 126.7 (Ar-C3, Ar-C5), 86.3 (d, $J_{C\text{-}Rh}$ = 14.4 Hz, Ar-*C*=C, C2 & C6), 72.8 (d, $J_{C\text{-}Rh}$ = 11.5 Hz, C=*C*H, C3 & C7), 41.6 (CH_2, C4 & C8), 34.7 (CH, C1 & C5), 33.1 (CH_2, C9) ppm

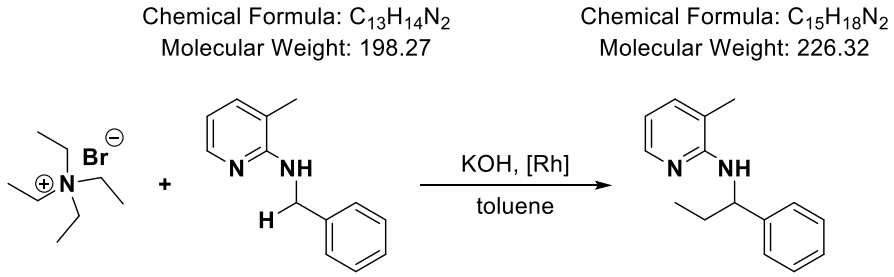
5.2.3 Model reactions for C-H functionalization

5.2.3.1 Assignment of chemical shifts



Scheme 30: General assignment of C-H functionalization products

5.2.3.2 3-Methyl-N-(1-phenylpropyl)pyridin-2-amine **13**



13

A suspension of *N*-benzyl-3-methylpyridin-2-amine (100 mg, 0.50 mmol, 1.00 eq.), tetraethylammonium bromide (105 mg, 0.50 mmol, 1.00 eq.), KOH (84 mg, 1.50 mmol, 3.00 eq.) and rhodium catalyst (0.025 mmol, 0.05 eq.) in toluene (dry, 2 ml) was stirred for 16 h at 150 °C. The solid material was separated *via* filtration over Celite® with DCM and removal of the solvent in *vacuo* afforded crude **13** as beige oil. Purification *via* column chromatography using silica gel, applying a gradient of EtOAc in LP from 0% to 10%, afforded **13** as a colorless solid.

The analytical data is in accordance to the literature. [43]

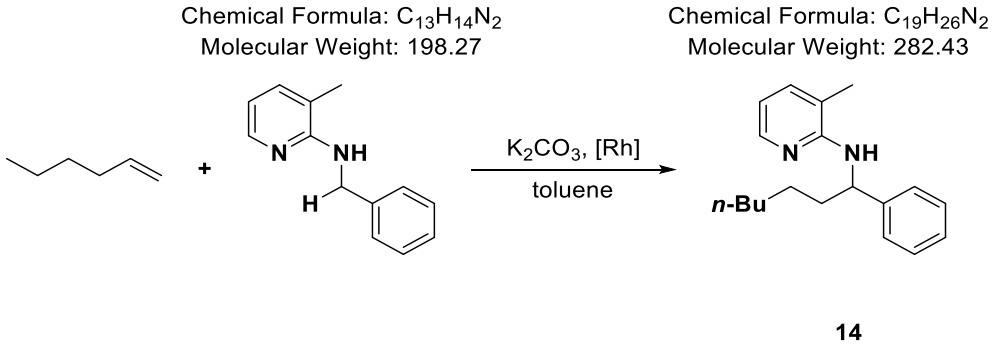
3-Methyl-N-(1-phenylpropyl)pyridin-2-amine (13): colorless solid

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3H, H4), 1.82 – 2.04 (m, 2H, H3), 2.12 (s, 3H, H7a), 4.40 (d, *J* = 7.7 Hz, 1H, N1), 5.19 (q, *J* = 7.2 Hz, 1H, H2), 6.48 (dd, *J* = 7.1, 5.1 Hz, 1H, H5a), 7.17 – 7.41 (m, 6H, H4a, H2b, H3b, H4b, H5b, H6b), 7.97 (dd, *J* = 5.1, 1.7 Hz, 1H, H6a) ppm

^{13}C-NMR (101 MHz, $CDCl_3$): δ = 10.9 (CH_3, C4), 17.2 (CH_3, C7a), 30.3 (CH_2, C3), 56.1 (CH, C2), 112.7 (CH, C5a), 116.4 (CH_3*C*=C, C3a), 126.7 (CH, C2b), 126.9 (CH, C6b), 127.7 (CH, C4b), 128.5 (CH, C3b), 128.6 (CH, C5b), 136.9 (CH, C4a), 144.3 (N1CH*C(sp^2)*, C1b), 145.6 (CH, C6a), 156.3 (N=C-N, C2a) ppm

R_f = 0.29 in LP/EtOAc 10:1; **mp** = 41.5 – 42.5 °C

5.2.3.3 3-Methyl-N-(1-phenylheptyl)pyridin-2-amine **14**



14

A suspension of *N*-benzyl-3-methylpyridin-2-amine (100 mg, 0.50 mmol, 1.00 eq.), 1-hexene (42 mg, 0.50 mmol, 1.00 eq.), K_2CO_3 (209 mg, 1.50 mmol, 3.00 eq.) and rhodium catalyst (0.025 mmol, 0.05 eq.) in toluene (dry, 2 ml) was stirred for 16 h at 150 °C. The solid material was separated *via* filtration over Celite® with DCM and removal of the solvent in *vacuo* afforded crude **14** as beige oil. Purification *via* column chromatography using silica gel, applying a gradient of EtOAc in LP from 0% to 10%, afforded **14** as a colorless oil.
The analytical data is in accordance to the literature. [43,44]

3-Methyl-N-(1-phenylheptyl)pyridin-2-amine (14): colorless oil
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.7 Hz, 3H, H8), 1.23 – 1.45 (m, 8H, H4, H5, H6, H7), 1.80 – 1.99 (m, 2H, H3), 2.13 (s, 3H, H7a), 4.39 (d, *J* = 7.7 Hz, 1H, N1), 5.26 (q, *J* = 7.3 Hz, 1H, H2), 6.48 (dd, *J* = 7.1, 5.0 Hz, 1H, H5a), 7.14 – 7.45 (m, 6H, H4a, H2b, H3b, H4b, H5b, H6b), 7.97 (dd, *J* = 5.1, 1.8 Hz, 1H, H6a) ppm
^{13}C-NMR (101 MHz, $CDCl_3$): δ = 14.2 (CH_3, C8), 17.2 (CH_3, C7a), 22.7 (CH_2, C7), 26.5 (CH_2, C6), 29.4 (CH_2, C5), 31.9 (CH_2, C4), 37.7 (CH_2, C3), 54.7 (CH, C2), 112.6 (CH, C5a), 116.2 (CH_3*C*=C, C3a), 126.6 (CH, C2b & C6b), 126.8 (CH, C4b), 128.5 (CH, C3b & C5b), 136.8 (CH, C4a), 144.7 (N1CH*C(sp^2)*, C1b), 145.7 (CH, C6a), 156.3 (N=C-N, C2a) ppm
R_f = 0.38 in LP/EtOAc 10:1

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