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FULL PAPER

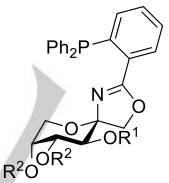
D-fructose based spiro-fused PHOX ligands: Palladium complexes and application in catalysis

Michael R. Imrich,[a] Cäcilia Maichle-Mössmer [b] and Thomas Ziegler *[a]

Abstract: Phosphinooxazoline (PHOX) ligands are an important class of ligands in asymmetric catalysis. Recently we reported on the synthesis of D-fructose based spiro-fused PHOX ligands. Here, we now present the application of these ligands in asymmetric alkylation. In addition, we prepared palladium complexes of our previous spiro-PHOX ligands and characterized them by x-ray crystallography. With the knowledge of the molecular structure of these spiro-PHOX palladium complexes we prepared two "improved" D-fructose based spiro-fused PHOX ligands the application of which in asymmetric alkylation resulted in high enantioselectivities (*er* up to 93:7) in a broad substrate range.

Introduction

The efficient synthesis of enantiopure compounds is still a main challenge in organic chemistry because the majority of biologically active molecules are chiral compounds and, in most cases, only one enantiomer has the desired biological effect. The most important approach to the synthesis of enantiopure compounds is asymmetric catalysis which is a still a fiercely embattled field in chemical research. In this context the design of new effective ligands for metal catalyzed enantioselective reactions remains a fundamental goal for further progress in this broad area of research.[1] During the past decades numerous different ligands have been prepared among which the so-called privileged ligands are especially notable. One important class of these privileged ligands in particular are the phosphinooxazoline-ligands (PHOX-ligands) which were originally developed by Helmchen, Pfaltz and Williams in 1993.[2] Various different PHOX-ligands have been synthesized and used in a wide variety of enantioselective reactions as well as in the total synthesis of complex natural products.[3] In general, a crucial aspect for the design of new ligands for metal catalyzed enantioselective reactions appears to be molecular rigidity of the backbone of the ligands.[4] Spiro-fusion of bicyclic compounds provides very rigid molecules in this respect and has already been applied to the construction of ligands for stereoselective catalysis.[3b, 5] Recently, we have extended the concept of spiro-fusion to carbohydrate based ligands and reported the synthesis of D-fructose derived spiro-fused pyridyloxazoline-ligands[6] and the respective PHOX-ligands (Figure 1, **1a**-**1i**).[7] These PHOX ligands were prepared in four to six steps starting from D-fructose where the key steps had been first a Ritter reaction of 1,2-isopropylidene protected fructose derivatives with 2-bromo benzonitrile in order to construct the oxazoline followed by an Ullmann coupling to introduce the diphenyl phosphine moiety. Previously, we obtained high conversion rates (> 99 %) and promising enantiomeric ratios (up to 84:16) with these PHOX-ligands in a Tsuji-Trost reaction of diphenylallyl acetate with dimethyl malonate as a model system.[7] These auspicious results motivated us to further investigate the application of our spiro-fused PHOX-ligands in asymmetric allylic alkylation. Here we present the screening of our ligands **1a**-**1i** in Tsuji-Trost reactions as well as the synthesis and x-ray crystal structures of palladium complexes of **1a** and **1e**. Furthermore, we used these results for mechanistic considerations which led us to construction and preparation of two improved ligands. In order to demonstrate the value of such improved ligands we used them in Pd catalyzed allylic alkylation with various allyl acetates and different nucleophiles.



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1a: $R^1 = R^2$ = Ac
1b: $R^1 = R^2$ = Bn
1c: $R^1 = R^2$ = Bz
1d: $R^1 = R^2$ = Me
1e: $R^1 = R^2$ = Piv

1f: R^1 = Ac, $R^2 = C(CH_3)_2$
1g: R^1 = Bn, $R^2 = C(CH_3)_2$
1h: R^1 = Bn, R^2 = Me
1i: R^1 = Me, R^2 = Bn

Figure 1. Structures of previously reported D-fructose based spiro-fused PHOX-ligands.

Results and Discussion

We chose to apply PHOX-ligands **1a**-**1i** in a Tsuji-Trost reaction between diphenylallyl acetate (**2**) as the electrophile and dimethyl malonate (**3**) as the nucleophile. The reaction has already been studied in detail with other ligands and has often been used as a benchmark test for new ligands.[3e, 8] The allylic alkylation was performed according to a standard procedure with $[PdCl(C_3H_5)]_2$ as palladium source and *N,O*-bis(trimethylsilyl)acetamide (BSA) as base (Scheme 1).[9]

We screened ligands **1a**-**1i** under different reaction conditions, *i.e.* in different solvents and at different temperatures, and evaluated the respective conversion rate and the enantioselectivity. The temperature was varied between 0 °C and room temperature and as solvents CH_2Cl_2, MeCN, PhMe and Et_2O were applied. The solvents were chosen due to their different properties: a halogenated solvent, a solvent which is capable of coordinating metal centers, an aromatic solvent and an ether. All reactions were run for 24 h in order to achieve comparable results. The detailed results of the screening of ligands **1a**-**1i** under the

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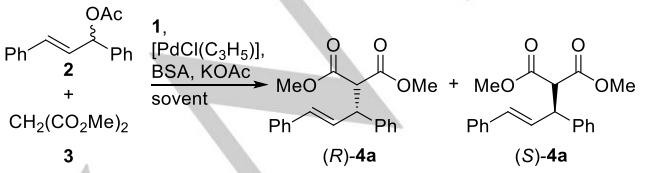
mentioned conditions can be found in the supporting information. (*R*)-**4a** was the main enantiomer in all reactions. Regarding the reaction temperature, it can be concluded that the enantioselectivity increased slightly (maximum from *er* 77:23 to 83:17) whereas the conversion decreased heavily (maximum drop from >99 % to 9 %) when the temperature was lowered from room temperature to 0 °C. By talking a look at the effect of the solvent, we found that the *er* in MeCN and in PhMe was higher than in CH_2Cl_2 or Et_2O in most cases. At room temperature the conversion in all solvents was good. Some key results of the screening of ligands **1a**-**1i** in the Tsuji-Trost reaction are depicted in Table 1.

Table 1. Screening of ligands **1a**-**i** in allylic alkylation.

entry	1	temperature	solvent	conversion[a]	*er* (*R*:*S*)[b]
1[c]	**1a**	rt	PhMe	>99 %	78:22
2[d]	**1a**	rt	PhMe	0 %	n.d.
3	**1a**	rt	MeCN	>99 %	77:23
4[d, e]	**1a**	rt	MeCN	49 %	75:25
5	**1b**	rt	PhMe	>99 %	82:18
6[c]	**1c**	rt	PhMe	>99 %	79:21
7	**1d**	rt	PhMe	>99 %	76:24
8	**1e**	rt	PhMe	53 %	89:11
9[f]	**1e**	rt	PhMe	0 %	n.d.
10	**1e**	rt	MeCN	>99 %	82:18
11[e, f]	**1e**	rt	MeCN	70 %	83:17
12	**1f**	rt	PhMe	74 %	67:33
13	**1g**	rt	PhMe	>99 %	73:27
14	**1h**	rt	PhMe	>99 %	87:13
15	**1i**	rt	PhMe	>99 %	81:19

[a] Determined by HPLC. [b] *er* was determined by chiral HPLC, absolute configuration was assigned by comparison of the optical rotation values with the literature data.[10] [c] Adapted from literature data.[7] [d] **5** was used instead of **1a** and $[PdCl(C_3H_5)]_2$. [e] 20 mol% $AgSbF_6$ were added. [f] **6** was used instead of **1e** and $[PdCl(C_3H_5)]_2$. n.d: not determined.



Scheme 1. Asymmetric allylic alkylation of diphenylallyl acetate.

The substitution pattern at the fructose moiety of the ligands had a significant influence on the enantioselectivity of the reaction. An increase in selectivity was obtained for bulky substituents like the sterically demanding pivaloyl protective groups in ligand **1e**, which provided an *er* of 89:11 in PhMe at room temperature (Table 1, entry 8). **1a** with the less sterically demanding acetyl protective groups provided an *er* of just 78:22 at the same conditions. The same trend could be found by comparing ligand **1b** with bulky benzyl protective groups at the carbohydrate moiety with ligand **1d** with small methyl groups at the fructose ring. A rigid and sterically demanding isopropylidene group at position 4 and 5 of the fructose part even had a negative effect on the stereoselectivity of the reaction. Ligands **1f** and **1g** resulted in low *er* values (Table1, entries 12 and 13). In case of ligand **1h** which has a benzyl group at position 3 and methyl groups at positions 4 and 5, the found *er* value (Table 1, entry 14) was a little higher as for ligand **1b** (Table 1, entry 5) which bears benzyl groups at position 3, 4 and 5. Ligand **1i** carries a small methyl substituent at position 3 and benzyl substituents at positions 4 and 5. The stereoselectivity of ligand **1i** (Table 1, entry 15) is a little smaller than the stereoselectivity of the perbenzylated ligand **1b** (Table 1, entries 5). This led us to the assumption that a bulky substituent at position 3 and small substituents at positions 4 und 5 may have a positive influence on the stereoselectivity of the D-fructose based spiro-fused PHOX ligands. In order to confirm this presumption we decided to prepare palladium complexes of our ligands and determine their respective x-ray crystal structures, thus providing more insight into the mechanism of the Tsuji-Trost reaction with D-fructose based spiro-fused PHOX ligands.

We first attempted to synthesize complexes of our ligands by using $[PdCl(C_3H_5)]_2$ as palladium source. The downfield shift in ^{31}P NMR and mass spectra (see supporting information for details) indicated the formation of palladium PHOX complexes of **1a**, **1c** and **1e** but we were not able to obtain crystals which were suitable for x-ray crystallography. Next, we used $PdCl_2(COD)$ instead of $[PdCl(C_3H_5)]_2$ (Scheme 2) and could finally obtain crystals suitable for x-ray crystallography[11] of the Pd-complexes of **1a** and **1e** by covering a saturated solution of the complex in CH_2Cl_2 with *n*-heptane. The complex derived from ligand **1a** was of the type $PdCl_2$(PHOX) and crystallized as monomer **5b** exhibiting a $^5C_2$ conformation of the pyranose ring instead of a $^2C_5$ conformation as depicted in **5a** (Scheme 2, Figure 2). The formation of complexes of the type $PdCl_2$(PHOX) is common for PHOX ligands and there are some examples of similar complexes with other PHOX ligands in the literature.[12] The pivaloyl protected ligand **1e** afforded the complex **6c** which crystallized as a dimeric complex of the type $[PdCl_2(PHOX)]_2$ (Scheme 2, Figure 3) with the sugar in a $^2C_5$ conformation. Similar dimeric Pd-complexes of the type $[PdCl_2(PHOX)]_2$ are reported in the literature for similar P,N-ligands[13] where the nitrogen does not coordinate the palladium ion while the phosphorous does and the dimeric form is built up by bridging via the two chlorines like in our complex **6c**. We suppose that there are equilibria of the monomeric and the dimeric form for both complexes **5a-d** and **6a-d** in solution because mass spectra indicated the existence of a monomer and

a dimer for both complexes (Scheme 2). Most lilkely, there are equilibria between different conformations of the pyranose chair for the monomeric forms, **5a** and **5b** and **6a** and **6b**, respectively as well as for the dimeric forms **5c** and **5d**, respectively **6c** and **6d** (Scheme 2).

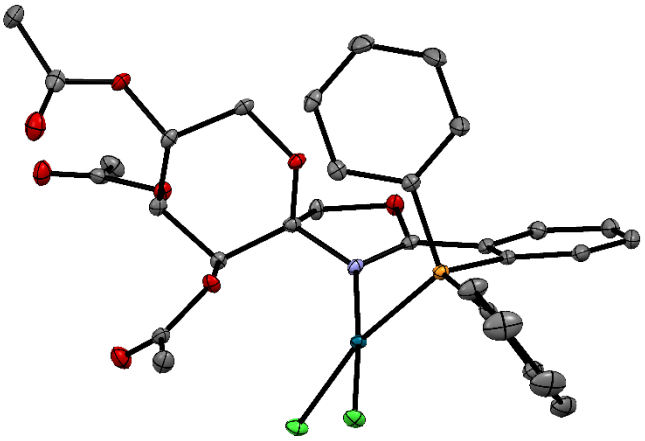


Figure 2. Molecular structure of complex **5b**. Ellipsoids are given at the 50 % probability level. Grey = carbon, red = oxygen, purple = nitrogen, orange = phosphorus, blue = palladium, green = chlorine, hydrogens are omitted for better clarity.

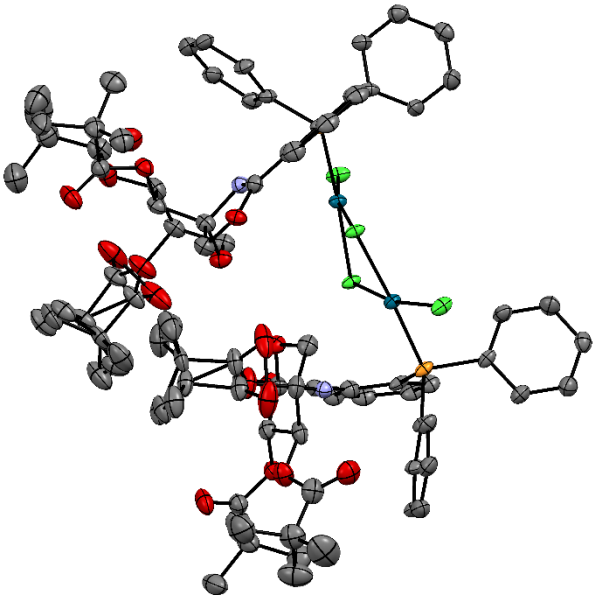
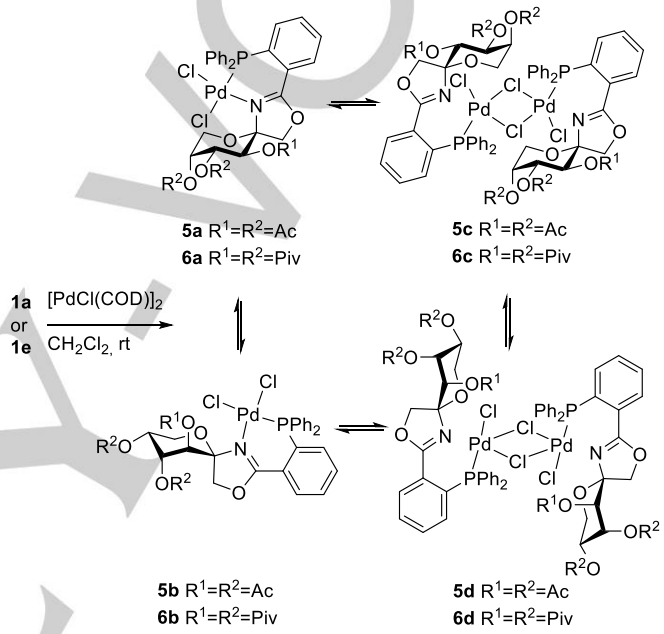


Figure 3. Molecular structure of complex **6c**. Ellipsoids are given at the 50 % probability level. Grey = carbon, red = oxygen, purple = nitrogen, orange = phosphorus, blue = palladium, green = chlorine, hydrogens are omitted for better clarity. The asymmetric units consist four dimers for better clarity only one dimer is shown. For full crystallographic data see supporting information.

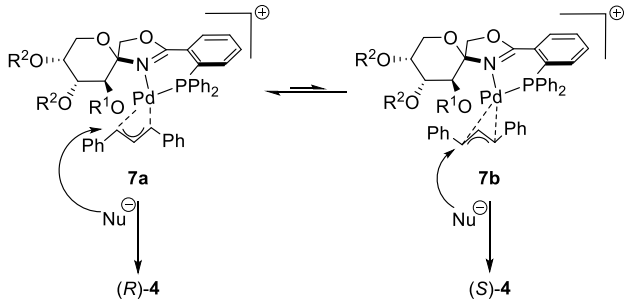
To prove that the molecular structures of the isolated complexes **5** and **6** can act as model system for transition state of the allylic alkylation we decided to use these complexes in the Tsuji-Trost reaction (Scheme 1) instead of a ligand and $[PdCl(C_3H_5)]_2$. With the complexes in PhMe as solvent no conversion was obtained (Table 1, entries 2 and 9). *In situ* dehalogenation with $AgSbF_6$ in MeCN as previously described[8a] provided more reactive derivatives of **5** and **6** which showed *er*'s in a comparable range as for the *in situ* formed complexes of **1a** and **1e** with $[PdCl(C_3H_5)]_2$ (Table 1, entries 4 and 11).



Scheme 2. Preparation of palladium complexes **5** and **6** of **1a** and **1e**.

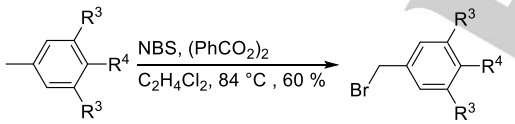
The mechanism of the Tsuji-Trost reaction has been thoroughly studied in detail with various ligands and reasonable models for the transition state of this reaction have been proposed.[3a, 5d, 6b, 14] Taking into account the proposed modes for the transition state of Tsuji-Trost reactions and our crystal structures we propose the following transition state for our fructose derived spiro-fused Pd-PHOX ligands (Scheme 3). Our model implies that after oxidative addition of the allyl acetate (**2**) to the palladium PHOX complex an intermediate allyl palladium species is formed. This intermediate exists as an equilibrium of two diasteromers **7a** and **7b**. Diastereomer **7a** is most likely the main isomer. Diastereomer **7b** should be disfavored due to the steric repulsion between R^1 and the phenyl moiety of the allylic system. The nucleophile preferably attacks the allylic system trans to the phosphorous atom.[3a, 8f, 15] Intermediate **7a** leads to (*R*)-**4** and intermediate **7b** to (*S*)-**4**. Under these assumptions the equilibrium should be forced towards **7a** when R^1 is bulky and accordingly the enantiomeric ratio of the products should be increased. This is in good accordance with our results shown in Table 1. Those ligands having bulky protective groups at all positions (**1b**, **1e**) or a bulky

protective group at position 3 (**1e**) gave higher *er*'s than the ligands with small substituents (for instance **1d** or **1i**).



Scheme 3. Plausible transition state for the Tsuji-Trost reaction with D-fructose based spiro-fused PHOX ligands.

Considering the aforementioned proposed stereo-directing effect of a substituent at position 3 of the spiro-PHOX ligands we prepared some ligands with bulkier substituents at position 3. Although ligand **1e** which bears bulky pivaloy groups gave the highest *er* in our screening (Table 1, entry 8) we chose ether substituents instead because for acyl protecting groups at the carbohydrate moiety the overall yields in the synthesis of the ligands were significantly lower.[7] Thus, we prepared benzylbromides **9a** and **9b** in one step from known **8**[16] (Scheme 4). Compound **9b** is also commercially available. Next, bromides **9a** and **9b** were reacted with diisopropyl-fructose[16] **10** to afford fructose derivatives **11a** and **11b** in 88% and 84% yield, respectively (Scheme 5). Selective hydrolysis of the 4,5-di-*O*-siopeopylidene group in the latter with diluted hydrochloric acid gave **12a** and **12b** in high yields which were finally methylated to afford fructosides **13a** and **13b** in almost quantitative yields.



Scheme 4. Synthesis of benzyl bromide **9a** and structure of **9b**.

For the construction of the oxazoline moiety we used the previously reported Ritter reaction of the 1,2-isopropylidene protected pyranoses **13a** and **13b** with 2-bromobenzonitrile and $BF_3 \cdot OEt_2$.[7] In the final steps we applied Stoltz' protocol for the copper catalyzed coupling of an arylbromide with diphenylphosphine to give PHOX ligands **15a** and **15b** in 86 % and 88 % yield, respectively.

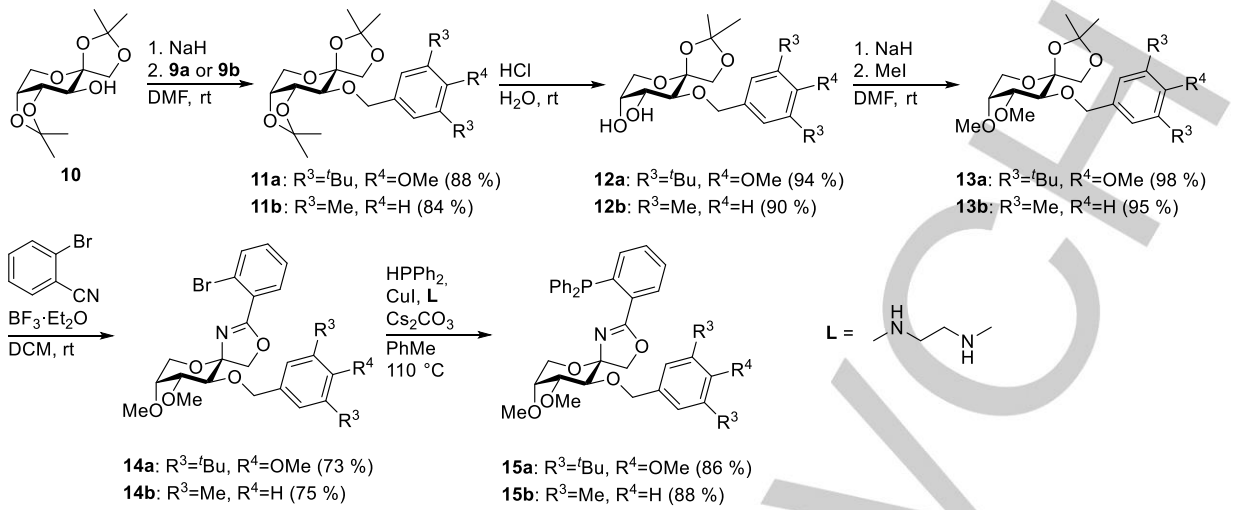
Table 2 summarizes some results (for screening of more solvents see supporting information) of the Tsuji-Trost reaction between diphenylallyl acetate (**2**) and dimethyl malonate (**3**) under catalysis with ligands **15a** and **15b** under identical conditions as depicted in Scheme 1. In almost all tested solvents the *er* of the substitution products was higher than 80:20. The highest enantioselectivities for both ligands **15a** and **15b** were obtained in nonpolar aromatic solvents like toluene or benzene (Table 2, entries 3, 4, 5, 8 and 9) while yields after 24 h were between 19 % and 36 % due to incomplete turnover. All other solvents resulted in lower *er's,* whereas the yields were much higher in these cases. Once again, by lowering the reaction temperature the enatioselectivity increased slightly but the yield decreased rapidly (Table 2, entries 1, 6, 7, 10). Best results (96 % yield, *er* 93:7) were obtained with **15a** in toluene at room temperature after 72 h (Table 2, entry 5). In summary, the *er*'s of the products of the allylic Tsuji-Trost alkylation was significantly higher under catalysis with our improved ligands **15a** and **15b** than with ligands **1a**-**1i**.

Finally, we also reacted a variety of different allylic substrates with dimethyl or diethyl or dibenzyl malonate, malonyldinitrile and 1,3-dimethyl barbituric acid using the optimized reaction conditions with ligand **15a** (Table 3). In all cases yields were high and *er* ranged from 85:15 to 93:7 with (*R*) configuration for the main enantiomer. A noteworthy influence of substituents at the aromatic rings of the allylic acetates on the enantioselectivity of the Tsuji-Trost reaction is not observed. Likewise, we did not find any significant dependence of the enatatioselectivity on the nucleophile.

Table 2. Ligands **15a** and **15b** in allylic alkylation.

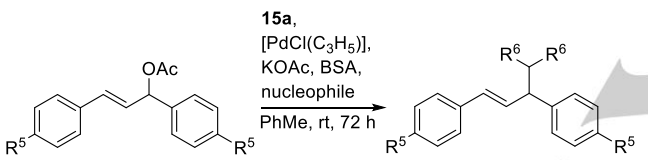
entry	ligand	temp.	solvent	time	Yield [a]	*er* (*R*:*S*)[b]
1	**15a**	rt	CH_2Cl_2	24 h	95 %	82:18
2	**15a**	rt	MeCN	24 h	99 %	82:18
3	**15a**	rt	PhMe	24 h	36 %	93:7
4	**15a**	rt	PhH	24 h	19 %	93:7
5	**15a**	rt	PhMe	72 h	96 %	93:7
6	**15a**	0 °C	CH_2Cl_2	24 h	67 %	85:15
7	**15b**	rt	CH_2Cl_2	24 h	97 %	85:15
8	**15b**	rt	PhMe	24 h	33 %	91:9
9	**15b**	rt	PhH	24 h	22 %	92:8
10	**15b**	0 °C	CH_2Cl_2	24 h	75 %	89:11

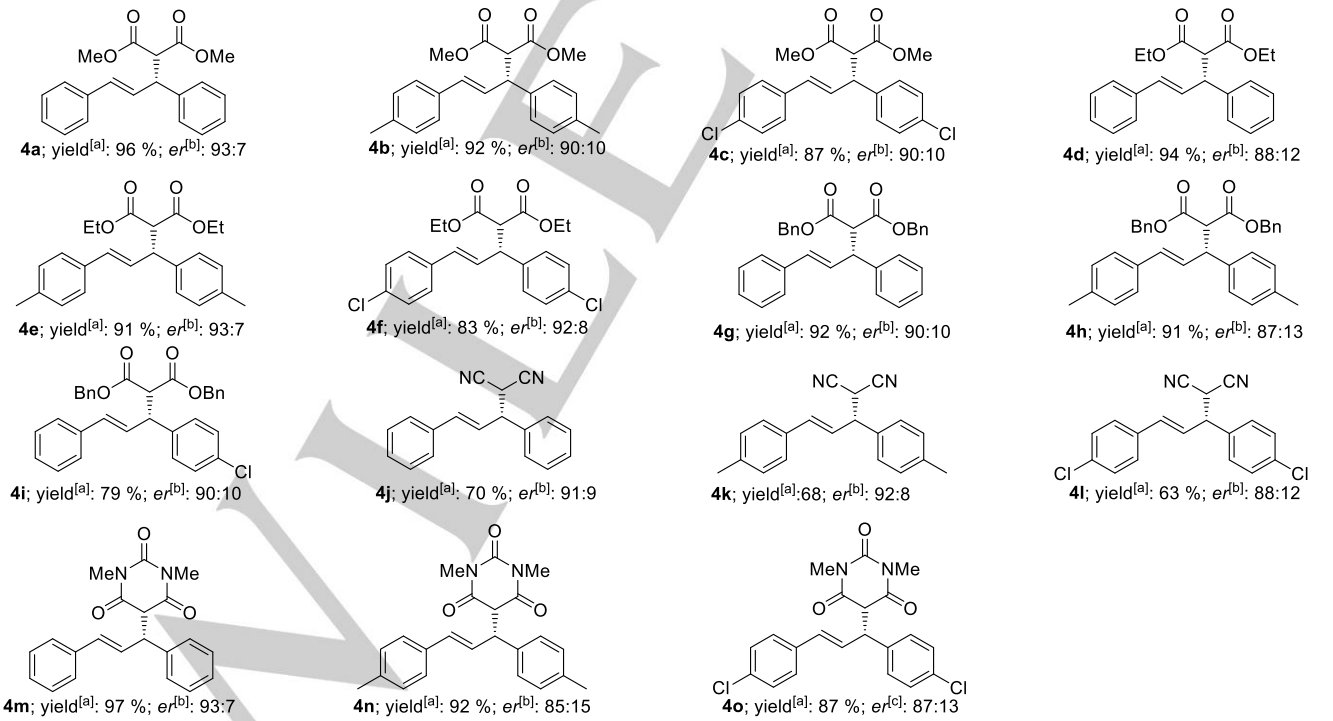
[a] Isolated yield. [b] *er* was determined by chiral HPLC, absolute configuration was assigned by comparison of the optical rotation values with the literature data.[10]



Scheme 5. Synthesis of improved PHOX ligands **15a** and **15b**.

Table 3. Scope of the allylic alkylation using **15a** as ligand.





[a] Isolated yield, reaction was performed on a 100 mg scale, [b] Determined by chiral HPLC, [c] Determined by NMR with $Eu(hfc)_3$ a chiral shift reagent.

Conclusions

We studied previously reported D-fructose based spiro-fused PHOX ligands as catalysts in asymmetric allylic alkylations (Tsuji-Trost reactions) in different solvents and at different temperatures. Furthermore, we could obtain x-ray structures of two palladium-PHOX complexes which allowed a better understanding of the reaction mechanism and the factors influencing the enantioselectivity of this reaction. Based on these studies we developed a second generation of two D-fructose based spiro-fused PHOX ligands having bulky benzyl groups at position 3 of the fructose moiety. This second generation of spiro-fused PHOX ligands allowed to prepare a series of diarylallyl malonates with high enantiomeric ratios (*er*'s up to 93:7). Further improvement (for instance by modification of the electronically environment at the phosphorous) may lead to D-fructose based spiro-fused PHOX ligands with an enantioselectivity comparable to classical PHOX ligands.[2]

Experimental Section

General

All reactions were carried out under an atmosphere of nitrogen. Dry toluene and THF were distilled from sodium, dry CH_2Cl_2, $C_2H_4Cl_2$, MeCN and DMF were distilled from P_4O_{10}. Chlorobenzene, nitrobenzene and benzonitrile were dried with a column of basic aluminium oxide. Dry solvents were stored over molecular sieves under an atmosphere of nitrogen. For reaction monitoring TLC plates from Macherey–Nagel "Polygram Sil G/U_{254}" were used. Preparative column chromatography was performed with silica gel "60 M" which was purchased from Macherey–Nagel. Solvents used as eluents were technical grade and distilled prior to their use. Petroleum ether (PE) refers to the fraction boiling at 60 – 90 °C. NMR spectra were recorded on a Bruker "Avance III HD 400" spectrometer and calibrated to the solvent signal ($CDCl_3$: ^{1}H 7.27 ppm, ^{13}C 77.0 ppm; CD_3OD: ^{1}H 3.31 ppm, ^{13}C 49.2 ppm) or to the internal standard TMS (^{1}H 0.00 ppm, ^{13}C 0.0 ppm). For peak assignment additional NMR spectra (DEPT-135, ^{1}*H*,^{1}*H*-COSY, ^{1}*H*,^{13}*C* -HMBC, ^{1}*H*,^{13}*C*-HSQC) were used and atoms were numbered according to the carbohydrate nomenclature. High resolution mass spectra were measured on a Bruker "maXis 4G" with electrospray ionization and a time of flight detector or on a Finnigan "MAT95" with electronic ionization. Mass spectra were recorded on a "Bruker Esquire 3000 Plus". Optical rotations were measured with a Perkin-Elmer "Polarimeter 341". Melting points were determined with a Büchi "Melting Point M-560" apparatus. Elemental analysis was performed on a HEKAtech "Euro 3000 CHN". X-ray data were collected on a Bruker "SMART APEX II DUO" diffractometer. Crystallographic data have been deposited to the Cambridge Crystallographic Data Centre, CCDC (1906320 for **5b**; 1906321 for **6c**). Enantiomeric ratio was determined by HLPC, using a Sykam "S 1121" chromatograph equipped with a Dr Maisch "Reprosil Chiral-NR, 8 µm, 150 × 4.6 mm" column or a Dr Maisch "Reprosil Chiral-AM, 5 µm, 125 × 4.6 mm" column. Conversions were measured by HPLC using a Sykam "S 1121" chromatograph equipped with a Grom "Saphir 65 Si, 5 µm, 250 × 4.6 mm" column.

Dichloro[(5*R*,8*R*,9*R*,10*S*)-2-(2-(diphenylphosphaneyl)phenyl)-3,6-dioxa-1-azaspiro[4.5]dec-1-ene-8,9,10-triyl-triacetate]palladium(II) (**5**)**:** To a solution of **1a** (102 mg, 0.177 mmol) in 5 ml dry CH_2Cl_2 was $PdCl_2COD$ (50.5 mg, 0.177 mmol) added and the reaction mixture was stirred at room temperature for 90 min. The solvent was evaporated in vacuo and the residue was recrystallized from CH_2Cl_2 and *n*-hexanes. **5** (130 mg, 98 %) was obtained as orange solid. Crystals for x-ray crystallography were prepared by covering a saturated solution of **5** in CH_2Cl_2 with *n*-heptane. R_f = 0.11 (EtOAc + 2 % Et_3N); $[\alpha]^{20}_D$ + 241° (c = 0.1, CH_2Cl_2); mp = > 207 °C (decomposition, CH_2Cl_2/*n*-heptane); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 28.48, 22.36 ppm; MS (ESI): *m/z* 716.0 $[M\text{-}Cl]^+$, 1468.9 $[2M\text{-}Cl]^+$; HRMS (ESI-TOF) m/z $[M\text{-}Cl]^+$: calcd for $C_{31}H_{30}NClO_8PPd$: 716.04269, found: 716.04220; Anal calcd for $C_{31}H_{30}NCl_2O_8PPd$: C 49.46, H 4.02, N 1.86, found: C 49.34, H 4.31, N 1.85.

Dichloro[(5*R*,8*R*,9*R*,10*S*)-2-(2-(diphenylphosphaneyl)phenyl)-3,6-dioxa-1-azaspiro[4.5]dec-1-ene-8,9,10-triyl-tris(2,2-dimethylpropanoate)] palladium(II) (**6**)**:** To a solution of **1e** (23 mg, 0.033 mmol) in 1.5 ml dry CH_2Cl_2 $PdCl_2COD$ (9.4 mg, 0.033 mmol) was added and the reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated in vacuo and the residue was recrystallized from CH_2Cl_2 and *n*-hexanes. **6** (25 mg, 86 %) was obtained as orange solid. Crystals for x-ray crystallography were prepared by covering a saturated solution of **6** in CH_2Cl_2 with *n*-heptane. R_f = 0.75 (EtOAc/2-propanol 1/1 + 2 % Et_3N); $[\alpha]^{20}_D$ -260 ° (c = 0.1, CH_2Cl_2); mp = > 230 °C (decomposition, CH_2Cl_2/*n*-heptane); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 26.62, 23.76 ppm; HRMS (ESI-TOF) m/z $[M\text{-}Cl]^+$: calcd for $C_{40}H_{48}NClO_8PPd$: 842.18354, found: 842.1895, m/z $[2M\text{-}Cl]^+$: calcd for $C_{80}H_{96}N_2Cl_2O_{16}P_2Pd_2$: 1719.34405, found: 1719.33649; Anal calcd for $C_{40}H_{48}NCl_2O_8PPd$: C 54.65, H 5.50, N 1.59, found: C 54.40, H 5.74, N 1.40.

5-(Bromomethyl)-1,3-di-*tert*-butyl-2-methoxybenzene (**9a**)**:** A mixture of **8**[16] (5.30 g, 22.6 mmol), *N*-bromosuccinimide (4.03 g, 22.6 mmol) and benzoyl peroxide (219 mg, 0.68 mmol; 75 %, remainder water) in dry $C_2H_4Cl_2$ was heated at reflux (oil bath: 90 °C) for 90 min, after 60 min again benzoyl peroxide (219 mg, 0.68 mmol; 75 %, remainder water) was added. The reaction mixture was cooled to room temperature, filtered and the solvent evaporated in vacuo. Column chromatography (PE) provided **9a** (4.23 g, 60 %) as a colorless solid. R_f = 0.25 (PE); mp = 58 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (s, 2 H, H-Ar), 4.50 (s, 2 H, CH_2Br), 3.70 (s, 3 H, OCH_3), 1.44 (s, 18 H, $C(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.7 (*C*OCH_3), 144.1 (*C*CH_2Br), 131.6 (*C*$C(CH_3)_3$), 127.7 (CH), 64.3 (OCH_3), 35.8 (*C*$(CH_3)_3$), 34.82 (CH_2Br), 32.0 (*C*$(CH_3)_3$) ppm; HRMS (EI) m/z $[M]^+$ calcd for $C_{16}H_{25}BrO$: 312.10833, found: 312.11107; Anal calcd for $C_{16}H_{25}BrO$: C 61.34, H 8.04, found: C 61.55, H 8.10.

3-*O*-(3,5-Di-*tert*-butyl-4-methoxy)benzyl-1,2:4,5-*O*-diisopropylidene-β-D-fructopyranose (**11a**): To a solution of **10**[17] (3.22 g, 12.4 mmol) 35 ml dry DMF NaH (904 mg, 22.6 mmol; 60 % dispersion in mineral oil) was added. The solution was cooled to 0 °C and a solution of **9a** (3.63 g, 11.6 mmol) in 20 ml dry DMF was added over a period of 10 min. The cooling was removed, the reaction mixture was stirred at room temperature for 2 h, quenched with MeOH and concentrated in vacuo. The residue was re-dissolved in EtOAc (150 ml) and washed with water (1 × 75 ml). After drying over Na_2SO_4 the solvent was evaporated in vacuo. Column chromatography (PE/EtOAc, 10/1) provided **11a** (5.04 g, 88 %) as a colorless syrup. R_f = 0.42 (PE/EtOAc, 8/1); $[\alpha]^{20}_D$ - 61.5° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (s, 2 H, H-Ar), 4.92 (d, *J*=11.9 Hz, 1 H, CH_2Ar), 4.61 (d, *J*=11.9 Hz, 1 H, CH_2Ar), 4.36 – 4.42 (m, 1 H, H-4), 4.21 – 4.25 (m, 1 H, H-5), 4.10 – 4.19 (m, 2 H, H-1a, H-6a), 4.02 (d, *J*=13.3 Hz, 1 H, H-6b), 3.90 (d, *J*=8.4 Hz, 1 H, H-1b), 3.68 (s, 3 H, OCH_3), 3.51 (d, *J*=7.3 Hz, 1 H, H-3), 1.56 (s, 3 H, $C(CH_3)_2$), 1.51 (s, 3 H, $C(CH_3)_2$), 1.45 (s, 3 H, $C(CH_3)_2$), 1.43 (s, 18 H, $C(CH_3)_3$), 1.40 (s, 3 H, $C(CH_3)_2$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.9, 143.4, 132.1, 125.8 (C-Ar), 112.1, 108.9 (*C*$(CH_3)_2$), 104.5 (C-2), 77.9 (C-5), 76.1 (C-3), 73.9 (C-4), 73.5 (CH_2Ar), 71.9 (C-1), 64.2 (OCH_3), 60.1 (C-6), 35.7 (*C*$(CH_3)_3$), 32.1 (C$(CH_3)_3$), 28.3, 26.8, 26.3, 26.1 (C$(CH_3)_2$) ppm; HRMS (ESI-TOF) m/z $[M+Na]^+$: calcd for $C_{28}H_{44}O_7Na$: 515.29792, found: 515.29813; Anal calcd for $C_{28}H_{44}O_7$: C 68.26, H 9.00, found: C 68.14, H 9.07.

3-*O*-(3,5-Dimethyl)benzyl-1,2:4,5-*O*-diisopropylidene-β-D-fructopyranose (**11b**): To a solution of **10**[17] (3.22g, 12.4 mmol) 40 ml in dry NaH (904 mg, 22.6 mmol; 60 % dispersion in mineral oil) DMF was added. The solution was cooled to 0 °C and a solution of **9b** (2.24 g, 11.3 mmol) in 20 ml dry DMF was added over a period of 10 min. The cooling was removed, the reaction mixture was stirred at room temperature for 2 h and poured into 50 ml of ice-water. The resulting solution was extracted with EtOAc (3 × 100 ml), dried over Na_2SO_4 and the solvent evaporated in vacuo. Column chromatography (PE/EtOAc, 8/1) provided **11b** (3.94 g, 84 %) as a colorless oil. R_f = 0.33 (PE/EtOAc, 8/1); $[\alpha]^{20}_D$ - 73.3° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.99 (s, 2 H, H-Ar), 6.92 (s, 1 H, H-Ar), 4.91 (d, *J* = 11.9 Hz, 1 H, CH_2Ar), 4.60 (d, *J* = 11.9 Hz, 1 H, CH_2Ar), 4.39 (dd, *J* = 7.1, 5.9 Hz, 1 H, H-4), , 4.23 (dd, *J* = 5.9, 2.2 Hz, 1 H, H-5), 4.15 (dd, *J* = 13.3, 2.2 Hz, 1 H, H-6a), 4.09 (d, *J* = 8.4 Hz, 1 H, H-1a), 3.00 (d, *J* =13.3 Hz, 1 H, H-6b), 3.88 (d, *J* = 8.4 Hz, 1 H, H-1b), 3.49 (d, *J* = 7.1 Hz, 1 H, H-3), 2.31 (s, 6 H, CH_3Ar), 1.55 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.0, 137.7, 129.1, 125.7 (C-Ar), 112.1, 109.0 (*C*(CH_3)$_2$), 104.4 (C-2), 77.8 (C-4), 75.6 (C-3), 73.8 (C-5), 73.0 (CH_2Ar), 71.8 (C-1), 60.1 (C-6), 28.1, 26.9, 26.2, 26.0 (C(*C*H_3)$_2$), 21.2 (CH_3Ar) ppm; HRMS (ESI-TOF) m/z $[M+Na]^+$: calcd for $C_{21}H_{30}O_6Na$: 401.19346, found: 401.19356; Anal calcd for $C_{21}H_{30}O_6$: C 66.65, H 7.99, found: C 66.87, H 8.06.

3-*O*-(3,5-Di-*tert*-butyl-4-methoxy)benzyl-1,2-*O*-isopropylidene-β-D-fructo-pyranose (**12a**): **11a** (4.10 g, 8.32 mmol) was dissolved in 250 ml THF, 200 ml hydrochloric acid (0.1 % in water) were added and the mixture was stirred at room temperature for 13 d. The reaction mixture was neutralized with Na_2CO_3 and the THF was evaporated in vacuo. The resulting aqueous suspension was extracted with EtOAc (3 × 250 ml), dried over Na_2SO_4 and concentrated in vacuo. Column chromatography of the residue (PE/EtOAc, 1/1) provided **12a** (3.54 g, 94 %) as a colorless solid. R_f = 0.36 (PE/EtOAc, 1/1); mp = 62 °C (CH_2Cl_2); $[\alpha]^{20}_D$ – 79.4° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (s, 2 H, H-Ar), 4.70 (s, 2 H, CH_2Ar), 4.06 (d, *J* = 8.7 Hz, 1 H, H-1a), 4.03 – 3.98 (m, 2 H, H-1b, H-4), 3.97 – 3.91 (m, 2 H, H-5, H-6a), 3.77 (dd, *J* = 2.0, 13.0 Hz, 1 H, H-6b), 3.70 – 3.65 (m, 4 H, H-3, OCH_3), 2.50 (bs, 2 H, 2×OH), 1.50 (s, 3 H, C(CH_3)$_2$), 1.45 (s, 3 H, C(CH_3)$_2$), 1.42 (s, 18 H, C(CH_3)$_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.4, 144.0, 131.7, 126.5 (C-Ar), 111.8 (*C*(CH_3)$_2$), 105.6 (C-2), 76.3 (C-3), 75.9 (CH_2Ph), 71.7 (C-1), 71.2 (C-4), 69.6 (C-5), 64.2 (OCH_3), 63.5 (C-6), 35.7 (*C*(CH_3)$_3$), 32.0 (C(*C*H_3)$_3$), 26.8, 26.2 (C(*C*H_3)$_2$) ppm; HRMS (ESI-TOF) m/z $[M+Na]^+$: calcd for $C_{25}H_{40}O_7Na$: 475.26662, found: 475.26672; Anal calcd for $C_{25}H_{40}O_7$: C 66.35, H 8.91, found: C 66.35, H 9.07.

3-*O*-(3,5-Dimethyl)benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose (**12b**): **11b** (3.75 g, 9.9 mmol) was dissolved in 250 ml THF and 150 ml hydrochloric acid (0.1 % in water) were added and the mixture was stirred at room temperature for 4 d. The reaction mixture was neutralized with Na_2CO_3 and the solvents were evaporated in vacuo. Column chromatography (PE/EtOAc, 1/2) provided **12b** (3.03 g, 90 %) as a colorless solid. R_f = 0.39 (PE/EtOAc, 1/2); mp = 103 °C (CH_2Cl_2); $[\alpha]^{20}_D$ - 124.5° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.98 (s, 2 H, H-Ar), 6.95 (s, 1 H, H-Ar), 4.69 (s, 2 H, CH_2Ar), 4.06 (d, *J* = 8.7 Hz; 1 H, H-1a), 3.90 – 4.03 (m, 4 H, H-1b, H-4, H-5, H-6a), 3.75 (dd, *J* = 2.0, 13.0 Hz, 1 H, H-6b), 3.67 (d, J = 9.5 Hz, 1 H, H-3), 2.54 (bs, 2 H, 2×OH), 2.31 (s, 6 H, CH_3Ar), 1.50 (s, 3 H, C(CH_3)$_2$), 1.45 (s, 3 H, C(CH_3)$_2$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.2, 137.7, 129.7, 125.7 (C-Ar), 111.9 (*C*(CH_3)$_2$), 105.6 (C-2), 76.4 (C-3), 75.4 (CH_2Ar), 71.7 (C-1), 71.1 (C-4), 69.6 (C-5), 63.5 (C-6), 26.8, 26.1 (C(CH_3)$_2$), 21.2 (CH_3Ar) ppm; HRMS (ESI-TOF) m/z $[M+Na]^+$: calcd for $C_{18}H_{26}O_6Na$: 361.16212, found: 361.16225; Anal calcd for $C_{18}H_{26}O_6$: C 63.89, H 7.74, found: C 63.84, H 7.82.

3-*O*-(3,5-Di-*tert*-butyl-4-methoxy)benzyl-1,2-*O*-isopropylidene-4,5-di-*O*-methyl-β-D-fructopyranose (**13a**): To a solution of **12a** (2.96 g, 6.55 mmol) in 40 ml dry DMF NaH (1.05 g, 26.2 mmol, 60 % dispersion in mineral oil) was added over a period of 20 min. After complete addition the reaction mixture was cooled to 0 °C and MeI (1.6 ml, 26 mmol) was added over a period of 10 min. The reaction was allowed to reach room temperature and it was stirred at this temperature for 4 h. The reaction mixture was quenched with MeOH and concentrated in vacuo. The residue was dissolved in EtOAc (100 ml), washed with water (2 × 50 ml), dried over Na_2SO_4 and the solvent was evaporated in vacuo. Column chromatography (PE/EtOAc, 5/1) provided **13a** (2.09 g, 95 %) as a colorless oil. R_f = 0.30 (PE/EtOAc, 4/1); $[\alpha]^{20}_D$ - 76.8 ° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 (s, 2 H, H-Ar), 4.90 (d, *J* = 11.2 Hz, 1 H, CH_2Ar), 4.53 (d, *J* = 11.2 Hz, 1 H, CH_2Ar), 3.96 (d, *J* = 8.4 Hz, 1 H, H-1a), 3.93 – 3.86 (m, 2 H, H-1b, H-6a), 3.80 – 3.63 (m, 7 H, H-3, H-4, H-5, H-6b, OCH_3), 3.52 (s, 3 H, OCH_3), 3.49 (s, 3 H, OCH_3), 1.48 (s, 3 H, C(CH_3)$_2$), 1.43 (s, 3 H, C(CH_3)$_2$), 1.42 (s, 18 H, C(CH_3)$_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.0, 143.4, 132.3, 126.3 (C-Ar), 111.8 (*C*(CH_3)$_2$), 105.7 (C-2), 81.4 (C-5), 75.9 (CH_2Ar), 75.6 (C-4), 74.9 (C-3), 71.8 (C-1), 64.2 (OCH_3), 59.9 (C-6), 57.5 (OCH_3), 57.2 (OCH_3), 35.6 (*C*(CH_3)$_3$), 31.9 (C(*C*H_3)$_3$), 27.0 (C(*C*H_3)$_2$), 26.2 (C(CH_3)$_2$) ppm; HRMS (ESI-TOF) m/z $[M+Na]^+$: calcd for $C_{27}H_{44}O_7Na$: 503.29792, found: 503.29768 ; Anal calcd for $C_{20}H_{30}O_6$: C 67.47, H 9.23, found: C 67.47, H 9.33.

3-*O*-(3,5-Dimethyl)benzyl-1,2-*O*-isopropylidene-4,5-di-*O*-methyl-β-D-fructopyranose (**13b**): To a solution of **12b** (2.04 g, 6.03 mmol) in 50 ml dry DMF NaH (964 mg, 24.1 mmol; 60 % dispersion in mineral oil) was added and the reaction mixture was stirred for 60 min at room temperature. MeI (1.5 ml, 24 mmol) was added and the resulting solution was stirred at room temperature for 4 h. The reaction was quenched with MeOH and concentrated in vacuo. The residue was dissolved in EtOAc (100 ml), washed with water (2 × 50 ml), dried over Na_2SO_4 and the solvent was evaporated in vacuo. Column chromatography (PE/EtOAc, 3/1) provided **13b** (2.09 g, 95 %) as a colorless oil. R_f = 0.32 (PE/EtOAc, 3/1); $[\alpha]^{20}_D$ – 106.4° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.99 (s, 2 H, H-Ar), 6.91 (s, 1 H, H-Ar), 4.93 (d, *J* = 11.5 Hz, 1 H, CH_2Ar), 4.54 (d, *J* = 11.5 Hz, 1 H, CH_2Ar), 4.01 – 3.85 (m, 3 H, H-1a, H-1b, H-6a), 3.82 – 3.63 (m, 4 H, H-3, H-4, H-5, H-6b), 3.52 (s, 3 H, OCH_3), 3.49 (s, 3 H, OCH_3), 2.30 (s, 6 H, CH_3Ar), 1.49 (s, 3 H, C(CH_3)$_2$), 1.44 (s, 3 H, C(CH_3)$_2$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.4, 137.7, 129.0, 125.5 (C-Ar), 111.8 (*C*(CH_3)$_2$), 105.7 (C-2), 81.4 (C-4 or C-5), 75.7 (C-4 or C-5), 75.4 (CH_2Ar), 74.9 (C-3), 71.8 (C-1), 59.8 (C-6), 57.4 (OCH_3), 57.3 (OCH_3), 27.1 (C(*C*H_3)$_2$), 26.1 (C(*C*H_3)$_2$), 21.2 (CH_3Ar) ppm; HRMS (ESI-TOF) m/z $[M+Na]^+$: calcd for $C_{20}H_{30}O_6Na$: 389.19346, found: 389.19344 ; Anal calcd for $C_{20}H_{30}O_6$: C 65.55, H 8.25, found: C 65.17, H 8.22.

(5*R*,8*R*,9*R*,10*S*)-2-(2-Bromophenyl)-10-((3,5-di-*tert*-butyl-4-methoxy-benzyl)oxy)-8,9-dimethoxy-3,6-dioxa-1-azaspiro[4.5]dec-1-ene (**14a**): **13a** (900 mg, 1.87 mmol) and 2-bromobenzonitrile (5.11 g, 28.1 mmol) were dissolved in 5 ml dry CH_2Cl_2 and $BF_3{\cdot}OEt_2$ (0.50 ml, 1.9 mmol; 48 % in Et_2O) was added. After stirring at room temperature for 90 min the reaction was quenched with Et_3N (3 ml) und the solvent was evaporated in vacuo. Column chromatography of the residue (PE + 2 % Et_3N → PE/EtOAc, 5/1 + 2% Et_3N) provided **14a** (825 mg, 73 %) as colorless oil. R_f = 0.40 (PE/EtOAc, 3/1 + 2 % Et_3N); $[\alpha]^{20}_D$ - 110.0° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 – 7.70 (m, 1 H, H-Ar), 7.66 – 7.60 (m, 1 H, H-Ar), 7.35 – 7.24 (m, 2 H, H-Ar), 7.18 (s, 2 H, H-Ar), 4.94 (d, *J* = 11.6 Hz, 1 H, CH_2Ar), 4.62 (d, *J* = 11.6 Hz, 1 H, CH_2Ar), 4.25 – 4.08 (m, 3 H, H-1a, H-1b, H-6a), 4.04 – 3.94 (m, 2 H, H-4, H-6b), 3.87 (d, *J* = 9.7 Hz, 1 H, H-3), 3.80 – 3.75 (m, 1 H, H-5), 3.65 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3), 3.54 (s, 3 H, OCH_3), 1.38 (s, 18 H, C(CH_3)$_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 165.8 (OCN), 158.9, 143.4, 133.9, 132.5, 131.8, 131.7, 129.4, 126.9, 126.2, 122.1 (C-Ar), 103.2 (C-2), 81.8 (C-4), 77.1 (C-3), 76.2 (C-5), 75.4 (CH_2Ar), 74.6 (C-1), 64.2 (OCH_3), 61.6 (C-6), 57.7 (OCH_3), 57.3 (OCH_3), 35.6 (*C*(CH_3)$_3$), 32.0 (C(*C*H_3)$_3$) ppm; HRMS (ESI-TOF) m/z $[M+H]^+$: calcd for $C_{31}H_{43}NBrO_6$: 604.22683, found: 604.22647; Anal calcd for $C_{31}H_{42}NBrO_6$: C 61.59, H 7.00, N: 2.32 found: C 61.87, H 7.15, N 2.19.

(5*R*,8*R*,9*R*,10*S*)-2-(2-Bromophenyl)-10-((3,5-dimethylbenzyl)oxy)-8,9-dimethoxy-3,6-dioxa-1-azaspiro[4.5]dec-1-ene (**14b**): **13b** (902 mg, 2.46 mmol) and 2-bromobenzonitrile (6.72 g, 36.9 mmol) were dissolved in 5 ml dry CH_2Cl_2 and $BF_3{\cdot}OEt_2$ (0.65 ml, 2.5 mmol; 48 % in Et_2O) was added. After stirring at room temperature for 120 min the reaction was quenched with Et_3N (3 ml) und the solvent was evaporated in vacuo. Column chromatography of the residue (PE + 2 % Et_3N → PE/EtOAc, 3/1 + 2% Et_3N) provided **14b** (898 mg, 75 %) as colorless oil. R_f = 0.29 (PE/EtOAc, 3/1 + 2 % Et_3N); $[\alpha]^{20}_D$ - 148.1° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (dd, *J* = 1.8, 7.6 Hz, 1 H, H-Ar), 7.64 (dd, *J* = 1.2, 7.8 Hz, 1 H, H-Ar), 7.38 – 7.26 (m, 2 H, H-Ar), 6.95 (s, 2 H, H-Ar), 6.89 (s, 1 H, H-Ar), 4.98 (d, *J* = 11.9 Hz, 1 H, CH_2Ar), 4.62 (d, *J* = 11.9 Hz, 1 H, CH_2Ar), 4.22 – 4.14 (m, 3 H, H-1a. H-1b, H-6a), 4.03 – 3.94 (m, 2 H, H-4, H-6b), 3.87 (d, *J* = 9.7 Hz, 1 H, H-3), 3.80 – 3.75 (m, 1 H, H-5), 3.54 (s, 3 H, OCH_3), 3.54 (s, 3 H, OCH_3), 2.27 (s, 6 H, CH_3Ar) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.0, 138.6, 137.7, 133.8, 131.8, 131.6, 129.7, 129.0, 126.9, 125.3, 122.0 (C-Ar), 103.1 (C-2), 81.7 (C-4), 77.2 (C-3), 76.2 (C-5), 74.9 (CH_2Ar), 74.8 (C-1), 61.5 (C-6), 57.7 (OCH_3), 57.4 (OCH_3), 21.2 (CH_3Ar) ppm; HRMS (ESI-TOF) m/z $[M+H]^+$: calcd for $C_{24}H_{29}NBrO_5$: 490.12236, found: 490.12222; Anal calcd for $C_{24}H_{28}NBrO_5$: C 58.78, H 5.76, N: 2.86 found: C 58.77, H 5.89, N 2.68.

(5*R*,8*R*,9*R*,10*S*)-10-((3,5-di-*tert*-butyl-4-methoxybenzyl)oxy)-2-(2-(di-phenylphosphaneyl)phenyl)-8,9-dimethoxy-3,6-dioxa-1-azaspiro[4.5]dec-1-ene (**15a**): A solution of CuI (16.5 mg, 87µmol), *N*,*N*'-dimethylethylenediamine (65 µl, 0.61 mmol) and diphenylphosphine (230 µl, 1.31 mmol) in 3 ml dry toluene was stirred at room temperature for 20 min. Cs_2CO_3 (849 mg, 2.61 mmol) and **14a** (420 mg, 0.70 mmol; 0.1 M in dry toluene) were added and the mixture was heated to 110 °C for 17 h. The reaction mixture was cooled to room temperature, filtered and concentrated. Column chromatography of the residue (*n*-hexanes/EtOAc, 5/1 + 2% Et_3N) provided **15a** (434 mg, 86 %) as colorless solid. R_f = 0.45 (*n*-hexanes/EtOAc, 3/1 + 2% Et_3N); mp = 86 °C (CH_2Cl_2); $[\alpha]^{20}_D$ - 162.7° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 – 7.96 (m, 1 H, H-Ar), 7.44 – 7.37 (m, 1 H, H-Ar), 7.36 – 7.18 (m, 11 H, H-Ar), 7.14 (s, 2 H, H-Ar), 6.92 – 6.86 (m, 1 H, H-Ar), 4.84 (d, *J* = 12.0 Hz, 1 H, CH_2Ar), 4.51 (d, *J* = 12.0 Hz, 1 H, CH_2Ar), 4.17 (d, *J* = 9.5 Hz, 1 H, H-1a), 4.08 (d, *J* = 9.5 Hz, 1 H, H-1b), 3.74 – 3.65 (m, 5 H, H-3, H-6a, OCH_3), 3.60 – 3.51 (m, 1 H, H-6b), 3.46 (s, 3 H, OCH_3), 3.44 – 3.41 (m, 1 H, H-5), 3.36 (s, 3 H, OCH_3), 3.29 (dd, *J* = 3.4, 9.7 Hz, 1 H), 1.38 (s, 18 H, $C(CH_3)_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.3 (d, *J* = 2.2 Hz, OCN), 158.5, 143.2, 139.6 (d, *J* = 12.5 Hz), 139.3 (d, *J* = 6.6 Hz), 139.0 (d, *J* = 10.3 Hz), 134.4 (d, *J* = 64.6 Hz), 133.8 (d, *J* = 8.8 Hz), 133.3 (d, *J* = 65.3 Hz), 131.8, 131.6, 130.9, 129.7, 128.3, 128.2, 128.1, 128.0, 125.4 (C-Ar), 103.8 (C-2), 81.3 (C-4), 77.2 (C-3) 76.6 (C-5), 74.1 (CH_2Ar), 74.1 (C-1), 64.2 (OCH_3), 61.8 (C-6), 57.6 (OCH_3), 57.4 (OCH_3), 35.7 ($C(CH_3)_3$), 32.0 ($C(CH_3)_3$) ppm; ^{31}P NMR (126 MHz, $CDCl_3$) δ = -5.56 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$: calcd for $C_{43}H_{53}NPO_6$: 710.36050, found: 710.35992; Anal calcd for $C_{43}H_{52}NPO_6$: C 72.76, H 7.38, N: 1.97 found: C 72.67, H 7.60, N 1.96.

(5*R*,8*R*,9*R*,10*S*)-10-((3,5-Dimethylbenzyl)oxy)-2-(2-(diphenyl-phosphaneyl)phenyl)-8,9-dimethoxy-3,6-dioxa-1-azaspiro[4.5]dec-1-ene (**15b**): A solution of CuI (14.5 mg, 77µmol), *N*,*N*'-dimethylethylenediamine (57 µl, 0.54 mmol) and diphenylphosphine (200 µl, 1.15 mmol) in 3 ml dry toluene was stirred at room temperature for 20 min. Cs_2CO_3 (748 mg, 2.30 mmol) and **14b** (300 mg, 0.61 mmol; 0.1 M in dry toluene) were added and the mixture was heated to 110 °C for 20 h. The reaction mixture was cooled to room temperature, filtered and concentrated. Column chromatography of the residue (PE/EtOAc, 3/1 + 2% Et_3N) provided **15b** (321 mg, 88 %) as colorless solid. R_f = 0.39 (PE/EtOAc, 4/1 2% Et_3N); mp = 62 °C (CH_2Cl_2); $[\alpha]^{20}_D$ - 126.7° (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 – 7.88 (m, 1 H, H-Ar), 7.31 – 7.11 (m, 12 H, H-Ar), 6.83 – 6.75 (m, 4 H, H-Ar), 4.72 (d, *J* = 12.1 Hz, 1 H, CH_2Ar), 4.40 (d, *J* = 12.1 Hz, 1 H, CH_2Ar), 4.08 (d, *J* = 9.4 Hz, 1 H, H-1a), 3.99 (d, *J* = 9.4 Hz, 1 H, H-1b), 3.70 – 3.53 (m, 3 H, H-3, H-6a, H-6b), 3.37 (s, 3 H, OCH_3), 3.35 – 3.32 (m, 1 H, H-5), 3.23 (s, 3 H, OCH_3), 3.15 (dd, *J* = 3.3, 9.7 Hz, 1 H, H-4), 2.17 (s, 6 H, CH_3Ar) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.4 (d, *J* = 2.2 Hz, OCN), 139.4 (d, *J* = 13.2 Hz) 139.2 (d, *J* = 6.6 Hz), 139.1 (d, *J* = 9.5 Hz), 137.5, 134.1 (d, *J* = 20.5 Hz), 133.5 (d, *J* = 19.0 Hz), 131.9 (d, *J* = 21.3 Hz), 130.9, 129.6, 128.7, 128.3, 128.3, 128.2, 128.1, 125.0 (C-Ar), 103.6 (C-2), 81.0 (C-4), 77.1 (C-3), 76.5 (C-5), 74.2 (C-1), 73.7 (CH_2Ar), 61.7 (C-6), 57.6 (OCH_3), 57.3 (OCH_3), 21.2 (CH_3Ar) ppm; ^{31}P NMR (126 MHz, $CDCl_3$) δ = -5.77 ppm; HRMS (ESI-TOF) m/z $[M+H]^+$: calcd for $C_{36}H_{39}NPO_5$: 596.25604, found: 596.25662; Anal calcd for $C_{36}H_{38}NPO_5$: C 72.59, H 6.43, N: 2.35 found: C 72.29, H 6.55, N 2.32.

General procedure for the small scale allylic alkylation: A mixture of $[PdCl(C_3H_5)]_2$ (0.5 ml, 29 µmol; 5.7 mM in dry CH_2Cl) and ligand (0.5 ml, 66 µmol; 13.2 mM in dry CH_2Cl) was stirred at room temperature for 30 min and the solvent was evaporated in vacuo. A solution of dimethyl malonate (**3**) (20 µl, 174 µmol), rac-diphenylallyl acetate (**2**) (14.6 mg, 58 µmol), KOAc (0.3 mg, 3 µmol) and *N,O*-bis(trimethylsilyl)acetamide (43 µl, 174 µmol) in 1 ml dry solvent was added to the residue. After stirring at room temperature or 0 °C for 24 h the reaction was quenched with saturated NH_4Cl solution (2 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (reactions performed in CH_2Cl_2) or EtOAc (reactions performed in other solvents). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. Conversion was determined by HPLC (*n*-hexane/2-propanol, 9/1; 1.6 ml/min) t_R(**2**) = 2.0 min ; t_R(**4a**) = 2.4 min. Enantiomeric ratio was determined by chiral HPLC (*n*-hexanes/2-propanol, 9/1; 1.6 ml/min) t_R((*R*)-**4a**) = 5.2 min, t_R((*S*)-**4a**) = 6.8 min.

General procedure for the allylic alkylation with isolated yields: A mixture of $[PdCl(C_3H_5)]_2$ (5 mol% relating to the allyl acetate) and ligand (11 mol % relating to the allyl acetate) in 3 ml dry solvent was stirred at room temperature for 30 min. *N,O*-bis(trimethylsilyl)acetamide (3 equiv.), nucleophile (3 equiv.), KOAc (5 mol% relating to the allyl acetate) and allyl acetate (100 mg, 1 equiv.; solution in 4 ml solvent) were added and the reaction mixture was stirred at the temperature indicated in Table 2 for the time noted in Table 2. The reaction was quenched with saturated NH_4Cl solution (5 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (reactions performed in CH_2Cl_2) or EtOAc (reactions performed in other solvents). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo. The products were isolated after column chromatography using mixtures of PE/EtOAc.

The analytical data for **4a** - **4j**, **4l** and **4m** are in accordance with the literature. Absolute configurations were assigned by comparison of optical rotations with literature values.[5e, 6b, 8a, 9-10, 14d, 18] For the determination of *er*'s see supporting information.

(*E*)-2-(1,3-Di-*p*-tolylallyl)malononitrile (**4k**): light yellow oil, R_f = 0.36 (PE/EtOAc, 6/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.06 (m, 8 H, H-Ar), 6.57 (d, J = 15.8 Hz, 1 H, H-olefin), 6.32 (dd, J = 7.9, 15.7 Hz, 1 H, H-Olefin), 4.02 – 3.86 (m, 2 H, 2 × CH), 2.28 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.8, 138.5, 135.4, 133.6, 132.7, 130.0, 129.4, 127.5, 126.7, 123.0 (C-Ar, C-olefin), 111.8, 111.7 (CN), 49.5 (CH), 30.3($C(CN)_2$), 21.2, 21.1(CH_3) ppm; HRMS (ESI-TOF) m/z $[M+Na]^+$: calcd for $C_{20}H_{18}N_2Na$: 309.13622, found: 309.13622; Anal calcd for $C_{20}H_{18}N_2$: C 83.88, H 6.34, N 9.78, found: C 83.43, H 6.53, N: 9.56.

(*E*)-5-(1,3-Di-*p*-tolylallyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4n**): white solid, R_f = 0.20 (PE/EtOAc, 6/1); mp = 133 °C (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 8.1 Hz, 2 H, H-Ar), 7.15 – 7.04 (m, 4 H, H-Ar), 7.02 – 6.93 (m, 2 H, H-Ar), 6.75 (dd, *J* = 8.8, 15.8 Hz, 1 H, H-olefin), 6.54 (d, *J* = 15.8 Hz, 1 H, H-olefin), 4.36 (dd, *J* = 3.7, 8.7 Hz, 1 H, CH), 3.84 (d, *J* = 3.8 Hz, 1 H, $CH(CO)_2$), 3.15 – 3.06 (2 s, 6 H, NCH_3), 2.31

(2 s, 6 H, Ar-CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.0, 167.2, 151.0 (CO), 137.8, 137.6, 134.9, 133.9, 132.5, 129.3, 129.2, 127.4, 126.6, 126.4 (C-Ar, C-olefin), 56.3 ($CH(CO)_2$), 52.9 (CH), 28.2, 28.1 (NCH_3), 21.2, 21.1 (Ar-CH_3) ppm; HRMS (ESI-TOF) m/z $[M+Na]^+$: calcd for $C_{23}H_{24}N_2O_3Na$: 399.16.91, found: 399.16813; Anal calcd for $C_{23}H_{24}N_2O_3$: C 73.38, H 6.43, N: 7.44 found: C 73.38, H 6.45, N 7.49.

(*E*)-5-(1,3-Bis(4-chlorophenyl)allyl)-1,3-dimethylpyrimidine-2,4,6(1*H*, 3*H*, 5*H*)-trione (**4o**): white solid; R_f = 0.31 (PE/EtOAc, 4/1); mp = 148 °C (CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.14 (m, 6 H, H-Ar), 7.06 – 6.95 (m, 2 H, H-Ar), 6.70 (dd, *J* = 8.7, 15.8 Hz, 1 H, H-olefin), 6.44 (d, *J* = 15.7 Hz, 1 H, H-olefin), 4.36 (dd, *J* = 3.7, 8.6 Hz, 1 H, CH), 3.79 (d, *J* = 3.7 Hz, 1 H, $CH(CO)_2$), 3.08 (s, 3 H, NCH_3), 3.07 (s, 3 H, NCH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.4, 166.8, 150.8 (CO), 136.5, 134.9, 134.1, 133.6, 131.9, 129.0, 128.9, 128.8, 128.0, 127.7 (C-Ar, C-olefin), 55.5 ($CH(CO)_2$), 51.5 (CH), 28.3, 28.2 (NCH_3) ppm; HRMS (ESI-TOF) m/z $[M+Na]^+$: calcd for $C_{21}H_{18}N_2Cl_2O_3Na$: 439.05867, found: 439.05918; Anal calcd for $C_{21}H_{18}N_2Cl_2O_3$: C 60.45, H 4.35, N: 6.71 found: C 60.16, H 4.38, N 6.75.

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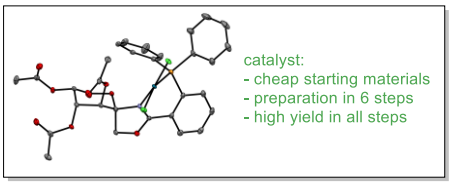

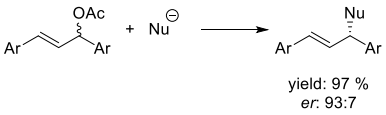

PHOX-ligands

*Michael R. Imrich, Cäcilia Maichle-Mössmer, Thomas Ziegler**

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D-fructose based spiro-fused PHOX ligands: Palladium complexes and application in catalysis

The x-ray crystal structure of Pd-complexes of D-fructose based spiro-fused PHOX is described. Furthermore, the synthesis of two new, improved ligands is reported. These ligands were applied in asymmetric allylic alkylation with various substrates.