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Aminophosphine–oxazoline and phosphoramidite–oxazoline ligands and their application in asymmetric catalysis

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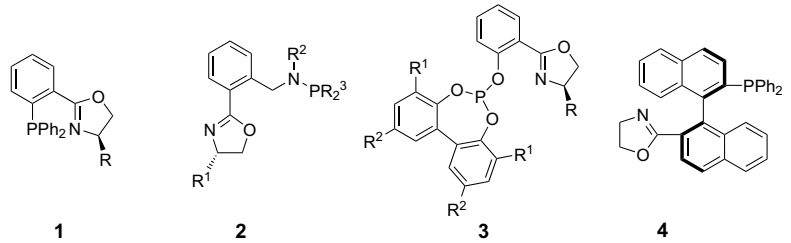
Abstract—The synthesis of a novel series of aminophosphine–oxazoline and phosphoramidite–oxazoline is described. The efficacy of these aminophosphine–oxazoline ligands was investigated in the palladium catalysed asymmetric allylic alkylation of 1,3-diphenyl-prop-2-enyl acetate leading to a maximum of 38% ee at 64% conversion. Phosphoramidite–oxazoline ligands, however, gave ees of up to 87% at 71% conversion in the same reaction and also proved to be effective in the palladium catalysed asymmetric Suzuki coupling between 2-methylnaphthylboronic acid and 1-bromonaphthalene, leading to a maximum of 46% ee in 54% isolated yield at room temperature.

1. Introduction

In recent years, it has been shown that sterically and electronically unsymmetrical ligands are very efficient in many transition metal mediated asymmetric transformations.[1,2] In particular, phosphine–oxazoline ligands represent a versatile and successful class. For example, the PHOX-type ligands **1**, which were reported independently by Pfaltz,[3] Helmchen[4] and Williams,[5] give excellent conversions and enantioselection in allylic substitution reactions, intermolecular Heck reaction, iridium catalysed hydrogenations and enantioselective Diels–Alder reactions, among others.[6–8] Following the success of these phosphino-oxazoline ligands, many groups have shown that phosphite– and phosphinite–oxazoline ligands can be equally efficient in a wide range of reactions, exhibiting excellent conversions and enantioselection.[9–20] Research on aminophosphine–oxazoline[21] and phosphoramidite–oxazoline ligands, however, has hardly been reported, while ligands containing an aminophosphine[22–25] or a phosphoramidite[26] sub-unit have been highly successful in many catalytic applications.



1 **2** **3** **4**

Interested by this relatively unexplored class of ligands, we herein wish to report the synthesis of heterodonor aminophosphine–oxazoline and phosphoramidite–oxazoline ligands of general formula **2** and the preliminary evaluation of their corresponding palladium complexes as catalysts for asymmetric allylic alkylation and Suzuki couplings. Compared to the PHOX ligands **1**, which form a 6-membered chelate, and Claver's phosphite–oxazoline ligands **3**,[27] which form a 7-membered chelate, PN-oxazoline ligands **2** form an 8-membered chelate, similar to Hayashi's and Ikeda's binaphthyl-based oxazoline–phosphine ligands

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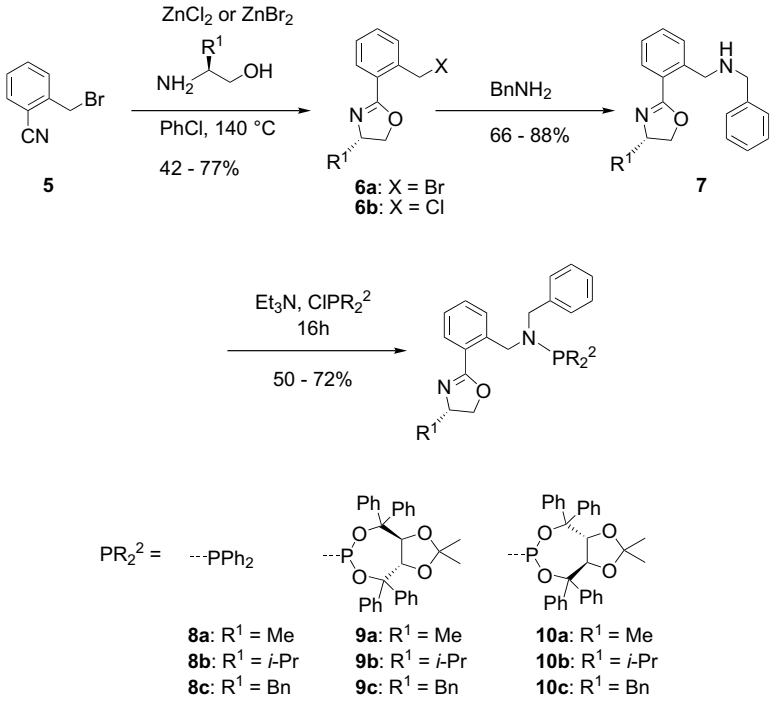


Scheme 1. Synthesis of ligands **8**–**10**.

4,[28,29] which we hoped to be beneficial in obtaining high enantioselectivities by creating a chiral pocket, that is, more confined than ligands with a smaller chelate ring size. The ligands were prepared in a modular way, which allows facile independent structural variations at different parts of the molecule during each step of synthesis.

Thus, aminophosphine–oxazoline ligands **8** and phosphoramidite–oxazoline ligands **9** and **10** were readily prepared starting from commercially available α-bromo-*o*-tolunitrile and the appropriate enantiopure aminoalcohols in a $ZnCl_2$ catalysed cyclocondensation (Scheme 1). During this reaction we observed partial exchange of the α-bromo-group for an α-chloro-group resulting in the formation of **6b**. To circumvent the formation of this side product, $ZnBr_2$ instead of $ZnCl_2$ can be used as catalyst, although this only worked well for the formation of **6a** (R = *i*-Pr, Bn). For ligand **6a** (R = Me), significant amounts of undetermined side products were formed when $ZnBr_2$ was used. Although mixtures of **6a** and **6b** can be separated by column chromatography on silica, the subsequent nucleophilic substitution with benzylamine operates well with this mixture to yield secondary amine **7**. Subsequent reaction of **7** with chlorodiphenylphosphine or with in situ prepared TADDOL-derived phosphorchloridites[30] in the presence of Et_3N gave ligand classes **8** and **9**–**10**, respectively. Although these ligands are sensitive towards hydrolysis, especially the members of ligand class **8**, we found that they can be purified by quick column chromatography on silica using solvents as received without noticeable loss of yield.

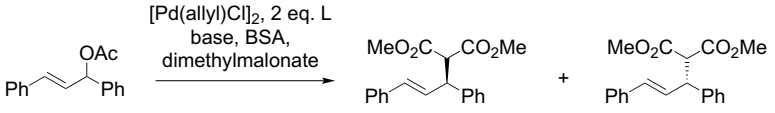
1.1. Asymmetric allylic alkylation

The formation of asymmetric carbon–carbon linkages catalysed by palladium complexes of chiral ligands is a useful way of assessing the ability of the ligand to induce enantioselectivity.[31,32] One of the most typically used systems involves nucleophilic attack of the dimethylmalonate anion on 1,3-diphenylprop-2-enyl acetate **11**. This reaction has been used extensively by many groups for testing the potential of new chiral ligands, because of its high synthetic utility and a detailed understanding of its mechanism. Palladium complexes of homobidentate ligands have proven to be successful in this transformation by creating a chiral environment that influences the orientation of the reactants sufficiently to cause one enantiomer of the product to predominate. Heterobidentate ligands, such as phosphine–oxazolines **1**, affect the stereochemical outcome of the bond forming process by the desymmetrisation of the substrate allyl through electronic effects. The incoming nucleophile then reacts preferentially at the more electrophilic end of the substrate, giving rise to the observed enantioselectivity.[33–38]

The enantio-differentiating abilities of **8**–**10** were initially assessed in the palladium catalysed allylic alkylation of 1,3-diphenylprop-2-enyl acetate using in situ generated dimethylmalonate anion as the nucleophile. The results obtained with ligands **8a**–**10c** are summarised in Table 1.

During preliminary work we investigated a range of solvents, including coordinating solvents such as diethyl ether and tetrahydrofuran, but these afforded low levels of enantioselectivities (in the range up to 25% ee). However, dichloromethane proved to be our optimal solvent and of the aminophosphine–oxazoline ligands **8** tested, ligand **8b** afforded the highest ee of 38% in a good yield of 64%. Unfortunately, the levels of enantioselectivities observed with ligand **8c** were poor (up to 10% ee). The nature of the base had a large impact on enantioselectivity; higher

Table 1. Pd-Catalysed allylic alkylation with **8a**–**10c**[a]



(±)-**11** (*S*)-**12** (*R*)-**12**

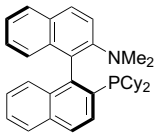
Entry	Ligand	Base	Solvent	Conversion[b] (%)	ee[c] (%)
1	**8a**	KOAc	CH_2Cl_2	59	25 (*R*)
2	**8b**	KOAc[d]	CH_2Cl_2	11	38 (*R*)
3	**8b**	LiOAc	CH_2Cl_2	30	6 (*R*)
4	**8b**	NaOAc	CH_2Cl_2	76	17 (*R*)
5	**8b**	KOAc	CH_2Cl_2	68	29 (*R*)
6	**8b**	Cs_2CO_3	CH_2Cl_2	64	38 (*R*)
7	**8c**	KOAc	CH_2Cl_2	87	4 (*S*)
8	**9a**	KOAc	CH_2Cl_2	22	64 (*R*)
9	**9b**	KOAc	CH_2Cl_2	86	73 (*R*)
10	**9c**	KOAc	CH_2Cl_2	68	78 (*R*)
11	**10a**	KOAc	CH_2Cl_2	71	87 (*S*)
12	**10b**	KOAc	CH_2Cl_2	46	81 (*S*)
13	**10c**	KOAc	CH_2Cl_2	41	88 (*S*)

[a] Reaction conditions: $[[Pd(allyl)(\mu\text{-}Cl)]_2] = 2.5$ mM in CH_2Cl_2, L/Pd = 1.1, substrate/Pd = 200, KOAc/Pd = 10, BSA/Pd = 300, dimethylmalonate/Pd = 300, $T = 20$ °C, $t = 48$ h.
[b] Conversion determined by ^{1}H NMR.
[c] Ee determined by Chiral HPLC (Chiralcel OD column). Specific rotations were compared to literature values.
[d] KOAc/Pd = 1.

ees were obtained with softer bases, whereas conversions were hardly affected (entries 3–6). Since KOAc is the most commonly applied base for allylic alkylation, we used this base for all our other experiments. However, we were pleased to determine that improved results could be obtained with TADDOL-based ligands **9** and **10** (entries 6–11). The configuration of the product was mainly determined by the configuration of the TADDOL-moiety: (+)-TADDOL derived ligands **9a**–c led to (*R*)-**12**, whereas (−)-TADDOL derived ligands **10a**–c resulted in (*S*)-**12**. Consistently higher enantiopurities of **12** were obtained using **10a**–**c** compared to **9a**–**c**, indicating that the (*S*)-configurations of the oxazoline-unit and (−)-TADDOL-unit are matched.

1.2. Asymmetric Suzuki reaction

In recent years, much research has been devoted to the synthesis of axially chiral biaryls. Many useful methods use either chiral auxiliaries or start from chiral materials.[39] The asymmetric Suzuki coupling is a powerful method for the synthesis of axially chiral biaryls starting from achiral materials and using mild methods, additionally the Suzuki coupling shows high functional group tolerance. Especially successful is the procedure by Buchwald, who used phosphinamine binaphthyl ligands **13** for the preparation of functionalised biaryls in high conversion and with high ees.[40] Cammidge also reported an asymmetric Suzuki protocol in a study that tested a range of chiral ligands, with the ferrocene-derived P,N ligand **14**, affording ees of up to 64% in 44% yield.[41] It is known that monodentate phosphoramidite ligands can effect the Suzuki coupling at room temperature in high yields and thus we became interested in the application of ligands **9** and **10** in this reaction.[42,43] As a model reaction we studied the coupling between 2-methylnaphthylboronic acid **15** with 1-bromonaphthalene **16** in DME/H_2O (10/1)[41,43] using various bases (Table 2). We did not test ligand class **8** under these reaction conditions in view of their potential instability under these reaction conditions.



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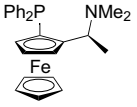

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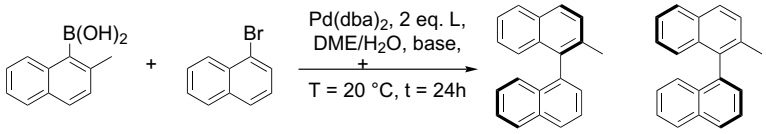
The nature of the base had a large impact both on conversion and ee. The influence between the different ligands was non-consistent, for example, for **9b** the best conversion and ee were obtained with Cs_2CO_3, while for **10b** the use of Cs_2CO_3 resulted in racemic product, whereas CsOH gave the best combination of both conversion and ee. Similarly, **9a** and **9c** and **10a** and **10c** were tested using different bases. While **9a** gave no or low ees in all cases (yield = 30–63%, ee = 0–17%), **10a** showed some promising results with $Ba(OH)_2$ as base (yield = 57%, ee = 34%). **9c** and **10c** gave low conversions independent of the applied base (yield = 0–36%, ee = 0–34%). The role of the base is still unclear although in the case of softer (larger) bases with Cs, and to a lesser extent with Ba, the complex is clearly less able to distinguish between different approaches of the boronic acid species.

Surprisingly, for all ligands (*R*)-2-methyl-1,1′-binaphthyl was formed preferentially suggesting that in this reaction,

Table 2. Pd-Catalysed asymmetric Suzuki coupling using ligands **9b** and **10b**[a]



15 **16** (*R*)-**17** (*S*)-**17**

Entry	Ligand	Base	Yield[b] (%)	ee[c] (%)
1	**9b**	KOH	30	38 (*R*)
2	**9b**	NaOH	25	36 (*R*)
3	**9b**	CsOH	16	37 (*R*)
4	**9b**	CsF	19	40 (*R*)
5	**9b**	Cs_2CO_3	54	46 (*R*)
6	**9b**	$Ba(OH)_2$	31	43 (*R*)
7	**10b**	KOH	45	35 (*R*)
8	**10b**	NaOH	43	34 (*R*)
9	**10b**	CsOH	61	33 (*R*)
10	**10b**	Cs_2CO_3	49	0
11	**10b**	$Ba(OH)_2$	25	18 (*R*)

[a] Reaction conditions: $[Pd(dba)_2] = 5$ mM in DME/H_2O (10:1), L/Pd = 2, 1-bromonaphthalene/Pd = 250, 2-methyl-1-naphthaleneboronic acid/Pd = 300, base/Pd = 500, $T = 20$ °C, $t = 24$ h.
[b] Isolated yield after column chromatography on silica.
[c] ees determined by Chiral HPLC (Chiralcel OJ column), optical rotations were compared to literature values.

the configuration of the oxazoline-unit determined the chirality of the product.

2. Conclusion

In conclusion, we have shown a facile synthesis of a new class of modular P–N ligands. The results obtained with phosphoramidite–oxazoline ligands **9** and **10** in asymmetric allylic alkylation and asymmetric Suzuki coupling show the potential of this type of ligands in asymmetric catalysis. Work is currently underway in order to fine-tune the ligand structure and its use in other asymmetric transformations and the results of these investigations will be reported in due time.

3. Experimental

3.1. General

All air- or water-sensitive reactions were performed using standard Schlenk techniques under a nitrogen atmosphere. THF and diethyl ether were distilled from sodium/benzophenone, toluene and dichloromethane were distilled from calcium hydride. Chlorodiphenylphosphine was distilled prior to use. All other solvents were of reagent grade and were used as received. Chemicals were purchased form Aldrich Chemical Co. Melting points were determined using a Gallenkamp melting point apparatus in open capillaries and are uncorrected. Optical rotation values were measured on a Perkin–Elmer 343 polarimeter. ^{1}H NMR spectra were obtained on a 300 MHz Varian-Unity spectrometer and a 500 MHz Varian-Unity spectrometer. ^{1}H–^{1}H COSY spectra were recorded on a 300 MHz Varian Unity spectrometer and a 500 MHz Varian-Unity spectrometer. ^{31}P and ^{13}C spectra were measured in ^{1}H decoupled mode. TMS was used as the external standard for ^{1}H and ^{13}C NMR and 85% H_3PO_4 in H_2O as an external standard for ^{31}P NMR. HPLC analysis was carried out on a Shimadzu LC-10AT$_{vp}$ machine and Shimadzu LC-2010A machine equipped with a UV–vis detector employing Chiralcel® OD and OJ columns from Diacel Chemical Industries.

3.2. General synthesis of 2-(2-bromomethylphenyl)-(4*S*)-4-*R*-4,5-dihydrooxazole (R = Me, *i*-Pr, Benzyl) 6a

To a mixture of 1.0 g of α-bromo-*o*-tolunitrile (5.2 mmol) and the appropriate (*S*)-2-aminoalcohol (5.2 mmol) in 8 mL of chlorobenzene was added 0.22 mL of a 1 M solution of $ZnCl_2$ in Et_2O (0.22 mmol) at 50 °C. Thereafter, the mixture was heated at 134 °C. After 24 h, the reaction mixture was diluted with 30 mL of CH_2Cl_2 and washed with a saturated solution of $NaHCO_3$ in water (3×20 mL). The organic layer was dried over Na_2SO_4 and subsequently concentrated in vacuo to yield either a white solid (R = Me, Bn) or a colourless oil (R = *i*-Pr) after purification by column chromatography on silica (pentane:ethylacetate 3:1). (Yield: 42–77%).

3.3. 2-(2-Bromomethylphenyl)-(4*S*)-4-methyl-4,5-dihydrooxazole 6a (R = Me)

Yield: 42% as an off-white solid; mp: 83–84 °C; $[\alpha]_D^{20} = +14.4$ (*c* 0.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 7.86$ (d, ^3J(H,H) = 7.2 Hz, 1H), 7.55 (m, 1H), 7.47 (m, 2H), 4.74 (m, 1H), 4.54 (d, ^2J(H,H) = 16.7 Hz, 1H), 4.41 (d, ^2J(H,H) = 16.6 Hz, 1H), 3.71–3.58 (m, 2H), 1.46 (d, ^3J(H,H) = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): $\delta = 168.5$ (s), 141.2 (s), 132.6 (s), 131.4 (s), 128.1 (s), 123.7 (s), 122.8 (s), 48.1 (s), 46.8 (s), 36.1 (s), 17.4 (s); IR (NaCl): $\nu = 3055$, 2978, 2933, 2875, 1664, 1470, 1454,

1409 cm^{-1}; HRMS (ES-I) Calcd for $C_{11}H_{13}NOBr$ (M+1) 254.0181. Found: 254.0192.

3.4. 2-(2-Bromomethylphenyl)-(4*S*)-4-isopropyl-4,5-dihydrooxazole 6a (R = *i*-Pr)

Yield: 77% as a colourless oil; $[\alpha]_D^{20} = -13.0$ (*c* 0.32, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 7.83$ (d, $^3J(H,H) = 7.2$ Hz, 1H), 7.54–7.46 (m, 1H), 7.46–7.38 (m, 2H), 4.56 (d, ($^2J(H,H) = 17.1$ Hz, 1H), 4.32 (d, $^2J(H,H) = 16.8$ Hz, 1H), 4.20 (td, $^3J(H,H) = 9.0$ Hz, $^3J(H,H) = 3.6$ Hz, 1H), 3.74 (dd, $^2J(H,H) = 11.4$ Hz, $^3J(H,H) = 3.6$ Hz, 1H), 3.67 (dd, $^2J(H,H) = 11.1$ Hz, $^3J(H,H) = 8.7$ Hz, 1H), 2.09 (m, 1H), 1.04 (d, $^3J(H,H) = 6.6$ Hz, 3H), 0.87 (d, $^3J(H,H) = 6.6$ Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 168.97$ (s), 141.16 (s), 132.21 (s), 131.29 (s), 127.85 (s), 123.69 (s), 122.64 (s), 58.28 (s), 47.22 (s), 34.11 (s), 30.15 (s), 19.88 (s), 19.63 (s); IR (NaCl): $\nu = 2966$, 2873, 1686, 1470, 1452, 1410, 1223, 737 cm^{-1}; HRMS (ES-I) calcd for $C_{13}H_{17}NOBr$ (M+1) 282.0494. Found: 282.0498.

3.5. 2-(2-Bromomethylphenyl)-(4*S*)-4-benzyl-4,5-dihydrooxazole 6a (R = Bn)

Yield: 73% as a white solid; mp: 78–79 °C; $[\alpha]_D^{20} = -45.8$ (*c* 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 7.86$ (d, $^3J(H,H) = 7.2$ Hz, 1H), 7.56–7.39 (m, 3H), 7.31–7.19 (m, 5H), 4.72 (m, 1H), 4.41 (d, $^2J(H,H) = 16.5$ Hz, 1H), 4.35 (d, $^2J(H,H) = 16.8$ Hz, 1H), 3.78 (dd, $^2J(H,H) = 10.8$ Hz, $^3J(H,H) = 7.2$ Hz, 1H), 3.72 (dd, $^2J(H,H) = 10.8$ Hz, $^3J(H,H) = 4.8$ Hz, 1H), 3.22 (dd, $^2J(H,H) = 14.1$ Hz, $^3J(H,H) = 8.1$ Hz, H), 3.15 (dd, $^2J(H,H) = 13.8$ Hz, $^3J(H,H) = 7.5$ Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 168.28$ (s), 140.863 (s), 136.48 (s), 132.04 (s), 130.95 (s), 128.36 (s), 128.27 (s), 127.50 (s), 126.43 (s), 123.19 (s), 122.22 (s), 54.51 (s), 48.10 (s), 37.03 (s), 33.80 (s); IR (NaCl): $\nu = 3058$, 3026, 2926, 1680, 1470, 1452, 1408, 1365, 1213, 737, 700 cm^{-1}; HRMS (ES-I) Calcd for $C_{17}H_{17}NOBr$ (M+1) 330.0484. Found: 330.0482.

3.6. General synthesis of 2-(*N*-benzyl-2-aminomethylphenyl)-(4*S*)-4-*R*-4,5-dihydrooxazole (R = Me, *i*-Pr, *t*-Bu, Benzyl) 7

Compound **6a** (8.5 mmol) was dissolved in 10 mL of benzylamine (9.8 g, 92 mmol) and both reactants were allowed to react for 16–96 h at 60 °C until full conversion of **6a** was observed by TLC and GC–MS. Thereafter, the product was purified by column chromatography on silica (ethylacetate:triethylamine 7:1) to yield a pale yellow oil. (Yield: 66–88%).

3.7. 2-(*N*-Benzyl-2-aminomethylphenyl)-(4*S*)-4-methyl-4,5-dihydrooxazole 7 (R = Me)

Yield: 66% as a pale yellow oil; $[\alpha]_D^{20} = +17$ (*c* 0.29, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 7.77$ (d, $^3J(H,H) = 7.5$ Hz, 1H), 7.46–7.26 (m, 3H), 7.25–7.09 (m, 5H), 4.58 (m, 1H), 4.20 (s, 1H), 3.76 (d, $^2J(H,H) = 13.5$ Hz, 1H), 3.66 (d, $^2J(H,H) = 13.2$ Hz, 1H), 2.73–2.71 (m, 2H), 1.56 (br s, 1H), 1.18 (d, $^3J(H,H) = 6.9$ Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 168.78$ (s), 141.41 (s), 140.25 (s), 133.11 (s), 131.11 (s), 128.32 (s), 128.11 (s), 127.92 (s), 126.91 (s), 123.61 (s), 122.73 (s), 53.37 (s), 52.46 (s), 46.59 (s), 45.56 (s), 17.06 (s); IR (NaCl): $\nu = 3273$, 2975, 2937, 2877, 1662, 1470, 1452, 1414, 1215, 1026, 746 cm^{-1}; HRMS (ES-I) Calcd for $C_{18}H_{21}N_2O$ (M+1) 281.1654. Found: 281.1664.

3.8. 2-(*N*-Benzyl-2-aminomethylphenyl)-(4*S*)-4-*i*-propyl-4,5-dihydrooxazole 7 (R = *i*-Pr)

Yield: 87% as a pale yellow oil; $[\alpha]_D^{20} = +2.1$ (*c* 0.54, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 7.81$ (d, $^3J(H,H) = 7.5$ Hz, 1H), 7.45–7.4 (m, 1H), 7.39–7.35 (m, 2H), 7.16–7.13 (m, 5H), 4.2–4.1 (m, 3H), 3.78 (d, $^2J(H,H) = 13.5$ Hz, 1H), 3.61 (d, $^2J(H,H) = 13.5$ Hz, 1H), 2.91 (dd, $^2J(H,H) = 12.6$ Hz, $^3J(H,H) = 3.9$ Hz, 1H), 2.73 (dd, $^2J(H,H) = 12.3$ Hz, $^3J(H,H) = 10.5$ Hz, 1H), 1.81 (m, 1H), 1.37 (br s, 1H), 0.95 (d, $^3J(H,H) = 6.6$ Hz, 3H), 0.78 (d, $^3J(H,H) = 6.9$ Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 169.54$ (s), 141.52 (s), 140.33 (s), 132.82 (s), 131.11 (s), 128.24 (s), 128.07 (s), 127.82 (s), 126.83 (s), 123.62 (s), 122.77 (s), 57.05 (s), 53.32 (s), 48.78 (s), 46.33 (s), 29.87 (s), 20.08 (s), 20.02 (s); IR (NaCl): $\nu = 3288$, 2962, 2929, 2873, 1678, 1470, 1452, 1411, 1213, 737 cm^{-1}; HRMS (ES-I) Calcd for $C_{20}H_{25}N_2O$ (M+1) 309.1967. Found: 309.1970.

3.9. 2-(*N*-Benzyl-2-aminomethylphenyl)-(4*S*)-4-benzyl-4,5-dihydrooxazole 7 (R = Bn)

Yield: 88% as a pale yellow oil; $[\alpha]_D^{20} = -17.2$ (*c* 0.31, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 7.83$ (d, $^3J(H,H) = 7.2$ Hz, 1H), 7.52–7.43 (m, 2H), 7.39 (d, $^3J(H,H) = 9$ Hz, 1H), 7.35–7.14 (m, 10H), 4.79 (m, 1H), 4.20 (s, 2H), 3.84 (d, $^2J(H,H) = 13.2$ Hz, 1H), 3.72 (d, $^2J(H,H) = 13.2$ Hz, 1H), 3.03–2.88 (m, 4H), 1.62 (br s, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 169.11$ (s), 141.43 (s), 140.15 (s), 137.86 (s), 132.95 (s), 131.12 (s), 128.80 (s), 128.55 (s), 128.33 (s), 128.15 (s), 127.86 (s), 126.50 (s), 123.63 (s), 122.65 (s), 53.44 (s), 52.87 (s), 50.59 (s), 46.99 (s), 37.50 (s); IR (NaCl): $\nu = 3305$, 3027, 2929, 2850, 1676, 1470, 1452, 1412, 1213, 735 cm^{-1}; HRMS (ES-I) Calcd for $C_{24}H_{25}N_2O$ (M+1) 357.1967. Found: 357.1964.

3.10. General synthesis of 2-(*N*-Benzyl-*N*-diphenylphosphino-2-aminomethylphenyl)-(4*S*)-4-*R*-4,5-dihydrooxazole (R = Me, *i*-Pr, *t*-Bu, Benzyl) 8

To 1.54 mmol of **7** in 15 mL of THF was added 0.26 mL of Et_3N (1.8 mmol, 1.2 equiv). Next 0.31 mL of chlorodiphenylphosphine (1.7 mmol, 1.1 equiv) was added dropwise at 0 °C, which immediately resulted in the formation of an $Et_3N{\cdot}HCl$ precipitate. The reaction mixture was allowed to react overnight. The salts were removed by filtration of the reaction mixture over $MgSO_4$, which was followed by the removal of the organics in vacuo. After column chromatography on silica (ethylacetate:pentane 1:3), the product was isolated as a white solid. (Yield: 50–60%).

3.11. 2-(*N*-Benzyl-*N*-diphenylphosphino-2-aminomethylphenyl)-(4*S*)-4-methyl-4,5-dihydrooxazole 8a

Yield: 50% as a white solid; mp: 62–65 °C; $[\alpha]_D^{20} = +88$ (*c* 0.28, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 7.76$ (m, 1H), 7.36

(m, 2H), 7.32 (td, $J = 7.0$ Hz, $J = 2.0$ Hz, 2H), 7.23–7.17 (m, 4H), 7.11 (br t, $J = 7.0$ Hz, 2H), 7.07 (m, 1H), 7.01–6.94 (m, 3H), 6.84–6.82 (m, 2H), 4.76 (m, 1H), 4.32 (dd, $J = 14.5$ Hz, $J = 5.0$ Hz, 1H), 4.20 (dd, $J = 15.0$ Hz, $J = 5.0$ Hz, 1H), 4.07 (s, 2H), 3.28 (m, 1H), 3.05 (ddd, $J = 14.5$ Hz, $J = 10.5$ Hz, $J = 4$ Hz, 1H), 0.94 (d, $J = 6.5$ Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 168.7$ (s), 141.5 (s), 140.3 (d, $J = 13.9$ Hz), 139.6 (d, $J = 13.4$ Hz), 137.9 (s), 133.2 (s), 132.9 (d, $J = 21.3$ Hz), 131.3 (d, $J = 20.5$ Hz), 130.9 (s), 129.0 (s), 128.8 (s), 128.4 (d, $J = 6.2$ Hz), 128.14 (s), 128.12 (s), 127.9 (d, $J = 5.5$ Hz), 127.7 (s), 126.9 (s), 123.5 (s), 122.7 (s), 55.3 (d, $J = 32.2$ Hz), 52.8 (s), 45.1 (d, $J = 6.2$ Hz), 44.4 (d, $J = 3.8$ Hz), 16.9 (s); $^{31}P\{^1H\}$ ($CDCl_3$): $\delta = 68.16$; IR (NaCl): $\nu = 3057$, 3003, 2970, 2929, 2852, 1678, 1470, 1452, 1433, 1412, 1215, 1147, 1092, 958, 742, 696 cm^{-1}; HRMS (ES-I) Calcd for $C_{30}H_{30}N_2OP$ (M+1) 465.2096. Found: 465.2098; Anal. Calcd for $C_{30}H_{29}N_2OP$: C, 77.57; H, 6.22; N, 5.82. Found: C, 76.67; H, 6.22; N, 5.82.

3.12. 2-(*N*-Benzyl-*N*-diphenylphosphino-2-aminomethylphenyl)-(4*S*)-4-*i*-propyl-4,5-dihydrooxazole 8b

Yield: 60% as a white solid; mp: 70–72 °C; $[\alpha]_D^{20} = +114$ (*c* 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 7.78$ (m, 1H), 7.37–7.34 (m, 4H), 7.25–7.21 (m, 3H), 7.15–7.12 (m, 1H), 7.06–7.04 (m, 3H), 7.01 (br t, $J = 7.0$ Hz, 2H), 6.92 (br t, $J = 7.0$ Hz), 6.84 (td, $J = 8.0$ Hz, $J = 1.5$ Hz), 2H), 6.78–6.76 (m, 2H), 4.30 (m, 1H), 4.25 (dd, $J = 14.5$ Hz, $J = 3.5$ Hz, 1H), 4.23 (dd, $J = 16.5$ Hz, $J = 3.5$ Hz, 1H), 4.14 (dd, $J = 14.5$ Hz, $J = 3.0$ Hz, 1H), 4.03 (d, $J = 16.5$ Hz, 1H), 3.33–3.24 (m, 2H), 1.57 (m, 1H), 0.65 (d, $J = 6.5$ Hz, 3H), 0.62 (d, $J = 6.5$ Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 169.6$ (s), 141.5 (s), 140.7 (d, $J = 14.3$ Hz), 139.3 (d, $J = 11.5$ Hz), 137.7 (s), 133.2 (d, $J = 21.8$ Hz), 133.0 (s), 130.87 (s), 130.85 (s), 130.7 (s), 129.2 (s), 129.0 (s), 128.5 (d, $J = 6.5$ Hz), 128.0 (s), 127.82 (s), 127.81 (s), 127.8 (s), 127.6 (s), 126.9 (s), 123.6 (s), 122.7 (s), 54.7 (s), 52.5 (d, $J = 38.9$ Hz), 51.9 (d, $J = 6.5$ Hz), 46.1 (d, $J = 7.9$ Hz), 30.3 (s), 20.0 (s), 19.8 (s); $^{31}P\{^1H\}$ ($CDCl_3$): $\delta = 68.31$; IR (NaCl): $\nu = 3058$, 3002, 2964, 2929, 2872, 1678, 1470, 1452, 1432, 1410, 1215, 1147, 1093, 947, 758, 698 cm^{-1}; HRMS (ES-I) Calcd for $C_{32}H_{34}N_2OP$ (M+1) 493.2409. Found: 493.2433. Anal. Calcd for $C_{32}H_{33}N_2OP$: C, 78.02; H, 6.75; N, 5.69. Found: C, 77.65; H, 6.69; N, 5.65.

3.13. 2-(*N*-Benzyl-*N*-diphenylphosphino-2-aminomethylphenyl)-(4*S*)-4-benzyl-4,5-dihydrooxazole 8c

Yield: 57% as a white solid; mp: 149–152 °C; $[\alpha]_D^{20} = +51$ (*c* 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 7.69$ (m, 1H), 7.33–7.24 (m, 4H), 7.21–7.18 (m, 3H), 7.13 (br t, $J = 7.0$ Hz, 3H), 7.06–6.97 (m, 9H), 6.90 (br d, $J = 7.0$ Hz, 2H), 6.75 (br d, $J = 6.5$ Hz, 2H), 4.78 (m, 1H), 4.24 (dd, $J = 14.5$ Hz, $J = 5.0$ Hz, 1H), 4.15 (dd, $J = 14.5$ Hz, $J = 5.5$ Hz, 1H), 3.99 (s, 2H), 3.40 (m, 1H), 3.19 (ddd, $J = 15.0$ Hz, $J = 11.0$ Hz, $J = 4.0$ Hz, 1H), 2.65–2.61 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 168.9$ (s), 141.5 (s), 140.2 (d, $J = 13.9$ Hz), 139.4 (d, $J = 13.4$ Hz), 138.1 (d, $J = 1.0$ Hz), 137.7 (s), 133.1 (s), 132.8 (d, $J = 20.9$ Hz), 1313.5 (d, $J = 19.9$ Hz), 128.9 (s), 128.8 (s), 128.6 (s), 128.4 (s), 128.39 (s), 128.35 (s), 128.2 (s), 127.8 (d, $J = 6.0$ Hz), 127.6 (s), 126.9 (s), 126.3 (s), 53.5 (d, $J = 30.1$ Hz), 53.5 (s), 50.8 (br s), 46.4 (d, $J = 5.1$ Hz), 37.5 (s); ($^{31}P\{^1H\}$ ($CDCl_3$): $\delta = 68.08$; IR (NaCl): $\nu = 3060$, 3026, 3002, 2920, 2854, 1680, 1470, 1452, 1433, 1410, 1215, 1093, 952, 744, 698 cm^{-1}; HRMS (ES-I) Calcd for $C_{36}H_{34}N_2OP$ (M+1) 541.2409. Found: 541.2418. Anal. Calcd for $C_{36}H_{33}N_2OP$: C, 79.98; H, 6.15; N, 5.18. Found: C, 79.45; H, 6.17; N, 4.97.

3.14. General synthesis of 2-(*N*-benzyl-*N*-(+)-TADDOL-2-aminomethylphenyl)-(4*S*)-4-*R*-4,5-dihydrooxazole (R = Me, *i*-Pr, Benzyl) (9)

To a stirred solution of 0.233 g of (+)-TADDOL (0.5 mmol) and 0.25 mL of Et_3N (0.182 g, 1.8 mmol) in 2 mL of CH_2Cl_2 was added 42 μL of PCl_3 at 0 °C. Immediately a precipitate was formed and the reaction mixture was allowed to react for 1 h. Next, a solution of **7** (0.5 mmol) in 2 mL of CH_2Cl_2 was added dropwise. The mixture was allowed to react for 2 days at room temperature. The salts were removed by filtration of the reaction mixture over $MgSO_4$, which was followed by the removal of the organics in vacuo. After column chromatography on silica (CH_2Cl_2), the product was isolated as a white solid. (Yield: 68–72%).

3.15. 2-(*N*-Benzyl-*N*-(+)-TADDOL-2-aminomethylphenyl)-(4*S*)-4-methyl-4,5-dihydrooxazole 9a

Yield: 68% as a white solid; mp: 125–128 °C; $[\alpha]_D^{20} = +97$ (*c* 0.28, $CHCl_3$); ^1H NMR (CD_2Cl_2): $\delta = 7.67$ (m, 1H), 7.66–7.63 (m, 2H), 7.50–7.47 (m, 2H), 7.38–7.31 (m, 9H), 7.24–7.10 (m, 14H), 7.06 (d, $J = 7.0$ Hz, 1H), 5.14 (dd, $J = 8.5$ Hz, $J = 3.5$ Hz, 1H), 4.75 (d, $J = 8.5$ Hz, 1H), 4.62 (m, 1H), 4.46 (dd, $J = 15.5$ Hz, $J = 10.0$ Hz, 1H), 4.27 (dd, $J = 10.0$ Hz, $J = 15.0$ Hz, 1H), 4.08 (d, $J = 16.5$ Hz, 1H), 4.02 (d, $J = 16.5$ Hz, 1H), 3.20 (m, 1H), 3.10 (m, 1H), 1.32 (s, 3H), 1.15 (d, $J = 7.0$ Hz, 3H), 0.17 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_2Cl_2): $\delta = 168.2$ (s), 147.3 (s), 146.6 (d, $J = 2.5$ Hz), 142.2 (d, $J = 1.5$ Hz), 142.0 (s), 141.9 (d, $J = 1.6$ Hz), 138.7 (2C or d), 133.5 (s), 131.3 (s), 129.6 (s), 129.2 (d, $J = 4.6$ Hz), 129.1 (s), 128.6 (s), 128.4 (s), 128.13 (s), 128.09 (s), 128.0 (s), 127.92 (s), 127.89 (s), 127.8 (s), 127.7 (s), 127.63 (s), 127.59 (s), 127.58 (s), 127.4 (s), 123.5 (s), 123.3 (s), 112.0 (s), 83.2 (d, $J = 3$ Hz), 82.6 (d, $J = 21.5$ Hz), 82.3 (d, $J = 8.2$ Hz), 82.1 (d, $J = 1.5$ Hz), 49.3 (d, $J = 19.0$ Hz), 48.3 (d, $J = 22.6$ Hz), 45.8 (s), 45.1 (d, $J = 4.0$ Hz), 27.7 (s), 25.3 (s), 17.0 (s); $^{31}P\{^1H\}$ NMR (CD_2Cl_2): $\delta = 140.67$; IR (NaCl): $\nu = 3089$, 3059, 2991, 2929, 1680, 1495, 1448, 1382, 1371, 1303, 1215, 1163, 1032, 1009, 760, 736, 698; HRMS (ES-I) Calcd for $C_{49}H_{48}N_2O_5P$ (M+1) 775.3301. Found 775.3337; Anal. Calcd for $C_{49}H_{47}N_2O_5P$: C, 75.95; H, 6.11; N, 3.62. Found: C, 75.85; H, 6.34; N, 3.34.

3.16. 2-(*N*-Benzyl-*N*-(+)-TADDOL-2-aminomethylphenyl)-(4*S*)-4-*i*-propyl-4,5-dihydrooxazole 9b

Yield: 67% as a white solid; mp: 130–134 °C; $[\alpha]_D^{20} = +95$ (*c* 0.29, $CHCl_3$); ^1H NMR (CD_2Cl_2) $\delta = 7.69$ (m, 1H), 7.57 (m, 2H), 7.39–7.05 (m, 23H), 6.99 (app. t, $J = 7.5$ Hz, 2H), 6.80 (br d, $J = 8.0$ Hz, 1H), 5.12 (dd, $J = 8.5$ Hz,

$J = 3.5$ Hz, 1H), 4.76 (d, $J = 8.5$ Hz, 1H), 4.33 (dd, $J = 15.5$ Hz, $J = 10.5$ Hz, 1H), 4.23 (dd, $J = 15.0$ Hz, $J = 13.5$ Hz, 1H), 4.17 (m, 1H), 4.13 (d, $J = 17.0$ Hz, 1H), 3.84 (d, $J = 17.0$ Hz, 1H), 3.39 (m, 1H), 3.21 (m, 1H), 1.74 (m, 1H), 1.32 (s, 3H), 0.72 (d, $J = 7.0$ Hz, 3H), 0.64 (d, $J = 7.0$ Hz, 3H), 0.15 (s, 3H). $^{13}C\{^1H\}$ NMR (CD_2Cl_2): $\delta = 169.2$ (s), 147.1 (s), 146.5 (d, $J = 1.9$ Hz), 142.2 (s), 142.1 (d, $J = 2.0$ Hz), 141.8 (d, $J = 1.7$ Hz), 138.4 (d, $J = 1.9$ Hz), 133.3 (s), 131.2 (s), 129.7 (s), 129.31 (s), 129.28 (d, $J = 4.6$ Hz), 128.5 (s), 128.3 (s), 128.1 (s), 128.03 (s), 128.0 (s), 127.9 (s), 127.8 (s), 127.62 (s), 127.59 (s), 127.5 (s), 127.3 (s), 123.7 (s), 123.3 (s), 111.9 (s), 82.3 (d, $J = 7.8$ Hz), 82.2 (d, $J = 21.8$ Hz), 82.1 (d, $J = 2.3$ Hz), 55.3 (br s), 49.2 (d, $J = 22.2$ Hz), 46.8 (br s), 44.2 (d, $J = 18.6$ Hz), 30.7 (s), 27.8 (s), 25.3 (s), 20.3 (s), 20.0 (s); $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta = 140.80$; IR (NaCl): $\nu = 3090$, 3065, 2915, 1678, 1495, 1446, 1382, 1371, 1217, 1084, 1049, 1032, 1012, 947, 877, 754, 698 cm^{-1}; HRMS (ES-I) Calcd for $C_{51}H_{52}N_2O_5P$ (M+1) 803.3614. Found: 803.3643; Anal. Calcd for $C_{51}H_{51}N_2O_5P$: C, 76.29; H, 6.40; N, 3.49. Found: C, 76.06; H, 6.38; N, 3.25.

3.17. 2-(*N*-Benzyl-*N*-(+)-TADDOL-2-aminomethylphenyl)-(4*S*)-4-benzyl-4,5-dihydrooxazole 9c

Yield: 72% as a white solid; mp: 156–159 °C; $[\alpha]_D^{20} = +55$ (*c* 0.29, $CHCl_3$); ^1H NMR (CD_2Cl_2): $\delta = 7.65$–7.60 (m, 3H), 7.48–7.46 (m, 2H), 7.35–7.28 (m, 8H), 7.21–7.09 (m, 15H), 7.06–6.98 (m, 3H), 6.96–6.94 (m, 1H), 6.93–6.91 (m, 1H), 5.16 (dd, $J = 8.5$ Hz, $J = 3.5$ Hz, 1H), 4.77 (d, $J = 8.5$ Hz, 1H), 4.64 (m, 1H), 4.40 (dd, $J = 15.0$ Hz, $J = 10.5$ Hz, 1H), 4.29 (dd, $J = 15.0$ Hz, $J = 10.5$ Hz, 1H), 3.93 (s, 2H), 3.38 (m, 1H), 3.31 (m, 1H), 2.97 (dd, $J = 14.5$ Hz, $J = 5.0$ Hz, 1H), 2.82 (dd, $J = 14.5$ Hz, $J = 10.5$ Hz, 1H), 1.31 (s, 3H), 0.18 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_2Cl_2): $\delta = 168.6$ (s), 147.2 (s), 146.5 (d, $J = 1.9$ Hz), 142.2 (d, $J = 1.8$ Hz), 142.0 (s), 141.9 (d, $J = 1.4$ Hz), 138.9 (d, $J = 2.1$ Hz), 138.6 (d, $J = 2.1$ Hz), 133.4 (s), 131.3 (s), 129.23 (d, $J = 4.9$ Hz), 129.2 (s), 129.0 (s), 128.7 (s), 128.5 (s), 128.2 (s), 128.04 (s), 127.96 (s), 127.9 (s), 127.8 (s), 127.7 (s), 127.6 (s), 127.5 (s), 126.6 (s), 123.5 (s), 123.2 (s), 112.1 (s), 83.2 (d, $J = 3.8$ Hz), 82.5 (d, $J = 21.3$ Hz), 82.4 (d, $J = 8.4$ Hz), 82.3 (d, $J = 1.4$ Hz), 52.2 (br s), 50.0 (d, $J = 19.9$ Hz), 47.4 (br s), 47.4 (d, $J = 20.9$ Hz), 37.1 (s), 27.8 (s), 25.3 (s); $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta = 141.06$; IR (NaCl): $\nu = 3087$, 3062, 3006, 2912, 1680, 1495, 1448, 1383, 1372, 1215, 1162, 1084, 1049, 1032, 1011, 877, 755, 736, 698 cm^{-1}; HRMS (ES-I) calcd for $C_{55}H_{52}N_2O_5P$ (M+1) 851.3614. Found: 851.3649; Anal. Calcd for $C_{55}H_{52}N_2O_5P$: C, 77.63; H, 6.04; N, 3.29. Found: C, 77.38; H, 6.11; N, 3.24.

3.18. General synthesis of 2-(*N*-benzyl-*N*-(−)-TADDOL-2-aminomethylphenyl)-(4*S*)-4-*R*-4,5-dihydrooxazole (R = Me, *i*-Pr, Benzyl) 10

To a stirred solution of 0.233 g of (−)-TADDOL (0.5 mmol) and 0.25 mL of Et_3N (0.182 g, 1.8 mmol) in 2 mL of CH_2Cl_2 was added 42 μL of PCl_3 at 0 °C. Immediately, a precipitate was formed and the reaction mixture was allowed to react for 1 h. Next, a solution of **7** (0.5 mmol) in 2 mL of CH_2Cl_2 was added dropwise. The mixture was allowed to react for 2 days at room temperature. The salts were removed by filtration of the reaction mixture over $MgSO_4$, which was followed by removal of the organics in vacuo. After column chromatography on silica (CH_2Cl_2), the product was isolated as a white solid. (Yield: 64–71%).

3.19. 2-(*N*-Benzyl-*N*-(−)-TADDOL-2-aminomethylphenyl)-(4*S*)-4-methyl-4,5-dihydrooxazole 10a

Yield: 71% as a white solid; mp: 126–129 °C; $[\alpha]_D^{20} = -121.2$ (*c* 0.33, $CHCl_3$); ^1H NMR (CD_2Cl_2): 7.66–7.64 (m, 1H), 7.46–7.41 (m, 4H), 7.37–7.34 (m, 2H), 7.30–7.26 (m, 5H), 7.30–7.25 (m, 4H), 7.18–7.09 (m, 11H), 7.07–7.03 (m, 3H), 4.99 (dd, $J = 8.5$ Hz, $J = 3.5$ Hz, 1H), 4.74 (d, $J = 8.5$ Hz, 1H), 4.65 (m, 1H), 4.47 (dd, $J = 15.5$ Hz, $J = 8.0$ Hz, 1H), 4.35 (d, $J = 16.5$ Hz, 1H), 4.27 (dd, $J = 15.5$ Hz, $J = 5.0$ Hz, 1H), 4.16 (d, $J = 16.5$ Hz, 1H), 3.27 (m, 1H), 2.89 (m, 1H), 1.17 (s, 3H), 1.03 (d, $J = 7.0$ Hz, 3H), 0.20 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_2Cl_2): $\delta = 168.3$ (s), 147.3 (s), 146.6 (d, $J = 1.5$ Hz), 142.4 (s), 141.9 (s), 141.7 (d, $J = 1.7$ Hz), 138.7 (d, 1.7 Hz), 133.6 (s), 131.3 (s), 129.5 (s), 129.2 (s), 129.0 (d, $J = 6.1$ Hz), 128.7 (s), 128.5 (s), 128.1 (s), 128.0 (s), 127.8 (s), 127.7 (s), 127.53 (br s), 127.48 (s), 127.4 (s), 123.5 (s), 123.2 (s), 112.2 (s), 82.8 (s), 82.7 (d, $J = 20.4$ Hz), 82.3 (d, $J = 3.6$ Hz), 82.1 (d, $J = 9.3$ Hz), 48.4 (d, $J = 15.5$ Hz), 48.2 (d, $J = 28.5$ Hz), 45.6 (d, $J = 3.1$ Hz), 44.2 (d, $J = 4.1$ Hz), 27.6 (s), 25.5 (s), 16.9 (s); $^{31}P\{^1H\}$ NMR (CD_2Cl_2): $\delta = 140.85$; IR (NaCl): $\nu = 3089$, 3056, 2989, 2933, 1680, 1495, 1470, 1448, 1304, 1265, 1213, 1162, 1088, 1036, 1007, 737, 698 cm^{-1}; HRMS (ES-I) Calcd for $C_{49}H_{48}N_2O_5P$ (M+1) 775.3301. Found: 775.3286; Anal. Calcd for $C_{49}H_{47}N_2O_5P$: C, 75.95; H, 6.11; N, 3.62. Found: C, 76.15; H, 6.40; N, 3.18.

3.20. 2-(*N*-Benzyl-*N*-(−)-TADDOL-2-aminomethylphenyl)-(4*S*)-4-*i*-propyl-4,5-dihydrooxazole 10b

Yield: 64% as a white solid; mp: 136–139 °C; $[\alpha]_D^{20} = -145$ (*c* 0.31, $CHCl_3$); ^1H NMR (CD_2Cl_2): $\delta = 7.68$–7.66 (m, 1H), 7.48–7.44 (m, 2H), 7.36–7.24 (m, 4H), 7.24–7.20 (m, 7H), 7.17–7.01 (m, 12H), 7.00–6.98 (m, 2H), 6.95 (d, $J = 6.5$ Hz, 1H), 4.93 (dd, $J = 8.0$ Hz, $J = 3.5$ Hz, 1H), 4.75 (d, $J = 8.5$ Hz, 1H), 4.50 (d, $J = 16.0$ Hz, 1H), 4.48 (dd, $J = 16.0$ Hz, $J = 7.0$ Hz, 1H), 4.16 (m, 1H), 4.09 (dd, $J = 15.5$ Hz, $J = 11.5$ Hz, 1H), 4.06 (d, $J = 17.0$ Hz, 1H), 3.30 (m, 1H), 3.04 (m, 1H), 1.69 (m, 1H), 1.08 (s, 3H), 0.65 (d, $J = 6.5$ Hz, 6H), 0.23 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_2Cl_2): $\delta = 169.2$ (s), 147.3 (s), 146.8 (d, $J = 1.4$ Hz), 142.4 (d, $J = 1.4$ Hz), 142.0 (s), 141.7 (d, $J = 1.8$ Hz), 138.6 (br s), 129.5 (s), 129.4 (s), 129.0 (d, $J = 11.7$ Hz), 128.7 (s), 128.5 (s), 128.1 (s), 128.0 (s), 127.8 (s), 127.7 (s), 127.6 (s), 127.5–127.4 (multiple signals), 123.7 (s), 123.2 (s), 112.3 (s), 83.3 (d, $J = 2.3$ Hz), 82.7 (d, $J = 20.1$ Hz), 82.1 (d, $J = 8.8$ Hz), 82.0 (d, $J = 3.8$ Hz), 54.5 (br s), 48.1 (d, $J = 14.5$ Hz), 46.7 (br s), 44.5 (d, $J = 29.4$ Hz), 30.4 (s), 27.5 (s), 25.6 (s), 20.2 (s), 20.1 (s); $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta = 141.43$; IR (NaCl): $\nu = 3087$, 3060, 3005, 2966, 2935, 2873, 1680, 1495, 1470, 1448, 1412, 1371, 1248, 1217, 1165, 1086, 1051, 1011, 945, 883, 750, 698 cm^{-1}; HRMS (ES-I) Calcd for $C_{51}H_{52}N_2O_5P$

(M+1) 803.3614. Found: 803.3608; Anal. Calcd for $C_{51}H_{51}N_2O_5P$: C, 76.29; H, 6.40; N, 3.49. Found: C, 75.82; H, 6.36; N, 3.23.

3.21. 2-(*N*-Benzyl-*N*-(−)-TADDOL-2-aminomethylphenyl)-(4*S*)-4-benzyl-4,5-dihydrooxazole 10c

Yield: 70% as a white solid; mp: 136–139 °C; $[\alpha]_D^{20} = -112$ (*c* 0.28, $CHCl_3$); ^1H NMR (CD_2Cl_2): $\delta = 7.60$–7.58 (m, 1H), 7.45 (bd, $J = 7.5$ Hz, 2H), 7.35 (m, 4H), 7.30–7.00 (m, 24H), 6.98–6.96 (m, 1H), 6.94–6.92 (m, 2H), 4.99 (dd, $J = 8.5$ Hz, $J = 3.5$ Hz, 1H), 4.78 (d, $J = 8.5$ Hz, 1H), 4.70 (m, 1H), 4.45 (dd, $J = 15.0$ Hz, $J = 8.0$ Hz, 1H), 4.25–4.20 (m, 2H), 4.04 (d, $J = 16.5$ Hz, 1H), 3.41 (m, 1H), 3.08 (m, 1H), 2.77–2.70 (m, 2H), 1.15 (s, 3H), 0.22 (s, 3H); $^{13}C\{^1H\}$ NMR (CD_2Cl_2): $\delta = 168.7$ (s), 147.3 (s), 146.7 (d, $J = 1.9$ Hz), 142.3 (d, $J = 1.9$ Hz), 141.9 (s), 141.7 (d, $J = 1.9$ Hz), 138.7 (d, $J = 1.6$ Hz), 138.4 (s), 131.3 (s), 129.6 (s), 129.3 (s), 129.1 (d, $J = 6.1$ Hz), 129.0 (s), 128.8 (s), 128.7 (s), 128.5 (s), 128.1 (s), 128.0 (s), 127.9 (s), 127.7 (s), 127.6 (multiple C's), 127.4 (s), 126.6 (s), 123.6 (s), 123.1 (s), 112.3 (s), 83.1 (d, $J = 0.9$ Hz), 82.6 (d, $J = 20.4$ Hz), 82.3 (d, $J = 3.8$ Hz), 82.2 (d, $J = 8.8$ Hz), 50.9 (br s), 49.0 (d, $J = 15.9$ Hz), 47.1 (d, $J = 26.5$ Hz), 47.0 (br s), 37.3 (s), 27.6 (s), 25.5 (s); $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta = 141.40$; IR (NaCl): $\nu = 3087$, 3062, 3008, 2915, 1680, 1494, 1448, 1217, 1163, 1103, 1088, 947, 883, 756, 737, 700 cm^{-1}; HRMS (ES-I) calcd for $C_{55}H_{52}N_2O_5P$ (M+1) 851.3614. Found: 851.3623; Anal. Calcd for $C_{55}H_{52}N_2O_5P$: C, 77.63; H, 6.04; N, 3.29. Found: C, 77.51; H, 6.31; N, 3.15.

3.22. Asymmetric allylic alkylation

To 5 mg of KOAc (51 μmol) in a flame-dried Schlenk tube were added $[Pd(allyl)(\mu\text{-}Cl)]_2$ (1.84 mg, 5 μmol) and ligand (11 μmol, 1.1 equiv) through freshly prepared stock-solutions in CH_2Cl_2 (1 mL per experiment). After the addition of the allylic substrate (1.0 mmol) in 1 mL of CH_2Cl_2, the mixture was stirred for 15 min. Subsequently, dimethylmalonate (171 μL, 1.5 mmol) and *N*,*O*-bis(trimethylsilyl) acetamide (371 μL, 1.5 mmol) were added. The reaction was monitored by NMR and HPLC. After the desired reaction time, the mixture was diluted with Et_2O, washed with saturated ammonium chloride solution and dried over $MgSO_4$. The conversion was determined by ^1H NMR. The enantiomeric excess was determined by chiral HPLC (Chiralcel OD, pentane/2-propanol = 99/1, flow = 0.3 mL min^{-1}, $t_r(R) = 36.3$ min, $t_r(S) = 38.2$ min, $\lambda = 254$ nm).

3.23. Asymmetric Suzuki coupling

To a flame-dried Schlenk tube was added a mixture of $Pd(dba)_2$ (2.9 mg, 5 μmol), ligand (10 μmol, 2.0 equiv) and 1-bromonaphthalene (35 μL, 0.25 mmol) through freshly prepared stock-solutions in DME (2 mL per experiment). Next, the mixture was stirred for 15 min at 40 °C. After cooling to room temperature, 2-methyl-1-naphthaleneboronic acid (56 mg, 0.30 mmol), base (0.5 mmol) and degassed water (0.2 mL) were added. After 24 h, the mixture was diluted with Et_2O, washed with saturated ammonium chloride solution and dried over $MgSO_4$. Column chromatography on silica gave pure product **17** as a white crystalline solid. The enantiomeric excess was determined by chiral HPLC (Chiralcel OJ, hexanes/ethanol/methanol = 1000/5/3.5, flow = 1.0 mL min^{-1}, $t_r(R) = 7.0$ min, $t_r(S) = 10.6$ min, $\lambda = 254$ nm). Specific rotations were compared to literature values. It is crucial to remove all 1-bromonaphthalene starting material as this compound overlaps with the (*R*)-enantiomer of the product in HPLC.

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