Catalytic asymmetric conjugate additions and Heck reactions

Imbos, Rosalinde

Chapter 7

Intramolecular Asymmetric Heck Reactions*

New applications of phosphoramidite ligands

In this chapter our efforts to introduce phosphoramidites as ligands for the intramolecular asymmetric Heck reaction are described. For this purpose, a new multi-functional substrate was designed. It was shown that phosphoramidites are suitable ligands in the asymmetric Heck reaction and, more important, that monodentate ligands have been successfully employed for the first time. We could obtain the coupling product with 96% ee using a very simple, easily accessible and modular Taddol-based phosphoramidite.

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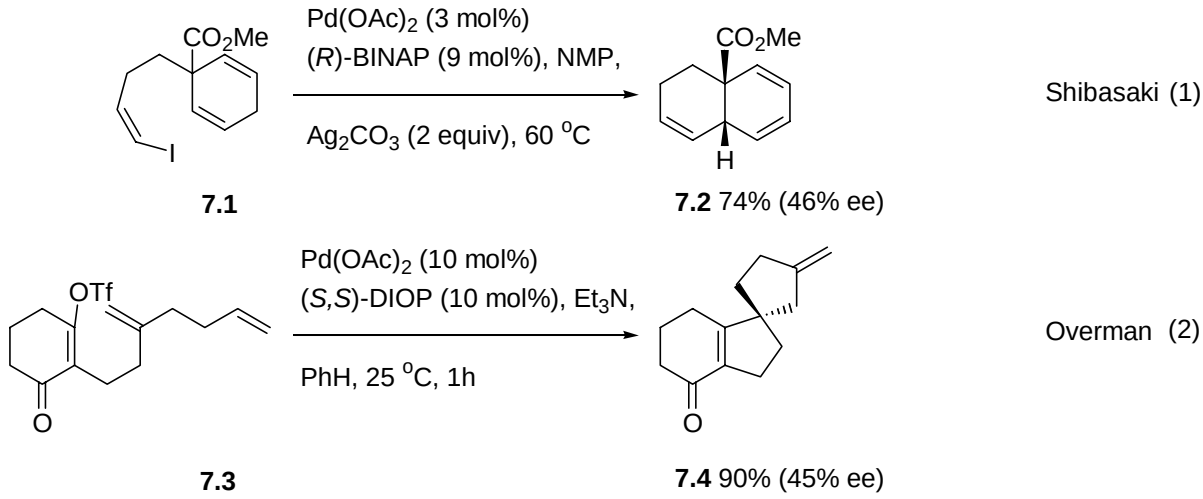
7.1 Introduction

Over the years, an asymmetric version of the classical Heck reaction[1] (the reaction of a vinyl- or aryl halide with an activated alkene) has been developed. In the previous chapter the intermolecular AHR was discussed, and in this chapter the intramolecular AHR will be described. This intramolecular asymmetric Heck reaction is an interesting new method of asymmetric C-C bond formation.[2,3,4,5,6] In the following sections a brief literature overview will be given of the results achieved in this field.

7.2 The intramolecular AHR

7.2.1 The first examples

The first two reports on intramolecular asymmetric Heck reactions (AHR) appeared in 1989 (see Scheme 7.1). Shibasaki[7] reported on the intramolecular AHR of prochiral vinyl iodide **7.1**, leading to chiral decalin system **7.2**, using a catalyst prepared *in situ* from $Pd(OAc)_2$ and (*R*)-BINAP.[8] The product contains two stereogenic centres and is obtained in 74% yield with 46% ee. The initially modest ee was later improved to 98%, by varying the Pd-source and changing to the vinyl triflate.[9]

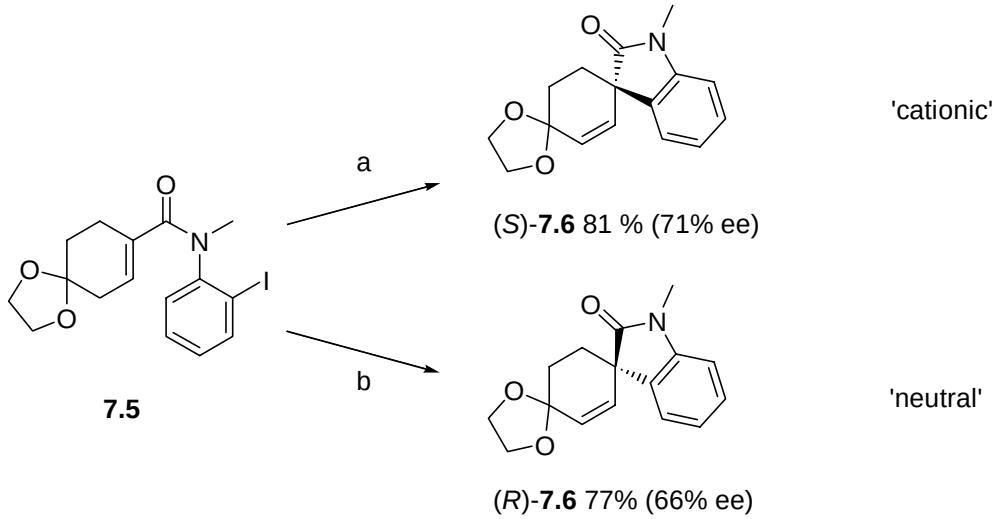


Scheme 7.1 *First reported examples of intramolecular AHR as reported by Shibasaki (1)[7] and Overman (2).[10]*

The catalyst used by Overman[10] was an *in situ* formed complex from $Pd(OAc)_2$ and (*S,S*)-DIOP. This catalyst induces an elegant example of spirocyclisation wherein the initial Heck coupling of **7.3** is followed by another intramolecular Pd-catalysed cyclisation, resulting in tricyclic product **7.4**. The enantioselectivity was modest (45% ee).

The potential of this asymmetric spirocyclisation did not become fully apparent until the appearance of new results, dealing with the synthesis of spiro-oxindoles **7.6**.[11] The AHR of

iodoanilide **7.5** was studied in the presence of a catalyst prepared from (*R*)-BINAP and Pd_2dba_3.
Using 'cationic' conditions (addition of silver salts will provide a cationic Pd-complex, *vide infra*) the enantiomer (*S*)-**7.6** (81%yield, 71% ee) of the product was formed. Performing the reaction under 'neutral'[12] conditions resulted in the formation of (*R*)-**7.6** in 77% yield and 66% ee, although the reaction was much slower and a higher catalyst loading was required (Scheme 7.2).



Scheme 7.2 *AHR of spiroxindole **7.5** using a catalyst prepared from (R)-BINAP and Pd_2dba_3. Conditions: (a) 5 mol% Pd_2dba_3, 10 mol% (R)-BINAP, 1.2 equiv. Ag_2CO_3, DMA, 80°C, 24h. (b) 10 mol% Pd_2dba_3, 20 mol% (R)-BINAP, 5 equiv. PMP, DMA, 80°C, 140h. PMP = pentamethylpiperidine.*

A few additional examples of this effect of the nature of the catalyst, i.e. cationic or neutral, have appeared, indicating that influence of change in base or additive is less strong than the 'geometry' effect determined by the nature of the chiral complex (i.e. the chiral environment created by the complex).[13] In general this effect is less pronounced, resulting in higher ee for one of the two complexes, and usually this is the case for the cationic species.[9a,14] Overman observed an important exception to this rule. Using the aryl triflate analogue of **7.5** a dramatic increase in ee of the product for the neutral pathway was observed.[15]

7.2.2 Mechanistic considerations

In an excellent mechanistic investigation reported by the Overman group,[16] detailed information about the cationic/neutral pathways was obtained. The cationic pathway is only valid for complexes containing very weakly coordinating anions (usually the triflate anion). The weak nucleophilicity of the anion renders the four-coordinated Pd-complex **7.10** cationic. When a halide (more coordinating) is used, the cationic complex can be generated by exchange with e.g. AgOTf or TlOTf (**7.9**→**7.10**). The AgX precipitates, giving the cationic

Pd-complex **7.10** with a triflate counterion. In this pathway, the bidentate phosphine ligand is always coordinated through both phosphorus atoms.

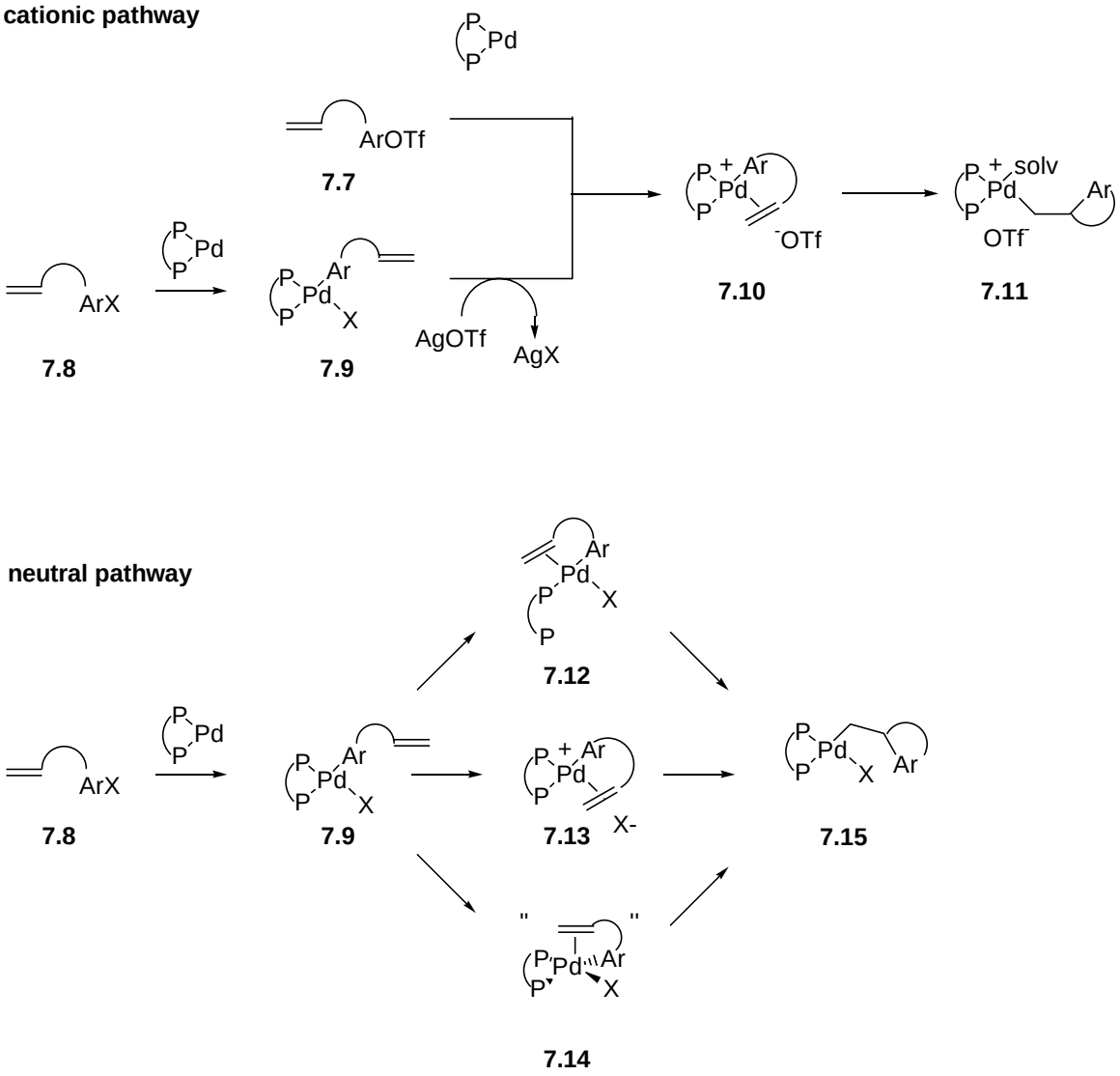


Figure 7.1 *Cationic and neutral Heck manifolds.*[16]

The general scheme for the neutral pathway involves sequence **7.9→7.12→7.15**, which proceeds through phosphine dissociation (Figure 7.1).[2,1,17] This automatically implies that monodentate phosphines would provide the product with the same or similar ee's. However, monodentate phosphines have been rarely used in AHR's. Therefore, Overman studied a number of monodentate phosphines (mainly monodentate analogues of BINAP), and observed ee's of max. 27% (whereas BINAP provided the product in 97% ee). Also chiral amplification[18] studies showed a linear relationship between the enantiomeric purity of the ligand and enantioselectivity of the product in both the neutral and cationic pathways. This results in the conclusion that the ligand -in this case- always coordinates through both phosphorus atoms in the case of a bidentate ligand and in the case of a monodentate ligand,

both ligands are coordinating to palladium. For the neutral pathway to proceed, a mechanism different from the phosphine dissociation must take place, since the cationic pathway **7.9→7.13→7.15** is very unlikely. Therefore, the sequence proposed by Overman (**7.9→7.14→7.15**) includes a neutral five-coordinate palladium species **7.14**, with a bidentate coordinating bisphosphine and axial coordination of the alkene. Related axial coordination of an alkene has been previously reported for other Pd-systems.[19]

7.3 Applications

The AHR has evolved over the years into a powerful way of introducing stereogenic centers. Especially BINAP has been employed as chiral ligand and several natural products have been synthesised with the AHR being one of the key steps in which chirality is introduced during C-C bond formation.[20,21,22,23]
Illustrative examples include Xestoquinone **7.16**,[24] Capnellene **7.17**,[25] Physostigmine **7.18**,[26] 5-epi-inodolizidine 167B **7.19**,[27] Spirotryprostatin B **7.20**[28] and Baccatin III **7.21** (the core structure of Taxol).[29] The structures are given in Figure 7.2. The C-C bonds that were formed using the AHR are marked with an arrow.

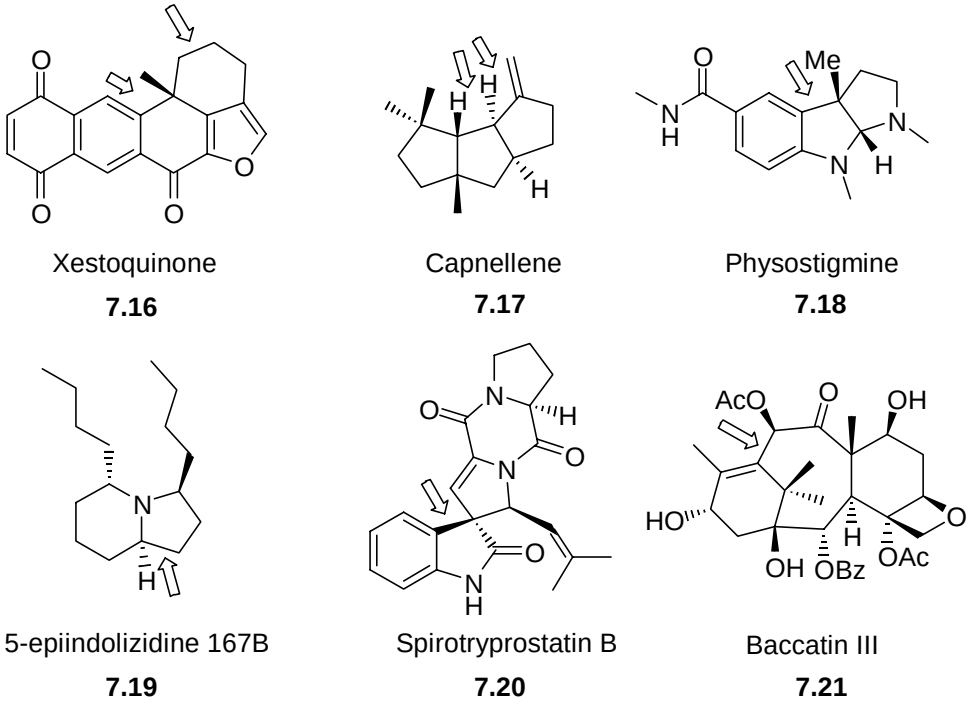
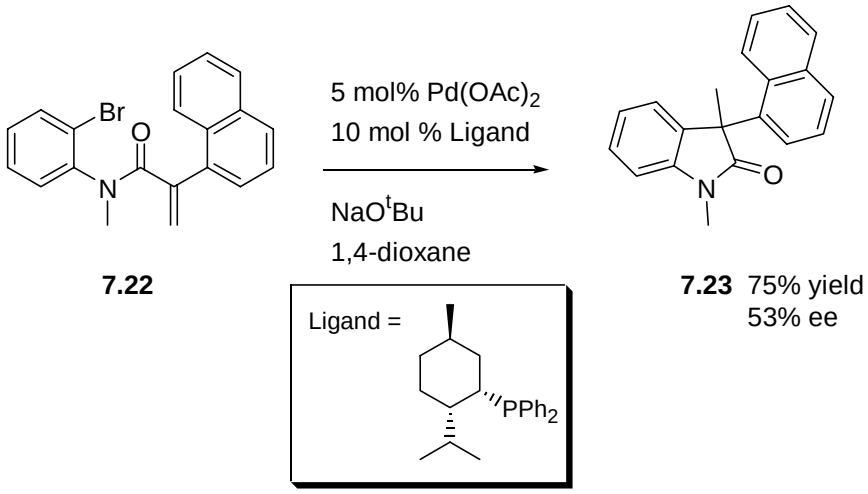


Figure 7.2 *Several natural products that were synthesised using the AHR. The bonds that were constructed using the AHR, are marked with an arrow.*

7.4 Scope

As is apparent from the previous section, the applicability of the intramolecular AHR is very broad. It is an ideal tool for creating quaternary carbon centres.[30] In contrast to the intermolecular AHR there is no standard substrate to test if a new catalytic system is suitable for the intramolecular AHR, altough sometimes the Overman-system is used.[11]
Because of their increased reactivity, usually iodides or triflates are studied[2], whereas mainly BINAP has been used as ligand. The intramolecular Heck reaction using BINAs[31] as well as BINAPFu[32] as ligands has also been reported. Bisoxazolines and pymox-Ph[33] were used in the asymmetric Heck coupling of γ-butyrolactones.[34]
Lee and Hartwig have reported the use of several monodentate phosphines as ligand in an asymmetric Pd-catalysed cyclisation, but ee's were generally very low with one exception wherein 53% ee was obtained.[35] (See Scheme 7.3)

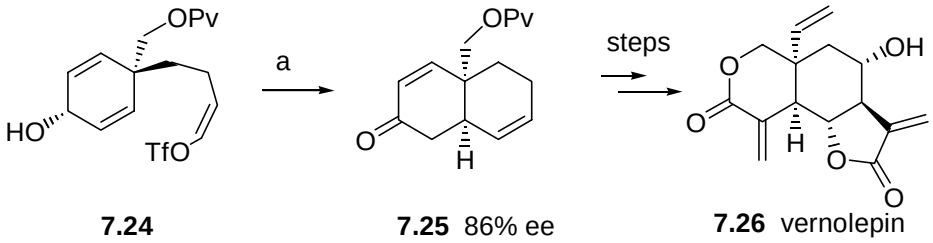


Scheme 7.3 *Asymmetric cyclisation using a monodentate phosphine-ligand resulting in 53% ee, as reported by Lee and Hartwig.*[35]

Although phosphoramidites have been reported to be very successful ligands for the classical –non chiral- Heck reaction,[36] the only AHR using phosphoramidites as ligands yielded nearly racemic product (2% ee).[35]

7.5 Goal of this research

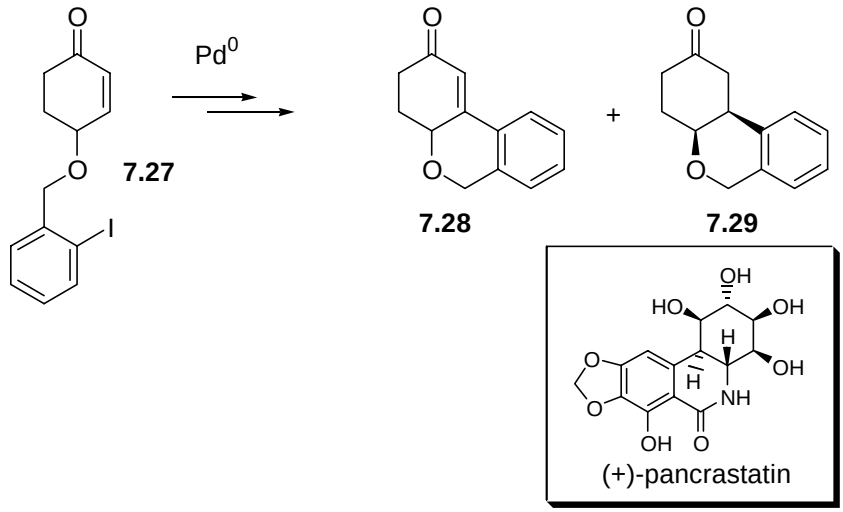
One of the substrates reported by Shibasaki *et al*[37] has a strong resemblance to the cyclohexadienones used as substrates for the catalytic asymmetric 1,4-addition described in the previous chapters (See Scheme 7.4). The Pd-BINAP catalysed AHR of dienol **7.24** provided the Heck-product **7.25**, which was converted in a number of steps to vernolepin **7.26**.[38]



7.24 **7.25** 86% ee **7.26** vernolepin

Scheme 7.4 *Dienol **7.24** employed by Shibasaki as substrate for the asymmetric synthesis of the core structure of Vernolepin using an intramolecular Heck coupling.*[37]

Furthermore, our attention was drawn by a report of Friestad and Branchaud, [39] dealing with the intramolecular Heck reaction of enone **7.27**. The Heck reaction, although not performed enantioselectively, was considered by this model-reaction as the C-C bond-forming step in the total synthesis of the anticancer *Amaryllidaceae* alkaloid pancrastatin.[40] The Heck reaction was successful although considerable amounts of the reduced product **7.29** were also formed.



Scheme 7.5 *Model reaction for the total synthesis of (+)-pancrastatin, as studied by Friestad et al.*[39]

Combining the structural features of these two substrates (**7.24** and **7.27**) results in prochiral cyclohexadienone **7.30** as a new substrate for the AHR (see Figure 7.3). Upon AHR, the stereogenic centre is not created at the site of C-C bond formation, but instead the cyclohexadienone is desymmetrised resulting in **7.31**.

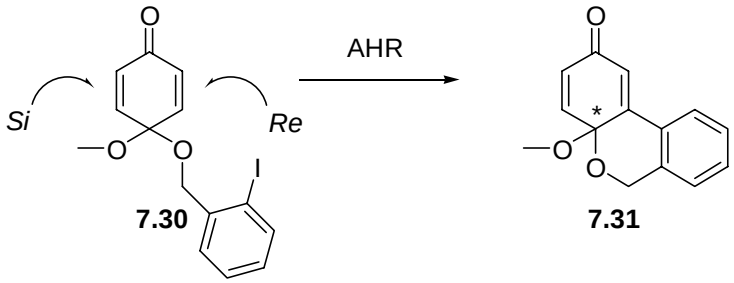
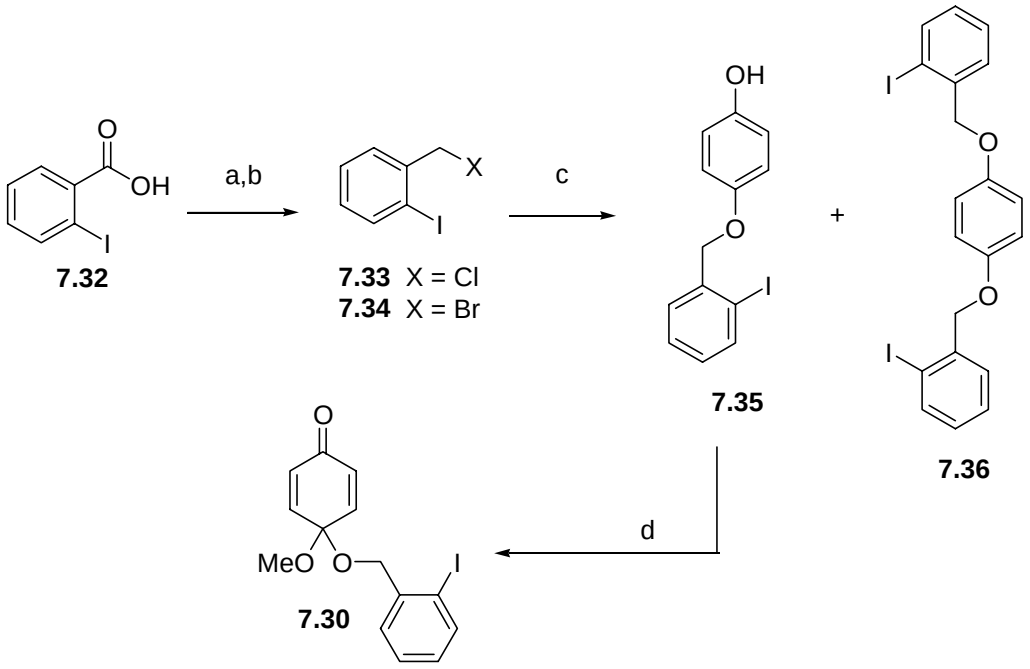


Figure 7.3 *Newly designed substrate **7.30** for the intramolecular AHR.*

The goal of the research reported in this chapter is the application of phosphoramidites as ligands in the intramolecular AHR, using this newly designed dienone-based substrate.
We expect the chiral catalyst to show high face-selectivity, (based on the excellent face-selectivity already observed in asymmetric 1,4-additions to cyclohexadienones[41]) leading to 4a-methoxy-4a*H*-benzo[*c*]chromen-2(6*H*)-one **7.31**. The AHR will also be a critical test for the stability of the substrate **7.30**.

7.6 Synthesis of the new substrate

Cyclohexadienone **7.30** is efficiently synthesised in four steps from commercially available 2-iodobenzoic acid **7.32**. Reduction of **7.32** using $NaBH_4/I_2$ as reducing agent[42] provided 2-iodobenzylalcohol in 98% yield. Formation of corresponding benzyl chloride **7.33** using $SOCl_2$,[43] or benzyl bromide **7.34** using CBr_4 and PPh_3[44] proceeded smoothly. (97% and 94% yield, respectively) The monoether of hydroquinone **7.35** was easily formed by refluxing the benzyl halide and a 10-fold excess of hydroquinone in acetone in the presence of K_2CO_3. The remaining hydroquinone and the formed diether **7.36** are easily removed by precipitation, yielding the monoether **7.35** (91%) as an orange oil. Phenolic oxidation with phenyl iodo diacetate (PIDA) in MeOH[45] provided the desired dienone **7.30** in 83% yield after column chromatography.

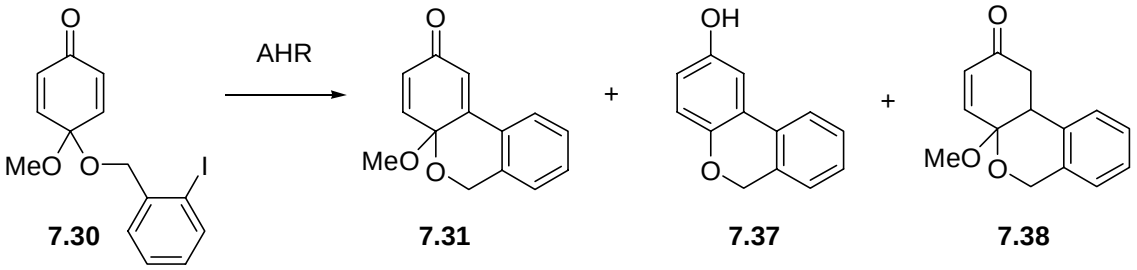


Scheme 7.6 *Synthetic route to the new substrate for the AHR. Conditions: (a) $NaBH_4$, I_2, 98%. (b) Et_3N, $SOCl_2$, 94% or CBr_4, PPh_3, 97%. (c) Hydroquinone (10 equiv.) K_2CO_3, acetone, Δ, 91%. (d) PIDA, MeOH, 83%.*

7.7 Preliminary experiments

To obtain the racemate needed to establish an accurate method for determination of enantiomeric excesses, a Heck reaction of **7.30** was performed in DMSO using only $Pd(OAc)_2$ as a catalyst. Et_3N (2 equivalents) was added to neutralise the acid formed, and, much to our surprise, the conversion was complete after 10 min at 50°C. The only product formed was **7.31** and the racemate was isolated as a yellow oil. The AHR of **7.30** could have led to the side-products **7.37** and **7.38**, also shown in Figure 7.7.

The AHR with dienone **7.30** could also to the elimination product **7.37**. Furthermore, small quantities of the reduced product **7.38** might be formed in the process. The reduced product **7.38** would probably not isolated, because of fast aromatisation to **7.37**.



Scheme 7.7 *Possible products in AHR of dienone 7.30.*

7.8 Mechanistic considerations

Based on extensive mechanistic studies of Heck couplings, the formation of **7.31** can be rationalised as shown in Figure 7.4. Initially, a chiral Pd(0) complex **A** is formed. Oxidative addition of dienone **7.30** results in Pd(II) complex **B**. Subsequent C-C bond formation (association and insertion into Pd-C), leads to complex **C** which does not have a *syn* β-hydride. To reach the final product **7.31** epimerisation of the C-2 centre, leading to **D**, followed by *syn* β-hydride elimination to complex **E** needs to take place. The net *trans* elimination can be explained via a mechanism involving oxo-π-allylpalladium intermediates, similar to enolisation in normal ketones, which have found precedent in the Pd-catalysed dehydrosilylation of silyl enolethers.[46] In addition it should be noted that several examples of apparent *trans* β-hydride elimination have appeared in literature.[47] Finally, reductive elimination of HI with base leads to the starting complex **A**.

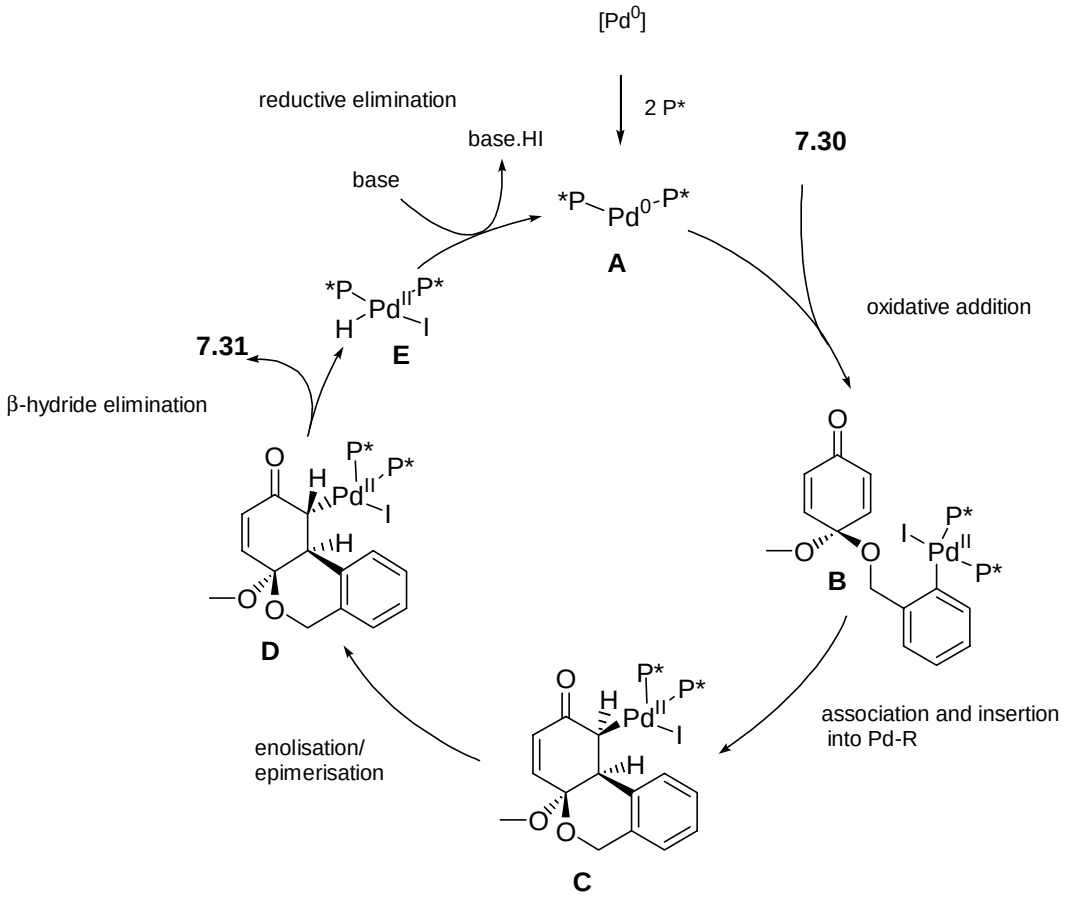
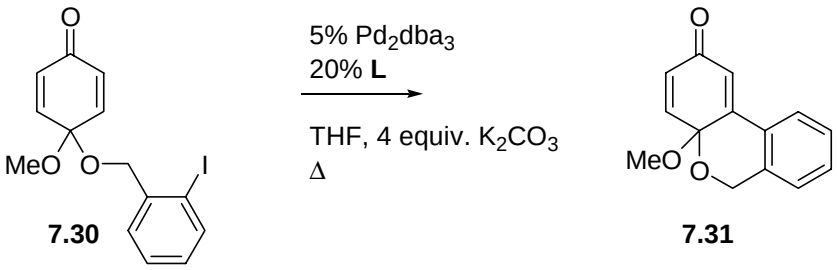


Figure 7.4 *Possible mechanistic pathway for the AHR of dienone **7.30***

7.9 Optimisation

7.9.1 Ligand screening

For the optimisation of our reaction we chose a linear approach. To confirm the possibility of using phosphoramidites as ligand in this AHR, we screened a number of BINOL and TADDOL[48] based ligands present in our lab.[49,50] We chose to perform the reaction in THF, since this is a frequently used solvent for the AHR, has coordinating properties and therefore the catalytically active complex might be stabilised by solvent coordination. K_2CO_3 was used as a base (as is often done); the low solubility of this inorganic base in THF keeps the level of base at all times low. (For general reaction scheme see Scheme 7.8) As a palladium-source Pd_2dba_3 was chosen, since Pd is already in the zero oxidation state and no $Pd^{II} \rightarrow Pd^0$ interconversion needs to take place prior to the start of the catalysic cycle. The catalyst was preformed *in situ*, i.e. a solution of Pd_2dba_3 and 2 equiv of the monodentate ligand (or 1 of a bidentate ligand) in THF was stirred at room temperature untill the purple solution (Pd_2dba_3) turned into a bright yellow (Pd-phosphorus complex). Furthermore, the reaction mixture was heated, since AHR's often need prolonged heating for complete conversion.



7.30 **7.31**

Scheme 7.8 *General scheme for the AHR of **7.30** using several phosphoramidites as ligand.*

The first set of ligands tested were monodentate phosphoramidites based on Binol or Taddol (see Figure 7.5 for abbreviations) containing non-chiral amine substituents (see Figure 7.6 for ligands). The results are shown in Table 7.1. All catalysts based on these ligands give full conversion after 48h, so phosphoramidites seem to be appropriate ligands for this reaction. The reaction is quite clean: at full conversion usually less than 10% side-products (mainly **7.37** and <1% of unidentified compounds) are detected by NMR analysis.

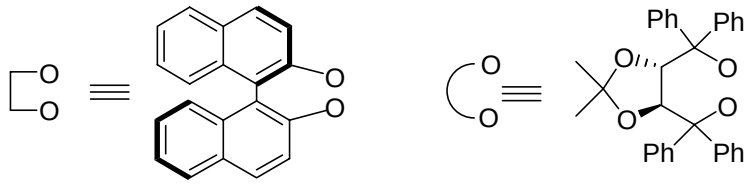


Figure 7.5 *Abbreviations for the BINOL-backbone and the TADDOL-backbone.*

For the BINOL based phosphoramidites a trend is observed: upon increasing the bulk on the amine moiety, the ee of the product is increased to a maximum value of 21% ee for **L4**. For the TADDOL-based phosphoramidite series exactly the opposite was observed: upon decreasing the bulk of the amine moiety, the ee of the product increased to 40% for the dimethyl-Taddol based phosphoramidite **L5**. Attempts to synthesise the even smaller mono-methylamine substituted Taddol based phosphoramidite failed due to fast hydrolysis, although Alexakis *et al*[49b] reported the successful preparation of this compound.

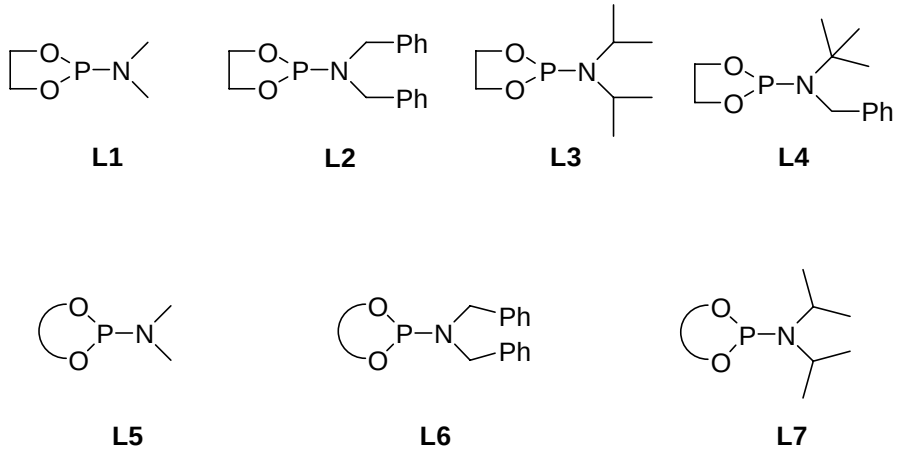


Figure 7.6 *Monodentate phosphoramidites containing non-chiral amine substituents used as ligands for the AHR.*

The second series of ligands tested were the monodentate Binol-based phosphoramidites containing chiral amine-backbones (see Figure 7.7). The results were disappointing and although all ligands gave full conversion, the ee's of the product were generally low (<10%). The best results were obtained when **L15** (with (*S,R,R)* configuration) and **L17** were used. The ee of the product was 26% and 27%, respectively. Employing the other diastereomers of the ligands (**L16**, (*S,S,S)* and **L18**, (*S,S,S)*), the product was obtained as a racemate. There is a clear and strong matched-mismatched effect in these cases. This means that with Binol based phosphoramidites not only the chiral Binol backbone is important for stereocontrol, but the nature of the chiral amine as well.

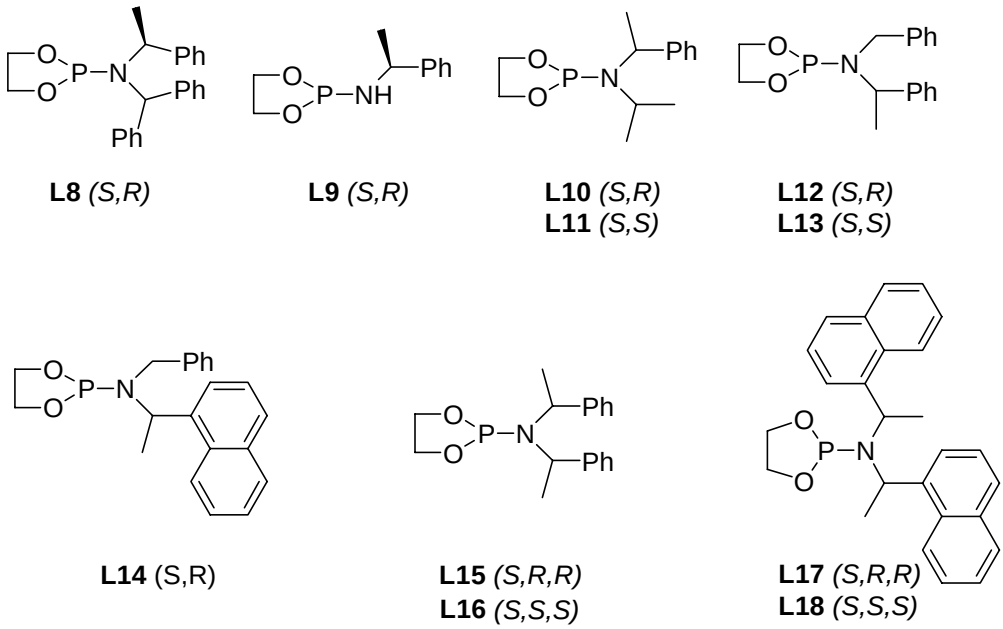


Figure 7.7 *Monodentate Binol-based phosphoramidites containing chiral amine moieties used as ligands in the AHR.*

The final class of ligands studied in this series was a number of bidentate phosphoramidites, since these are still believed to be superior to monodentate ligands because of their limited structural flexibility.[51] (Thus enhancing the asymmetric induction). We chose bidentate analogues of the best monodentate ligands found sofar, i.e. bidentate C_2 and C_3 bridged analogues **L19** and **L20**, respectively, of Taddol-based phosphoramidite **L5**. Bulky bidentate Binol-based phosphoramidites **L21** (with the best chiral amine-moiety and a C_2 spacer), **L22** (with a C_3 spacer and diisopropyl-groups) and **L23** which contains a very rigid urea bridge were also employed.[52] The Taddol based C2-bridged **L21** gave complete conversion in 24h, (the monodentate analogue **L5** needed 48h for complete conversion) and the product was isolated with a similar ee (39%). Apparently, anchoring the second phosphoramidite to the first, provides extra activity of the complex (the second phosphoramidite is on average less likely to diffuse away from the palladium core, giving a more active species)

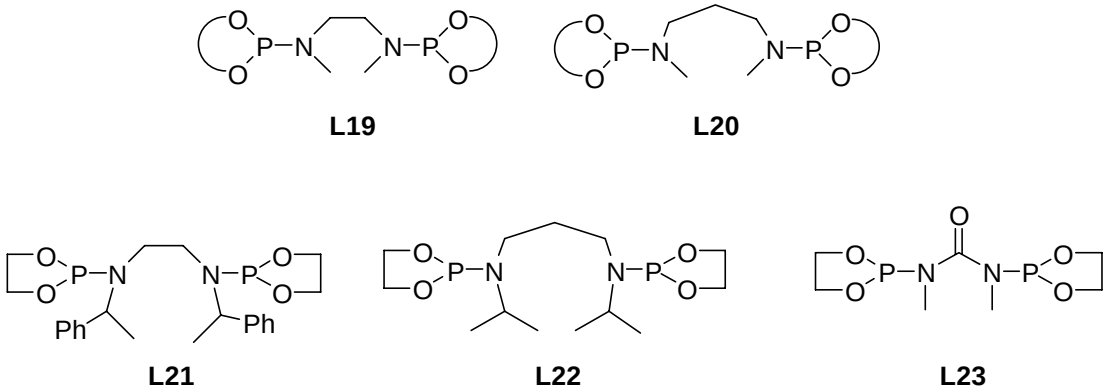


Figure 7.8 *Bidentate phosphoramidites used as ligands in the AHR.*

Surprisingly, **L20** failed to show any conversion. The phosphoramidite must be arranged around the Pd in such a way that reaction is no longer possible anymore. Maybe the palladium-complex of this ligand is too bulky to provide space for the substrate to add. The Binol based bidentate analogues **L21** and **L22** are capable of giving complete conversion within 48h, but the ee's were low (4 and 12%, respectively) Much to our surprise, urea bridged ligand **L23** was able to form a stable complex (since no Pd-black was formed during the reaction) and give full conversion to the product, albeit in low ee (4%).

Table 7.1 *Results for the AHR of **7.30** with various ligands, at full conversion.*[a]

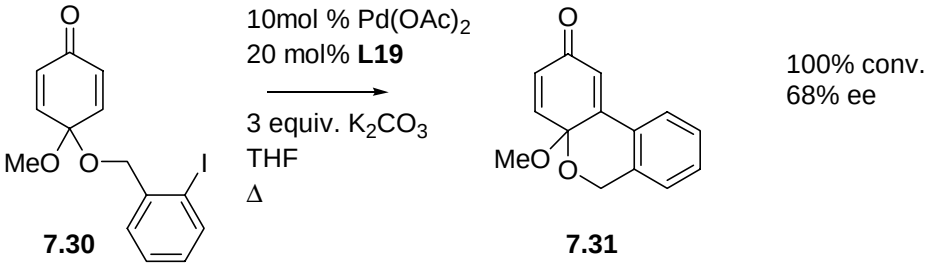
Ligand	Ee (%)[b]	Ligand	Ee (%)[b]	Ligand	Ee (%)[b]
L1	6	**L9**	8	**L17**	27
L2	4	**L10**	2	**L18**	3
L3	10	**L11**	0	**L19**	39
L4	21	**L12**	5	**L20**	0
L5	40	**L13**	0	**L21**	4
L6	22	**L14**	0	**L22**	12
L7	3	**L15**	26	**L23**	4
L8	12	**L16**	0		

[a]*Conversion was determined by 1H NMR* [b] *Ee's were determined by chiral HPLC.*

7.9.2 Change of Pd-source

It is known that dibenzylidenacetone (dba) can have a negative effect on the enantioselectivity in asymmetric catalysis (of course dba is a bidentate ligand itself and can compete[53] with any (chiral) ligand) Therefore an experiment, using 10 mol% of an *in situ* prepared catalyst starting from $Pd(OAc)_2$ and **L19** was performed. In case of a Pd^{II}-precursor, one extra equivalent of ligand is needed to reduce the Pd^{II}- precatalyst to the active Pd^0-complex. The acetate anions are too weakly nucleophilic to give any competition in coordinating to the palladium. There was indeed a deleterious effect of the dba as we observed a higher enantioselectivity for this AHR of **7.30** and the ee increased to 68% (compared to 39% for Pd_2dba_3). (see Scheme 7.9) Other Pd^{II}-salts were tested as well, ($PdCl_2$, $PdCl_2(PhCN)_2$) but $Pd(OAc)_2$ was clearly superior in rate and selectivity.

With all these results in hands, we decided to continue our optimisation experiments using bidentate Taddol based phosphoramidite **L19**, because of the superior rate to **L5** and the same order of selectivity compared to **L5**. (*vide supra*)



Scheme 7.9 *Improved selectivity using $Pd(OAc)_2$ as metal source.*

7.9.3 Solvent-dependence

Since selectivity and rate are not only dependent on the nature of the catalyst system, but also on the solvent (e.g. the coordination properties and polarity) a number of frequently used solvents for AHR were compared in the $Pd(OAc)_2$ /**L19** catalysed AHR of **7.30**. In all cases K_2CO_3 was used as a base and all reaction mixtures were heated to 80°C for 48 h, or to their boiling point if this was lower than 80°C.

In DMA, DMF, DMAE, DMSO, CH_3CN and NMP very fast reactions were observed as Pd-black formation occurred in the first 3h, and full conversion was also achieved. The product **7.31** was always isolated with <10% ee. This is probably due to the fact that these solvents are also very good ligands for Pd and thus compete with the phosphoramidites. For a selected number of other solvents, the results are shown in Table 7.2.

Table 7.2 *Solvent variation in AHR of **7.30**.*[a]

	solvent	T (°C)	Ee (%)[b]
1	THF	80	68
2	$CHCl_3$	65	86
3	CH_2Cl_2	35	85
4	Toluene	80	80
5	PhCl	80	70
6	$ClCH_2CH_2Cl$	80	68

[a] *Conditions: 10 mol% of a catalyst prepared from $Pd(OAc)_2$ and **L19** was used with K_2CO_3 as base, and the reaction mixtures were stirred for 48h at the indicated temperatures. Results shown are at full conversion.* [b] *Determined by chiral HPLC.*

Chlorobenzene and toluene give rise to an increase in ee to 70 and 80%, respectively. As can be seen from the table, non-coordinating solvents like dichloromethane and chloroform give a dramatic increase in ee to 85 and 86%, respectively. The AHR performed in dichloromethane needed 48h for complete conversion, whereas the AHR performed in $CHCl_3$ was completed within 36 h, so we continued our research using this solvent.

7.9.4 Different bases

As can be seen from Table 7.3, there is a dramatic effect on both conversion and ee of the reaction, when a number of different organic and inorganic bases were used for the AHR of **7.30**. The very bulky PMP gave a slow reaction, resulting in only 68% conversion after 48h. However, the reaction was highly selective, as an ee of 87% was observed for the product. The inorganic bases that were studied (K_2CO_3 and K_3PO_4) both gave full conversion to the product and in both cases an ee of 86% was obtained.

We observed a very high ee when Et_3N and PS[54] were used as base (92 and 91% ee, respectively). However, conversions were low and even prolonged stirring did not increase the conversion. Apparently using these bases, the reaction stops at the maximum conversion, although no Pd-black was formed. It is possible that the catalyst is 'poisoned' by the amine. For DABCO, conversion was also low, but in this case only 9% ee was observed for **7.31**. No conversion at all was obtained with pyridine and DBU.

Table 7.3 *Effect of base on ee in the AHR of **7.30**.*[a]

Entry	Base	Conv (%)[b]	Ee (%)[c]
1	PMP[d]	68	87
2	Et_3N	35	92
3	*i*Pr_2EtN	100	89
4	Cy_2MeN	100	90
5	DABCO[e]	36	9
6	K_3PO_4	100	86
7	K_2CO_3	100	86
8	PS[f]	25	91
9	Pyridine	0	-
10	DBU[g]	0	-

*[a]Conditions: a catalyst prepared from $Pd(OAc)_2$ and **L19** was used, in $CHCl_3$ at 80°C for 48h. [b]determined by ^1H NMR. [c]determined by chiral HPLC [d]Pentamethylpiperidine [e]1,4-diazabicyclo[2.2.2]octane [f] Proton Sponge[54] [g]1,8-diazabicyclo[5.4.0]undec-7-ene*

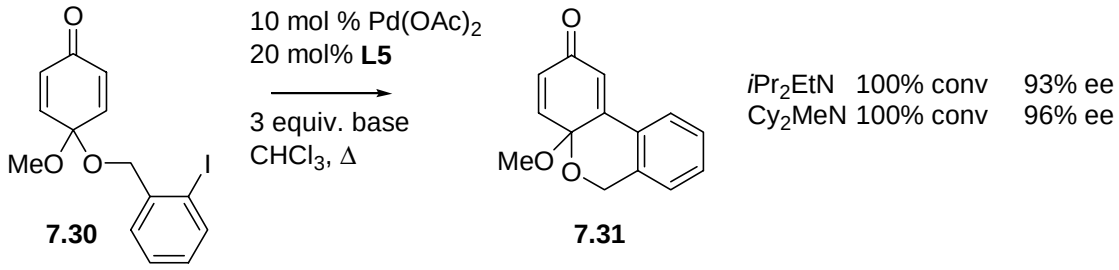
The best results were obtained using *i*Pr_2EtN and especially Cy_2MeN (based on recent reports of the effectiveness of this bulky tertiary amine[55]), both with full conversion and high enantioselectivities of 89% and 90%, respectively.

Although the stereogenic centre in the product has already been created when the β-hydride is eliminated under the influence of the base present in the reaction mixture, the base used in the AHR clearly has a strong effect on conversion, product distribution and ee.[56,57] This might be due to competition in coordination to Pd, generating a non-chiral complex, but might also be due to changes in solvent polarity.

7.9.5 Back to a monodentate ligand!

Recent developments in asymmetric catalysis show that high enantioselectivities can be induced by monodentate chiral ligands,[58,59] and that monodentate BINOL based phosphoramidites are excellent ligands for rhodium catalysed asymmetric hydrogenations.[60] Although monodentate ligands were never very successful in inter- as well as intramolecular AHR's, we examined the monodentate analogue **L5**[61] of bidentate ligand **L19** in the Heck coupling of **7.30** using the best conditions we obtained for **L19**. (These two ligands were at the start of this research already comparable in reactivity and selectivity)

Much to our delight the use of monodentate ligand **L5** resulted in an improved enantioselective conversion of **7.30** to **7.31** compared to the Heck coupling employing bidentate ligand **L19**. Again Cy_2MeN was the base of choice. Using $Pd(OAc)_2$ in the presence of **L5** and Cy_2MeN, full conversion was reached, providing **7.31** in 71% isolated yield with an excellent ee of 96%.[62]



Scheme 7.10 *AHR of **7.30** using monodentate Taddol based phosphoramidite **L5** results in very efficient catalysis.*

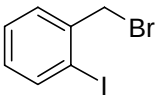
In summary, this is the first time that monodentate ligands have been succesfully used in the AHR, and the first time that high ee's were observed. Also noteworthy is the fact that these results are also the first description of the use of phosphoramidites in AHR's.

7.10 Conclusions

In conclusion, an efficient enantioselective intramolecular Heck reaction of cyclohexadienones, using readily available and modular TADDOL-based mono- and bidentate phosphoramidites as chiral ligands, has been developed. Excellent enantioselectivities up to 96% ee are reached for the first time in a Heck reaction with an easily synthesised monodentate phosphoramidite. However, the good results described in this chapter are only limited to one substrate, using one chiral ligand. Furthermore, it is unknown whether the reaction proceeds through a 'neutral' or 'cationic' pathway. Extension of the scope of this reaction and some mechanistic studies will be discussed in Chapter 8.

7.11 Experimental Section

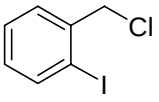
For general remarks, see previous chapters.



(2-Iodo)-benzylbromide (7.33)

To a stirred solution of 40 mmol (9.9 g) of (2-iodo)-benzoic acid at ambient temperature in 50 ml of CH_3CN was added 40 mmol (13.3 g) of CBr_4 in one portion and 40 mmol (10.5 g) of PPh_3 was added in small portions over 30 min. The mixture was refluxed overnight, the solvent evaporated and the crude product was purified by column chromatography (SiO_2, pentane/EtOAc = 95/5). The product was isolated as a pinkish oil, which solidified upon standing. (11.5 g, 97%) m.p. 51-53 °C (lit. 55.5°C)[63]

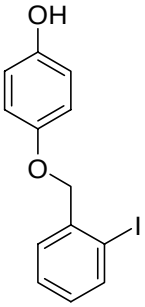
^{1}H NMR δ 4.55 (s, 2H), 6.95 (t, *J* = 7 Hz, 1H), 7.26 (t, *J* = 7 Hz, 1H), 7.42 (d, *J* = 9 Hz, 1H), 7.79, (d, *J* = 9 Hz, 1H). ^{13}C NMR δ 38.27 (t), 100.02 (s), 128.84 (d), 130.04 (d), 130.46 (d), 140.04 (d), 140.15 (s). HRMS calcd. for C_7H_6BrI 295.870, found 295.871.



(2-Iodo)-benzylchloride (7.34)

To a stirred solution of 20.0 g (85.5 mmol) of (2-iodo)-benzylalcohol in 250 ml CH_2Cl_2 was added 16.1 g (120.0 mmol) of triethylamine and 13.6 g of $SOCl_2$ (114 mmol). After 2h, the mixture was poured into 250 ml of saturated aq. $NaHCO_3$. The aqueous layer was extracted two times with 100 ml of CH_2Cl_2. The combined organic layers were dried on Na_2SO_4 and the solvent evaporated to yield the product (20.2 g, 80 mmol, 94%), m.p. 28.5-29.0°C (lit. 28-29°C).[64]

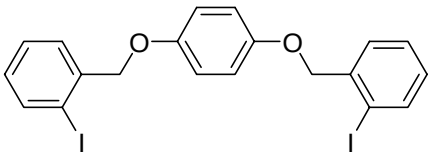
^{1}H NMR δ 4.63 (s, 2H), 6.98 (t, *J* = 6 Hz, 1H), 7.28 (t, *J* = 6 Hz, 1H), 7.33 (d, *J* = 6 Hz, 1H), 7.81 (d, *J* = 6 Hz, 1H). ^{13}C NMR δ 51.01 (t), 99.48 (s), 128.74 (d), 130.08 (d),130.10 (s), 130.19 (d), 139.84 (d). HRMS calcd. for C_9H_8ClI 251.920, found 251.921.



4-(2-Iodo)benzyloxyphenol (7.35)

A solution of 8.0 g (27 mmol) (2-iodo)-benzylbromide **7.33** (or 27 mmol of the 2-iodobenzylchloride **7.34**) 14.9 g (135 mmol) hydroquinone and 6.6 g (40.5 mmol) K_2CO_3 in 100 ml of acetone was stirred under reflux overnight. The mixture was cooled to room temperature and the solid was removed by filtration. The remaining solution was concentrated and the residue subsequently dissolved in $CHCl_3$. The hydroquinone precipitated and could be removed by filtration. After evaporation of the $CHCl_3$, the remaining oil was suspended in MeOH, after which the diether **7.36** precipitated (0.65 g, 4.5%). Another filtration and evaporation yields the pure mono-ether **7.35** as an orange oil (91% starting with the benzylbromide and 85% starting with the benzylchloride).

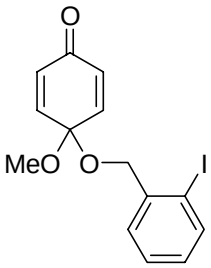
^{1}H NMR δ 4.93 (s, 2H), 6.72 (d, *J* = 9Hz, 2H), 6.82 (d, *J* = 9 Hz, 2H), 7.28 (m, 1H), 7.40 (m, 2H), 7.84 (m, 1H). ^{13}C NMR δ 73.17 (t), 95.88 (s),114.62 (d), 126.87 (d), 127.17 (d), 127.94 (d), 137.95 (d), 138.14 (s), 148.47 (s), 151.78 (s). HRMS calcd for $C_{13}H_{11}O_2I$ 325.980, found 325.980.



1,4-Di-(2-iodo)benzyloxybenzene (7.36)

Isolated as white fluffy needles, m.p. 189.5-191.3 °C.

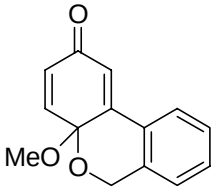
^{1}H NMR δ 4.95 (s, 4H), 6.88 (s, 4 H), 6.99 (m, 2H), 7.38 (m, 2H), 7.46 (m, 2H), 7.81 (m, 2H).73.05 (t), 95.65 (s), 114.41 (d), 126.87 (d), 127.13 (d), 127.92 (d), 137.72 (d), 139,41 (s), 151.71 (s). ^{13}C NMR δ 72.3 (t), 96.1 (s), 115.1 (d), 127.6 (d), 128.9 (d), 129.0 (d), 137.6 (d), 149.8 (s), 154.3 (s) HRMS calcd. for $C_{20}H_{16}O_2I_2$ 541.924, found 541.923.



4-(2-Iodo)benzyloxy-4-methoxycyclohexa-2,5-dien-2-one (7.30)

To a stirred solution of 5.0 g (15.3 mmol) of **7.35** in dry MeOH (10 ml) was added over 30 min a solution of 5.0 g (15.3 mmol) phenyl-iodo-diacetate in MeOH (50 ml). After 17h, the mixture was diluted with water (150 ml) and extracted with Et_2O (3x 50 ml). The combined organic layers were extracted with 2N NaOH (50 ml, brine (50 ml), dried on Na_2SO_4 and the solvent evaporated. The remaining oil was purified by column chromatography (SiO_2, Hexane/EtOAc = 8/1), yielding the product as an orange oil (4.5 g, 83%) which solidified upon standing; m.p.39.7-41.0°C.

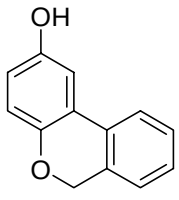
^{1}H NMR δ 3.39 (s, 3H), 4.58 (s, 2H), 6.22 (d, *J* = 6Hz, 2H), 6.85 (d, *J* = 6 Hz, 2H), 6.94 (m, 1H), 7.38 (m, 2H), 7.67 (d, *J* = 4 Hz, 1H).^{13}C NMR δ 50.78 (q), 68.81 (t), 97.75 (s), 97.38 (s), 128.27 (d), 128.39 (s), 128.60 (d), 139.10 (d), 139.65 (s), 143.16 (d), 185.04 (s). HRMS calcd. for $C_{14}H_{13}O_3I$ 355.991, found 355.992.



4a-Methoxy-4a*H*-benzo[c]chromen-2(6*H*)-one (7.31)

Light yellow oil. Isolated yield 72% (for an experiment using **L5** and Cy_2MeN), 95.7% ee, $[\alpha]_D$ 56.8 (c = 1.05, $CHCl_3$)

^{1}H NMR δ 3.21 (s, 3H), 4.82 (d, *J* = 13 Hz, 1H), 5.10 (d, *J* = 14 Hz, 1H), 6.33 (d, *J* = 10 Hz, 1H), 6.53 (s, 1H), 6.82 (d, *J* = 10 Hz, 1H), 7.09 (d, *J* = 8 Hz, 1H), 7.38 (m, 2H), 7.62 (d, *J* = 8 Hz, 1 H). ^{13}C NMR 51.09 (q), 62.60 (t), 120.00 (d), 124.06 (d), 124.74 (d), 126.73 (d), 127.41 (s), 129.96 (d), 135.00 (s), 142.38 (d), 147.38 (s), 185.85 (s). δ HRMS calcd. for $C_{14}H_{12}O_3$ 228.079, found 228.077. E.e. determination on HPLC DAICEL OD column, Heptane: EtOH = 75: 25, rt 6.69 min, 8.60 min. E.e. determination on HPLC DAICEL AS column: Heptane: IPA = 90: 10, rt 32.12 min, 38.67 min.



6*H*-Benzo[*c*]chromen-2-ol (7.37)

^{1}H NMR δ 5.01 (s, 2H), 6.62 (d, *J* = 5Hz, 1H), 6.73 (s, 1H), 6.82 (d, *J* = 5 Hz, 1H), 7.20 (m, 3H), 7.51 (d, *J* = 8Hz, 1H). ^{13}C NMR δ 69.17 (t), 110.33 (d), 115.46 (d), 116.67 (d), 122.69 (d), 124.42 (s), 125.63 (d), 128.47 (d), 129.00 (d), 130.54 (s), 132.37 (s), 149.83 (s), 151.23 (s). HRMS calcd. for $C_{13}H_{10}O_2$ 198.068, found 198.068.

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