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Phosphinooxazolines Derived from 3-Amino-1,2-diols: Highly Efficient Modular *P-N* Ligands

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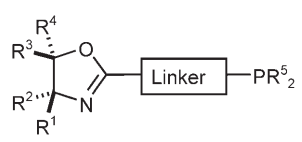
Abstract: A family of chiral phosphinooxazolines (**12a–e)** derived from modular, enantiopure β-amino alcohols has been prepared, and their palladium complexes have been used as chiral mediators in the asymmetric allylic alkylation reaction. The oxazoline moiety in **12** contains a C-4 aryl and a C-5 alkoxymethyl substituent that can be independently optimized for high catalytic activity and enantioselectivity. A methoxymethyl substituent at C-5 has been found to provide the best results in terms of enantioselectivity and activity in the alkylation of a diverse family of allylic substrates under both thermal and microwave-assisted activation. The palladium-phosphinooxazoline complexes described in this work are remarkably robust, as the enantioselectivity recorded in the asymmetric allylic alkylation remains essentially unchanged in the temperature range between 20 and 130 °C. An unprecedented reversal in enantioselectivity has been observed between 1,3-diphenylallyl and 1,3-dimethylallyl alkylation substrates, and the origin of this behavior has been explained by means of ONIOM QM/MM calculations.

Keywords: allylic alkylation; asymmetric catalysis; microwave-induced alkylation; ONIOM calculations

Introduction

Phosphinooxazolines **1** and **2** belong to a non-C_2-symmetric class of ligands which combine the characteristics of a "soft" phosphorus donor group with π-acceptor properties and a "hard" nitrogen sigma donor group.[1] The oxazoline and phosphorus groups are separated by a linker which corresponded, in the seminal work by Pfaltz,[2] Helmchen[3] and Williams,[4] to a 1,2-disubstituted benzene ring, **2**.



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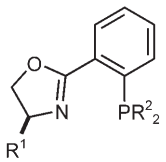

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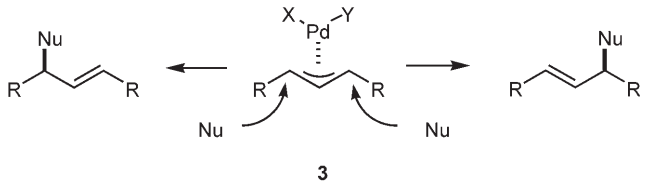
Although C_2-symmetric ligands have dominated the field of asymmetric catalysis because they facilitate the analysis of the catalyst-substrate interactions, for reactions where the two enantiomeric products arise from the regioselectivity of the process, C_1 ligands possessing two different coordinating atoms should allow a more effective regiocontrol.[5] The palladium-catalyzed asymmetric allylic alkylation of symmetrical π-allyl ligands (**3**) falls into this category, since the enantioselectivity of the reaction depends on the ability of the ligand in inducing a different reactivity in the two terminal allyl carbons (Scheme 1).

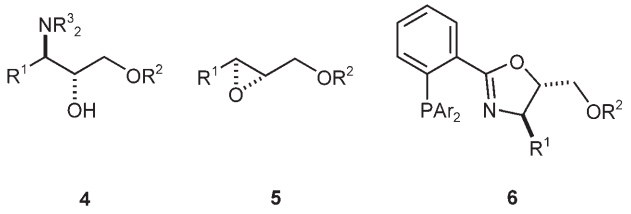
Following the initial studies by Pfaltz[2], Helmchen[3] and Williams,[4] a great variety of phosphinooxazolines has been developed and studied in the asymmetric allylic alkylation with excellent results.[1b,e–g,6] However, modular β-amino alcohols, suitable for the fine-tuning of catalytic properties, have never been used as chiral building blocks for the preparation of phosphinooxazolines.



Scheme 1.

Synthetic, yet enantiopure amino alcohols **4** arising from Sharpless epoxides **5** present several elements of structural diversity and have been developed by our group as very efficient mediators for the asymmetric addition of diethylzinc onto carbonyl compounds[7] and imines[8] and enantioselective transfer hydrogenation.[9] Their derived oxazaborolidines have been used in the enantioselective borane reduction of prochiral ketones[10] and the derived bisoxazolines in the asymmetric allylic alkylation.[11] In all these cases, the fine-tuning of catalytic properties is greatly facilitated by the complete modular nature of **4** which allows independent optimization of the different structural elements. Along with this strategy, we report in this paper the preparation of a new family of modular phosphinooxazolines **6**, incorporating an alkoxymethyl substituent at C-5 of the oxazoline ring and the performance of their π-allylpalladium complexes as catalysts for the asymmetric alkylation of a diverse family of allylic substrates.

Whereas known phosphinooxazoline libraries incorporate modularity at the phosphorus atom or at the



substituent of the carbon atom next to nitrogen, the study of the effects of the substituents at C-5 of the oxazoline moiety (such as the R^2OCH_2 group in **6**) remains unexplored. Besides its primary effect on catalytic activity and on enantioselectivity, the alkoxymethyl substituent in **6** offers the additional interest of allowing the heterogeneization of the phosphinooxazoline ligand onto insoluble organic resins. From this perspective, the optimization of the R^2OCH_2- moiety in **6** is of paramount importance: On one hand, the primary hydroxy group in these structures is the obvious point for polymer anchoring with minimal perturbation of the reaction site.[12] On the other hand, the optimal OR^2 group will dictate the optimal nature for the resin onto which **6** can be anchored.

Results and Discussion

Synthesis of the Phosphinooxazolines and their Palladium Complexes

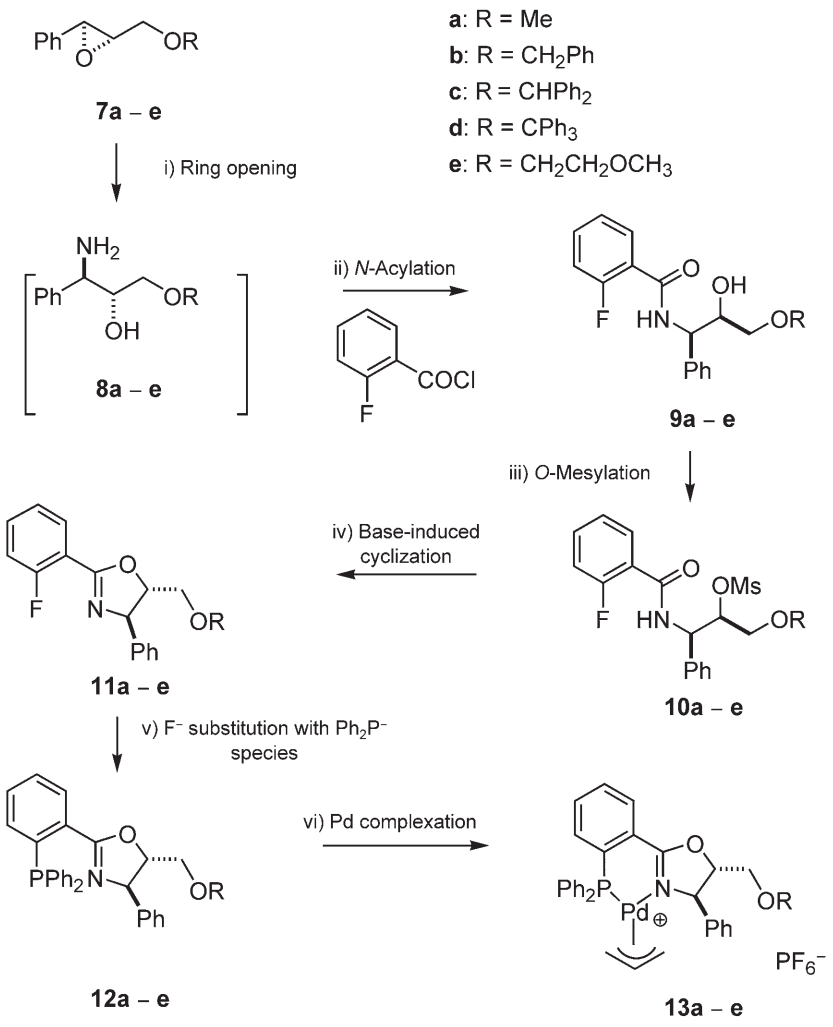
The preparation of phosphinooxazolines **12** and of their π-allyl palladium complexes **13** was planned from Sharpless epoxy ethers **7** through well documented synthetic transformations (Scheme 2).

Both the ready availability of enantiopure epoxy alcohols through Sharpless epoxidation and the ease for selective derivatization of the primary alcohol in these structures render this approach highly attractive in terms of the introduction of molecular diversity. Moreover, the substitution scheme in **7** should provide access to *trans*-4,5 disubstitued modular phosphinooxazolines, whose synthesis and catalytic properties have remained practically unexplored.[2,13]

Amino alcohols **8** were readily prepared by aminolysis of epoxy ethers **7** under pressure either by microwave irradiation or by simple thermal activation.[14] With microwave activation, the ring opening proceeded satisfactorily just by dissolving **7a** (R = Me), **7b** ($R = CH_2Ph$) and **7e** [$R = (CH_2)_2OMe$] in 25% aqueous ammonia (50 equivs.) and irradiating the corresponding solution for 8 min at 125 °C. Epoxy ethers **7c** and **7d**, which bear bulkier R groups, were not soluble in aqueous ammonia and a co-solvent (*i*-PrOH) was required to facilitate the reaction. In those cases, 1 equivalent of lithium perchlorate was also added to the reaction mixture in order to accelerate the ring-opening reaction. Full conversion was achieved in this manner after not more than 20 min. It is worth noting that, under thermal conditions, these reactions required 5 h for complete conversion (entries 4 and 6, Table 1). Independent of the ring-opening method which was used, all the reactions took place stereospecifically and with complete regiocontrol.

The crude amino alcohols **8** were simply dried with $MgSO_4$ (in dichloromethane solution) and directly submitted to the next step without further purification. The *N*-acylation step was carried out using 2-fluorobenzoyl chloride as the limiting reagent and triethylamine as the auxiliary base in dry tetrahydrofuran. At this stage, the intermediate hydroxy benzamides **9** were purified and characterized. The overall yields (referred to the ring opening and benzoylation steps) range from 53% to 80% and have been summarized in Table 1.

Conversion of **9a–e** into oxazolines **11a–e** was carried out through a two-step sequence[11] involving: activation of the hydroxy group in **9** as a mesylate (MsCl, NEt_3 as auxiliary base) and base-induced cyclization (5% KOH/MeOH) of the intermediate mesylates **10a–e** through an S_N2 mechanism. Due to the limited stability of mesylates **10**, these compounds were not stored, and the base-induced cyclization to-



i) Microwave-assisted: 50 equivs. 25% NH_3 or thermally induced: 50 equivs. 25% NH_3, 1 equiv. $LiClO_4$, 100 °C
ii) 0.95 equivs. *o*-FC_6H_4COCl (referred to **7**), THF, 1.95 equivs. NEt_3, 0 °C to r.t., 2 h
iii) MsCl (1,1 equivs.), Et_3N (2.2 equivs.), DCM, 0 °C to r.t., 2 h
iv) 5% aq. KOH (6.2 equivs.), MeOH, 15 h, r.t.
v) $KPPh_2$ (1.5 equivs.), THF, –78 °C up to –20 °C, 2 h
vi) $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.53 equivs.), NH_4PF_6 (1.02 equivs.), EtOH, 14 h

Scheme 2. Preparation of phosphinooxazolines **12a–e** and of their π-allyl Pd complexes **13a–e** from epoxy ethers **7a–e**.

wards **11** was carried out within a few hours after their preparation. The overall activation-cyclization sequence took place in a straightforward way, and high overall yields for the two steps (68–80%, see Table 2) were observed in all cases. The relative *trans* stereochemistry of the oxazoline substituents could be confirmed by means of a NOESY experiment on **11b**, where a cross-peak indicating NOE between the C*H*-N and the CH_2 units could be observed (See Supporting Information).

The nucleophilic displacement of fluoride from **11** with potassium diphenylphosphide proceeded uneventfully in THF at −20 °C. Quenching of the reaction mixture with sodium sulfate decahydrate followed by a short filtration through deoxygenated SiO_2 afforded pure phosphinooxazolines **12** in 62–97% yield (Table 2). ^{31}P NMR data were in agreement with the proposed structure, as a singlet at around −3 ppm was observed for the diphenylphosphino group along the whole series of compounds.

Table 1. Ring-opening and acylation of epoxy ethers **7a–e**.

Entry	Epoxy ether	Aminolysis conditions	2-Fluorobenz-amide	Overall yield
1	**7a**, R = Me	Microwave irradiation: 125 °C, 8 min	**9a**, R = Me	53 %
2	**7b**, R = CH_2Ph	Microwave irradiation: 125 °C, 8 min	**9b**, R = CH_2Ph	69 %
3	**7c**, R = $CHPh_2$	Microwave irradiation: 125 °C, *i*-PrOH, 8 min	**9c**, R = $CHPh_2$	61 %
4	**7c**, R = $CHPh_2$	Thermal conditions: 100 °C, *i*-PrOH, 5 h; 1 equiv. $LiClO_4$	**9c**, R = $CHPh_2$	80 %
5	**7d**, R = CPh_3	Microwave irradiation: 130 °C, *i*-PrOH, 20 min; 1 equiv. $LiClO_4$,	**9d**, R = CPh_3	67 %
6	**7d**, R = CPh_3	Thermal conditions: 100 °C, *i*-PrOH, 5 h; 1 equiv. $LiClO_4$	**9d**, R = CPh_3	60 %
7	**7e**, R = $(CH_2)_2OMe$	Microwave irradiation: 125 °C, 8 min	**9e**, R = $(CH_2)_2OMe$	59 %

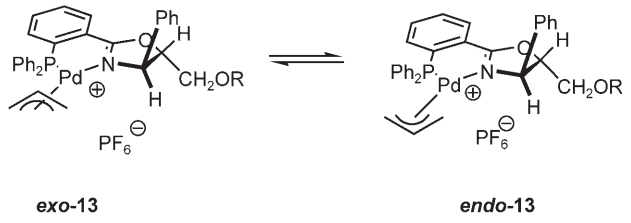
Table 2. Transformation of hydroxybenzamides **9** into the palladium complexes **13**.

Entry	Hydroxy amide	Overall yield steps iii and iv	Yield of step v	Yield of step vi	Palladium complex
1	**9a**, R = Me	76 %	93 %	76 %	**13a**, R = Me
2	**9b**, R = CH_2Ph	68 %	97 %	65 %.	**13b**, R = CH_2Ph
3	**9c**, R = $CHPh_2$	70 %	62 %	64 %	**13c**, R = $CHPh_2$
4	**9d**, R = CPh_3	80 %	76 %	63 %	**13d**, R = CPh_3
5	**9e**, R = $(CH_2)_2OMe$	68 %	85 %	63 %	**13e**, R = $(CH_2)_2OMe$

The phosphinooxazolines were finally converted into the ionic π-allylpalladium complexes immediately after isolation. The complexes were prepared by reacting the palladium dimer $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and the appropriate phosphinooxazoline **12** in ethanol in the presence of NH_4PF_6.[11] The metal complexes of general formula $[Pd(\eta^3\text{-allyl})(L)]PF_6$ **13** precipitated from the solution at 4 °C and could be isolated as crystalline materials. Yields of isolated material are given in Table 2.

As far as the structure of **13a–e** in solution is concerned, it is well known that palladium η^3-allyl complexes normally exist as two isomeric species which interconvert through a fluxional process of the allyl group.[15] In the case of an unsymmetrical palladium complex such as **13a–e**, *endo*- and *exo*-isomers are possible (Scheme 3).[16] The interconversion of *endo*- and *exo P-N*-palladium η^3-C_3H_5[15b–c,17] and allyl substituted[15e,f,16,18] species is a well studied process which involves, in most of the cases, a η^3-η^1-η^3 isomerization, with rotation of the sp^3-sp^2 bond of the allyl moiety in the palladium sigma complex followed by a final coordination of the olefin to the palladium center.

A detailed NMR study (see Supporting Information) strongly suggests that **13a–e** predominantly occur in solution as *endo*-isomers. In addition, the solid state structure of one of the complexes could be determined by X-ray crystallography (Figure 1), since crystals of anion exchanged complex **13a** could be grown in methanol.[19] Selected geometrical bond distances for the allyl moiety have been summarized in



Scheme 3.

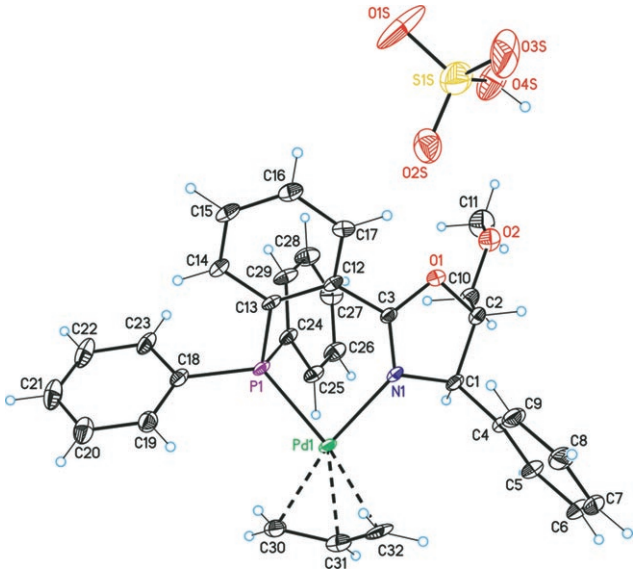


Figure 1. X-Ray structure of ***endo*-13a.**

Table 3. As anticipated from what has been observed in other palladium-allyl complexes,[17] the Pd–C bonds to the terminal allylic C-atom *trans* to the *P*-atom are significantly longer (2.217 Å for the *endo* isomer and 2.225 Å for the *exo* one) than the Pd–C bonds *trans* to the *N*-atom (2.125 Å for both the *endo* and *exo* isomers).

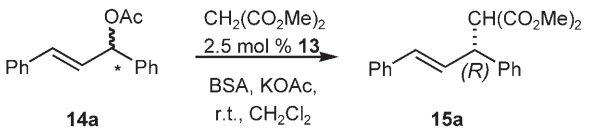
Table 3. Selected bond lengths [Å] for the ***endo-*** and ***exo-*13a-bis**.

Pd(1)–N(1)	2.109(3)
Pd(1)–C(30)	2.125(4)
Pd(1)–C(31)	2.137(7)
Pd(1)-C(31′)	2.206(8)
Pd(1)–C(32)	2.217(7)
Pd(1)–C(32′)	2.225(8)
Pd(1)–P(1)	2.289(8)

The allyl ligand was found to be disordered and refined with only one position for one terminal allyl carbon (C-30, see Figure 1) and two positions for the other terminal (C-32) and the central (C-31) allyl carbon atoms. Refining the occupancy factors afforded an *endo:exo* ratio of 58:42. This result fits reasonably well with the *endo:exo* ratio measured in solution by integration of the central allyl proton signals, which was found to be 65:35.

Allylic Alkylation Catalyzed by Pd/ Phosphinooxazoline Complexes

To test the effect of structural variation in the modular phosphinooxazolines (CH_2OR group) on the catalytic activity in the asymmetric allylic alkylation reaction, palladium complexes **13** containing an unsubstituted allyl moiety were used as catalytic precursors in model asymmetric allylic alkylation reactions. In this way, *rac*-(*E*)-3-acetoxy-1,3-diphenyl-1-propene (**14a**) was alkylated in dichloromethane at room temperature in the presence of 2.5 mol% of **13** (Scheme 4), the nucleophile being generated from dimethyl malonate with *N,O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate. The results of the enantioselective allylic alkylation are collected in Table 4.



Scheme 4. Asymmetric allylic alkylation of *rac-(E)*-3-acetoxy-1,3-diphenyl-1-propene (**14a**).

Table 4. Ligand fine-tuning in the catalytic asymmetric allylic alkylation with **13**.

Entry	Catalyst	Time [h]	Conversion [%][a]	*ee* [%][b]
1	**13a** (R = Me)	4	>99	96
2	**13b** (R = CH_2Ph)	4.3	>99	85
3	**13c** (R = $CHPh_2$)	27	87	87
4	**13d** (R = CPh_3)	27	60	83
5	**13e** (R = CH_2CH_2OMe)	4.5	>99	86

[a] Conversion was measured by NMR.
[b] The product had the *R* configuration, which was established by comparison of the sign of the optical rotation of **15a** with the reported value.[20] Enantiomeric excesses were measured by chiral HPLC.

When 2.5 mol% of catalyst were used, total conversion of **14a** was observed at room temperature after 4 h with catalysts **13a, b** and **13e** (R = Me, CH_2Ph and CH_2CH_2OMe respectively, entries 1, 2 and 5 in Table 4). The activity of the catalysts in terms of conversion decreased with the size of the protecting group, and lower conversions were observed for the ligands with bulkier protecting groups (R = $CHPh_2$ and CPh_3, entries 3 and 4, Table 4). The best enantioselectivity (96% *ee*, entry 1 in Table 4) was observed in the case of the catalyst **13a** which bears the less bulky substituent at C-5 in the oxazoline ring. The enantioselectivity for the rest of the members of the family ranged from 83 to 87% *ee*, the lower value being recorded for the catalyst with the bulkier substituent (83% *ee*, entry 4 in Table 4, R = CPh_3). It is clear from these results that **13a**, containing a methoxymethyl substituent, is the optimal ligand among those in the studied series.

For this ligand (**13a**), the reaction temperature was optimized, and alternative activation methods such as microwave irradiation were also studied.[21] The results are summarized in Table 5.

The reaction was carried out at different temperatures (from −10 °C to 55 °C) and very good selectivities were observed throughout the whole temperature range (94–97% *ee*). With **13a**, the best performance in terms of enantioselectivity was achieved at 35 °C (97% *ee*, entry 4). The reaction was also studied under microwave irradiation and, in this case, the reaction time could be dramatically shortened (15 min for complete conversion) without any loss in enantioselectivity (entry 7 in Table 5). All together, this result represents a remarkable example of good performance of the asymmetric allylic alkylation under microwave irradiation. The remarkably good temperature/selectivity profile renders catalyst **13a** optimal for future applications in larger scale because almost no temperature control would be required in order to achieve high enantioselectivities.

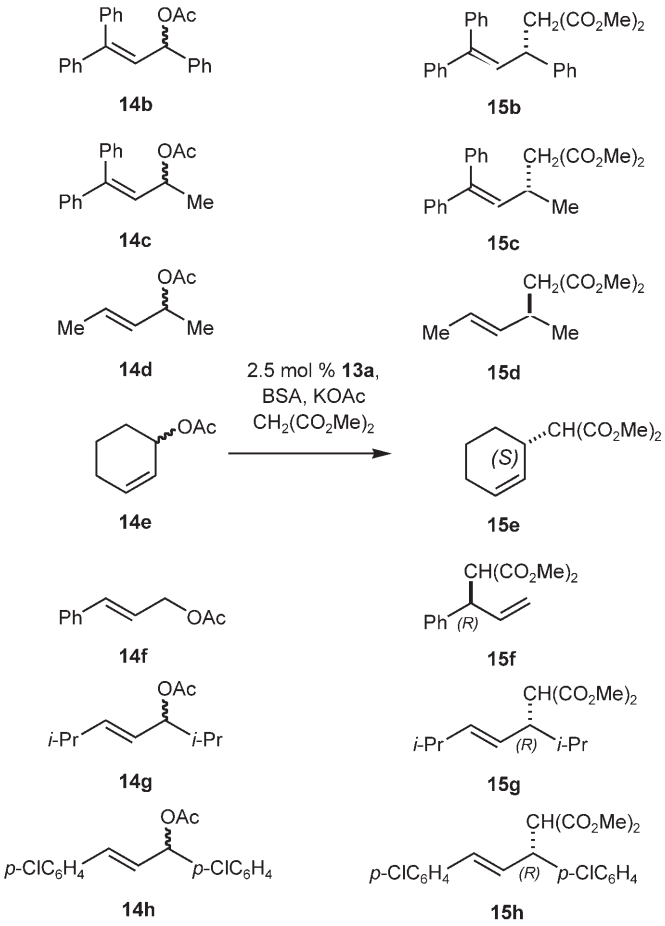
Table 5. Optimization procedure for catalyst **13a** in the asymmetric allylic alkylation of **14a**.

Entry	Temperature [°C]	Time [h]	Conversion [%][a]	*ee* [%][b]
1	−10	24	>99	94
2	0	7	>99	95
3	r.t.	4	>99	96
4	35	2.5	>99	97
5	35, MW irradiation	1	96	95
6	45	2	>99	95
7	55[c], MW irradiation	15 min	99	95

[a] Conversion was measured by NMR.
[b] The product had the *R* configuration, which was established by comparison of the sign of the optical rotation of **15a** with the reported value.[20] Enantiomeric excesses were measured by chiral HPLC.
[c] The reaction was carried out in acetonitrile.

With the optimized catalyst in hand, the asymmetric alkylation reaction of substrates **14b–h** mediated by the π-allylpalladium-phosphinooxazoline complex **13a** was studied (Scheme 5). These results are collected in the Table 6.

Excellent results were obtained in terms of enantioselectivity in the alkylation of allylic systems bearing a bulky substituent at the carbon atom undergoing alkylation, such as **14b**, **14f**, and **14g**. For all these systems, the enantioselectivities recorded with catalyst **13a** are amongst the highest recorded with phosphi-



Scheme 5. Asymmetric allylic alkylation of substrates **14b–h** with **13a**.

Table 6. Asymmetric allylic alkylation of substrates **14b–h** with catalyst **13a**.

Entry	Substrate	Product	Solvent/Temperature	Reaction time [h]	Conversion [%][a]	*ee* [%][b]
1	**14b**	(*R*)-**15b**	DMF/30 °C	96	42	94
2	**14b**	(*R*)-**15b**	THF/70 °C	38	90	94
3	**14b**	(*R*)-**15b**	MeCN/130 °C, MW	2	99	94
4	**14c**	(*R*)-**15c**	MeCN/100 °C, MW	2	64	72
5	**14c**	(*R*)-**15c**	MeCN/130 °C, MW	2	>99	70
6	**14d**	(*S*)-**15d**	CH_2Cl_2/r.t.	24	87	43
7	**14d**	(*S*)-**15d**	MeCN/60 °C, MW	3.5	>99	35
8	**14e**	(*S*)-**15e**	CH_2Cl_2/r.t.	24	40	56
9	**14e**	(*S*)-**15e**	MeCN/60 °C, MW	3.5	>99	34
10	**14f**	(*R*)-**15f**	CH_2Cl_2/rt	4	>99[c]	82
11	**14g**	(*R*)-**15g**	MeCN/80 °C, MW	8	54[d]	92
12	**14h**	(*R*)-**15h**	THF/−10 °C	17	95	98
13	**14h**	(*R*)-**15h**	THF/r.t.	1.5	>99	91
14	**14h**	(*R*)-**15h**	THF/85 °C, MW	2.5	>99	93

[a] Conversions were measured by NMR.
[b] The configurations for **15–g** were established by comparison with either reported chromatographic elution orders or optical rotations. Compound **15h** was assumed to have the (*R*) configuration by comparing its elution order with the one for (*R*)-**15a** in the Chiralcel OD-H and AD-H columns. Enantiomeric excesses were measured by chiral HPLC for **15b**, **15f** and **15h**, by GC for **15d** and **15e** and by NMR for **15c** and **15g** (see Experimental Section for details).
[c] The linear to branched product ratio was 93/7.
[d] It refers to isolated yield.

nooxazoline ligands in the considered reaction.[1g,2,28] Excellent enantioselectivities have also been achieved in the allylic alkylation of substrate **14h**, which had not previously been studied with phosphinooxazoline-based catalysts. The very good results with this substrate and **14a** render catalyst **13a** as very suited for the allylic alkylation of 1,3-diaryl-substituted allyl acetates.

The influence of the bulkiness of the *ipso* substituent on enantioselectivity becomes clear when the results on **14b**/**14c** or **14a** (Table 5)/**14d** are compared. In these cases, replacement of a phenyl substituent by a less bulky methyl group at the reaction site is accompanied by an important decrease in enantioselectivity.

The tolerance of **13a** towards temperature changes is of paramount importance for the determination of optimal reaction conditions. Thus, while the enantioselectivity was high for substrate **14b** at room temperature (94% *ee*, entry 1), conversion was rather low under these conditions even after long reaction times. Microwave-assisted allylic alkylation turned out to be more effective for this kind of substrates, and complete conversion was achieved in acetonitrile at 130 °C in only 2 h. Very gratifyingly, the enantioselectivity achieved under these conditions was the same recorded at room temperature (compare entries 3 and 1 in Table 6). To conclude with, microwave activation is the technique of choice for the allylic alkylation reaction of hindered allyl substrates mediated by **13a** (see entries 5, 7, 11, and 14 in Table 6). In particular, the results obtained with **13a** for substrates **14a**, at 55 °C, **14b** and **14c**, at 130 °C, and for **14g** and **14h**, at 80–85 °C, confirm the remarkably wide selectivity-temperature profile of this catalyst.

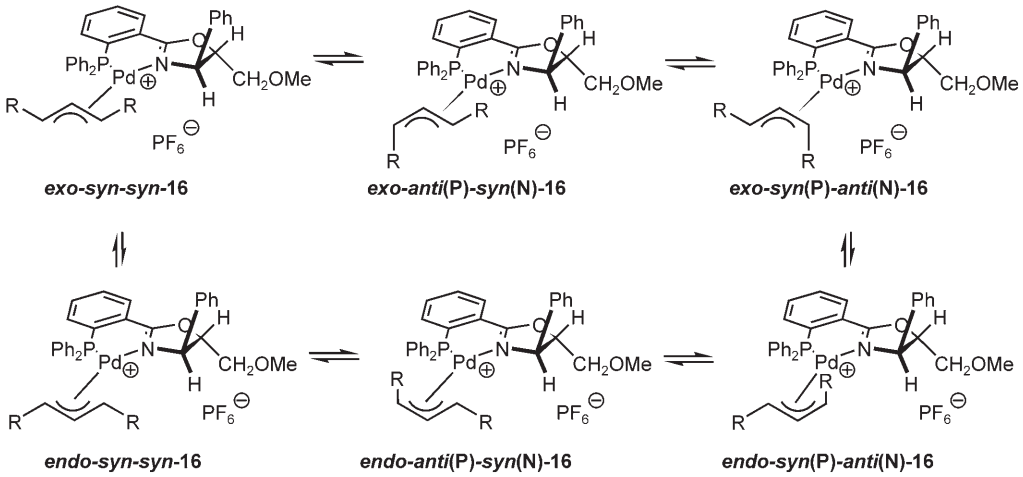
On the other hand, substrates **14d** and **14e** showed low enantioselectivities in the alkylation reaction (entries 6 and 8 in Table 6). Conversion could be improved under microwave irradiation but selectivities remained low (entries 7 and 9 in Table 6). In any case, it should be recalled that the selectivities observed for these two substrates in the present work are similar to the best ones achieved using well established phosphinooxazolines.[22] Also on the negative side, it is to be noted that with the unsymmetrical substrate **14f**, although the branched product is formed with high enantioselectivity, the ratio of branched to linear product is low. Thus, the challenge of simultaneously achieving high regiocontrol in favour of the branched product and high enantiocontrol in the major regioisomer posed by non-symmetrical substrates does not find a definitive solution with the use of **13a**.

Among these results, the reversal in the sign of enantioselectivity observed when passing from substrate **14a** (Table 5) to **14d** is particularly noteworthy, since a parallel behavior has never been observed before in this reaction. It is interesting to realize that a similar reversal in enantioselectivity is not observed in the case of **14g**, where the allyl system bears bulkier alkyl substituents. Thus, this behavior appears to be related to the small size of the methyl substituents, and to the possible changes that this can provoke in the stereochemistry/reactivity of the reactive intermediate.

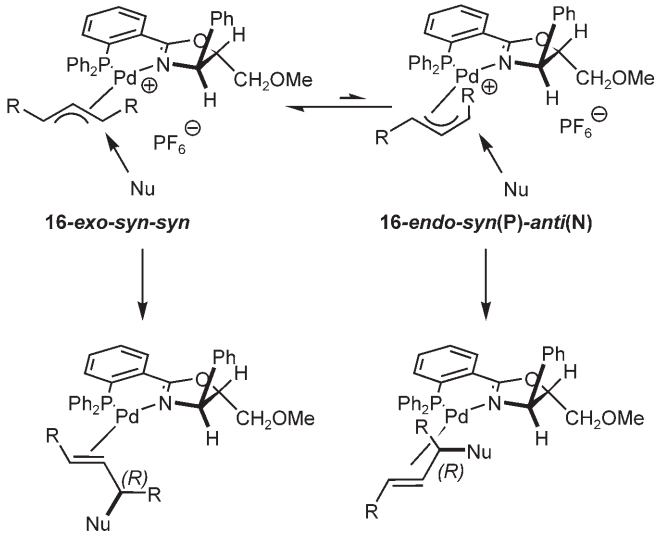
Mechanistic Rationalization

The Pd-catalyzed enantioselective C–C bond-forming reactions that have been studied in this work start from racemic substrates and proceed *via* symmetrical Pd-allyl complexes **16**. It should be recalled that complexes **16** containing the 1,3-disubstituted allyl moiety can give rise to several isomers, depending on the stereochemical relationship between the substituents of the allyl group and the central allyl hydrogen: *syn-syn*; *syn-anti*, *anti-syn* and *anti-anti* isomers.[15a,f,18a,c–e,23] Furthermore, each of those isomers can have an *exo* or *endo* arrangement of the allyl moiety. These isomeric species are interconverting due to several fluxional processes (Scheme 6). The *anti-anti* isomers (not depicted in Scheme 6) have a very limited abundance given their lower stability and are normally not detected.[18d] It has been reported in the literature that the most abundant isomer in the case of 1,3-diphenyl substituted allyl systems corresponds to the *exo-syn-syn* isomer, followed by the *endo-syn-syn* one, the ratio among them ranging from 4:1 to 12:1.[15a,16,18e,23b–c] The same trend has been found for the 1,3-dimethylallyl precursor,[18d,23a] although *syn-anti* diastereomers are stable enough as to be also observed as minor components of the equilibrium mixture in this case. Furthermore, the relative abundance of the different diastereomers of the 1,3-dimethylallyl system depends on the substitution pattern of the sp^3 carbon next to nitrogen in the oxazoline ring: if this carbon is a quaternary one, the *syn-anti* isomers predominate.[23c]

In the asymmetric allylic alkylation, the enantioselectivity of the process is determined by the regioselectivity of the attack of the nucleophile onto the palladium allylic intermediate. The higher ability a ligand has to differentiate the two allyl termini towards the incoming nucleophile, the higher selectivity will be induced. In this complex scenario of reaction pathways arising from the different precursors and attack positions, it is normally accepted that the major ongoing process arises from the ***exo-syn-syn*-16** precursor by attack of the nucleophile onto the allyl carbon *trans* to the phosphorus atom (Scheme 7).[1e,15a] The *R* configuration of the final product **15a** for the 1,3-diphenyl-substituted starting material **14a** (Scheme 4) would be in agreement with this assumption. In an analogous way, the attack of the nucleophile onto the allyl carbon *trans* to the phosphorus



Scheme 6.



Scheme 7.

substituent in precursor ***endo-syn*(P)-*anti*(N)-16** would lead to the major enantiomer of the substitution product **15a** as well. However, this reaction pathway is probably less important as the previous one, since the ***endo-syn*(P)-*anti*(N)-16** precursor is predicted to be much less abundant than the ***exo-syn-syn*** one.[24] In principle, the substitution product with the *R* configuration could also arise from attack of the nucleophile onto the allyl carbon *trans* to nitrogen in precursors ***endo-syn-syn*-16** and ***exo-anti*(P)-*syn*(N)-16** as well. However, it is normally accepted that these last two reaction pathways are irrelevant, as the allyl carbon *trans* to phosphorus is much more reactive towards nucleophiles (The chemical shift of the carbon atom *trans* to phosphorus was observed at 103.1 ppm in ^{13}C NMR for ***exo-syn-syn*-16** (R = Ph), whereas the chemical shift of the carbon atom *trans* to the nitrogen was observed at 69.1 ppm).

In order to understand the reversal in the sign of the enantioselection when moving from the 1,3-diphenylallyl to the 1,3-dimethylallyl substrate, we have performed and report here the results of a theoretical study on the relevant *syn:anti* isomers of the π-allylpalladium complexes of phosphinooxazoline **12a** (**16aMe** and **16aPh**). A two-layer ONIOM approach has been used for these studies,[25] with the partitioning shown in Figure 2. The high-level layer was treated at the highest, B3LYP/LanL2DZ level. The rest of the molecule was included into the low-level layer and treated at the semi-empirical AM1 level. Therefore, the two-layer ONIOM approach used in the present studies is denoted as ONIOM (B3LYP/LanL2DZ: AM1). The considered geometries were optimized with respect to all geometrical parameters, and the ONIOM total energy was computed. All calculations were performed without symmetry constraints using the Gaussian 03 program.[26]

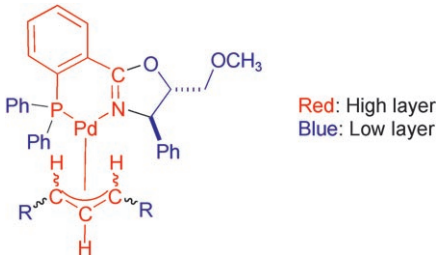


Figure 2. Molecular partition for ONIOM calculations.

The *syn-syn* and the two possible *syn-anti* diastereomers were calculated for both *exo* and *endo* arrangements of **16aMe** and **16aPh**.[27] Results on ONIOM total energy and relative energy have been summarized in Table 7.

The molecular structures of the minimal energy isomers of **16aPh** and **16aMe** are shown in Figure 3 along with some key atomic distances. From the

Table 7. ONIOM total energy (in atomic units) and relative energy (in kcal·mol^{-1}) of the relevant stereoisomers of **16aPh** and **16aMe**.

	16aPh (1,3-Diphenylallyl)		**16aMe** (1,3-Dimethylallyl)	
	ONIOM Total Energy [a.u.]	Rel. Energy [kcal·mol^{-1}]	ONIOM Total Energy [a.u.]	Rel. Energy [kcal·mol^{-1}]
***endo-anti*(P)-*syn*(N)**[a]	−576.5771334	3.04	−576.6357478	3.13
***endo-syn*(P)-*anti*(N)**	−576.5670563	9.36	−576.6285414	7.65
endo-syn-syn	−576.5793477	1.65	−576.6310965	6.05
***exo-anti*(P)-*syn*(N)**	−576.5706163	7.13	−576.6312656	5.94
***exo-syn*(P)-*anti*(N)**	−576.5738638	5.09	−576.6407325	0.00
exo-syn-syn	−576.5819787	0.00	-576.6336009	4.48

[a] This denotes that the substituent in the allyl terminus proximal to P is in *anti* arrangement and the substituent in the allyl terminus proximal to N is *syn*.

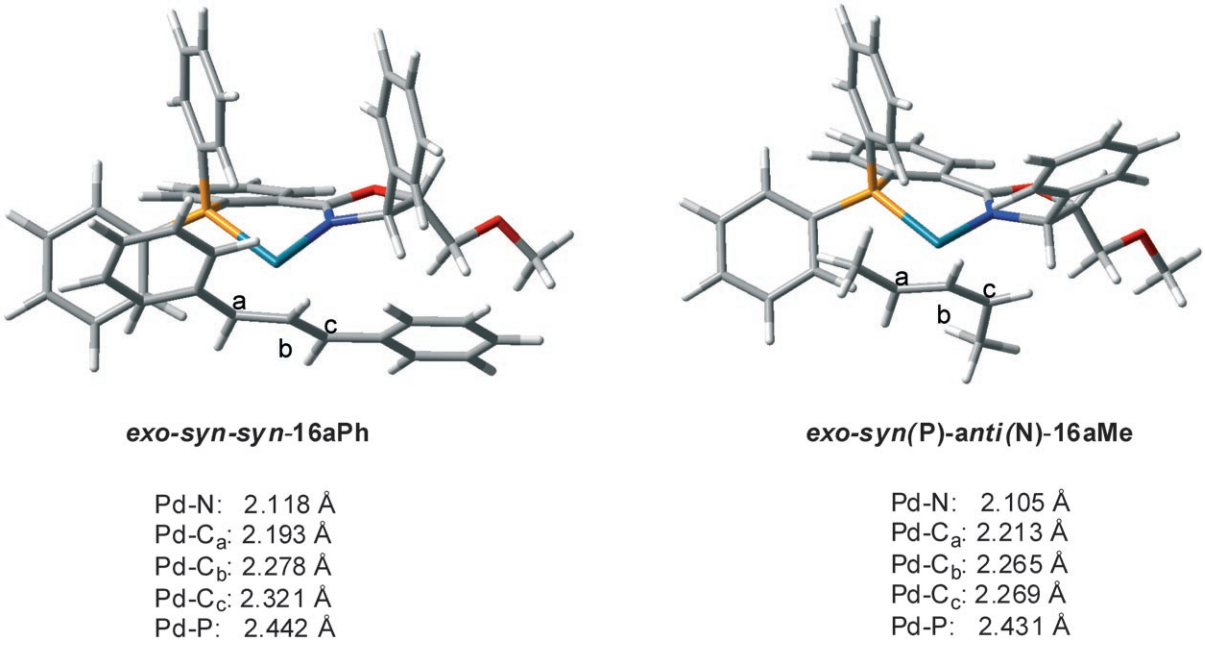


Figure 3. ONIOM optimized molecular structures of the minimal energy stereoisomers of **16aPh** and **16aMe**.

methodological point of view, it is important to note that the optimized distances show a good overall agreement with those found in the crystal structure of **13a** (see Table 3), only the Pd-P distance in the π-allyl complexes being slightly overestimated by the calculations.

With respect to the stereochemical outcome of the reactions, and assuming a reactant-like character of the transition states for the malonate attack to the cationic complexes **16a**, the energetic ordering of the different stereoisomers and the well-based[1e,15a] assumption that the nucleophilic attack will take place at the allyl terminus *trans* to phosphorus dictate the stereochemistry of the reaction product.

Very interestingly, the calculations predict that the alkylation of 1,3-diphenylallyl acetate will take place through intermediate ***exo-syn-syn*-16aPh** and will lead to an *R* product, as experimentally observed. In the same manner, the calculations predict that the alkylation of 1,3-dimethylallyl acetate will take place through intermediate ***exo-syn*(P)-*anti*(N)-16aMe** and will lead to an *S* product, as experimentally observed. Thus, the ONIOM calculations provide an explanation for the reversal of enantioselectivity in the alkylations of 1,3-diphenylallyl and 1,3-dimethylallyl acetate with the same catalytic system based on the nature of the most stable π-allylpalladium intermediates containing these systems. The stability of the different stereoisomers contributing to the description of these intermediates appears to be importantly controlled by the size of the 1,3-substituents in the allyl system.[28]

Noteworthy, the ONIOM calculations provide also a clue for the understanding of the different reactivity recorded with the 1,3-diphenylallyl and 1,3-dimethylallyl substrates. Taking the 1,3-diphenylallyl system (**16aPh**) as a reference (see Figure 3), a comparison of the distance between palladium and the carbon atom *trans* to phosphorus (Pd–C_c) in the *exo-syn-syn* stereoisomer with that found in the minimal energy stereoisomer of **16aMe** (2.321 Å *vs.* 2.269 Å) tends to indicate that substrate **14a** should exhibit a higher reactivity than **14d**.

Conclusions

In summary, the synthesis of a family of enantiopure modular phosphinooxazolines, containing a *trans*-4-phenyl-5-alkoxymethyl-disubstituted oxazoline ring and arising from purely synthetic, yet enantiopure precursors has been achieved, and their π-allylpalladium complexes have been evaluated as ligands in the asymmetric allylic alkylation reaction. From a practical point of view, we have been able to identify a phosphinooxazoline ligand (**12a**) that efficiently controls the enantioselectivity of the alkylation of allylic substrates over a very broad range of temperatures, thus allowing performing the reaction in extremely short times (minutes). From a more general perspective, the presence of an additional substituent at C-5 in the oxazoline ring leads to improved catalytic characteristics in the phosphinooxazoline ligands with respect to those bearing a phenyl substituent at C-4, but lacking the alkoxymethyl substituent at C-5, and this could be related to conformational control of the phenyl group by the alkoxymethyl substituent at the level of the reactive intermediate. The remarkably good performance of the catalysts makes them attractive for future applications. In view of immobilization, the results of the benchmark-guided structure optimization suggest that linear, non-bulky linkers should lead to minimal deterioration of catalytic properties in polymer-supported phosphinooxazolines **12**.

Experimental Section

General remarks about the experimental section can be found in the Supporting Information.

Microwave Assisted Epoxide Ring Opening with Aqueous Ammonia; Synthesis of Amino Alcohols 8a-e; General Procedure

The corresponding epoxide (1.0 mmol), 30% aqueous NH_3 (50 mmol), $LiClO_4$ (1 mmol) and of isopropyl alcohol (5 mL) if required were irradiated at 125 °C for the period of time indicated in Table 1. The mixture was left to reach room temperature and the solvent was removed under vacuum. The raw material was dissolved in CH_2Cl_2 (5 mL) and washed with water (3×5 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The corresponding amino alcohols **8a–e** were used in the next step without further purification.

Epoxide Ring Opening with Aqueous Ammonia under Thermal Conditions; Synthesis of Amino Alcohols 8a–e; General Procedure

The corresponding epoxide (1.0 mmol), 30% aqueous NH_3 (50 mmol), $LiClO_4$ (1 mmol) and isopropyl alcohol (5 mL) if required were heated in a sealed pressure at 100 °C for the period of time indicated in Table 1. The mixture was left to reach room temperature and the solvent was removed under reduced pressure. The raw material was dissolved in CH_2Cl_2 (5 mL) and washed with water (3×5 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed at reduced pressure. The corresponding amino alcohols **8a–e** were used in the next step without further purification.

Synthesis of (2-Fluoro)phenyl Hydroxy Amides 9a-e; General Procedure

Et_3N (1.95 mmol) was added under Ar to a solution of the corresponding amino alcohol **8a–e** (1.0 mmol) in anhydrous THF (1.5 mL) and the mixture was cooled at 0 °C. A solution of 2-fluorobenzoyl chloride (0.95 mmol) in anhydrous THF (1.3 mL) was slowly added to the previous solution. The mixture was left to reach room temperature and further stirred for two hours. The solvents were removed under vacuum. The raw material was diluted with CH_2Cl_2 (5 mL) and washed with brine (3×5 mL). The organic phase was dried over anhydrous Na_2SO_4, the drying agent was filtered off and the solvent removed under reduced pressure. The raw material was purified by chromatography over SiO_2 eluting with a mixture of hexanes/AcOEt of increasing polarity: from 100:0 to 60:40.

See Supporting Information for the physical and spectroscopical data of compounds **9a–e**.

As a representative example, **2-fluoro-*N*-[(1*R*,2*R*)-2-hydroxy-3-methoxy-1-phenylpropyl]-benzamide (9a):** $[\alpha]_D^{23}$: +32.9 (*c* 0.74 in $CHCl_3$); ^{1}H NMR: δ = 8.22 (bs, 1H, NH), 8.08 (dt, J = 7.9, 1.9 Hz, 1H), 7.50–7.10 (m, 8H), 5.45 (ddd, J = 8.4, 4.8, 2.4 Hz, 1H), 4.14–4.07 (m, 1H), 3.45 (dd, J = 9.5, 3.3 Hz, 1H), 3.38 (s, 3H), 3.28 (dd, J = 9.9, 5.1 Hz, 1H), 2.58 (d, J = 6.6 Hz, 1H); ^{13}C NMR: δ = 162.8 (C), 160.7 (d, $J_{C,F}$ = 246.0 Hz, C), 138.5 (C), 133.2 (d, $J_{C,F}$ = 9.6 Hz, CH), 132.1 (d, $J_{C,F}$ = 1.8 Hz, CH), 128.6 (CH), 127.6 (CH), 127.1 (CH), 124.7 (d, $J_{C,F}$ = 3.2 Hz, CH), 120.9 (d, $J_{C,F}$ = 11.0 Hz, C), 115.9 (d, $J_{C,F}$ = 24.5 Hz, CH), 73.4 (CH_2), 72.1 (CH), 59.2 (CH_3), 57.1 (CHNH); IR (film): ν = 3340, 1638, 1615, 1534, 1482, 1453, 1100, 754, 702 cm^{-1}; MS (CI, NH_3): m/z = 304 ($C_{17}H_{19}NO_3F{\cdot}H^+$, 100); HRMS (CI): m/z = 304.1371, calcd. for $C_{17}H_{19}NO_3F{\cdot}H^+$: 304.1349.

Synthesis of (2-Fluoro)phenyloxazolines 11a–e; General Procedure

Methanesulfonyl chloride (1.1 mmol) was slowly added to a solution of compounds **9a–e** (1.0 mmol) and Et_3N (2.2 mmol) in CH_2Cl_2 (8.2 mL) under an argon atmosphere

at 0 °C. The mixture was left to reach room temperature and further stirred for two hours. This mixture was added over a saturated aqueous solution of NH_4Cl (9 mL), the two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×6 mL). The organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4. The drying agent was filtered off and solvent removed under reduced pressure. This raw material was added to a 5% solution of KOH in MeOH (9 mL, 2.0 mmol), and the mixture was stirred 15 h at room temperature. The reaction was quenched with water (5 mL) and extracted with CH_2Cl_2 (3× 5 mL). The organic phases were dried over anhydrous Na_2SO_4. The drying agent was filtered off and solvent removed under reduced pressure. The purification of the products **11a–e** was carried by flash column chromatography.

See Supporting Information for the physical and spectroscopical data of compounds **11a–e**.

As a representative example, **(4*R*,5*S*)-2-(2-fluorophenyl)-5-methoxymethyl-4-phenyl-4,5-dihydrooxazole (11a):** $[\alpha]_D^{23}$: +47.6 (*c* 0.68 in $CHCl_3$); ^{1}H NMR: δ=8.04 (ddd, *J*=8.0, 1.6, 1.6 Hz, 1H), 7.55–7.13 (m, 8H), 5.17 (d, *J*=7.6 Hz, 1H), 4.66 (ddd, *J*=7.6, 4.7, 4.7 Hz, 1H), 3.73–3.71 (m, 2H), 3.47 (s, 3H); ^{13}C NMR: δ=161.2 (d, $J_{C,F}$=257.0 Hz, C), 160.8 (d, $J_{C,F}$=5.4 Hz, C), 141.6 (C), 133.0 (d, $J_{C,F}$=8.6 Hz, CH), 131.2 (d, $J_{C,F}$=1.3 Hz, CH), 128.6 (CH), 127.6 (CH), 126.6 (CH), 123.8 (d, $J_{C,F}$=4.1 Hz, CH), 116.6 (d, $J_{C,F}$=21.0 Hz, CH), 115.8 (d, $J_{C,F}$=10.4 Hz, C), 85.6 (CH), 73.5 (CH_2), 72.3 (CH), 59.5 (CH_3); IR (film): ν=1652, 1497, 1457, 1055, 764, 700 cm^{-1}; MS (CI, NH_3): *m/z*=304 (M^++18, 2%), 286 (M^++1, 100%); HRMS (CI): *m/z*=286.1241, calcd. for $C_{17}H_{17}NO_2F$ (M^++1): 286.1243.

Synthesis of the Phosphinooxazoline Ligands 12a–e; General Procedure

A solution of Ph_2PK (1.45 mmol, 2.8 mL of 0.5 M solution in THF) was slowly added under argon at −78 °C *via* cannula to an oven-dried Schlenk flask which contained the corresponding fluorooxazoline **11a–e** (1.0 mmol) in THF (2 mL). The temperature was allowed to reach −20 °C. The reaction mixture was further stirred for 2 h at this temperature, allowed then to reach room temperature, further stirred for 12 h at this temperature, quenched with $Na_2SO_4{\cdot}10H_2O$ in order to hydrolyze the excess of diphosphine, and filtered through a short SiO_2 pad eluting with CH_2Cl_2. The residue after removing the solvents was further purified by column chromatography over SiO_2 under argon. SiO_2 and the solvents which were involved in the chromotagraphic purifications were previously deoxygenated either by flushing or bubbling argon. Compounds **12** were not fully characterized (only ^{1}H and ^{31}P NMR were recorded, see Supporting Information) and were immediately transformed into the corresponding palladium complexes **13**.

Synthesis of the Phosphinooxazoline Allylpalladium Complexes 13a–e. General Procedure

A solution of compound **12a–e** (1.0 mmol) in deoxygenated ethanol (2 mL) was added *via* cannula to a Schlenk flask which contained a solution of $[Pd(C_3H_5)Cl]_2$ (0.53 mmol) in ethanol (5 mL). The reaction mixture was stirred 1 hour under argon at room temperature, NH_4PF_6 (1.02 mmol) was added. The resulting solution was further stirred for 14 h and allowed to stand at −20 °C for several hours. The palladium complexes precipitated were filtered off, washed with cold ethanol (3 mL) and dried under vacuum.

See Supporting Information for the physical and spectroscopical data of compounds **13a–e**.

As a representative example, **(η^3-allyl)[(4*R*,5*S*)-5-methoxymethyl-4-phenyl-2-(2-diphenyl-phosphinophenyl)-4,5-dihydrooxazol]palladium(II) hexafluorophosphate (13a):** $[\alpha]_D^{23}$: −70.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR: δ=8.31 (ddd, *J*=8.0, 4.4,1.2 Hz, 2H), 7.71–7.06 (m, 32H), 4.63 (bs, 2), 3.83–3.67 (m, 5H); *endo*: 6.96 (d, *J*=7.3 Hz, 2H), 5.73 (tt, *J*=13.0, 7.0 Hz, 1H), 5.34 (d, *J*=7.5 Hz, 1H), 4.60 (bs, 1H), 3.39 (s, 3H), 3.22 (d, *J*=6.3 Hz, 1H), 2.74 (d, *J*=11.0 Hz, 1H), 2.61 (d, *J*=12.5 Hz, 1H); *exo*: 6.92 (d, *J*=7.5 Hz, 2H), 5.38 (d, *J*=7.5 Hz, 1H), 5.15 (tt, *J*=13.3, 6.7 Hz, 1H,), 4.22 (bs, 1H), 3.38 (s, 3H), 3.31 (d, *J*=6.3 Hz, 1H), 2.78 (t, *J*=12.0 Hz, 1H); ^{13}C NMR: δ=134.4 (CH), 134.3 (CH), 133.7 (CH), 133.6 (CH), 133.5 (CH), 133.4 (CH), 133.0 (CH), 132.2 (CH), 132.1 (CH), 132.1 (CH), 129.9 (CH), 129.8 (CH), 129.7 (CH), 129.6 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 128.9 (CH), 126.9 (CH), 87.5 (CH), 76. (CH), 72.2 (CH_2), 59.5 (CH_3); *endo*: 165.2 (CN), 139.3 (C), 121.2 (CH), 79.2 (d, *J*=29.0 Hz CH_2), 57.2 (CH_2); *exo*: 165.2 (CN), 139.1 (C, Ph), 121.3 (CH), 80.9 (d, *J*=30.3 Hz CH_2), 56.2 (CH_2); ^{31}P NMR: δ=25.0 (s, PPh_2 *exo*), 24.5 (s, PPh_2 *endo*:), −141.2 (h, *J*=712.5 Hz, PF_6); IR (KBr): ν=3064, 2933, 1627, 1482, 1437, 1121, 1100, 839, 731, 698 cm^{-1}; MS (FAB): *m/z*=598 (M^+-PF_6, 100%); anal. calcd. for $C_{32}H_{31}NO_2PPdPF_6$: C 51.66, H 4.20, N 1.88; found: C 51.17, H 4.30, N 1.96.

(η^3-1,3-Diphenylallyl)[(4*R*,5*S*)-5-methoxymethyl-4-phenyl-2-(2-diphenylphosphinophenyl)-4,5-dihydrooxazol]palladium(II) Hexafluorophosphate (16)

Following the general method from ligand **12a** (0.06 g, 0.13 mmol), complex $[Pd(C_3H_5)(C_6H_5)_2Cl]_2$ (0.047 g, 0.07 mmol) and NH_4PF_6 (0.033 g, 0.2 mmol), compound **16** was obtained after filtration as a yellow solid; yield: 0.060 g (0.06 mmol, 50%). $[\alpha]_D^{23}$: −325.3 (*c* 0.34, $CHCl_3$); ^{1}H NMR: δ=7.70–6.60 (m, 56H), 4.34–4.31 (m, 2H); *endo*: 8.22 (ddd, *J*=8.0, 4.2, 1.0 Hz, 1H), 6.53–6.48 (m, 1H), 4.78 (t, *J*=11.2 Hz, 1H), 4.68 (d, *J*=12 Hz, 1H), 4.46 (d, *J*=5.5 Hz, 1H), 3.29–3.20 (m, 2H), 3.22 (s, 3H); *exo*: 8.26 (ddd, *J*=8.0, 4.0, 1.2 Hz, 1H), 6.29 (dd, *J*=14.0, 10.5 Hz, 1H), 6.20 (d, *J*=8.5 Hz, 1H), 4.26 (d, *J*=11.0 Hz, 1H), 4.23 (d, *J*=5.0 Hz, 1H), 3.53 (dd, *J*=11.0, 5.2 Hz, 1H), 3.50 (dd, *J*=11.0, 4.5 Hz, 1H), 3.47 (s, 3H); ^{13}C NMR: δ=165.1 (C), 139.2 (C), 138.9 (C), 137.9 (C), 135.8 (C), 135.3 (CH), 133.4 (CH), 133.2 (CH), 133.0 (CH), 132.1 (CH), 131.6 (CH), 131.2 (CH), 129.6 (CH), 129.3 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 127.8 (CH), 127.1 (CH), 126.8 (CH), 126.7 (CH), 125.9 (CH), 125.7 (CH), 86.1 (CH), 72.3 (CH_2), 59.6 (CH_3); *endo*: 111.2 (CH), 95.7 (CH), 74.8 (CH), 71.2 (CH); *exo*: 110.7 (d, $J_{C,P}$=5.2 Hz, CH), 103.1 (d, $J_{C,P}$=22.1 Hz, CH), 70.2 (CH), 69.1 (d, $J_{C,P}$=7.0 Hz, CH); ^{31}P NMR: δ=22.5 (s, PPh_2 *endo*), 17.7 (s, PPh_2 *exo*), −140.6 (h, *J*=713.2 Hz, PF_6); IR (KBr): ν=3062, 2929, 1628, 1491, 1437, 1119, 1100, 837, 735, 695 cm^{-1}; MS (FAB): *m/z*=750 (M^+-PF_6, 100%).

General Procedure for Palladium-Catalyzed Allylic Alkylation; Thermal Conditions

Allylic alkylation of 14a: A solution of **14a** (0,25 g, 1.0 mmol) in CH_2Cl_2 (2 mL) was added at room temperature to a solution **13a–e** (0.02 mmol) in CH_2Cl_2 (2 mL) under argon. Dimethyl malonate (0.396 g, 0.350 mL, 3.0 mmol) and BSA (0.610 g, 0.740 mL, 3.0 mmol) were syringed into the above solution and a catalytic amount of KOAc (0.004 g, 0.04 mmol) was lastly added under argon. The mixture was stirred at room temperature for 48 h (unless stated otherwise stated). The reaction mixture was then diluted with diethyl ether, filtered over Celite, and washed with water (4× 10 mL). The organic phase was dried over anhydrous Na_2SO_4. The drying agent was filtered off and the solvent was removed under reduced pressure. The crude mixture was filtered through a short SiO_2 pad eluting with ethyl acetate. The conversion of the reaction was measured after removing the solvent by ^{1}H NMR of the crude mixture. Dimethyl malonate was mostly removed under vacuum (130 °C, 0.4 mbar) and the enantiomeric excesses were determined from the residue by HPLC on a OD-H column (0.5 mL min^{-1} *n*-hexane/isopropyl alcohol, 99:1): (*R*)-**15a** Rt = 23 min, (*S*)-**15a** Rt = 25 min.

Allylic alkylation of 14b: The procedure was analogous to the one described for **14a** but using **13a** as the catalyst, **14b** as starting material, and DMF or THF as solvents at the temperatures indicated in Table 6. The enantiomeric excesses were determined by HPLC on a AD-H column (0.3 mL min^{-1} *n*-hexane/isopropyl alcohol, 97:3): (*R*)-**15b** Rt = 49.4 min, (*S*)-**15b** Rt = 51.6 min.

Allylic alkylation of 14d: The procedure was analogous to the one described for **14a** but using **13a** as catalyst and **14d** as starting material, and CH_2Cl_2 at room temperature. The enantiomeric excesses were determined by GC on a FS-cyclodex-β-Dex column (80 °C): (*R*)-**15d** Rt = 68.0 min, (*S*)-**15d** Rt = 69.2 min.

Allylic alkylation of 14e: The procedure was analogous to the one described for **14a** but using **13a** as catalyst and **14e** as starting material, and CH_2Cl_2 at room temperature. The enantiomeric excesses were determined by GC on a FS-cyclodex-β-Dex column (10 min at 90 °C, 1 °C min^{-1} up to 130 °C, 15 min at 130 °C, 5 °C min^{-1} up to 150 °C, 15 min at 50 °C): (*S*)-**15e** Rt = 57.0 min, (*R*)-**15e** Rt = 57.4 min.

Allylic alkylation of 14f: The procedure was analogous to the one described for **14a** but using **13a** as the catalyst, **14f** as starting material, and CH_2Cl_2 at room temperature. The enantiomeric excesses were determined by HPLC on a OJ-H column (0.7 mL min^{-1} *n*-hexane/isopropyl alcohol 97:3): (*S*)-**15f** Rt = 26.7 min, (*R*)-**15f** Rt = 28.4 min.

Allylic alkylation of 14h: The procedure was analogous to the one described for **14a** but using **13a** as the catalyst, **14h** as starting material, and THF as solvent at the temperatures indicated in Table 6. The enantiomeric excesses were determined by HPLC on a AD-H column (0.8 mL min^{-1} *n*-hexane/isopropyl alcohol 85:15): (*R*)-**15h** Rt = 19.3 min, (*S*)-**15h** Rt = 29.5 min.

General Procedure for Palladium-Catalyzed Allylic Alkylation; Microwave-Assisted Conditions

The reaction mixture for racemic allylic acetates **14a**, **14b**, **14c**, **14d**, **14e, 14g**, and **14h** using **13a** as the catalyst was prepared in the appropriated solvent (see Table 6) in an analogous way as described before for the thermal conditions. The reaction mixture was heated in a microwave reactor for the reaction time and at the temperature indicated in Table 6. Enantiomeric excesses for **15a**, **15b**, **15d**, **15e** and **15h** were measured as described before. The enantiomeric excesses for **15c** and **15g** were determined by NMR using the Eu(hcf)$_3$ chiral chemical shift reagent. The spectra were of solutuins in $CDCl_3$ were taken using 6 equivalents of **15c** and **15g** with respect to one equivalent of the Eu(hcf)$_3$. The enantiomeric excess was measured by integrating suitable signals from the two diastereomeric complexes.

The configurations of the final products were established by comparison either with with either reported chromatographic elution orders or optical rotations: (+)-(*R*)-**15a**;[20] (+)-(*R*)-**15b**;[29] (+)-(*R*)-**15c**;[29] (−)-(*S*)-**15d**;[20] (−)-(*S*)-**15e**;[20] **15f** (Chiralcel OJ);[30] (*S*)-**15f** Rt = 24.9 min, (*R*)-**15f** Rt = 27.7 min and (−)-(*S*)-**15g**.[31]

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comparison of selected ^{1}H-, ^{13}C- and ^{31}P NMR data with reported values in the literature. The second most abundant one was assigned as the ***endo-syn-syn*-16** by the same arguments as before. No further assignments were possible due to heavy signal overlapping and low intensity of the signals of the rest of the isomers.

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