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Monodentate phosphoramidites; versatile ligands in catalytic asymmetric intramolecular Heck reactions †

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The Pd-catalysed intramolecular asymmetric Heck reaction (AHR) of cyclohexadienone monoacetals in the presence of chiral phosphoramidite ligands is described. High enantioselectivities (up to 96% ee) are reached with monodentate ligands. The highest selectivity is observed with Taddol-based phosphoramidites containing a small amine substituent. A study of the effect of the leaving group at the aryl moiety and a number of parameters in the AHR show that this AHR most likely proceeds through a neutral pathway and that two equiv. of ligand are necessary for optimal asymmetric induction.

Chiral bidentate ligands have dominated the field of asymmetric catalysis in past decades and a number of privileged ligands including Binol, Taddol, bisoxazolines and a variety of bisphosphines have found widespread application.[1] The pioneering work on rhodium catalyzed asymmetric hydrogenation producing optically active amino acids, as reported by Knowles, was however based on monodentate phosphine ligands.[2] A limited number of monodentate chiral ligands have found application in asymmetric catalysis.[3–5] Recently a number of new highly selective phosphorus based monodentate chiral ligands such as phosphines,[6] phosphonites,[7] phosphites[8] and phosphoramidites[9] have been introduced.

For instance the application of monodentate phosphites and phosphoramidites in asymmetric hydrogenation leading to α- and β-amino acids contradicts the general notion that bidentate ligands are a requirement to reach high enantioselectivities in these reactions.[10–12] We have shown that phosphoramidites provide excellent levels of ee in a number of other asymmetric transformations such as asymmetric 1,4-additions,[13] epoxide ring-opening[14] and kinetic resolutions.[15] Binol- and Taddol-based phosphoramidites **1**–**3** (Fig. 1) are among the most successful members of this new class of chiral ligands.

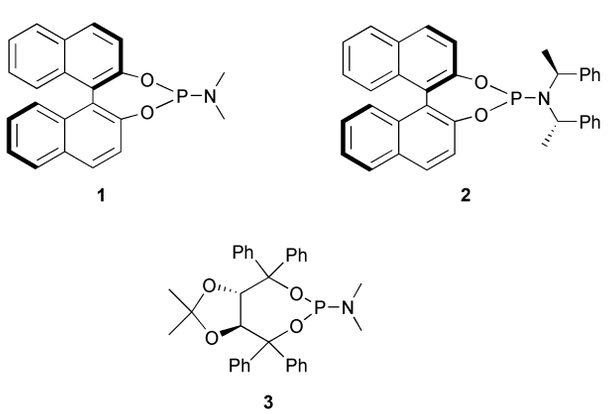
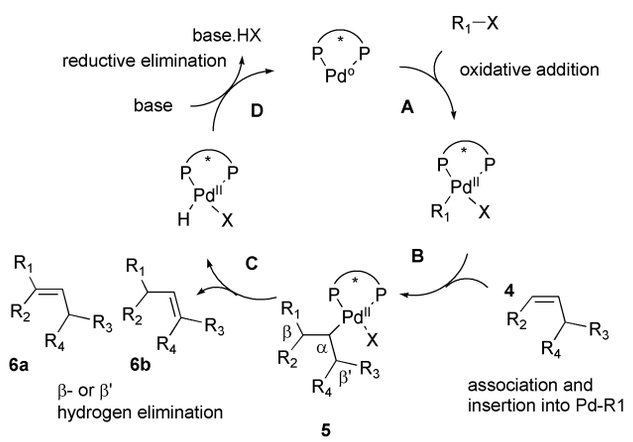


Fig. 1 Monodentate phosphoramidite ligands.

Important features of these phosphoramidites are the straightforward synthesis and the modular structure, which allows easy modification. Furthermore they are rather cheap and relatively stable towards hydrolysis and oxidation. As part of our program to develop catalytic asymmetric methodologies for carbon–carbon bond formation we have recently reported high enantioselectivity in the intramolecular asymmetric Heck reaction (AHR).[16]

The palladium catalysed arylation of olefins (Heck coupling) is an important method for C–C bond formation. The catalytic cycle is proposed to proceed according to Scheme 1:[17] Oxidative addition of an aryl or vinyl halide or triflate to a Pd^0-complex (step **A**) results in a Pd^{II} complex. Coordination of the alkene **4** followed by *cis*-insertion into the Pd–R_1 bond resulting in **5** (step **B**) is followed by β- or β′-hydrogen elimination (step **C**) providing **6a** or **6b**. Finally, reductive elimination of HX under influence of base (step **D**) results in regeneration of the starting Pd^0-complex.



Scheme 1

The regioselectivity depends heavily on the electronic and steric properties of the substituents present in the substrates. The key step regarding enantioselectivity in this reaction is obviously path **B**, which is dependent on the nature of the chiral ligand used. The nucleophilicity of the counterion (X) also plays a role.[18] If a halide is used the catalytic Pd-complex is neutral. In contrast, if a very weakly coordinating triflate anion is used a cationic Pd-complex is formed, which is considered to provide the pathway with higher stereoselectivity. Addition of silver[19] or thallium salts[20] to a reaction where an aryl halide is used as the aryl source leads to precipitation of the silver or thallium halides, resulting in the cationic Pd-complex, and as a consequence higher enantioselectivities are obtained for a number of examples.

Using monodentate phosphoramidite ligand **3** up to 96% ee was reached in the intramolecular Heck cyclization of cyclohexadienone monoacetal **7a** (Scheme 2).[16]

† Based on the presentation given at Dalton Discussion No. 5, 10–12th April 2003, Noordwijkerhout, The Netherlands.

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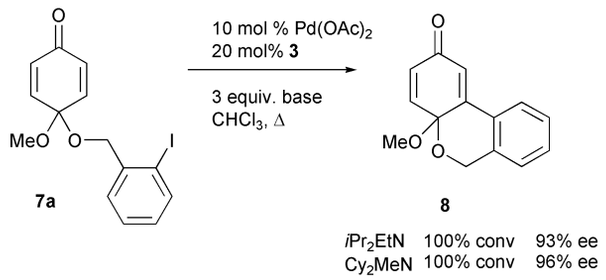


Scheme 2

We report here the results of a study on the effect of variations in leaving group and arene-substituents in the intramolecular asymmetric Heck reaction and the influence of a number of parameters that affect the reactivity and enantioselectivity of this catalytic conversion.

Results and discussion

Substrate variation

To study the scope of the reaction, several analogues of **7a** were synthesised and examined using the optimised conditions for this reaction as previously reported[16] (see Fig. 2 for a general structure). The size of the acetal, the nature of the leaving group, the substituents on the aryl group and the size of the ring that is formed during the AHR were varied.

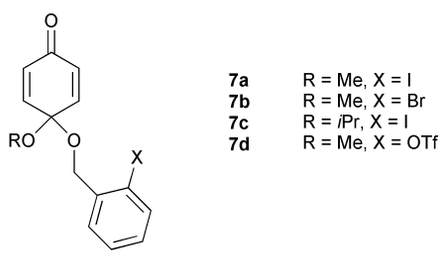
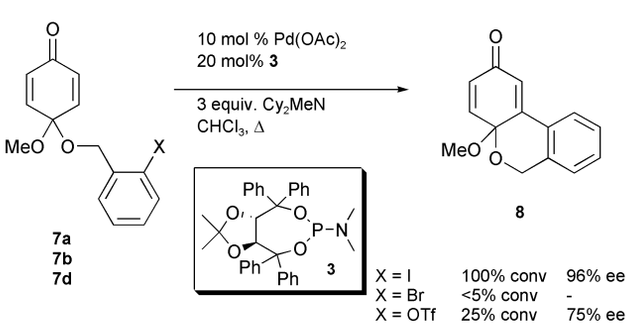


Fig. 2 Cyclohexadienone monoacetal substrates for the intramolecular AHR.

To study the effect of the leaving group bromide- **7b**, and triflate-substituted analogues **7d** of dienone **7a** were prepared using a phenyliododiacetate (PIDA) oxidation of the corresponding hydroquinone monoethers as a key step.[21,22] The AHR of dienones **7b** and **7d** was compared with the intramolecular coupling of iodo-dienone **7a** (see Scheme 3) reported earlier. The optimised conditions for the latter substrate were employed: an *in situ* formed catalyst of $Pd(OAc)_2$ and ligand **3** (10 mol%, Pd : L ratio = 1 : 2) was utilised and the reaction was performed in $CHCl_3$, using 3 equiv. of Cy_2MeN as a base. The reaction mixture was heated to 80 °C for 48 h under an inert atmosphere.



Scheme 3

The bromo-dienone **7b** showed only very low reactivity and less than 5% conversion was observed after a reaction time of 48 h. This decrease in reactivity in Heck reactions for bromides (and chlorides) compared to iodides is well known.[17d] In contrast the iodo-substituted dienone **7a** gave full conversion and the product **8** was isolated with an ee of 96%.

The triflate-analogue is expected to give rise to a cationic intermediate complex (*vide infra*), which might result in a different ee and could provide information on the pathway (cationic or neutral) leading to the highest enantioselectivity.[23] The triflate **7d** gave a very sluggish reaction: the mixture turned brown and a bit turbid. After 2 days only 25% conversion was observed (a considerable amount of side-product was formed as well) and the product showed only 75% ee. This indicates that in the case of these dienones, provided that the AHR of the triflate **7d** proceeds mainly through a cationic pathway, and the iodide dienone **7a** proceeds *via* the neutral pathway,[23] the 'neutral' complex results in the more reactive catalyst also leading to higher enantioselectivity (*vide infra*).

Next dienone **9** (Fig. 3), containing different substituents at the aromatic ring, or dienone **11** (Scheme 4) with a one carbon bridge, were examined.

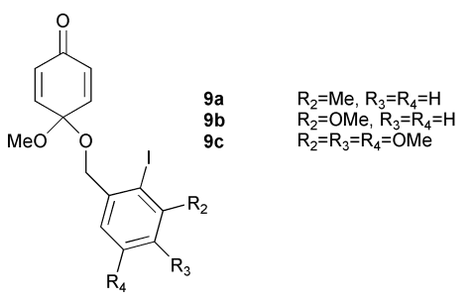
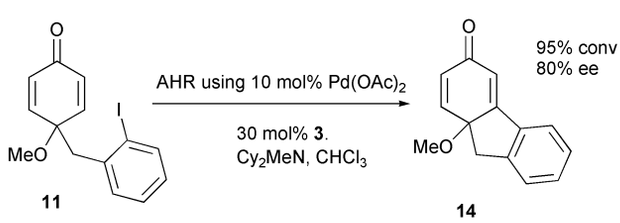


Fig. 3 Substituted cyclohexadienone monoacetals.



Scheme 4

For the AHR of dienones **9a**–**c** (and **7c**) monodentate ligand **3** (Fig. 1) as well as bidentate ligand **13** (Fig. 4) were used. The results are summarized in Table 1. In general, all reactions proceeded with good to complete conversion (<10% of side products were formed). In all cases the monodentate ligand **3** showed slightly higher enantioselectivities than the corresponding bidentate ligand **13** as ee's for the products were 2–5% lower when **14** was employed as a ligand.

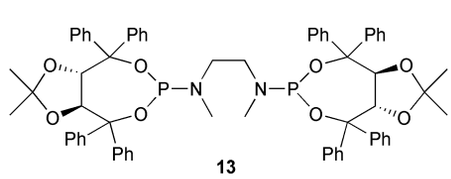


Fig. 4 Structure of bidentate ligand **13**.

By increasing the steric bulk around the prochiral centre (^{i}PrO based acetal dienone **7c**) a decrease in reactivity as well as enantioselectivity was observed (compare entry 1, Table 1 and Scheme 3). The product **10** was obtained with 89% conversion and with an ee of 78% using ligand **3**. The effect of changing the electronic and steric properties of the aryl moiety, strongly depends on the substituent pattern. For the 3-Me-substituted dienone **9a** the ee dropped to 73% for product **12a**. In contrast, the presence of a 3-MeO substituent in dienone **9b** results in product **12b** with an ee of 94%. The presence of three MeO-

Table 1 Results of AHR of dienones **7c** and **9a**–**c** using mono- or bi-dentate phosphoramidites as chiral ligands[a]

Entry	Dienone	Product	Conversion [b](ee)[c] ligand **3**	Conversion[b] (ee)[c] ligand **13**
1	**7c**	**10**	89 (78)	90 (73)
2	**9a**	**12a**	95 (73)	98 (70)
3	**9b**	**12b**	83 (94)	87 (92)
4	**9c**	**12c**	84 (87)	80 (83)

[a] Conditions: 10 mol% $Pd(OAc)_2$, 30 mol% **3** or 20 mol% **13**, $CHCl_3$, Cy_2MeN, Δ, 48 h. [b] Determined by ^1H NMR. [c] Determined by chiral HPLC.

groups at the aromatic ring (dienone **9c**) results in a highly electron rich aromatic iodide and the Heck product **12c** is obtained with 87% ee.

All substrates studied so far were dienone mono-acetals. To determine if the acetal-moiety is inextricably connected to the high ee in this intramolecular coupling reaction dienone **11**, which after AHR will result in an all carbon tricyclic system **14**, was prepared (Scheme 4).[22] This tricyclic system not only lacks an acetal moiety, but a five-membered ring is formed upon Heck cyclization instead of a six-membered ring. The AHR of this new dienone, using the same conditions as for the other dienones (*vide supra*), resulted in 95% conversion to **14** (employing ligand **3**) and 80% ee.

Although the comparison with **7** is not completely justified (five- *versus* six-membered ring formed), the presence of an acetal does not seem to be essential for high ee and good conversion.

Additives

Added salts can enhance reactivity and selectivity in palladium mediated processes.[24–26] A number of experiments using bidentate ligand **13** and the standard dienone **7a** were performed to examine additive effects and the results are shown in Fig. 5. As a base $^iPr_2EtN$ was used with 10 mol% of Pd-cat and $CHCl_3$ was employed as the solvent. This 'standard' reaction gives full conversion after 48 h and product **8** is obtained with an 89% ee.

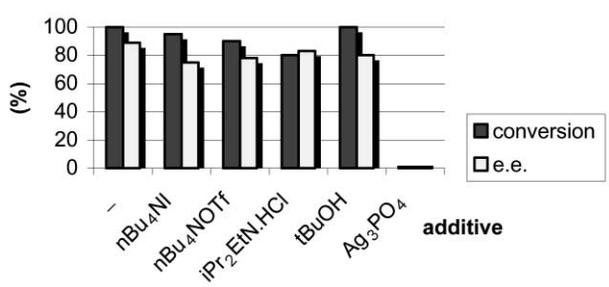


Fig. 5 The effect of additives on the AHR of **7a** using the palladium catalyst based on **13**. Conditions: 10 mol% $Pd(OAc)_2$, 20 mol% **13**, $^iPr_2EtN$, Δ, 48 h. In each case 1 equiv. of additive was used, with the exception of ^{t}BuOH, for which 10 equiv. were added.

In the first experiment $^nBu_4NI$ (1 equiv.) was added to the reaction mixture, to increase the I^- concentration. This reaction did not go to completion and the ee of the product (75%) was lower than for the 'standard' reaction. Adding $^nBu_4NOTf$ to the reaction mixture resulted in a comparable result; the reaction was not complete and the enantioselectivity was lower. Addition of $^iPr_2EtN{\cdot}HCl$ to the mixture (mimicking the solution after a longer reaction time, since $^iPr_2EtN{\cdot}HI$ is formed as the reaction progresses)[27] resulted in a conversion of only 80%, but the ee was not affected very much. Apparently the build-up of amine salts or the presence of chloride slows down the reaction, but has little effect on enantioselectivity. To our surprise, addition of ^{t}BuOH resulted in a clean reaction and no Pd-black was formed and full conversion was reached after 48 h. This means that this reaction (with a moisture sensitive acetal) can be run in a protic environment at elevated temperatures. The decrease of ee to 80% can therefore be attributed to a solvent effect. Generating the cationic complex by addition of Ag_3PO_4 or Ag_2CO_3 did not give any conversion, which leads to the conclusion that the cationic complex is not reactive in this case. This indicates that the enantioselective AHR of **7a**, when performed under the optimised conditions, will follow a neutral pathway. It appears that the addition of salts has only a marginal effect on the enantioselectivity and conversion.

Monitoring conversion and ee in time

To determine if the catalyst is uniformly defined throughout the reaction, the conversion and ee of the reaction were followed in time (using Cy_2MeN as a base and **3** or **13** as chiral ligands). From the results shown in Fig. 6 it is obvious that the ee is constant during the reaction for both ligands. From the conversion *vs*. time plots, it is evident that the monodentate and bidentate ligand show similar behaviour; there is no induction period, which is in accordance with the constant ee observed. When 70–80% conversion is reached, a 'levelling off' of the curve is observed, which is in accordance with the fact that the concentration of **7a** is much lower then, giving a lower rate.

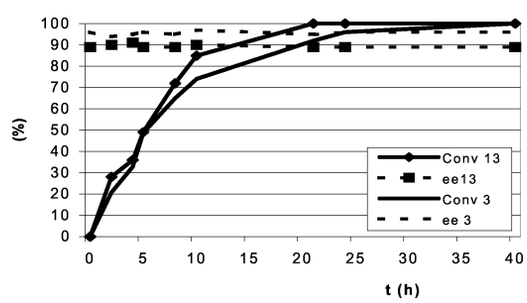


Fig. 6 Conversion and ee *vs*. time of the AHR of **7** using catalysts prepared from $Pd(OAc)_2$ and **3** or **13**.

Pd to ligand ratio

To examine if the presence of two or more equivalents of phosphoramidites is necessary for high asymmetric induction, a series of experiments was performed in which the Pd : L ratio was changed from 0–3 (Fig. 7). The ligand used for this reaction was monodentate ligand **3** and the reactions were performed in $CHCl_3$ using Cy_2MeN as a base, whereas the catalyst was prepared using $Pd(OAc)_2$. Since this is a Pd^{II}-source, one extra equivalent of ligand was necessary for reducing the Pd^{II} to Pd^0. This extra equivalent was not included in the ratio of Pd : L.

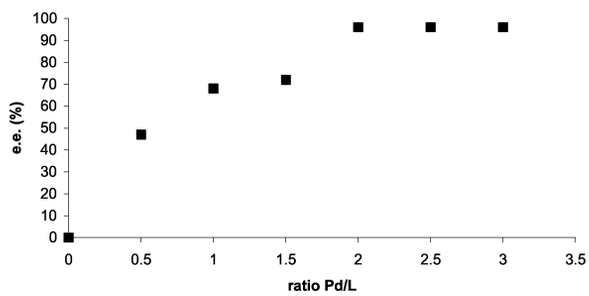


Fig. 7 Effect of Pd : **3** ratio on ee of the product at full conversion of **7a**, using a catalyst prepared from $Pd(OAc)_2$ and **3**.

It turned out, that even 0.5 equiv. (to Pd) of the ligand was able to induce significant ee (up to 50%) in the product. Upon increasing the ratio, also the ee of the product increased to a maximum value of 96% ee for a Pd : L ratio of 2 or higher. Increasing the amount of ligand to a Pd : L ratio of 1 : 3 did not cause a further change in enantioselectivity. From these results we can conclude that two equivalents of the ligand are necessary for optimal asymmetric induction, and that extra equivalents do not change the enantioselectivity of the catalyst.

Influence of ligand structure on reactivity and selectivity

The catalyst based on phosphoramidite **3** was superior with respect to enantioselectivity and activity to the bidentate ligand **13**. Two equivalents of ligand are necessary for optimal asymmetric induction. To examine the steric requirements of the chiral ligand, several analogues of ligand **3** were synthesised. The rigidity and steric effect of the amine part was subtly changed in **15** and **16** (Fig. 8). The bulk of the Taddol moiety was increased in the naphthyl-analogue **17**.[28] The cyclopentanone-acetal Taddol derivative, that is more constrained but less hindered due to the presence of the five-membered ring, was used to prepare the dimethylamine phosphoramidite **18**. All ligands were prepared according to known literature procedures.[29,30]

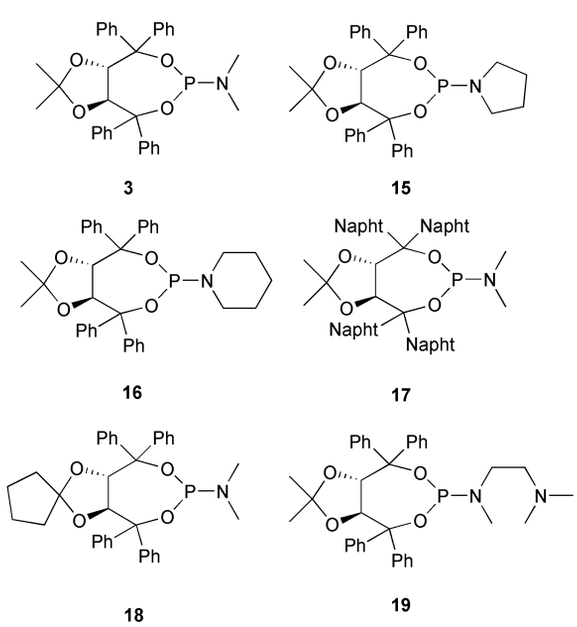
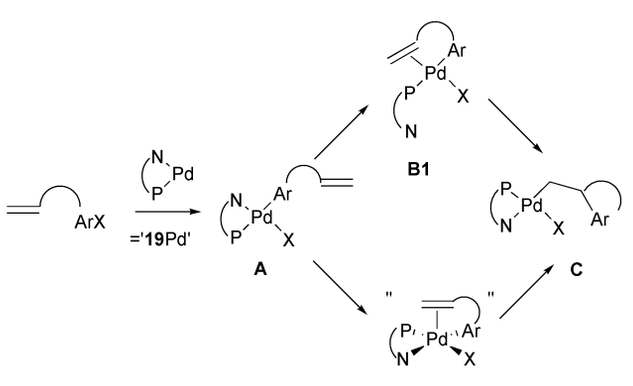


Fig. 8 Ligand **3** and analogues **15**–**19**.

To determine which neutral pathway (see Scheme 5) takes place, the analogue **19** of ligand **3** with a pendant amine functionality was designed. If the catalysis would occur through the neutral pathway, as shown in Scheme 5, where one of the ligands dissociates, the less strongly coordinating pendant amine group is expected to give a similar complex as when **3** would be used in this catalysis.



Scheme 5 Possible neutral pathways involved in the AHR of **7a** employing **19** as a ligand.

Table 2 Ligand variation in the AHR of **7a** [a]

Entry	Ligand	Conversion [b] (%)	Ee [c] (%)
1	**3**	100	96
2	**15**	100	92
3	**16**	85	85
4	**17**	100	88
5	**18**	100	58
6	**19**	60	26

[a] See Table 1. [b] Determined by NMR. [c] Determined by chiral HPLC.

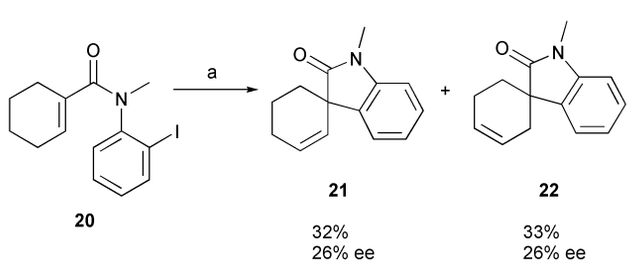
The AHR of substrate **7a** was studied with these new ligands using the optimised conditions and the results are shown in Table 2. Changing the bulk and flexibility of the amine-moiety in pyrrolidine based phosphoramidite ligand **15** provided the product with full conversion and 92% ee. By increasing the ring size as seen in **16**, both the reactivity and selectivity decreased (to 85% conversion and 85% ee, respectively). Increasing the bulk of the diol moiety in the ligand by changing from Taddol to Dinol (naphthyl-based Taddol) resulted in **17** that showed similar reactivity but lower enantioselectivity (full conversion, 88% ee). Changing the acetal moiety to the cyclopentanone-analogue as present in **18** displayed a remarkable decrease in ee to 58%, despite the remote position of modification. Excellent enantioselectivities are therefore only observed employing monodentate phosphoramidites (**3** and **15**) based on Taddol containing small amine moieties.

Finally, the monodentate mimic **19** resulted in a very slow reaction (only 60% conversion after 48 h) and a dramatic drop in ee (26%). The pendant dimethylamino group may coordinate too strongly to Pd in the neutral pathway, preventing dissociation taking place in path **B1** (Scheme 5).

A more likely explanation might be that the catalysis proceeds through the neutral five-coordinate palladium species **B2**, with a bidentate coordinating ligand and axial coordination of the alkene. This again supports the conclusion that two equiv. of phosphoramidite **3** are necessary for high asymmetric induction.

For comparison, the Overman substrate [31] **20** was also examined (Scheme 6). The reaction was performed under the same conditions as employed for the dienones, except for the temperature: $CHCl_3$ was used as a solvent, Cy_2MeN as a base and the catalyst was prepared from $Pd(OAc)_2$ and ligand **3**. The reaction mixture was stirred overnight at ambient temperature. The conversion was only 65% and the product was formed as a 1 : 1 mixture of the regioisomers **21** and **22**, both having an ee of only 26%. When the reaction was performed under the conditions used by Overman (DMA, PMP) similar results were obtained.

Based on extensive mechanistic studies of Heck couplings,[17] the formation of **8** can be rationalised as shown in Fig. 9.



Scheme 6 Application of the phosphoramidite ligand in the Overman AHR. (a) 10 mol% $Pd(OAc)_2$, 20 mol% **3**, Cy_2MeN (3 equiv.), $CHCl_3$, Δ, 18 h.

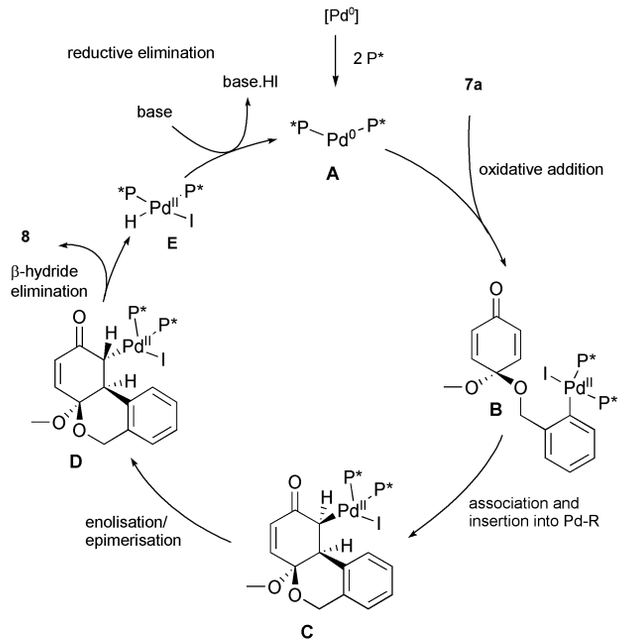


Fig. 9 Possible mechanistic pathway for the AHR of dienone **7a**.

Initially, a chiral Pd(0) complex **A** is formed. Oxidative addition of dienone **7a** 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 **8** 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.[32] In addition it should be noted that several examples of apparent *trans* β-hydride elimination have appeared in the literature.[33] Finally, reductive elimination of HI with base leads to the starting complex **A**.

Conclusions

We have shown that the AHR of iodide substituted dienone **7a** is very successful, resulting in full conversion and 96% ee. The cationic complex that was generated by adding silver salts to the catalyst did not give any conversion at all. However, the triflate analogue **7d** did show conversion albeit only 25% and an ee of 78% in the product was obtained. Since the cationic complex is likely to be formed for triflates,[34] and this was shown to be unreactive, a certain percentage (25% in this case) of the amount of dienone must lead to the neutral complex resulting in a respectable enantioselectivity.

The presence of substituents at the phenyl ring results in a slower and less enantioselective Heck coupling, although an *o*-MeO-substituent is tolerated. The complex is apparently uniformly defined throughout the reaction (no induction period is necessary) and two equivalents of Taddol-based ligand **3** are necessary for optimal asymmetric induction. Of course, this is a very interesting observation, since the bidentate version (**13**) of this ligand shows lower enantioselectivity. Furthermore, the experiments using ligand **19** show that it is likely that the $Pd(OAc)_2$/**3** catalysed AHR of **7a** proceeds through a pentacoordinate neutral pathway.

The extra flexibility and rotational freedom that is obtained by using mono- instead of bi-dentate ligands is beneficial for the enantioselectivity of this particular Heck coupling. Whether or not this feature has generality for other AHRs still needs to be determined.

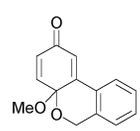
Experimental

All solvents were reagent grade and were dried and distilled, if necessary, following standard procedures. Reagents were purchased from Aldrich, Acros Chimica, Merck or Fluka and used as received unless stated otherwise. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer (at 300 and 75.4 MHz, respectively). Chemical shifts are reported in δ units (ppm) relative to the residual deuterated solvent signals of $CHCl_3$ (^{1}H: 7.24 ppm, ^{13}C: 77.0 ppm). Optical rotations were measured at ambient temperature using a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on an AEI-MS-902 mass spectrometer. HPLC measurements were performed on a Waters HPLC system equipped with a 600E solvent delivery system and a 996 photodiode array detector. To ensure accurate determination of ee's, racemic mixtures of all products were prepared.

General procedure for the AHR

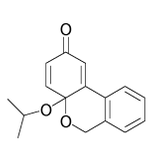
$Pd(OAc)_2$ (0.033 mmol) and 0.066 mmol of **13** or 0.099 mmol of **3** were dissolved under Ar in 3 ml of dry and degassed $CHCl_3$ and heated under reflux for 1–2 h, until a clear yellow solution was obtained. Next 1.2 mmol of base, the appropriate additive and 0.33 mmol of cyclohexadienone were added and the mixture was refluxed for 48 h. The solvent was evaporated, conversion was determined by ^{1}H NMR and the crude product was purified by column chromatography (SiO_2, petroleum ether (40:60)–EtOAc = 9 : 1).

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



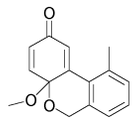
Light yellow oil. Isolated yield 72% (for an experiment using **3** and Cy_2MeN), 95.7% ee, $[\alpha]_D$ 56.8 (c = 1.05, $CHCl_3$). ^{1}H NMR δ 3.21 (s, 3H), 4.82 (d, J = 13 Hz, 1H), 5.10 (d, J = 14 Hz, 1H), 6.33 (d, J = 10 Hz, 1H), 6.53 (s, 1H), 6.82 (d, J = 10 Hz, 1H), 7.09 (d, J = 8 Hz, 1H), 7.38 (m, 2H), 7.62 (d, J = 8 Hz, 1H). ^{13}C NMR δ 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). HRMS calc. for $C_{14}H_{12}O_3$ 228.079, found *m*/*z* 228.077. E.e. determination on HPLC DAICEL OD column, Heptane : EtOH = 75 : 25, rt = 6.69, 8.60 min. E.e. determination on HPLC DAICEL AS column: heptane : IPA = 90 : 10, rt = 32.12, 38.67 min.

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



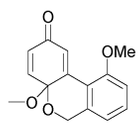
^{1}H NMR δ 0.82 (d, J = 6 Hz, 3H), 1.06 (d, J = 8 Hz, 3H), 3.83 (septet, J = 6 Hz, 1H), 4.80 (d, J = 15 Hz, 1H), 5.11 (d, J = 15 Hz, 1H), 6.26 (d, J = 8 Hz, 1H), 6.51 (s, 1H), 6.79 (d, J = 14 Hz, 1H), 7.04 (d, J = 8 Hz, 1 H), 7.34 (m, 2H), 7.62 (d, J = 7 Hz, 1H) ^{13}C NMR δ 23,74 (q), 24.02 (q), 62.61 (t), 66.531 (d), 119.92 (d), 123.93 (d), 124.74 (d), 127.33 (d), 128.34 (s), 129.50 (d), 130.47 (d), 135.18 (s), 144.20 (d), 14834 (s), 156.29 (s), 183.27 (s). HRMS calc. for $C_{16}H_{16}O_3$ 256.109 found *m*/*z* 256.107. E.e. determination on HPLC DAICEL OD column, heptane : ^{i}PrOH = 95 : 5, rt = 12.6, 25.3 min.

4a-Methoxy-10-methyl-4a*H*,6*H*-benzo[*c*]chromen-2-one



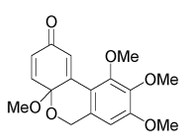
^{1}H NMR δ 2.24 (s), 3.42 (s), 4.81 (dd, J = 25, 13 Hz, 2H), 6.12 (d, J = 11 Hz, 1H), 6.71 (s, 1H), 6.86 (d, J = 11 Hz, 1H), 7.05–7.12 (m, 3H). ^{13}C NMR δ 17.89 (q), 42.71 (q), 63.78 (t), 114.77 (s), 121.56 (d), 126.46 (d), 129.03 (d), 130.59 (d), 131.33 (s), 131.69 (s), 135.65 (s), 142.65 (d), 149.97 (d), 164.45 (s), 198.36 (s). HRMS calc. for $C_{15}H_{14}O_3$ 242.094, found *m*/*z* 242.093. E.e. determination on HPLC DAICEL OD column, heptane : ^{i}PrOH = 95 : 5, rt = 10.9, 35.94 min.

4a,10-Dimethoxy-4a*H*,6*H*-benzo[*c*]chromen-2-one



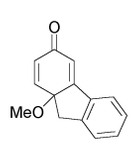
^{1}H NMR δ 3.63 (s, 3H), 3.85 (s, 3H), 5.05 (d, J = 10 Hz, 1H), 5.20 (d, J = 10 Hz, 1H), 6.55 (d, J = 8 Hz, 1H), 6.79 (s, 1H), 6.82 (d, J = 8 Hz, 1H), 6.87 (dd, J = 8, 2 Hz, 1H), 7.14–7.24 (m, 1H), 7.30 (dt, J = 2, 8 Hz, 1H). ^{13}C NMR δ 45.4 (q), 46.3 (q), 64.1 (t), 108.1 (s), 121.3 (d), 121.4 (d), 127.3 (d), 128.2 (d), 132.1 (s), 132.4 (d), 134.6 (s), 135.3 (s), 149.8 (d), 164.5 (s), 187.0 (s). HRMS calc. for $C_{15}H_{14}O_4$ 258.089, found *m*/*z* 258.088. E.e. determination on HPLC DAICEL OD column, heptane : ^{i}PrOH = 95 : 5, rt = 18.68, 24.95 min.

4a,8,9,10-Tetramethoxy-4a*H*-benzo[*c*]chromen-2(6*H*)-one



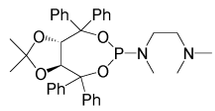
^{1}H NMR δ 3.24 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 4.98 (dd, J = 23, 12 Hz, 2H), 6.36 (d, J = 10 Hz, 1H), 6.39 (s, 1H), 6.76 (d, J = 9 Hz), 7.15 (d, J = 2 Hz). ^{13}C NMR δ 51.14 (q), 55.99 (q), 60.59 (t), 60.99 (q), 62.66 (q), 102.20 (d), 114.08 (q), 123.54 (d), 130.44 (d), 131.95 (s), 142.26 (d), 143.06 (s), 147.87 (s), 151.27 (s), 151.88 (s), 155.31 (s), 186.79 (s). HRMS calc. for C_{17} $H_{19}O_6I$ 446.022, found *m*/*z* 446.021. E.e. determination on HPLC DAICEL OD column, heptane : ^{i}PrOH = 95 : 5, rt = 15.9, 26.06 min.

9a-Methoxy-9,9a-dihydrofluoren-3-one



^{1}H NMR δ 2.86 (m, 2H), 3.64 (s, 3H), 6.38 (d, J = 9 Hz, 1H), 6.59 (s, 1H), 6.79 (d, J = 9 Hz, 1H), 7.05–7.08 (m, 1H), 7.28 (dt, J = 11, 2 Hz, 1H), 7.45–7.49 (m, 1H), 7.56–7.59 (m, 1H). ^{13}C NMR δ 42.0 (s), 49.7 (q), 83.8 (s), 121.4 (d), 125.6 (d), 126.1 (d), 127.6 (d), 127.8 (d),132.4 (d), 134.3 (s), 137.8 (s), 152.4 (d), 164.5 (s), 187.0 (s). HRMS calc. for $C_{14}H_{12}O_2$ 212.084, found *m*/*z* 212.084. E.e. determination on HPLC DAICEL OD column, heptane : ^{i}PrOH = 90 : 10, rt = 7.2, 9.4 min.

***N*-(2,2-Dimethyl-4,4,8,8-tetraphenyltetrahydro[1,3]dioxolo-[4,5-*e*][1,3,2]dioxaphosphepin-6-yl)-*N*,*N*′,*N*′-trimethylethane-1,2-diamine**



At 0 °C, 2.5 mmol (1.16 g) (−)Taddol was dissolved in 10 ml of THF and 8.5 mmol Et_3N (1.25 ml) was added. To the stirred mixture slowly 2.5 mmol (236 µl) PCl_3 was added. The mixture was stirred for 1 h, the salts were removed by filtration, and the chlorophosphine solution was cooled to −20 °C. A pre-made solution of the lithium amide of *N*,*N*′,*N*′-trimethylethylene-diamine (5 ml of THF, 3.0 mmol amine, 1.88 ml of 1.6 M ^{n}BuLi in hexane) was slowly added to the chlorophosphine solution, and the mixture was allowed to warm to ambient temperature, and stirred overnight. Salts were removed by filtration, the solvents were evaporated and the product was obtained as a white powder by crystallisation from acetone (193 mg, 13%). ^{1}H NMR δ 0.28 (s, 3H), 1.29 (s, 3H), 2.23 (s, 6H), 2.79 (d, J = 9 Hz, 3H), 4.80 (d, J = 9 Hz, 1H), 4.99 (dd, J = 9, 3 Hz, 1H), 7.18–7.82 (m, 20H). ^{13}C NMR δ 25.26, 27.51, 32.45 (d, J = 16 Hz), 45.56, 46.80 (d, J = 24 Hz), 57.87, 81.19, 82.20, 82.43, 127.14, 127.42, 127.65, 128.03, 128.73, 128.83, 128.97, 140.30 (d, J = 15 Hz), 145.48 (d, J = 15 Hz). HRMS calc. for $C_{36}H_{41}N_2O_4P$ 596.280, found *m*/*z* 596.281.

Acknowledgements

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