Palladium complexes of phosphinamine ligands in the intramolecular asymmetric Heck reaction

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Dedicated with respect to Jean-Pierre Genet — 'Allez les bleus'

Abstract

The synthesis of two novel cyclisation substrates for the asymmetric intramolecular Heck reaction is reported. Their cyclisation, in addition to a known substrate for *cis*-decalin formation, were tested with palladium complexes of BINAP and heterobidentate oxazoline-containing ligands. In general BINAP provides a more active catalyst system for the range of substrates tested although excellent enantioselectivities of up to 85% were obtained with the P,N ligands studied. A trend was noted whereby the *t*-leucine-derived oxazoline ligands were more reactive and enantioselective than the valine-derived analogues. Similarly, the diphenylphosphinoferrocenyloxazoline ligands were more reactive and selective than the corresponding diphenylphosphinophenyloxazoline ligands.
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1. Introduction

The Heck reaction is a versatile and useful palladium-catalysed elaboration of substituted alkenes by direct C–C bond formation at a vinylic carbon centre [1–4]. Its potential has been exploited in the key steps of many total syntheses [5] and a better understanding of the reaction mechanism continues to emerge [6–9]. Both intramolecular and intermolecular asymmetric variants have been extensively studied and have been the subject of numerous reviews [10–17]. The asymmetric intramolecular Heck reaction was reported initially in 1989 when Overman and Shibasaki independently described enantioselective cyclisations [18,19]. The asymmetric induction obtained was due to palladium complexes of the diphosphine ligands, DIOP and (*R*)-BINAP, respectively. Since those initial reports the methodology has been applied to the enantioselective synthesis of a range

of fused ring systems such as decalins **1** [19], hydrindans **2** [20], indolizidines **3** [21] and diquinanes **4**–**5** [22] (Fig. 1).

(*R*)-BINAP (**6**) proved to be the ligand of choice in the majority of the intramolecular Heck reactions studied although the related diphosphines BINAs (**7**) [23], BITIANP (**8**), TMBTP (**9**) [24] and BPPFOH (**10**) [21] have compared favourably to BINAP in selected cyclisations (Fig. 2).

Pfaltz and co-workers described the application of palladium complexes of diphenylphosphinooxazoline ligands **11**–**12** to the intermolecular Heck reaction with 2,3-dihydrofuran [25,26]. Hallberg subsequently employed ligands **11**–**12** in his enamide synthesis obtaining both excellent enantioselectivities and good regioselectivities [27]. More recently, Busacca and co-workers have applied related phosphinoimadazoline ligands to the preparation of spirooxindoles with enantioselectivities of up to 88% [28]. Metal complexes of ferrocene-based planar chiral ligands have proven to be highly effective for a range of catalytic asymmetric transformations [29]. Diphenylphosphinoferrocenyloxa-

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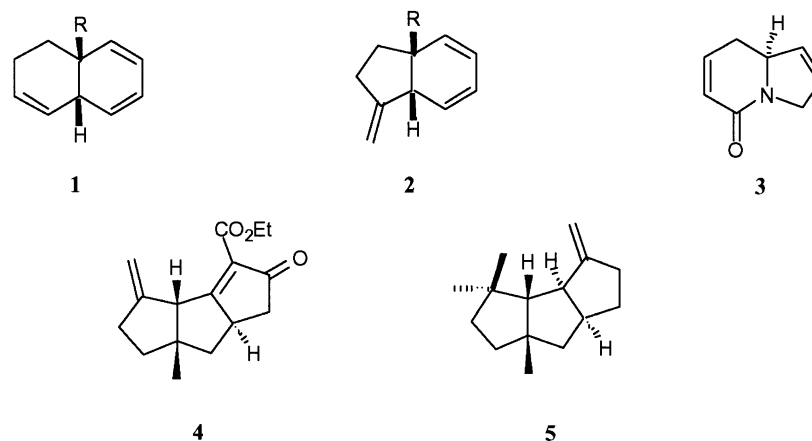*E-mail address:* p.guiry@ucd.ie (P.J. Guiry).

Fig. 1. Products of intramolecular asymmetric Heck reactions.

zoline ligands **13**–**14** were first reported by the groups of Uemura and Richards [30,31]. We had independently synthesised these ligands and observed enantioselectivities of up to 92% using ligand **14** in the palladium-catalysed allylic alkylation of 1,3-diphenyl-propenylacetate [32] and up to 72% ee in the allylic amination of ethyl (2E)-1,3-diphenylprop-2-enyl carbonate [33]. More recently, we have demonstrated the efficacy of the heterobidentate P–N systems **11**–**14** in the intermolecular Heck reaction with both 2,3-dihydrofuran and 2,2-dialkyl-2,3-dihydrofurans as substrates [34–37]. This led us to believe that P,N ligands **11**–**14** would have potential in the Pd-catalysed asymmetric intramolecular Heck reaction and we now wish to report in full our results on their application to this transformation [38,39].

2. Results and discussion

We intended to test the efficiency of palladium complexes of ligands **11**–**14** with both novel and known cyclisation substrates (**15**, **17**–**18**) for comparison purposes with related ligands and to expand the range of substrates studied (Fig. 3).

Specifically, we prepared the novel triflate **15** as the potentially complicated double bond isomerisation of the Heck reaction product is avoided with this substrate. This cyclisation precursor is therefore an excellent substrate for the direct screening and comparison of a range of ligand–palladium complexes. Triflate **15** was chosen as during the catalytic cycle the triflate anion spontaneously dissociates and acts as a counterion, thus stabilising the proposed cationic palladium intermediate
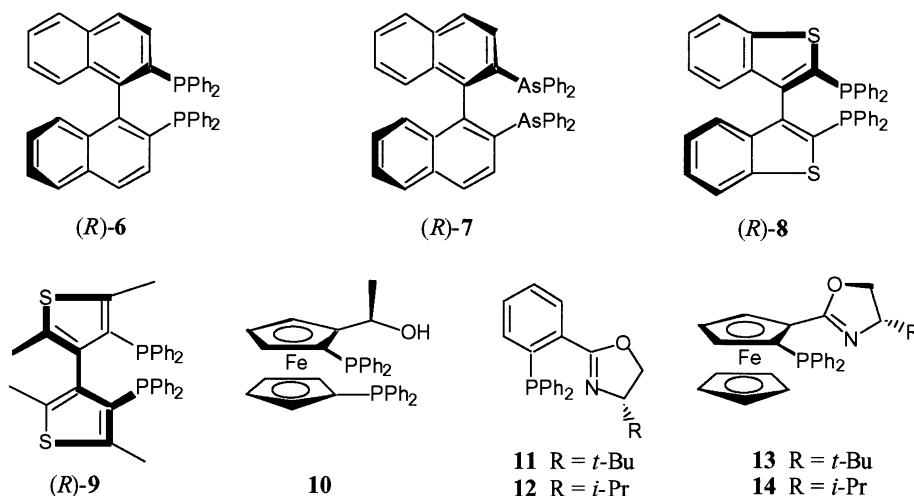

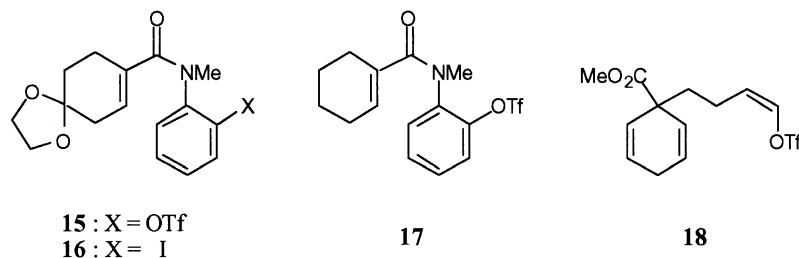Fig. 2. Ligands applied in the intramolecular asymmetric Heck reaction.

Fig. 3. Substrates for the intramolecular asymmetric Heck reaction.

and allowing the ligand to remain bidentate [40,41]. This cationic pathway proposal by Cabri [40] to effectively induce enantioselectivity in the Heck reaction was subsequently challenged by Overman where an apparently neutral pathway afforded high levels of enantioselectivities [42]. The proposed cationic square planar palladium intermediate may also be accessed from the corresponding iodide **16**, but generally requires the addition of silver salts to remove the halide ligand from the palladium coordination sphere. The novel triflate **17** was prepared in order to investigate the relative regioselectivity and stereoselectivity of cyclisation induced by palladium complexes of bisphosphine or phosphinamine ligands respectively, since with this substrate double bond isomerisation of the Heck reaction product is possible. Finally the alkenyl triflate **18** was screened using palladium complexes of phosphinamine ligands in order to further investigate the scope of heterobidentate ligands in asymmetric Heck reactions. This substrate had previously been extensively studied by the group of Shibasaki [20,43] using BINAP as the source of chiral induction, which would provide a useful comparative source for our study with phosphinamine ligands.

2.1. Synthesis of substrate 15

2-Trifluoromethanesulfonyloxy-(1,4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-N-methylaniline (**15**) was prepared in five steps from the known carboxylic acid, 1,4-dioxaspiro[4.5]dec-7-ene-8-carboxylic acid (**19**) [42] (Scheme 1). Coupling via the acid chloride with 2-aminophenol gave the corresponding enamide **20** in 60% yield. The remaining functional group manipulations required were amide N-methylation and conversion of the phenol to an aryl triflate. Methylation without protection of the alcohol resulted in significant competitive O-methylation. Following the general procedure of McKillop the phenol was protected as an allyl-ether **21** [44] and subsequent N-methylation yielded the required amide **22** in 85% yield. Following the procedure of Deziel, the allyl-ether was deprotected using catalytic quantities of tetrakis(triphenylphosphine)palladium(0) generating **23** in 84% yield [45]. Conversion of the phenol to the triflate **15** was achieved in 82% yield using

triflic anhydride and dimethylaminopyridine in dichloromethane, a protocol which we have used in our synthesis of axially chiral P,N ligands [46]. The required novel cyclic substrate **15** was thus prepared in five steps from carboxylic acid **19** in an overall yield of 35%.

2.2. Intramolecular Heck studies of substrate 15

Prior to the commencement of the study of the asymmetric cyclisation of substrate **15** it was necessary to prepare the cyclisation product **24** as a racemate in order to establish conditions for the separation of the enantiomers (Scheme 2).

The cyclised product was formed in a 90% isolated yield, although the reaction employed a high catalyst loading of 20 mol%. With this racemic mixture in hand separation of the enantiomers was now possible. Separation by chiral HPLC was initially attempted, however despite trying three different chiral columns (Daicel, Chiralpak OJ, OD, AD), sufficient baseline separation was not achieved. Resolution of the enantiomers could however be achieved by ^{1}H-NMR spectroscopy in the presence of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III). The N-methyl singlets of the two diastereomers formed appeared at different chemical shifts moving from 3.21 for the enantiomers to 3.6–4.0 for the diastereomers.

The results of our investigations on the asymmetric cyclisation of substrate **15** with BINAP **6** and the P,N ligands **11–14** (Scheme 3), are given in Table 1.

BINAP **6** was determined by Overman to be the ligand of choice in the cyclisation of the analogous aryl iodide giving an optimal enantioselectivity of 71% in 81% yield [43]. Following a similar procedure in the present study, cyclisations of **15** were carried out using 5 mol% of palladium precursor (Pd$_2$(dba)$_3$), 10 mol% of (R)-BINAP **6** and three equivalents of base (Scheme 3). Palladium complexes of ligand **6** were generated in situ prior to addition of solvent and base and the formation of the catalyst was assumed to be complete when an orange homogenous solution had formed (typically this took 1 h). The Heck reaction time was 2 days (to allow direct comparison with the iodide analogue) and the
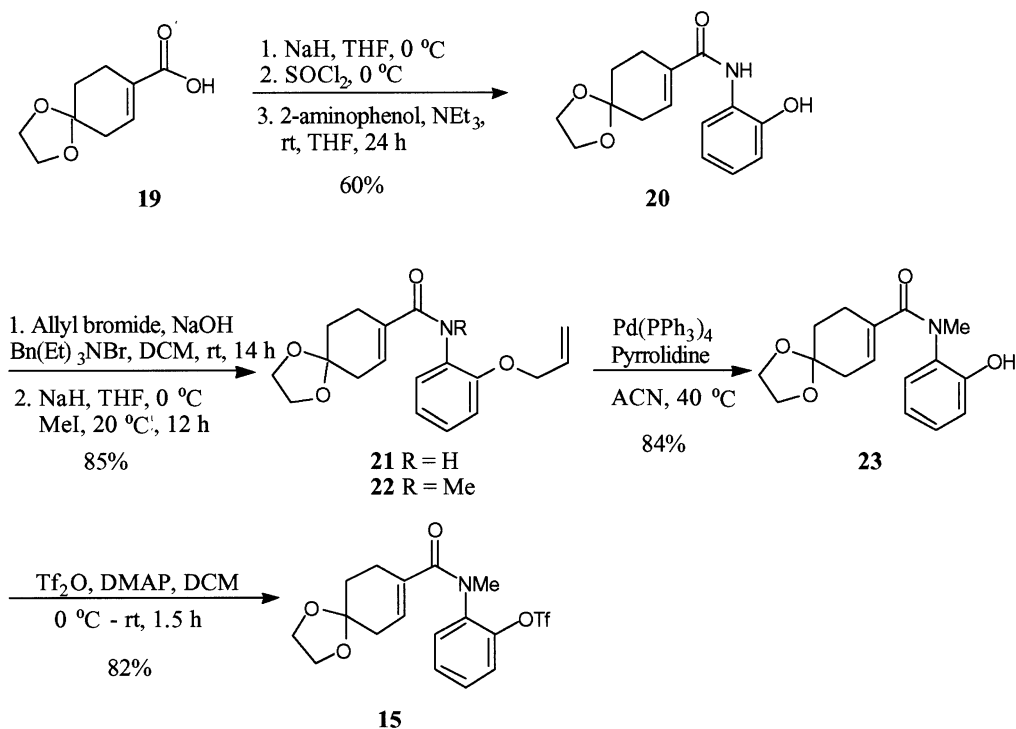
Scheme 1. Synthesis of substrate **15**.

reactions were observed to be proceeding when the precipitation of a salt (base.HOTf) was observed.

Heck reactions catalysed by palladium complexes of BINAP **6**, using toluene as solvent and PMP as base produced cyclised product in 23% yield and 35% ee (entry 1). A switch of solvent to benzene resulted in an increase in enantioselectivity to 45% with a similar reaction yield of 24% (entry 2). A combination of diisopropylethylamine and benzene resulted in an improved yield of 40% but again reduced enantioselectivity of 35% (entry 3). A combination of *N,N*-dimethylacetamide (DMA) and proton sponge promoted cyclisation in a reasonable yield of 38%, but with a poor 7% ee (entry 4). In Overman's study of the silver salt promoted cyclisation of the analogous aryl iodide, yields of > 80% were routinely obtained compared to a maximum yield of 40% in the present investigation [43]. However, our results are not completely unexpected as aryl triflates are generally less reactive than the corresponding aryl iodides. Enantioselectivities were also superior in cycli-

sations of the iodide analogue with an optimal ee of 71% compared to 45% for the triflate variant.

Cyclisations promoted by palladium complexes of the diphenylphosphinooxazoline ligand **11** were initially screened with PMP as base and toluene as solvent affording spirooxindole product in a poor 9% yield and 31% ee (entry 5). A slight increase in yield to 14% was observed for the corresponding reaction in benzene but also a slight decrease in ee to 27% (entry 6). Employing DMA as solvent gave an increased yield of 30% but again with a poor enantioselectivity of 25% (entry 7). Using toluene as solvent and triethylamine as base the enantioselectivity was improved to 46%, however with low catalyst activity (13% yield, entry 8). The corresponding palladium complexes of the *i*-propyl-substituted ligand **12** were less reactive and enantioselective than their *t*-butyl analogues with poor yields and enantioselectivities being observed under all of the conditions screened with our optimal result being obtained in toluene with PMP as base (entry 9). Similar
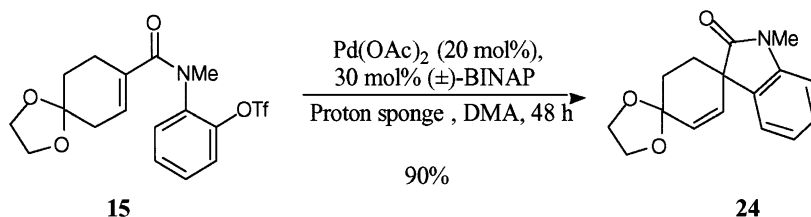
Scheme 2. Preparation of product **24** as a racemate.
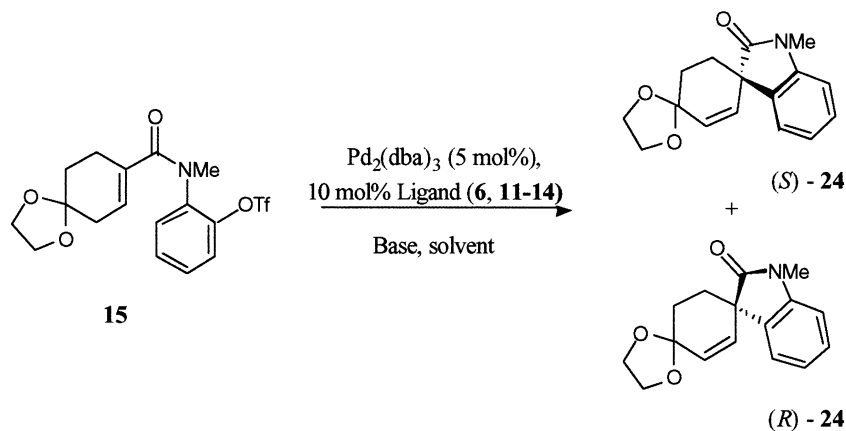
Scheme 3. Asymmetric cyclisation of substrate **15**.

lowering of reactivity and asymmetric induction in going from *t*-butyl- to *i*-propyl-substituted analogues was previously noted by Pfaltz in their study of the intermolecular asymmetric Heck reaction. Although yields obtained in reactions catalysed by palladium complexes of ligands **11–12** were poor in all cases, enantioselectivities were competitive when compared with BINAP (optimal ee of 46%, 45% for BINAP).

Employing palladium complexes of the *t*-butyl-substituted ferrocenyloxazoline ligand **13** in toluene as solvent with DIPEA as base produced cyclised product in 25% yield and 40% ee (entry 10). Changing the base to triethylamine resulted in an improved yield of 35% and increased enantioselectivity of 46%. With the more sterically demanding PMP as base, a vastly improved yield of 63% was observed, with an ee of 47%, our optimal result for substrate **15**. Switching the solvent to

benzene resulted in slightly lower yields and enantioselectivities compared to the analogous reactions in toluene. When Pd(OAc)$_2$ was used as the catalyst precursor a lower yield and enantioselectivity were observed (compare entries 10 and 15). A pronounced difference in reactivity and enantioselectivity was again observed between palladium complexes of **13** and **14**, with the more sterically demanding *t*-butyl-substituted ligand affording a significantly more reactive and also more selective catalyst. The palladium complexes of **14** with toluene and PMP afforded cyclised product in 14% yield and 39% ee (entry 16) and other combinations of solvent and base tested gave yields of less than 5%. However, despite one example (entry 12) the yields obtained with this novel substrate were poor to moderate and it may be that the ketal ring, which acts as a blocking group to double bond isomerisation, may have

Table 1
Heck cyclisations of aryl triflate **15**

Entry	Ligand	Solvent	Base [a]	Time (h)	Temp. (°C)	% Yield [b]	% Ee (config.) [c]
1	**6**	Toluene	PMP	48	80	23	35 (*S*)
2	**6**	Benzene	PMP	48	80	24	45 (*S*)
3	**6**	Benzene	*i*-Pr$_2$NEt	48	80	40	35 (*S*)
4	**6**	DMA	PS	48	110	38	7 (*S*)
5	**11**	Toluene	PMP	168	80	9	31 (*R*)
6	**11**	Benzene	PMP	168	80	14	27 (*R*)
7	**11**	DMA	PMP	168	80	30	25 (*R*)
8	**11**	Toluene	Et$_3$N	168	80	13	46 (*R*)
9	**12**	Toluene	PMP	168	80	14	12 (*R*)
10	**13**	Toluene	*i*-Pr$_2$NEt	168	80	25	40 (*R*)
11	**13**	Toluene	Et$_3$N	168	80	35	46 (*R*)
12	**13**	Toluene	PMP	168	80	63	47 (*R*)
13	**13**	Benzene	PMP	168	80	22	28 (*R*)
14	**13**	Benzene	*i*-Pr$_2$NEt	168	80	17	37 (*R*)
15 [d]	**13**	Toluene	*i*-Pr$_2$NEt	168	80	8	35 (*R*)
16	**14**	Toluene	PMP	168	80	14	39 (*R*)

[a] PMP = 1,2,2,6,6-pentamethylpiperidine, PS = proton sponge (1,8-bis(dimethylamino)naphthalene).
[b] Determined by ^{1}H-NMR.
[c] Absolute configuration inferred by comparing the optical rotation to literature values [42].
[d] Pd(OAc)$_2$ was used as the catalyst precursor.

an adverse effect on the reactivity of this substrate. There may be a steric clash between it and one of the phosphine phenyl groups of the ligand leading to a subsequent retardation of the migratory insertion step, and hence the relatively low yields observed in this study.

2.3. Synthesis of substrate 17

A second novel substrate for the intramolecular asymmetric Heck reaction, trifluoromethanesulfonyloxy-[4.5]-dec-7-en-8-yl-carbonyl-*N*-methylaniline (**17**) was prepared in order to investigate the relative regioselectivity and enantioselectivity of cyclisation promoted by palladium complexes of bisphosphine or phosphinamine ligands. We proposed to prepare this cyclic precursor via a similar route to that described in Scheme 1 for the preparation of triflate **15**. Therefore, 1-cyclohexene-1-carboxylic acid **25** was coupled via the acid chloride with 2-aminophenol yielding the corresponding amide **26** in 60% overall yield (Scheme 4). The remaining synthetic transformations required were amide *N*-methylation and conversion of the phenol to an aryl triflate. In order to achieve clean methylation it was again necessary to protect the phenol **26** as an allylether **27**, which was then treated with iodomethane yielding the tertiary amide **28** in 78% overall yield. Deprotection of the ether as before using catalytic quantities of tetrakis(triphenylphosphine)palladium(0) gave the phenol **29** in 93% yield. Conversion of the phenol to the aryl triflate **17** was realised in 85% yield using triflic anhydride and dimethylaminopyridine in

dichloromethane. Thus, the required novel cyclic substrate 2-trifluoromethanesulfonyloxy-[4.5]-dec-7-en-8-yl-carbonyl-*N*-methylaniline was prepared in five steps in an overall yield of 37% from 1-cyclohexene-1-carboxylic acid **25**.

### 2.4. Intramolecular Heck studies of substrate 17

The synthesis of the racemic Heck products from the cyclisation of substrate **17** was carried out using palladium complexes of racemic BINAP as ligand (Scheme 5).

As expected, a mixture of double bond isomers **30** and **31** was obtained. Unfortunately, despite numerous attempts, this mixture proved inseparable by column chromatography. The 270 MHz ^{1}H-NMR spectrum of this mixture shows characteristic alkene peaks for the alkene isomer **30** at 5.12 (H_2) and 6.13 (H_3) and for the alkene isomer **31** at 5.91 ($H_{3,4}$). However both sets of enantiomers could be resolved by chiral HPLC on a Daicel Chiralpak OJ column and with this information in hand asymmetric Heck reactions were then carried out using palladium complexes of (*R*)-BINAP **6** and phosphinamine ligands **11**–**14** (Scheme 6, Table 2).

Using palladium complexes generated in situ from (*R*)-BINAP **6** and Pd$_2$(dba)$_3$, cyclisation proceeded in a good yield of 77% employing dimethylacetamide (DMA) as solvent and PMP as base (entry 1). However, as expected, a mixture of spirooxindole double bond isomers **30** and **31** was obtained in a ratio of 23:77 in which the enantiomeric excess for **30** was 74%, whereas **31** was formed with a much decreased stereoselectivity
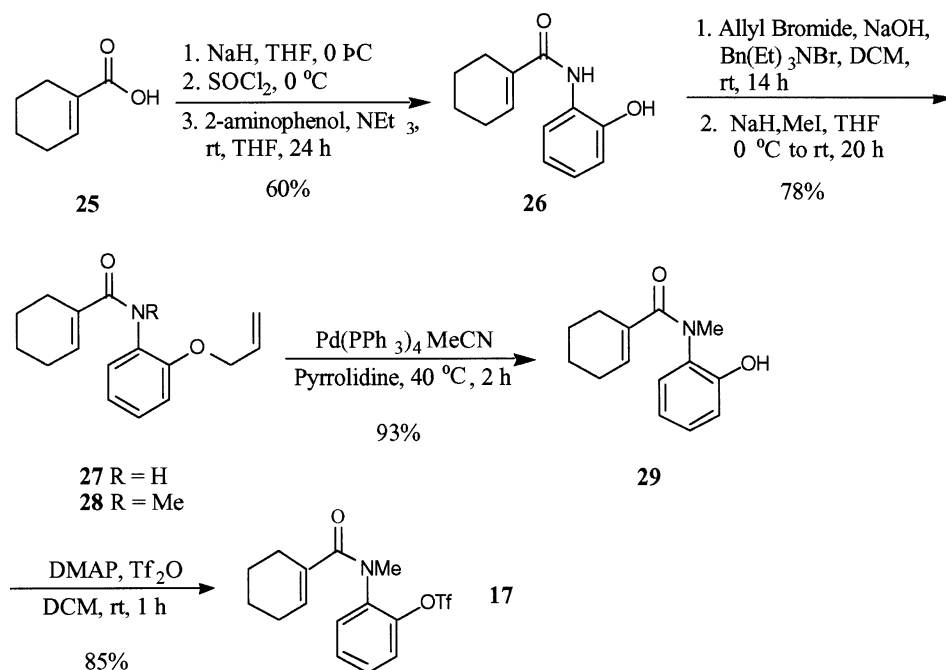
Scheme 4. Synthesis of substrate **17**.
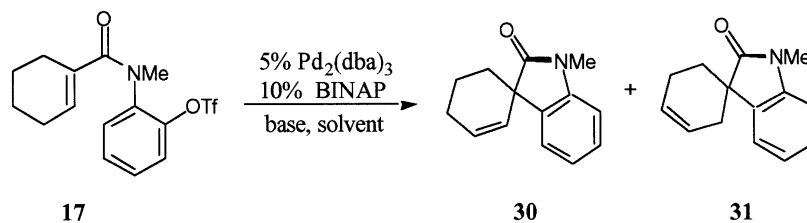
Scheme 5. Preparation of racemate product **30/31**.

of 31% ee. A switch of solvent to toluene caused the regioselectivity for isomer **30/31** to be reversed, which suggests a significant role for coordinating versus non-coordinating solvents in the cationic pathway (entry 2). Increased reactivity was also observed on switching to the non-polar solvent (compare entries 1 and 2). When employing dimethylformamide as solvent, excellent conversions were observed although the enantioselectivity was significantly lower, just 38% ee for isomer **30** and racemic for isomer **31**. In addition, an alternative inorganic base was utilised in toluene but in this case enantioselectivity was again moderate (47% ee for isomer **30**) and just 5% for isomer **31** (entry 4). The regioselectivity in this case was 91:9 in favour of isomer **31**, which highlights the significant role of the base (compare entries 2 and 4).

Palladium complexes of the diphenylphosphinoaryloxazoline ligands **11–12** were initially screened in PMP-promoted asymmetric Heck cyclisations of triflate **17**. The intramolecular Heck reaction of **17** in dimethylacetamide using palladium complexes of the *t*-butyl-substituted aryloxazoline ligand **11** proceeded in poor yield (20%), but with reasonable enantioselectivity (57%) (entry 5). Of particular note was the almost complete regioselectivity observed for the alkene double bond isomer **30**. Catalysts derived from palladium complexes of the *i*-propyl-substituted diphenylphosphinoaryloxazoline **12** proved even less reactive than their *t*-butyl analogues, affording just 7% of cyclised product (entry 7). Although PMP had proven to be an excellent

additive in the work of Overman, the results obtained with the diphenylphosphinoaryloxazolines in the present study were not encouraging. Therefore a variety of alternative bases were studied with these ligands in an attempt to improve reactivity and stereoselectivity.

Using dimethylacetamide as solvent (entry 8), palladium complexes of **11** afforded cyclised product in a yield of 20%, with a good enantioselectivity of 76% and with an excellent regioselectivity of > 99:1. The yield was again poor (10%) and the enantioselectivity moderate (54%) albeit with excellent regioselectivity (> 99:1) using palladium complexes of ligand **12** (entry 9). Improved yields were observed in Heck reactions promoted by DIPEA compared to the other amine bases screened. Enantioselectivities were moderate however, ranging from 12 to 39% with an optimal result of 39% ee in an excellent 96% yield for the *t*-Bu-substituted aryloxazoline ligand **11** with benzene as solvent (entry 11).

The cyclisation of initiate **16** was also investigated using palladium complexes of the diphenylphosphino-ferrocenyloxazoline-containing ligands **13** and **14** (Scheme 6, Table 3). Initially PMP was used as base as this proved to be the optimal additive in Overman's investigation, and also in the present study using (*R*)-BINAP as ligand.

Using DMA as solvent at 110 °C, palladium complexes of the *t*-butyl-substituted diphenylphosphinoferrocenyloxazoline ligand **13** induced cyclisation with almost complete regioselectivity for alkene isomer **30**,
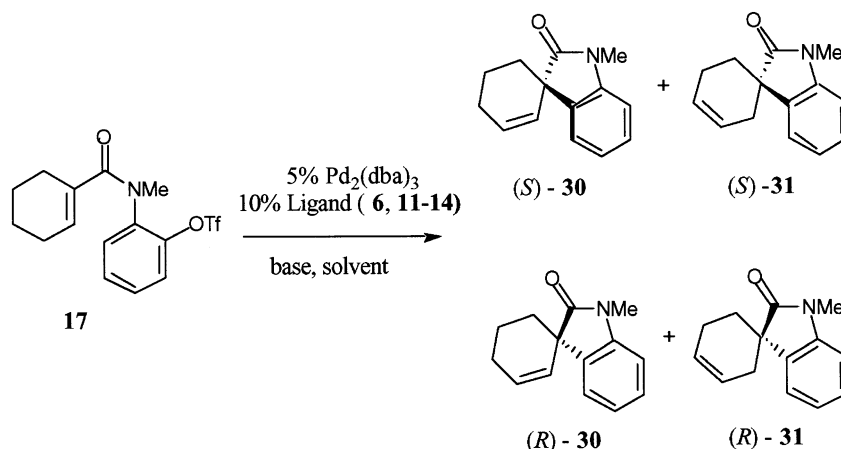

Scheme 6. Asymmetric cyclisation of substrate **17**.

Table 2
Heck cyclisations of aryl triflate **17**

Entry	Ligand	Solvent	Base	Time (h)	Temp. (°C)	% Yield [a]	**30:31** [a]	% Ee **30:31** (config.) [b]
1	**6**	DMA	PMP	48	110	77	23:77	74:31 (*S*)
2	**6**	Toluene	PMP	48	110	90	75:25	71:27 (*S*)
3	**6**	DMF	PMP	48	110	90	15.85	38.0 (*S*) [c]
4	**6**	Toluene	K_2CO_3	48	80	70	9:91	47:5 (*S*)
5	**11**	DMA	PMP	168	110	20	>99:1	57 (*R*) [c]
6	**11**	Toluene	PMP	168	80	20	90:10	19 (*R*) [c]
7	**12**	DMA	PMP	168	110	7	98:2	53 (*R*) [c]
8	**11**	DMA	PS	168	110	20	>99:1	76 (*R*) [c]
9	**12**	DMA	PS	168	110	10	>99:1	54 (*R*) [c]
10	**11**	Toluene	*i*-Pr$_2$NEt	168	80	35	92:8	36 (*R*) [c]
11	**11**	Benzene	*i*-Pr$_2$NEt	168	80	96	98:2	39 (*R*) [c]
12	**12**	Toluene	*i*-Pr$_2$NEt	168	80	20	94:6	12 (*R*) [c]

[a] Determined by ^{1}H-NMR.
[b] Enantioselectivities were determined by chiral HPLC analysis using a Daicel Chiralpak OJ column (0.4625 cm), hexane–2-propanol 99.5:0.5 (t_R = 41.5 (*S*)-**30** and 57.8 (*R*)-**30**; t_R = 28.1 (*S*)-**31** and 31.4 (*R*)-**31** min.
[c] Minor isomer formed as a racemate.

with a good enantioselectivity of 64% (entry 1). A drop in reactivity (13% yield), regioselectivity (71:29) and enantioselectivity (37%), was observed under similar reaction conditions, but employing palladium catalysts of the *i*-propyl-substituted ferrocenyl ligand (**14**, entry 2). Using **13**-derived catalysts and increasing the reaction temperature did not provide any significant accompanying increase in reactivity and was detrimental to regioselectivity and enantioselectivity (entry 3). Under these reaction conditions a significant deposition of palladium black was observed. Using the *t*-butyl-derived ferroceneoxazoline ligand **13** but switching the solvent to toluene, previously found by Shibasaki to lead to improved reactivity for initiate substrates, improved the yield to 70% albeit with slightly poorer regioselectivity and enantioselectivity (compare entries 1

and 4). Lowering the reaction temperature from reflux to 80 °C led to cyclised product in excellent regioselectivity (>99:1) and slightly improved enantioselectivity (compare entries 4 and 5). The pattern of lower reactivity and selectivity of the *i*-propyl-substituted ferrocenyloxazoline observed when using DMA was again repeated when toluene was used as solvent (entry 6). Using palladium complexes of **13** in refluxing benzene (entry 7), a slight increase in enantioselectivity was seen in comparison to the corresponding reaction in toluene (53 vs. 57%) with a slight reduction in yield (55 vs. 71%). Using proton sponge as base afforded a 30% yield in DMA at 110 °C with an excellent enantioselectivity of 85% using palladium complexes of ligand **13** (entry 9). Changing the solvent to toluene and reducing the temperature to 80 °C greatly improved the reactivity

Table 3
Heck cyclisations of aryl triflate **17**

Entry	Ligand	Solvent	Base	Time (h)	Temp. (°C)	% Yield [a]	**30:31** [a]	% Ee **30:31** (config.) [b]
1	**13**	DMA	PMP	168	110	36	>99:1	64 (*R*)
2	**14**	DMA	PMP	168	110	13	71:29	37 (*R*)
3	**13**	DMA	PMP	168	145	34	76.24	13 (*R*)
4	**13**	Toluene	PMP	168	110	70	94:6	51 (*R*)
5	**13**	Toluene	PMP	168	80	71	>99:1	53 (*R*) [c]
6	**14**	Toluene	PMP	168	110	20	90:10	19 (*R*) [c]
7	**13**	Benzene	PMP	168	80	55	98:2	57 (*R*) [c]
8	**14**	Benzene	PMP	168	80	20	76.24	47 (*R*) [c]
9	**13**	DMA	Proton sponge	168	110	30	>99:1	85 (*R*) [c]
10	**13**	Toluene	Proton sponge	168	80	71	>99:1	82 (*R*) [c]
11	**14**	DMA	Proton sponge	168	110	21	94:6	66 (*R*) [c]
12	**13**	Toluene	*i*-Pr$_2$NEt	168	80	55	98:2	57 (*R*) [c]
13	**13**	Benzene	*i*-Pr$_2$NEt	168	80	61	98:2	47 (*R*) [c]
14	**14**	Benzene	*i*-Pr$_2$NEt	168	80	25	95:5	15 (*R*) [c]

[a] Determined by ^{1}H-NMR.
[b] Enantioselectivities were determined by chiral HPLC analysis using a Daicel Chiralpak OJ column (0.4625 cm), hexane–2-propanol 99.5:0.5 (t_R = 41.5 (*S*)-**30** and 57.8 (*R*)-**30**; t_R = 28.1 (*S*)-**31** and 31.4 (*R*)-**31** min.
[c] Minor isomer formed as a racemate.

of the catalyst giving **30** in 71% yield with a regioselectivity of > 99:1, and with a high enantioselectivity of 82% (entry 10). Palladium complexes of **13** in toluene afforded cyclised product in good yield and good regioselectivity (98:2), with a reasonable enantioselectivity of 57% (entry 12) when employing Hünig's base. Switching to benzene resulted in a slight increase in yield but also to a decrease in enantioselectivity (entry 13). Palladium complexes of the *i*-propyl-substituted ferrocenyloxazoline (**14**) again afforded cyclic product in low yield (typically in the range 5–25%) and enantioselectivity (up to 15%) (entry 14).

This investigation of the novel substrate **17** shows that palladium catalysts of phosphinamine ligands provided products of good stereo- and excellent regioselectivity in its asymmetric Heck reaction. Interestingly, the product distribution obtained from cyclisations promoted by palladium catalysts of phosphinamine ligands differs appreciably from that obtained using the corresponding BINAP catalysts. For example, employing BINAP in DMA as solvent predominantly double bond isomer **31** was formed, whereas ligand **12** under analogous conditions yielded almost exclusively double bond isomer **30**. Thus with certain substrates such as the aryl initiate **17**, it may be possible to produce different isomers selectively, depending on the exact reaction conditions employed. It is also worth noting that palladium complexes of BINAP proved considerably more reactive than their corresponding phosphinamine analogues. Conversions of up to 90% were obtained after 48 h using BINAP-derived catalysts, whereas using the phosphinamine systems reaction times of up to 7 days were required to afford reasonable yields of product.

2.5. Intramolecular Heck studies of substrate **18** — the formation of cis-decalins

The original report on the asymmetric intramolecular Heck reaction from Shibasaki [19] involved the synthesis of *cis*-decalins **32** from the corresponding alkenyl iodides **33** (Scheme 7). The basic strategy involved enantioselective ring closure of the prochiral substrate resulting in the formation of a tertiary chiral centre. When alkenyl iodides were used as substrates it was necessary to add silver salts in order to achieve good enantioselectivity. Screening of a variety of salts yielded
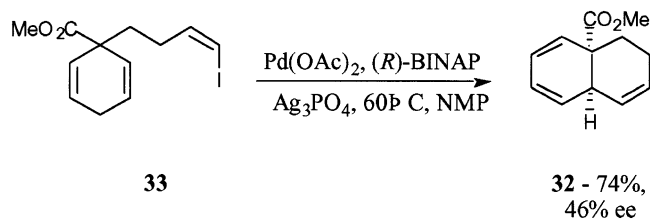
Scheme 7. Formation of *cis*-decalin **32**.
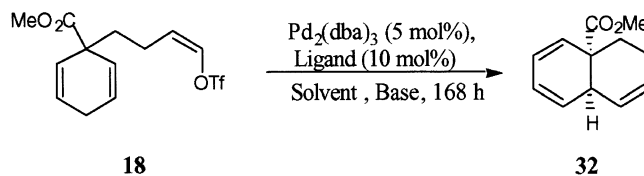
Scheme 8. Asymmetric cyclisation of substrate **18**.

silver phosphate as the optimal additive [47]. In a subsequent publication from the same group [20] the cyclisation of the analogous alkenyl initiates **18** was described (Scheme 8).

It was assumed that silver additives would not be required in the case of the triflate, as the triflate anion spontaneously dissociates, thus generating the required cationic 16 electron palladium species. These reaction conditions gave 91% ee as compared to the 46% ee from the corresponding iodide. Palladium complexes of BINAP, and its chiral arsine analogue BINAs **7** are the only catalyst systems reported to date which have proven successful for this system [23].

It is therefore of interest to test phosphinamine ligands of type **11**–**14** in this cyclisation and compare their reactivity and stereoselectivity to BINAP (Scheme 8). The results of our investigations are detailed in Table 4.

Using palladium complexes generated in situ from Pd₂(dba)₃ and (*R*)-BINAP **6**, cyclisation proceeded in reasonable yield (50%), and with good enantioselectivity (82% ee, entry 1). A similar yield (54%), albeit with higher enantioselectivity (91%), was obtained in Shibasaki's study which employed Pd(OAc)₂ as the precursor. Increasing the reaction temperature to 110 °C resulted in an improved yield (65%) without having an adverse effect on the stereoselectivity of the reaction (entry 2). Using *N*-methylpyrrolidine as solvent resulted in increased activity of the catalyst (80% yield) but also lowered enantioselectivity (46% ee, entry 3). Using palladium complexes of the *t*-butyl-substituted ferrocenyloxazoline ligand **13** cyclisation proceeded in lower yield (30%) but with an improved enantioselectivity of 85% (entry 4). In an attempt to increase yields, higher reaction temperatures of 80 °C and 110 °C were applied but this led to decreased yields (24% and 23%, respectively) and also decreased enantioselectivities (67% and 42% ee, respectively, entries 5–6). In both cases the mass balance was recovered unreacted starting initiate **18**. This, and the precipitation of palladium black, suggests that higher reaction temperatures lead to catalyst degradation. Alternative bases to potassium carbonate were screened using palladium complexes of ligand **13** (entries 7–9) but low yields of 10–11% were observed. However, there were marked differences in the enantioselectivities obtained as both sodium carbonate and 1,2,2,6,6-pentamethylpiperidine (PMP) gave good enantioselectivities (67% and 74%, respectively), whereas

Table 4
Heck cyclisations of alkenyl triflate **18**

Entry	Ligand	Solvent	Base	T (°C)	Yield (%) [a]	ee [b,c]
1	**6**	Toluene	K_2CO_3	60	50	82
2	**6**	Toluene	K_2CO_3	110	65	83
3	**6**	NMP	K_2CO_3	60	80	46
4	**13**	Toluene	K_2CO_3	60	30	85
5	**13**	Toluene	K_2CO_3	80	24	67
6	**13**	Toluene	K_2CO_3	110	23	42
7	**13**	Toluene	Na_2CO_3	60	11	67
8	**13**	Toluene	PMP	60	10	74
9	**13**	Toluene	Proton sponge	60	10	28
10	**14**	Toluene	K_2CO_3	60	< 5	–
11	**11**	Toluene	K_2CO_3	60	20	47
12	**11**	Toluene	K_2CO_3	110	17	42
13	**13**	Benzene	K_2CO_3	60	11	62
14	**13**	DMA	K_2CO_3	60	< 5	–
15	**13**	NMP	K_2CO_3	60	45	58
16	**11**	NMP	K_2CO_3	60	47	43

[a] Yields were determined by ^{1}H-NMR analysis of the reaction mixture.

[b] Enantioselectivities were determined by chiral HPLC analysis using a Daicel Chiralpak OJ column (0.4625 cm), hexane: 100% ($t_R = 84.2$ (−) and 93.7 (+) min).

[c] The specific rotation of the major enantiomer in entries 1–3 was (+) and in entries 4–16 was (−) and the absolute configuration was assigned by comparison with Shibasaki's original work [19].

proton sponge gave a poor ee of 28%. A similar trend was observed by Shibasaki when he screened a range of bases in the BINAP-promoted cyclisations of **33** and found that the use of tertiary amines as base led to less reactive systems [42]. Using palladium complexes of the *i*-propyl-substituted ferrocenyloxazoline ligand **14** afforded only trace amounts (< 5%) of cyclised product (entry 10).

Palladium complexes of the *t*-butyl-substituted aryloxazoline ligand **11** proved less reactive and enantioselective than the ferrocene analogue affording a yield of 20% and an enantioselectivity of 47% (compare entries 4 and 11). Increasing the reaction temperature to 110 °C again led to both a decrease in yield and enantioselectivity (entry 12), also attributable to catalyst inactivation at elevated temperatures. Using palladium complexes of ligand **13** but switching the solvent to benzene resulted in a significant attenuation of yield to 11%, with an enantioselectivity of 62% (entry 13). Similarly poor yields were observed in DMA (entry 14). Reactivity was improved using *N*-methylpyrrolidine (NMP) as solvent, as outlined by a yield of 45% (with palladium complexes of **13**), with a good enantioselectivity of 58% (entry 15). Improved activity was also seen with catalysts derived from the *t*-butyl-substituted aryloxazoline ligand **11** using NMP as solvent, but only moderate enantioselectivity (43%) was observed (entry 16).

In conclusion, BINAP and a range of phosphinamine ligands were screened in asymmetric Heck reactions of initiate **18**. Palladium complexes formed from $Pd_2(dba)_3$ and BINAP gave cyclised product in up to 65% yield and 85% ee. The *t*-butyl-substituted ferrocenyloxazoline

ligand **13** afforded our optimal enantioselectivity of 85% for the range of phosphinamine ligands tested. Variation of solvent and base appears to indicate that this system is very sensitive to catalyst deactivation and that a combination of either toluene or NMP with potassium carbonate as base was required for acceptable catalytic activity. However, the excellent enantioselectivities obtained (up to 85%) using phosphinamine ligands suggests that there is potential for the application of their palladium complexes in this reaction.

3. Mechanistic considerations

For the Heck cyclisation of the aryltriflates **15** and **17** the putative intermediates prior to migratory insertion in palladium complexes of the *tert*-butyl-substituted diphenylphosphinoferrocenyloxazoline **13** can have the alkene bound to palladium by either of its faces and can bind in a *trans*-fashion to either phosphorus (Scheme 9), or nitrogen (Scheme 10).

When the alkene approach is *trans* to phosphorus both of the possible intermediates (**34**, **35**) suffer from steric repulsion. When the alkene approach is *trans* to nitrogen as in intermediate **36**, which would lead to (*S*) configured product, there is steric repulsion between the cyclohexyl ring and one of the phenyl groups on the phosphine. Intermediate **37**, which would lead to (*R*) configured product is sterically unencumbered. Thus, intermediate **37** appears to be the most likely route to migratory insertion as this is the palladium complex of the lowest relative energy. This route should lead to
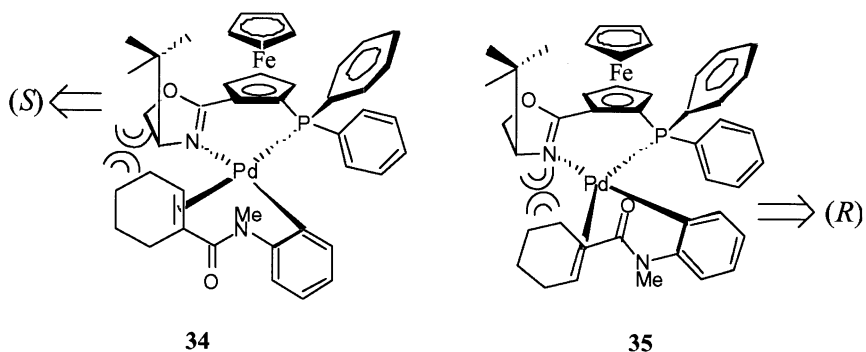
Scheme 9. Alkene approach *trans* to phosphorus.

cyclised product of (*R*) configuration with high enantioselectivity and this is what is seen experimentally.

4. Conclusions

We have prepared two novel substrates for the intramolecular asymmetric Heck reaction and have tested a range of palladium complexes of phosphinamine ligands and BINAP in their asymmetric intramolecular Heck reaction in addition to testing a known substrate for *cis*-decalin formation. A number of interesting trends appeared for the different ligand types during the course of this study.

Cyclisations of initiate **15** proceeded in poor to moderate yields for all of the catalyst systems screened. The optimal enantioselectivity (47%) was afforded with the *t*-butyl-substituted ferrocenyloxazoline ligand **13**. Reactions in nonpolar solvents (particularly toluene) proceeded with better yields than the corresponding reactions with polar solvents, a trend that was apparent for all of the triflate substrates screened. This would suggest that coordinating solvents can have a significant effect in the cationic Heck pathway. Another curious phenomenon is the higher reactivity of the *t*-butyl-substituted over the *i*-propyl-substituted oxazoline based ligands with all the substrates screened. The reason for this is unclear although similar trends were

reported by Pfaltz in the asymmetric intermolecular Heck reaction.

Mixtures of double bond isomers (75:25) were obtained in reasonable enantioselectivity (up to 74%) when using BINAP as ligand for the cyclisation of initiate **17**. Palladium complexes of the diphenylphosphinooxazolines afforded cyclised product with good enantioselectivity (up to 85%) and excellent regioselectivity (>99:1) in the cyclisation of this substrate. The *t*-butyl-substituted ferrocenyloxazoline ligand again proved to be the most enantioselective of all the ligands screened.

These results suggest that palladium complexes of phosphinamine ligands may be applied successfully in enantioselective Heck reactions, via the cationic Heck pathway, which is accessible from aryl or alkenyl initiates.

5. Experimental

[1]H and ^{13}C spectra were recorded at 270 (67.5) or 500 (125) MHz at ambient temperature on JEOL JNM-PMX-270 MHz or Varian-Unity 500 MHz spectrometers with Me$_4$Si as the internal standard. Peak assignments were aided by [1]H–[1]H correlation experiments. Coupling constants are given as absolute values. Low resolution electron-impact MS spectra were measured on a VG Analytical spectrometer with attached
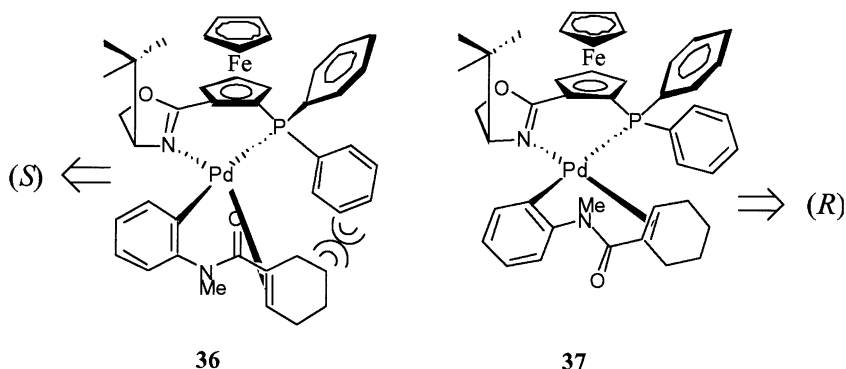
Scheme 10. Alkene approach *trans* to nitrogen.

INCOS 2400 data system at an ionisation potential of 70 eV. Isomers are assumed to have the same response factors. Elemental analyses were performed by Ms Anne Connolly, Department of Chemistry, University College Dublin. Infra-red spectra were recorded on a Perkin–Elmer Paragon 1000 Infra-red FT spectrometer. Optical rotation values were measured on a Perkin–Elmer 241 polarimeter. Melting points were determined in open capillary tubes in a Gallenkamp melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out on aluminium sheets pre-coated with silica gel 60 F 254 (0.25 mm, Macherey-Nagel). Column chromatography separations were performed using Merck Kieselgel 60 (Art. 7734), Merck Alumina (Art. 1097) or Merck Alumina (Art. 1104) as stated. Solvents were dried immediately prior to use by distillation from standard drying agents. 1,4-Dioxaspiro[4.5]dec-7-ene-8-carboxylic acid (**19**) was prepared according to literature method [48]. Methyl 1-[4-[[(trifluoromethyl)sulfonyl]-oxy]-3(*Z*)-butenyl-2,5-cyclohexadiene-1-carboxylate (**18**) was prepared according to the method of Shibasaki [43].

5.1. Preparation of 2-hydroxy-(1,4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-aniline (20)

1,4-Dioxaspiro[4.5]dec-7-ene-8-carboxylic acid (3.4 g, 18.4 mmol) in THF (30 ml) was added dropwise to a stirred suspension of sodium hydride (1.0 g, 25.0 mmol), in THF (30 ml) at 0 °C yielding a milky white suspension. Stirring was continued for a further 2 h at ambient temperature. The reaction was recooled to 0 °C and thionyl chloride (1.6 ml, 21.0 mmol), was added dropwise over approximately 5 min giving a light yellow almost transparent solution. This was stirred for a further 2.5 h at room temperature (r.t.). 2-Aminophenol (4.00 g, 18.4 mmol) was added as a solution in THF (30 ml), followed by triethylamine (2.7 ml, 19.0 mmol). Evolution of HCl was apparent at this stage and the light yellow solution became a deep mustard coloured suspension. The reaction mixture was then refluxed for a further 5 h. After cooling the deep yellow suspension was diluted with ether (300 ml) and washed consecutively with water (250 ml), saturated sodium bicarbonate (250 ml) and brine (250 ml). The organic layer was concentrated in vacuo yielding a dark brown solid which was purified by column chromatography giving 2-hydroxy-(1,4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-aniline, as a white solid (3.0 g, 60%), m.p. 158–160 °C, TLC (100% ethyl acetate) $R_f = 0.3$; IR (KBr disc cm^{-1}): 3410, 2961, 1685; ^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 9.75$ (s, 1H, OH), 7.83 (s, 1H, NH), 7.17 (dd, 1H, $J = 7.9$, 1.5 Hz, H$_6$), 7.08 (td, 1H, $J = 0.9$ Hz, 6.5 Hz, H$_5$), 6.98 (dd, 1H, $J = 6.7$, 1.4 Hz, H$_4$), 6.85 (td, 1H, $J = 7.9$, 1.5 Hz, H$_3$), 6.71 (m, 1H, H$_8$), 4.01 (s, 4H, (OCH$_2$)$_2$), 2.62 (m, 2H, H$_{12a,b}$), 2.48 (m, 2H, H$_{9a,b}$), 1.87 (t, 1H, $J = 6.4$ Hz,

H$_{11a,b}$); ^{13}C-NMR (75.4 MHz, CDCl$_3$): $\delta = 166.5$ (C(O)), 149.1 (C$_2$), 133.4 (C$_1$), 132.1 (C$_7$), 126.9 (C$_{10}$), 125.7 (C$_4$), 123.4 (C$_5$), 119.8 (C$_6$), 116.5 (C$_3$), 107.2 (C$_8$), 64.5 (O(CH$_2$)$_2$), 36.1 (C$_{12}$), 31.0 (C$_9$), 24.3 (C$_{10}$); MS (EI, 70 eV): m/z (%): 275 [M$^+$] (28%), 167 (89), 99 (58), 81 (100); Found: C, 64.8; H, 6.2; N, 5.1. C$_{15}$H$_{17}$O$_4$N requires C, 65.4; H, 6.2; N, 5.0%.

5.2. Preparation of 2-allyloxy-(1,4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-aniline (21)

Following the general method of McKillop, the amide **20** (0.85 g, 3.2 mmol), allyl bromide (0.8 ml, 8.0 mmol), benzyltriethylammonium chloride (0.075 g, 0.32 mmol), 1.0 M aqueous sodium hydroxide (3.5 ml), CH$_2$Cl$_2$ (20 ml) and water (7 ml) were placed in a 100 ml Schlenk flask. The flask was wrapped with aluminium foil to prevent exposure to light and the orange mixture was stirred vigorously for 14 h at r.t. The reaction was allowed to stand for 15 min and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (220 ml) and the combined organic layers were washed with saturated aqueous citric acid solution (100 ml), brine (100 ml), dried over magnesium sulfate and concentrated in vacuo. The crude residue thus obtained was carried through to the next reaction without further purification, IR (KBr disc cm^{-1}): 3423, 1673, 1634; ^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 8.42$ (dd, 1H, $J = 7.3$, 2.3 Hz, H$_6$), 8.20 (br. s, 1H, NH), 6.98 (m, 3H, H$_{3,4,5}$), 6.62 (m, 1H, H$_8$), 6.00 (m, 1H, H$_{2'}$), 5.40 (dd, 1H, $J = 15.8$, 1.5 Hz, H$_{3'a}$), 5.30 (dd, 1H, $J = 9.1$, 1.5 Hz, H$_{3'b}$), 4.61 (brd, 2H, $J = 2.0$ Hz, H$_{1'a,b}$), 4.01 (s, 4H, (OCH$_2$)$_2$), 2.64 (app t, 2H, $J = 1.5$ Hz, H$_{12a,b}$), 2.48 (m, 2H, H$_{9a,b}$), 1.87 (t, 1H, $J = 6.4$ Hz, H$_{10a,b}$) ^{13}C-NMR (75 MHz, CDCl$_3$): $\delta = 165.6$ (C(O)), 147.3 (C$_2$), 134.1 (C$_1$), 133.1 (Ar-CH), 131.4 (Ar-CH), 128.3 (C$_{10}$), 123.8 (C$_7$), 121.7 (Ar-CH), 120.2 (Ar-CH), 118.3 (C$_{3'}$), 111.6 (C$_{2'}$), 107.5 (C$_8$), 69.8 (C$_{1'}$), 64.81 (2CH$_2$), 36.2 (C$_{12}$), 31.0 (C$_9$), 23.9 (C$_{11}$); MS (EI, 70 eV): m/z (%): 315 [M$^+$] (26%), 229 (17), 188 (18), 167 (70), 135 (37), 99 (48), 81 (100); HRMS for C$_{18}$H$_{21}$O$_4$N: Requires 351.3690; found 351.3715.

5.3. Preparation of 2-allyloxy-(1,4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-N-methylaniline (22)

A mixture of the allyl ether **21** (0.89 g, 2.7 mmol), sodium hydride (60% paraffin dispersion, 200 mg, 4.9 mmol) and dry THF (20 ml) were stirred for 10 min at 0 °C under a nitrogen atmosphere and then for a further 3 h at r.t. Iodomethane (0.5 ml, 8.0 mmol) was then added in one portion and the mixture was stirred at r.t. overnight. Saturated sodium bicarbonate solution (50 ml) was then added followed by 20 ml of CH$_2$Cl$_2$. The layers were separated and the aqueous layer was extracted with ether (220 ml) and EtOAc (20 ml). The

combined organic layers were washed with brine (50 ml), dried over magnesium sulfate and concentrated in vacuo. The resultant brown residue was purified by column chromatography giving 2-allyloxy-(1,4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-*N*-methylaniline as a light yellow oil (0.89 g, 96%), TLC: (petroleum ether 40–60 °C–EtOAc = 2:1) $R_f = 0.05$; IR (neat, cm^{-1}): 2956, 1643; ^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.20$ (dt, 1H, $J = 7.0$, 1.7 Hz, H$_5$), 7.10 (brd, 1H, $J = 7.6$ Hz, H$_6$), 6.90 (m, 2H, Ar-H), 6.02 (m, 1H, H$_{2'}$), 5.64 (m, 1H, H$_8$), 5.43 (dd, 1H, $J = 18.1$, 1.5 Hz, H$_{3'a}$), 5.30 (dd, 1H, $J = 10.5$, 1.5 Hz, H$_{3'b}$), 4.54 (m, 2H, H$_{1'}$), 3.85 (s, 4H, (OCH$_2$)$_2$), 3.24 (s, 3H), 2.28 (m, 2H, H$_{12a,b}$), 2.04 (m, 2H, H$_{9a,b}$), 1.56 (t, 2H, $J = 6.3$ Hz, H$_{11a,b}$); ^{13}C-NMR (75 MHz, CDCl$_3$): $\delta = 172.3$ (C(O)), 153.5 (C$_2$), 134.0 (C$_1$), 133.0 (CH), 128.9 (C$_{10}$), 128.5 (CH), 128.2 (CH), 121.1 (C$_{3'}$), 117.7 (C$_{2'}$), 113.0 (C$_7$), 107.3 (C$_8$), 69.0 (CH), 64.4 (2CH$_2$), 35.6 (C$_{12}$), 30.9 (C$_9$), 25.2 (C$_{11}$); MS (EI, 70 eV): *m/z* (%): 329 [M$^+$] (27%), 202 (23), 186 (36), 167 (49), 122 (57), 99 (77), 81(96), 53 (100); Found C, 68.7; H, 6.91; N, 4.15. C$_{19}$H$_{23}$O$_4$N requires C, 69.3; H, 7.0; N, 4.3%.

5.4. Preparation of 2-hydroxy-(1,4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-N-methylaniline (23)

Following a modification of the procedure of Deziel, a mixture of 2-allyloxy-(1,4-dioxaspiro[4.5]-dec-7-en-8-yl-carbonyl)-*N*-methylaniline (1.03 g, 3.4 mmol), Pd(PPh$_3$)$_4$ (0.14 g, 0.12 mmol), triphenylphosphine (0.04 g, 0.16 mmol) and dry MeCN (15 ml) were stirred for 5 min at 0 °C. A solution of pyrrolidine (1.2 ml, 14.0 mmol), in MeCN (10 ml) was then added and the solution was stirred for a further 10 min at 0 °C. The solution was heated at 40 °C for 2 h. After cooling to r.t. the reaction mixture was diluted with saturated citric acid solution (20 ml) and the layers were separated. The organic layer was washed with saturated citric acid solution (20 ml), brine (20 ml), dried over magnesium sulfate and concentrated in vacuo. The resulting crude orange residue was purified by column chromatography to give 2-hydroxy-(1,4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-*N*-methylaniline as a white solid (0.82 g, 84%), m.p. 125–127 °C, TLC: (petroleum ether 40–60 °C–EtOAc = 1:1) $R_f = 0.2$; IR (neat, cm^{-1}): 2927, 2362, 1612, 1459; ^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.52$ (s, 1H, m), 7.15 (dt, 1H, $J = 7.0$, 1.5 Hz, H$_6$), 7.00 (m, 2H, Ar-H), 6.85 (app. t, 1H, $J = 7.3$ Hz, H$_3$), 5.81 (m, 1H, H$_8$) 3.88 (s, 4H, (OCH$_2$)$_2$), 3.29 (s, 3H), 2.33 (m, 2H, H$_{12a,b}$), 2.18 (m, 2H, H$_{9a,b}$), 1.61 (m, 2H, H$_{11a,b}$); ^{13}C-NMR (75 MHz, CDCl$_3$): $\delta = 173.3$ (C(O)), 152.2 (C$_2$), 133.7 (C$_1$), 132.3 (C$_7$), 131.9 (Ar-CH), 129.1 (Ar-CH), 129.0 (Ar-CH), 128.8 (C$_{10}$), 120.6 (Ar-CH), 107.3 (C$_8$), 64.5 (2CH$_2$), 35.7 (C$_{12}$), 30.9 (C$_9$), 25.3 (C$_{11}$); MS (EI, 70 eV): *m/z* (%): 289 [M$^+$] (18%), 167 (62), 81 (100); Found

C, 66.7; H, 6.6; N, 4.5. C$_{16}$H$_{19}$O$_4$N requires C, 66.4; H, 6.6; N, 4.8%.

5.5. Preparation of 2-trifluoromethanesulfonyloxy-(1,4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-N-methylaniline (15)

2-Hydroxy-(1,4-dioxaspiro[4.5]dec-7-en-8-ylcarbonyl)-*N*-methylaniline (0.501 g, 2.00 mmol), dimethylaminopyridine (1.83 g, 15.0 mmol) and CH$_2$Cl$_2$ (5 ml) were added to a 10 ml Schlenk flask under a nitrogen atmosphere giving a light orange solution. The solution was cooled to 0 °C and triflic anhydride (0.85 ml, 5.0 mmol) was added dropwise yielding a green mixture with some precipitation. The reaction was allowed to stir at r.t. for a further 14 h, recooled to 0 °C and quenched with a saturated citric acid solution (10 ml). The contents of the Schlenk flask were transferred to a 100 ml separatory funnel. The organic layer was removed and the aqueous layer was extracted with 20 ml of CH$_2$Cl$_2$. The organic fractions were combined, dried over magnesium sulfate and concentrated in vacuo. The resulting light orange almost solid residue was purified by column chromatography yielding 2-trifluoromethanesulfonyloxy-[4.5]-dec-7-en-8-yl-carbonyl-*N*-methylaniline (0.67 g, 82%) as a clear oil, TLC: (100% ethyl acetate) $R_f = 0.7$; IR (neat, cm^{-1}): 2930, 1660, 1425, 1214, 1141; ^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.30–7.43$ (m, 4H, Ar-H), 5.61 (m, 1H, H$_8$), 3.90 (s, 4H, (OCH$_2$)$_2$), 3.35 (s, 3H, NMe), 2.42 (m, 2H, H$_{12a,b}$), 2.13 (m, 2H, H$_{9a,b}$), 1.67 (app. t, 2H, $J = 6.3$ Hz, H$_{11a,b}$); ^{13}C-NMR (75 MHz, CDCl$_3$): $\delta = 172.6$ (C(O)), 141.3 (C$_2$), 133.4 (C$_1$), 129.4 (C$_7$), 129.3 (C$_3$), 128.8 (C$_{10}$), 122.7 (C$_5$), 121.4 (C$_6$), 116.6 (C$_3$), 107.2 (C$_8$), 64.5 (2CH$_2$), 35.8 (C$_{12}$), 30.9 (C$_9$), 25.2 (C$_{11}$); MS (EI, 70 eV): *m/z* (%): 421 [M$^+$] (9%), 288 (32), 167 (44), 99 (78), 86 (100); Found: C, 48.0; H, 5.2; N, 2.9. C$_{17}$H$_{18}$O$_6$NSF$_3$ requires C, 48.4; H, 4.3; N, 3.3%.

5.6. Synthesis of 1',2'-dihydro-1'-methyl-2'-oxospiro[1,4-dioxaspiro[4.5]dec-6-ene-8,3'-3'H-indole (24)

Pd(OAc)$_2$ (10.5 mg, 0.048 mmol), (+/−)-B1NAP (40 mg, 0.064 mmol) and dimethylacetamide (1 ml) were added to a 10 ml Schlenk flask and stirred for 1 h. A dimethylacetamide (1 ml) solution of the triflate (130 mg, 0.24 mmol) was added along with proton sponge (0.2 g, 1.0 mmol) and the reaction was allowed to stir for 5 min at r.t. The reaction mixture was degassed (×3) by the pump–freeze–thaw method. The Schlenk flask was sealed and heated at 110 °C for 48 h. The deep red solution was quenched via addition of saturated sodium bicarbonate solution (5 ml). The contents of the flask were transferred to a separatory funnel, water (10 ml) and EtOAc (10 ml) were added and the layers were separated. The aqueous layer was extracted with EtOAc

(210 ml). The organic extracts were combined, washed with brine, dried over magnesium sulfate and concentrated in vacuo. The crude product thus obtained was further purified by preparative chromatography, TLC: (petroleum ether 40–60 °C/EtOAc = 3:1) $R_f = 0.35$; IR (KBr disc cm^{-1}): 1719, 1613; ^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.29$ (td, 1H, $J = 7.7$, 1.2 Hz, Ar-H), 7.25 (d, 1H, 1 = 7.6 Hz, Ar-H), 7.05 (td, 1H, $J = 7.2$, 0.9 Hz, Ar-H), 6.84 (d, 1H, $J = 7.9$ Hz, Ar-H), 5.96 (d, 1H, $J = 9.9$ Hz, H$_9$), 5.48 (d, 1H, $J = 9.9$ Hz, H$_8$), 3.98–4.06 (m, 4H), 3.21 (s, 3H), 2.45 (ddd, 1H, $J = 2.6$, 9.5, 13.1 Hz, H$_{12b}$), 2.16–2.26 (m, 1H, H$_{12a}$), 1.96–2.06 (m, 2H, H$_{11a,b}$); ^{13}C-NMR (75.4 MHz, CDCl$_3$): $\delta = 178.0$ (C(O)), 143.1 (C$_1$), 132.8 (CH), 131.1 (C$_{10}$), 129.9 (CH), 128.3 (CH), 123.8 (CH), 122.6 (CH), 108.0 (C$_6$), 104.3 (CH), 64.7 (OCH$_2$), 64.6 (OCH$_2$), 49.2 (C$_7$), 30.6 (NMe), 29.7 (C$_{12}$), 26.4 (C$_{11}$); Found: C, 70.6; H, 6.3; N, 5.1. Calc. for C$_{16}$H$_{17}$NO$_3$: C, 70.8; H, 6.3; N, 5.1%.

5.7. General procedure for the asymmetric cyclisation of triflate 15

Pd$_2$(dba)$_3$ (1.8 mg, 0.002 mmol), ligand (0.008 mmol) and benzene (0.4 ml) were charged to a 10 ml Schlenk flask and stirred for 1 h. A benzene (0.5 ml) solution of the triflate (30 mg, 0.08 mmol) and PMP (70 μl, 0.41 mmol) was added and the reaction was stirred for 5 min. The reaction mixture was degassed, sealed and heated for the appropriate reaction time at either 80 °C or 110 °C. Work-up was equivalent to the racemic variant and for the optimal result with (R)-BINAP, 1′,2′-dihydro-1′-methyl-2′-oxospiro[1,4-dioxaspiro[4.5]dec-6-ene-8,3′-3′H-indole] was isolated in 24% yield (5.2 mg) and 45% ee (S) with an optical rotation of $[\alpha]_D^{18} = +2.4°$ ($c = 0.25$ MeOH) and otherwise equivalent in all respects to a previously prepared sample.

5.8. Determination of enantiomeric excess of 1′,2′-dihydro-1′-methyl-2′-oxospiro[1,4-dioxaspiro[4.5]dec-6-ene-8,3′-3′H-indole (24)

A 0.1 M solution of Eu(hfc)$_3$ was prepared by dissolving 0.126 g of the reagent in 1.0 ml of CDCl$_3$. An NMR sample of **24** was prepared using 0.005 g of sample in 1.0 ml of CDCl$_3$. Approximately 30 μl of the Eu(hfc)$_3$ solution was added to the NMR tube and the N-methyl singlet at 3.21 ppm split into two singlets (3.6–3.8 ppm) which could then be integrated. If complete baseline separation is not apparent at this stage the Eu(hfc)$_3$ solution can be added dropwise, as required, although addition of an excess of shift reagent caused the N-methyl singlets to overlap with signals of the ethylene ketal.

5.9. Preparation of 2-hydroxy-[4.5]-dec-7-en-8-yl-carbonyl-aniline (26)

1-Cyclohexene-1-carboxylic acid (5.0 g, 40.0 mmol) in THF (30 ml) was added dropwise to a stirred suspension of sodium hydride (1.76 g, 44.0 mmol), in THF (50 ml) at 0 °C yielding a milky white suspension Stirring was continued for a further 2 h at ambient temperature. The reaction was recooled to 0 °C and thionyl chloride (3.2 ml, 42.0 mmol), was added dropwise over approximately 5 min giving a light yellow almost transparent suspension. This was stirred for a further 2.5 h at r.t. 2-Aminophenol (4.36 g, 40.0 mmol), was added as a solution in THF (30 ml), followed by Et$_3$N (6.4 ml, 43.0 mmol). Evolution of HCL was apparent at this stage and the light yellow solution became a deep mustard-coloured suspension. The reaction mixture was refluxed for a further 5 h. After cooling the reaction mixture was diluted with ether (300 ml) and washed consecutively with water (250 ml), saturated sodium bicarbonate (250 ml) and brine (250 ml). The organic layer was concentrated in vacuo yielding a dark brown solid. This was washed consecutively with petroleum spirits (50 ml), and then ice-cold EtOAc (20 ml), followed by recrystallisation from MeOH–hexanes yielding 2-hydroxy-[4.5]-dec-7-en-8-yl-carbonyl-aniline (3.4 g, 39.17%) as an off-white solid, m.p. 156–158 °C, IR (KBr cm^{-1}) 3409, 3100, 2957, 1661; ^{1}H-NMR (300 MHz, Me$_2$SO): $\delta = 9.77$ (s, 1H, OH), 8.76 (s, 1H, NH), 7.80 (dd, 1H, $J = 6.57$, 1.54 Hz, H$_6$), 7.00 (dt, 1H, $J = 1.5$ Hz, 5.6 Hz, H$_5$), 6.95–6.77 (m, 2H, H$_4$, H$_3$), 6.74 (m, 1H, H$_8$), 2.16–2.32 (m, 4H, H$_{12a,b}$, H$_{9a,b}$), 1.61 (m, 4H, H$_{11a,b}$, H$_{10a,b}$); ^{13}C-NMR (75.4 MHz Me$_2$SO): $\delta = 167.0$ (C(O)), 148.7 (C$_2$), 134.6 (Ar-CH), 133.9 (C$_1$), 127.1 (C$_7$), 125.4 (Ar-CH), 122.9 (Ar-CH), 119.8 (C$_8$), 116.4 (C$_3$), 25.6 (C$_9$), 24.6 (C$_{12}$), 22.4 (C$_{11}$), 21.8 (C$_{10}$); MS (EI, 70 eV): m/z (%): 217 [M$^+$] (13%), 109 (100), 81(56); Found: C, 71.7; H, 6.9; N, 6.4. C$_{13}$H$_{15}$O$_2$N requires C, 71.9; H, 6.9; N, 6.4%.

5.10. Preparation of 2-allyloxy-[4.5]-dec-7-en-8-yl-carbonyl-N-methylaniline (27)

To a well stirred solution of the 2-hydroxy-[4.5]-dec-7-en-8-yl-carbonyl-aniline (2.4 g, 10.1 mmol) in CH$_2$Cl$_2$ (60 ml) in a 250 ml Schlenk flask were added water (35 ml), 1 M NaOH (15 ml) and benzyltriethylammonium chloride (227 mg, 1.0 mmol). The flask was then wrapped in aluminium foil. Allyl bromide (1.9 ml, 20.2 mmol) was added and the reaction mixture was stirred vigorously for a further 16 h. The reaction mixture was then transferred to a 250 ml separatory funnel and the layers were separated. The aqueous layer was further extracted with CH$_2$Cl$_2$ (250 ml). The organic extracts were combined and then washed consecutively with saturated sodium bicarbonate (50 ml) and brine (50 ml),

concentrated in vacuo and then dried over magnesium sulfate. The crude 2-allyloxy-[4.5]-dec-7-en-8-yl-carbonyl-aniline (2.65 g, 97%) thus obtained was carried through to the next reaction without further purification. A solution of the allyl-amide (2.65 g, 9.8 mmol) in THF (10 ml) was added dropwise to a suspension of sodium hydride (0.82 g, 20.4 mmol) in THF (30 ml) at $0\,^{\circ}C$ under a nitrogen atmosphere. The resultant light yellow mixture was stirred for a further 10 min at $0\,^{\circ}C$ and then 3 h at r.t. Iodomethane (1.6 ml, 25.5 mmol) was added in one portion and the reaction was allowed to stir at r.t. for 14 h. Saturated sodium bicarbonate (25 ml) was added and the resultant mixture was extracted with ether (230 ml) and EtOAc (30 ml). The organic extracts were combined, washed with brine (50 ml), dried with magnesium sulfate and concentrated in vacuo. The crude product was purified by column chromatography on silica gel yielding 2-allyloxy-[4.5]-dec-7-en-8-yl-carbonyl-N-methylaniline (1.73 g, 70%) as a light yellow oil, TLC (petroleum ether 40:60 $^{\circ}C$–EtOAc = 1:1) $R_f = 0.25$; IR (neat, cm^{-1}): 2950, 1645; ^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.20$ (td, 1H, $J = 1.3$, 1.7, 7.9 Hz, H$_6$), 7.07 (dd, 1H, $J = 7.5$, 1.6 Hz, H$_5$), 6.94–6.86 (m, 2H, H$_{4,3}$), 6.02 (m, 1H, H$_8$), 5.76 (m, 1H), 5.40 (ddd, 1H, $J = 17.4$, 1.7, 1.5 Hz), 5.28 (ddd, 1H, $J = 10.4$, 1.5, 1.5 Hz), 4.56 (app. d, 2H, $J = 4.1$ Hz), 3.22 (s, 3H, NMe), 2.04 (m, 2H, H$_{12a,b}$), 1.81 (m, 2H, H$_{9a,b}$), 1.40 (m, 4H, H$_{10a,b}$, H$_{11a,b}$); ^{13}H-NMR (75 MHz, CDCl$_3$) $\delta = 172.2$ (C(O)), 154.6 (C$_2$), 134.8 (C$_1$), 133.0, 130.8, 129.3, 128.5 (C$_7$), 121.0, 117.7 (C$_3$), 112.9, 69.0 (allyl-CH$_2$), 35.8 (C$_{12}$), 25.0 (C$_9$), 22.3 (C$_{11}$), 21.8 (C$_{10}$); Found: C, 74.7; H, 7.7; N, 5.1. C$_{17}$H$_{21}$O$_2$N requires C, 75.2; H, 7.8; N, 5.2%.

5.11. Preparation of 2-hydroxy-[4.5]-dec-7-en-8-yl-carbonyl-N-methylaniline (28)

Following a modification of the procedure of Deziel, a mixture of 2-allyloxy-[4.5]-dec-7-en-8-yl-carbonyl-N-methylaniline (2.67 g, 9.8 mmol), Pd(PPh$_3$)$_4$ (0.3 g, 3.0 mmol), triphenylphosphine (0.09 g, 0.3 mmol) and dry MeCN (15 ml) were stirred for 5 min at $0\,^{\circ}C$. A solution of pyrrolidine (3.3 ml, 40.0 mmol), in MeCN (10 ml) was then added and the solution was stirred for a further 10 min at $0\,^{\circ}C$. The solution was heated at $4\,^{\circ}C$ for 2 h. After cooling to r.t. the reaction mixture was diluted with saturated citric acid solution (20 ml) and the layers were separated. The organic layer was washed with saturated citric acid solution (20 ml), brine (20 ml), dried with magnesium sulfate and concentrated in vacuo. The resulting crude orange residue was purified by column chromatography to give 2-hydroxy-[4.5]-dec-7-en-8-yl-carbonyl-N-methylaniline as a white solid (2.1 g, 93%), m.p. 164–166 $^{\circ}C$, TLC (2:1 pet spirits 40:60–EtOAc) $R_f = 0.17$; IR (KBr disc, cm^{-1}): 3121, 2931, 1656, 1614; ^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.51$ (s, 1H), 7.14

(ddd, 1H, $J = 5.7$, 1.6, 0.9 Hz, H$_6$), 7.01 (dd, 2H, $J = 6.8$, 1.3 Hz, H$_{4,5}$), 6.84 (m, 1H, H$_3$), 5.93 (m, 1H, H$_8$), 3.26 (s, 3H, NMe), 2.04 (m, 2H, H$_{12a,b}$), 1.89 (m, 2H, H$_{9a,b}$), 1.44 (m, 4H, H$_{10a,b}$, H$_{11a,b}$); ^{13}C-NMR (75.4 MHz, CDCl$_3$): $\delta = 174.6$ (C(O)), 152.8 (C$_2$), 134.3 (C$_1$), 132.0, 131.4, 129.1 (C$_7$), 120.7, 25.9 (C$_{12}$), 25.0 (C$_9$), 22.3 (C$_{11}$), 21.7 (C$_{10}$); MS (EI, 70 eV): m/z (%): 231 (M$^+$, 7%) 123 (66), 109 (90), 81 (100); Found: C, 72.4; H, 7.4; N, 5.9. C$_{14}$H$_{17}$O$_2$N requires C, 72.7; H, 7.4; N, 6.0%.

5.12. Preparation of 2-trifluoromethanesulfonyloxy-[4.5]-dec-7-en-8-yl-carbonyl-N-methylaniline (17)

2-Hydroxy-[4.5]-dec-7-en-8-yl-carbonyl-N-methylaniline (0.1 g, 0.4 mmol), dimethylaminopyridine (0.36 g, 3.0 mmol) and CH$_2$Cl$_2$ (5 ml) were added to a 10 ml Schlenk flask under a nitrogen atmosphere giving a light orange solution. The solution was cooled to $0\,^{\circ}C$ and triflic anhydride (0.17 ml, 1.0 mmol) was added dropwise yielding a green mixture with some precipitation. The reaction was allowed to stir at r.t. for a further hour then recooled to $0\,^{\circ}C$ and quenched with a saturated citric acid solution (3 ml). The contents of the Schlenk flask were transferred to a 100 ml separatory funnel. The organic layer was removed and the aqueous layer was extracted with a further 20 ml of CH$_2$Cl$_2$. The organic fractions were combined, dried over magnesium sulfate and concentrated in vacuo. The resulting brown residue was purified by column chromatography yielding 2-trifluoromethanesulfonyloxy-[4.5]-dec-7-en-8-yl-carbonyl-N-methylaniline (0.12 g, 83%) as a clear oil, TLC (EtOAc) $R_f = 0.7$; IR (neat, cm^{-1}): 2932, 1661, 1422, 1213, 1139; ^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.29$–7.43 (m, 4H, Ar-H), 5.72 (m, 1H, H$_8$), 3.34 (s, 3H, NMe), 2.16 (m, 2H, H$_{12a,b}$), 1.87 (m, 2H, H$_{9a,b}$), 1.45–1.64 (m, 4H, H$_{10a,b}$, H$_{11a,b}$) ^{13}C-NMR (75.4 MHz, CDCl$_3$) $\delta = 172.0$ (C(O)), 146.3 (C$_2$), 133.8 (C$_1$), 129.4 (CH), 129.3 (CH), 128.7 (C$_7$), 122.6 (C$_8$), 117.3 (C$_3$), 98.3, 87.9, 25.5 (C$_{12}$), 25.1 (C$_9$), 22.2 (C$_{11}$), 21.6 (C$_{10}$); MS (EI, 70 eV): m/z (%): 363 (M$^+$, 28%), 214 (51), 109 (78), 81 (100); Found: C, 49.5; H, 4.5; N, 3.7. C$_{15}$H$_{16}$O$_4$NSF$_3$ requires C, 49.6; H, 4.4; N, 3.8%.

5.13. Preparation of 1′,2′-dihydro-1′-methyl-2′-oxospiro-(cyclohex-2-ene-1,3′-3′-indoles) (30 and 31)

An oven-dried 10 ml Schlenk flask was charged with Pd$_2$(dba)$_3$ (11.5 mg, 0.013 mmol), racemic BINAP (16.8 mg, 0.027 mmol) and purged with nitrogen for 5 min. Dimethylacetamide (1 ml) was added giving a purple suspension which was allowed to stir for approximately 2 h until an orange solution had formed. A dimethylacetamide (1 ml) solution of the triflate 17 (100 mg, 0.275 mmol) was added followed by PMP (0.17 ml, 1.1 mmol). The resulting solution was frozen with liquid nitrogen, evacuated (0.1–0.01 mm) and allowed to warm to r.t.

This freeze–pump–thaw cycle was repeated three times. The Schlenk flask was sealed and heated to 110 °C for 36 h. The reaction was quenched with saturated aqueous sodium bicarbonate (5 ml), diluted with water (5 ml) and EtOAc (5 ml). The layers were separated and the aqueous layer was extracted with EtOAc (25 ml). The combined organic extracts were washed with brine (20 ml), dried over magnesium sulfate and concentrated in vacuo. The crude product was further purified by column chromatography to give 1′,2′-dihydro-1′-methyl-2′-oxospiro-(cyclohex-2-ene-1,3′-3′-indole), (0.045 g, 78%), as a white solid (mixture (23:72) of **30** and **31** double bond isomers), TLC (petroleum ether 40:60–ethyl acetate = 5:1) $R_f = 0.31$; IR (KBr disc, cm^{-1}): 2961, 1705, 1610, 1465; **31**: ^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.31$ (t, 1H, $J = 7.3$ Hz, H$_3$) 7.27–7.25 (m, 1H, H$_6$), 7.04 (t, 1H, $J = 7.5$ Hz, H$_5$), 6.86 (d, 1H, $J = 7.7$ Hz, H$_4$), 5.84–5.95 (m, 2H, H$_{9,10}$), 3.23 (s, 3H, NMe), 2.61–2.70 (m, 1H, H$_{12a}$), 2.30–2.36 (m, 2H, H$_7$), 1.91–2.00 (m, 2H, H$_{11}$), 1.49–1.58 (m, 1H, H$_{12b}$); ^{13}C-NMR (125 MHz, CDCl$_3$) $\delta = 175.9$ (C(O)), 135.0 (C$_1$), 127.9, 127.0, 125.1 (C$_8$), 124.2 (C$_9$), 122.6, 108.1, 101.4, 46.3 (C$_7$), 31.9 (C$_{10}$), 29.2 (C$_{12}$), 22.1 (C$_{11}$); MS (EI, 70 eV): m/z (EIMS 70 eV): 213 [M$^+$] (53%), 184 (31%), 159 (100%); Found: C, 78.3; H, 7.2; N, 6.0. Calc. for C$_{14}$H$_{15}$NO: C, 78.8; H, 7.1; N, 6.6%.

5.14. General procedure for the asymmetric cyclisation of triflate **17**

5.14.1. Using BINAP **6** as ligand

Pd$_2$(dba)$_3$ (1.8 mg, 0.002 mmol), (*R*)-BINAP **6** (5.1 mg, 0.008 mmol) and toluene (0.4 ml) were charged to a 10 ml Schlenk flask and stirred for 1 h. A toluene (0.5 ml) solution of the triflate (30 mg, 0.08 mmol) and PMP (70 μl, 0.41 mmol) was added and the reaction was stirred for 5 min. The reaction mixture was degassed, sealed and heated for 48 h at 110 °C. Work-up was equivalent to the racemic variant and 1′,2′-dihydro-1′-methyl-2′-oxospiro-(cyclohex-2-ene-1,3′-3′-indole) was isolated in 90% yield (16.8 mg) as a white solid with an enantioselectivity of 71% (*S*) and an optical rotation of $[\alpha]_D^{18} = +2.3°$ ($c = 0.25$ MeOH) and otherwise equivalent in all respects to a previously prepared sample.

5.14.2. Using ligand **13**

Pd$_2$(dba)$_3$ (1.8 mg, 0.002 mmol), **13** (4.0 mg, 0.008 mmol) and toluene (0.4 ml) were charged to a 10 ml Schlenk flask and stirred for 1 h. A toluene (0.5 ml) solution of the triflate **17** (27 mg, 0.08 mmol) and proton sponge (88.0 mg, 0.4 mmol) was added and the reaction was stirred for 5 min. The reaction mixture was degassed, sealed and heated for 48 h at 110 °C. Work-up was equivalent to the racemic variant and 1′,2′-dihydro-1′-methyl-2′-oxospiro-(cyclohex-2-ene-1,3′-3′-indole) was isolated in 71% yield (13.2 mg) and 82% ee

(*R*) solely as the double bond isomer **30**, ^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 7.30$–7.20 (m, 2H, H$_{5′,6′}$), 7.0 (m, 1H, H$_{4′}$), 6.83 (d, 1H, 17.6 Hz, H$_{3′}$), 6.13 (dt, 1H, $J = 9.8$, 4.0 Hz, H$_2$), 5.28 (d, 1H, $J = 9.9$ Hz, H$_3$), 3.21 (s, 3H, NMe), 2.25–2.20 (m, 2H, H$_{4a,b}$), 2.05–2.00 (m, 2H, H$_{6a,b}$), 1.65–1.95 (m, 2H, H$_{5a,b}$); $[\alpha]_D^{18} = -2.4°$ ($c = 0.25$ MeOH).

5.15. Preparation of methyl 3,8a-dihydro-4H-naphthalene-4a-carboxylate (**32**)

An oven-dried 10 ml Schlenk flask was flushed with nitrogen for 5 min and then charged with racemic BINAP (9.2 mg, 0.015 mmol), Pd$_2$(dba)$_3$ (6.7 mg, 0.0075 mmol) and toluene (0.5 ml). The purple suspension thus obtained was stirred for 1 h under a nitrogen atmosphere and had then become an orange solution. Methyl 1-[4-[[(trifluoromethyl)sulfonyl]oxy]-3(Z)-butenyl-2,5-cyclohexadiene-1-carboxylate (50 mg, 0.15 mmol) was then added in toluene (1.0 ml) followed by potassium carbonate (41.4 mg, 0.3 mmol). The reaction mixture was degassed by the freeze–thaw–pump method (×3), sealed and heated at 60 °C for 72 h. The reaction mixture was now allowed to cool to r.t., diluted with ether (5 ml), washed with brine (5 ml), dried over magnesium sulfate and concentrated in vacuo. The crude residue was then further purified by column chromatography on silica gel to give methyl 3,8a-dihydro-4a-4H-naphthalenecarboxylate as a colourless oil (14.0 mg, 51%), TLC (pet spirits 40:60–ethyl acetate = 10:1) $R_f = 0.2$; IR (neat, cm^{-1}): 1730; ^{1}H-NMR (300 MHz, CDCl$_3$): $\delta = 5.94$ (ddd, 1H, $J = 9.5$, 5.1, 0.7 Hz, H$_5$), 5.79 (m, 1H, H$_4$), 5.60–5.75 (m, 3H, H$_{4′}$, H$_3$, H$_6$), 5.56 (d, 1H, 9.7 Hz, H$_{3′}$), 3.72 (s, 3H, OMe), 3.61 (m, 1H, H$_2$), 1.93–2.10 (m, 2H, H$_{2′a,b}$), 1.85–1.90 (m, 2H, H$_{1′a,b}$); ^{13}C-NMR (75.4 MHz, CDCl$_3$): $\delta = 176.1$ (C(O)), 129.7 (CH), 128.9 (CH), 126.7 (CH), 125.7 (CH), 124.0 (CH), 120.6 (CH), 52.3 (OMe), 46.0 (C$_1$), 36.1 (C$_2$), 27.4 (C$_2$), 21.7 (C$_{2′}$); MS (EI, 70 eV): m/z (%): 190 [M$^+$] (35%), 131 (100%), 115 (23%).

5.16. General procedure for the asymmetric cyclisation of triflate **18**

An oven-dried 10 ml Schlenk flask was flushed with nitrogen for 5 min and then charged with (*R*)-BINAP (4.6 mg, 0.008 mmol), Pd$_2$(dba)$_3$ (1.8 mg, 0.002 mmol) and toluene (0.5 ml). The purple suspension thus obtained was stirred for 1 h under a nitrogen atmosphere and had then become an orange solution. Methyl 1-[4-[[(trifluoromethyl)sulfonyl]oxy]-3(Z)-butenyl-2,5-cyclohexadiene-1-carboxylate (26 mg, 0.08 mmol) was then added in toluene (0.5 ml) followed by potassium carbonate (20.4 mg, 0.15 mmol). The reaction mixture was degassed by the freeze–thaw–pump method (×3),

sealed and heated at 60 °C for 72 h. Work-up was as for the racemic variant and methyl 3,8a-dihydro-4H-naphthalene-4a-carboxylate **32** was isolated as a viscous colourless oil (7.4 mg, 50%), $[\alpha]_D^{18} = +39.7°$ ($c = 0.3$ MeOH) (82% ee).

5.17. Determination of enantiomeric excess of methyl 3,8a-dihydro-4H-naphthalene-4a-carboxylate (**32**)

Enantioselectivities were determined by chiral HPLC analysis using a Daicel Chiralpak OJ column (0.46 cm25 cm), 0.3 ml min^{-1}, hexane: 100% ($t_R = 84.2$ ($-$) and 93.7 ($+$) min).

Acknowledgements

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