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New Carbohydrate-Based Phosphite-Oxazoline Ligands as Highly Versatile Ligands for Palladium-Catalyzed Allylic Substitution Reactions

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Abstract: We have designed and synthesized a new family of readily available phosphite-oxazoline ligands for Pd-catalyzed asymmetric allylic substitution reactions. These ligands can be tuned in two regions to explore their effect on catalytic performance. By carefully selecting the ligand components, we obtained high enantioselectivities in the Pd-catalyzed allylic substitution in substrates with different steric properties

Keywords: allylic substitution; amination; asymmetric catalysis; C–C bond formation; palladium; phosphite-oxazoline ligand

Palladium-catalyzed allylic substitution is a useful synthetic method for the formation of carbon-carbon and carbon-heteroatom bonds.[1] The selection of chiral ligands for highly enantioselective allylic substitution has mainly focused on the use of mixed bidentate donor ligands.[1,2] Mixed phosphorus-nitrogen ligands have played a dominant role among the heterodonor ligands. However, one disadvantage of using these ligands is that they are often synthesized either from expensive chiral sources or in tedious synthetic steps. Another common disadvantage for the most successful ligands developed for this process is that they show a high substrate specificity (i.e., high ees are obtained in disubstituted linear hindered substrates and low ees are obtained in cyclic and unhindered linear substrates, or *vice versa*).[1]

Research into more versatile mixed P–N ligand systems from simple starting materials in this reaction is therefore of great importance nowadays. For this purpose, carbohydrates are particularly advantageous thanks to their low price and easy modular construction.[3] Although they have been successfully used in other enantioselective reactions, they have only very recently shown their huge potential as a source of highly effective chiral ligands in this process.[3] Notable examples include two types of phosphorus-oxazoline ligands.[4] In this context, Uemura and co-workers synthesized the phosphinite-oxazoline ligands **1** (Figure 1).[4b, c] These ligands proved to be effective in the allylic substitution of the hindered substrate 1,3-diphenyl-3-acetoxyprop-1-ene (**S1**) but showed low enantioselectivity for unhindered cyclic and linear substrates.[4c] Based on this structure, in this paper we have designed a new family of ligands in which the phosphinite group is replaced by a phosphite group (Scheme 1). The advantage of incorporating a phosphite moiety into the ligand is that substrate specificity decreases because the chiral pocket created (the chiral cavity where the allyl is embedded) is smaller than for ligands **1**[1c,5] yet flexible enough[6] to allow the perfect coordination of hindered and unhindered substrates.[7] These ligands also provide a more flexible ligand scaffold because they can be easily tuned in two different regions (phosphite and oxazoline substituents) to explore how they affect the catalytic performance. As a result, the Pd-allylic substitution reactions of several substrates with different steric properties are reached.

This new family of phosphite-oxazoline ligands **2**–**8** is derived from the commercially available D-glucosamine. Their synthesis is straightforward (Scheme 1). They are easily prepared by attaching several phosphor-

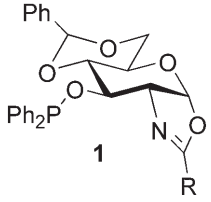
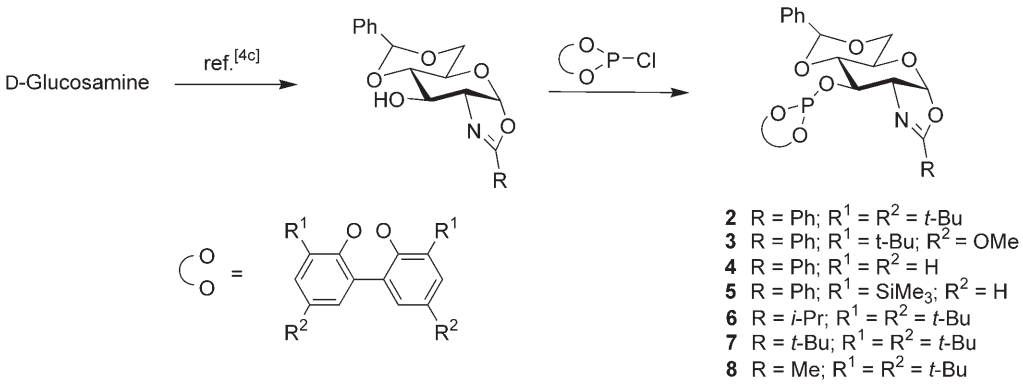
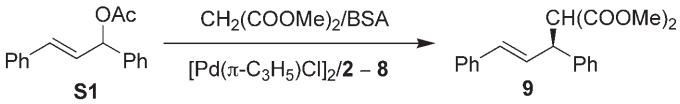


Figure 1. Phosphinite-oxazoline ligands developed by Uemura and co-workers.



Scheme 1. Synthesis of phosphite-oxazoline ligands **2**–**8**.

Table 1. Pd-catalyzed allylic alkylation of **S1** using ligands **2**–**8**.[a]



Entry	Solvent	Ligand	% Conversion[b] (min)	% ee[c]
1	CH_2Cl_2	**2**	100 (30)	92 (*S*)
2	CH_2Cl_2	**3**	89 (30)	84 (*S*)
3	CH_2Cl_2	**4**	57 (30)	86 (*S*)
4	CH_2Cl_2	**5**	95 (30)	86 (*S*)
5	CH_2Cl_2	**6**	91 (30)	86 (*S*)
6	CH_2Cl_2	**7**	67 (30)	45 (*S*)
7	CH_2Cl_2	**8**	100 (15)	85 (*S*)
8[d]	CH_2Cl_2	**2**	54 (300)	95 (*S*)
9[d, e]	Toluene	**2**	100 (360)	99 (*S*)

[a] 0.5 mol % $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 30 min, ligand/Pd = 0.9; 3 equivs. of $CH_2(COOMe)_2$ and *N,O*-bis(trimethylsilyl)acetamide (BSA)/KOAc as base, room temperature.
[b] Measured by ^1H NMR. Reaction time in minutes shown in parentheses. In all cases isolated yields > 95% based on recovered starting material were obtained.
[c] Determined by HPLC.
[d] $T = 0\,^\circ C$.
[e] 2 mol % of $[Pd(\pi\text{-}C_3H_5)Cl]_2$.

ochloridites[8] to the corresponding hydroxy-oxazoline scaffolds[4c].

We first tested the new ligands in the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-3-acetoxy-prop-1-ene (**S1**) with dimethyl malonate as a model reaction using standard conditions (Table 1).

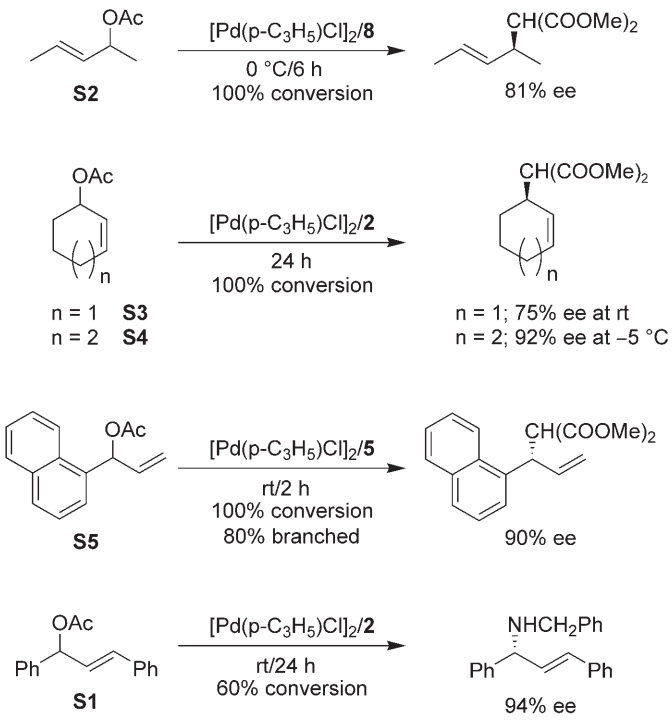
The effects of the phosphite moieties were studied using ligands **2**–**5** (Table 1, entries 1–4). We found that the substituents at the *ortho* positions of the biphenyl moiety affected activities, while enantioselectivities were mainly affected by the substituents at the *para* positions of the biphenyl moiety.[9] Activities and enantioselectivities were therefore highest when *tert*-butyl groups were present at both the *ortho* and *para* positions of the biphenyl-phosphite moiety.

The effect of the oxazoline substituent was studied with ligands **2**, **6**–**8** (Table 1, entries 1, 5–7). We found that these substituents affected both activities and enantioselectivities. The best enantioselectivities were obtained using ligand **2**, which contains a phenyl-oxazoline substituent. This behavior is in contrast with the oxazoline-substituent effect observed for related phosphinite-oxazoline ligands **1**, for which the enantioselectivity was higher when a methyl substituent was present.[4b, c] Concerning activities, they were higher when less sterically demanding substituents were present (i.e., Me > Ph > *i*-Pr > *t*-Bu).

Enantioselectivity was further improved (ees up to 95%) with ligand **2** by lowering the reaction temperature to 0 °C (Table 1, entry 8). Changing the solvent from dichloromethane to toluene increased the enantioselectivity even further (ees up to 99%, Table 1, entry 9).

To further study the potential of these readily available ligands, we also tested them in the allylic alkylation of unhindered linear substrate **S2**, cyclic substrates **S3** and **S4** and the monosubstituted linear substrate **S5**, and in the allylic amination of **S1** (Scheme 2).

The enantioselectivity in unhindered linear **S2** and cyclic **S3** and **S4** substrates is usually more difficult to control than for the hindered substrate **S1**. For high ees to be achieved it is crucial that ligands create a small chiral pocket around the metal center, mainly because of the presence of less sterically *syn* substituents.[1] Although highly enantioselective catalysts have been developed for these unhindered substrates, they generally provide low enantiocontrol in hindered substrates like **S1**. The development of enantioselective catalysts for both hindered and unhindered substrates is therefore still a challenge. The presence of the bulky biphenyl in the phosphite moiety in ligands **2**–**8**, which are known to be flexible and to provide large bite angles, can therefore also provide excellent results for unhindered substrates. Interestingly for the sterically undemanding substrates **S2**–**S4**, high enantioselectivities (81%, 75% and 92%,



Scheme 2. Pd-catalyzed allylic substitution of **S1**–**S5** using ligands **2**–**8**. In all cases products were isolated in yields > 95% based on recovered starting material.

respectively) were also achieved. These results are among the best reported for this type of unhindered substrate.[10]

For substrate **S5**, as well as controlling the enantioselectivity of the process, the regioselectivity is also a problem, because a mixture of regioisomers can be obtained. Most Pd catalysts developed to date favor the formation of the achiral linear product rather than the desired branched isomer.[11] Therefore, the development of highly regio- and enantioselective Pd-catalysts is still a challenge. Under non-optimized conditions, the catalytic system containing ligand **5** produced the desired branched isomer as the major product with high enantioselectivity (90% ee). This result is among the best reported so far.[11]

Finally, we evaluated this ligand library in the allylic amination process of **S1** using benzylamine as nucleophile. High enantioselectivities (even higher than in the alkylation of this substrate) were also achieved (ees up to 94% at room temperature and CH_2Cl_2 as solvent).

To sum up, we have successfully designed and synthesized a series of modular phosphite-oxazoline ligands prepared in a few steps from commercial D-glucosamine as an inexpensive chiral source. These ligands can be tuned in two regions to explore their effect on catalytic performance. By carefully selecting the ligand components, we obtained high enantioselectivities in the Pd-catalyzed allylic substitution in substrates with different steric properties. This is therefore an exceptional ligand family that competes with a few other ligand series that also provide high ees for hindered and unhindered disubstituted and monosubstituted substrates. These results open up the allylic alkylation of a wide range of substrates to the potentially effective use of readily available and highly modular sugar-based phosphite-oxazoline ligands. Further modifications at both the phosphite and oxazoline moieties and mechanistic studies are currently under way.

Experimental Section

General Procedure for the Preparation of Ligands 2–8

The corresponding phosphorochloridite[8] (3.0 mmol) produced *in situ* was dissolved in toluene (12.5 mL) and pyridine (1.14 mL, 14 mmol) was added. Hydroxy-oxazoline[4c] (2.8 mmol) was azeotropically dried with toluene (3 × 2 mL) and then dissolved in toluene (12.5 mL) to which pyridine (1.14 mL, 14 mmol) was added. The oxazoline solution was transferred slowly at 0 °C to the solution of phosphorochloridite. The reaction mixture was stirred overnight at 80 °C, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography (toluene/NEt_3 = 100/1) to produce the corresponding ligand as a white solid.

Characterization of all new ligands **2**–**8** are collected in the Supporting Information.

Typical Procedure for Allylic Alkylation of *rac*-1,3-Diphenyl-3-acetoxyprop-1-ene (S1)

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the phosphite-oxazoline (0.0045 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S1** (126 mg, 0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (370 μL, 1.5 mmol) and a pinch of the corresponding base were added. The reaction mixture was stirred at room temperature. After the desired reaction time the reaction mixture was diluted with Et_2O (5 mL) and saturated aqueous NH_4Cl (25 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion was measured by ^1H NMR. To determine the ee by HPLC (Chiralcel OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.

Typical Procedure for Allylic Alkylation of *rac*-1,3-Dimethyl-3-acetoxyprop-1-ene (S2)

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.9 mg, 0.0025 mmol) and the phosphite-oxazoline (0.0045 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S4** (64 mg, 0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of

KOAc were added. The reaction mixture was stirred at room temperature. After 30 min the reaction mixture was diluted with Et_2O (5 mL) and saturated aqueous NH_4Cl (25 mL) was added. The mixture was extracted with Et_2O (3×10 mL) and the extract dried over $MgSO_4$. Conversion and enantiomeric excess was determined by GC.

Typical Procedure for Allylic Alkylation of *rac*-3-Acetoxycycloheptene (S3) and *rac*-3-Acetoxycyclohexene (S4)

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol) and the phosphite-oxazoline **2** (0.009 mmol) in dichloromethane (0.5 mL) was stirred. After 30 minutes the solution was brought to the desired temperature and subsequently, a solution of racemic substrate (0.5 mmol) in dichloromethane (1.5 mL) at the desired temperature, dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of KOAc were added. The reaction mixture was stirred at the desired temperature. After 24 hours the reaction mixture was diluted with Et_2O (5 mL) and saturated aqueous NH_4Cl (25 mL) was added. The mixture was extracted with Et_2O (3×10 mL) and the extract dried over $MgSO_4$. Conversion was determined by GC. For substrate **S3**, to determine the ee by ^1H NMR (using $Eu(hfc)_3$ as resolving reagent), a sample was purified on silica using an Et_2O/hexane (1/4) mixture as the eluent. For substrate **S4**, the enantiomeric excess was determined by GC.

Typical Procedure for Allylic Alkylation of *rac*-1-(1-Naphthyl)allyl Acetate (S5)

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (3.6 mg, 0.01 mmol) and the phosphite-oxazoline **5** (0.018 mmol) in dichloromethane (0.5 mL) was stirred for 30 min at room temperature. Subsequently, a solution of *rac*-1-(1-naphthyl)allyl acetate (0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and a pinch of KOAc were added. After 2 hours the reaction mixture was diluted with Et_2O (5 mL) and saturated aqueous NH_4Cl (25 mL) was added. The mixture was extracted with Et_2O (3×10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion and regioselectivity were measured by ^1H NMR. To determine the ee by HPLC (Chiralcel OJ, 13% 2-propanol/hexane, flow 0.7 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.

Typical Procedure for Allylic Amination of *rac*-1,3-Diphenyl-3-acetoxyprop-1-ene (S1)

A degassed solution of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (3.6 mg, 0.01 mmol) and the phosphite-oxazoline **2** (0.018 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of **S1** (126 mg, 0.5 mmol) in dichloromethane (1.5 mL) and benzylamine (131 μL, 1.5 mmol) were added. The reaction mixture was stirred at room temperature. After 24 hours the reaction mixture was diluted with Et_2O (5 mL) and saturated aqueous NH_4Cl (25 mL) was added. The mixture was extracted with Et_2O (3×10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion was measured by ^1H NMR. To determine the ee by HPLC (Chiralcel OJ, 13% 2-propanol/hexane, flow 0.5 mL/min), a sample was filtered over silica using 10% Et_2O/hexane mixture as the eluent.

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