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Parallel and Modular Synthesis of P-Chirogenic *P,O*-Ligands

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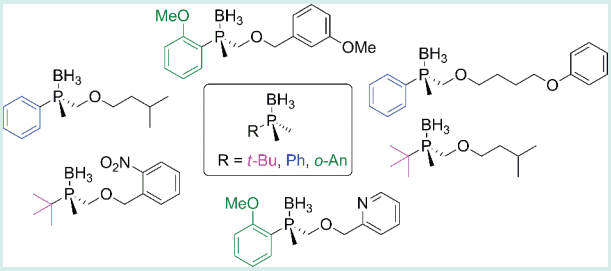
Supporting Information

ABSTRACT: A modular synthesis of P-chirogenic α-alkoxyphosphine ligands has been developed, allowing for the variation of two of the three groups on phosphorus. Oxidation and concomitant desymmetrization of a prochiral alkyl- or aryldimethylphosphine borane afforded α-hydroxyphosphines, which were subsequently deprotonated and alkylated in a parallel fashion. The choice of base and temperature for the alkylation step was found to be crucial for the outcome of the reaction. Selected ligands were subsequently screened in palladium catalyzed allylic substitution, affording product in good to excellent yield but moderate enantioselectivity, indicating that further optimization of the ligand structures is desirable to increase the stereoselectivity.



KEYWORDS: *chiral phosphine, parallel synthesis, O-alkylation, P-chiral, palladium catalyzed allylic substitution*

INTRODUCTION

The development of new methods for asymmetric synthesis and in particular asymmetric catalysis is of great importance because two enantiomers of a bioactive compound in many cases exhibit different biological properties.[1] The development of an asymmetric transition metal-catalyzed reaction often requires screening of a large number of chiral ligands, and methods for preparing such ligands either in parallel or in a library format are thus of interest.[2] Several research groups have focused specifically on the synthesis of phosphine- or phosphorus-containing ligand libraries,[3] both chiral[4] and nonchiral.[5] An elegant example in this context was described by Minnaard, de Vries, and Feringa, who prepared a library of 20 chiral phosphoramidite ligands in a parallel format and subsequently screened these in the rhodium-catalyzed asymmetric hydrogenation of a variety of alkene substrates, identifying two ligands that afforded exceptionally high enantioselectivity.[6] Gilbertson and co-workers have reported several examples of combinatorial libraries of chiral phosphines and their applications in asymmetric catalysis,[7] and Meldal has developed a solid phase synthesis of peptide-based phosphine ligands in a combinatorial format.[8] Combinatorial mixed-ligand and hybrid-ligand approaches have also been employed by several research groups.[9] However, examples of phosphine ligands with P-chirality prepared in a parallel format are far less common. In a P-chiral phosphine,[10] the chirality is placed closer to the reaction center in comparison to ligands with C-chirality, and P-chiral phosphines have given excellent results in the catalytic asymmetric hydrogenation of alkenes.[11] Because such ligands are more complex to prepare,[12] they have been less investigated in asymmetric synthesis in general however, and the efficient preparation of such ligands in a parallel format for screening purposes is thus highly important to increase their scope of application. We have during a number of years been devoted to the development of new methodology for the preparation of P-chiral phosphines,[13] and have also reported several examples of chiral phosphine ligand libraries incorporating pendant carboxy-,[14] triazolyl-[15] and amino-functionalities[16] (**1a**–**c**, Figure 1). We here report the synthesis of a different type of phosphine in a combinatorial format, that is, phosphines incorporating a pendant alkoxy-group. The application of these *P,O*-type ligands in palladium-catalyzed asymmetric allylic substitution is also described.

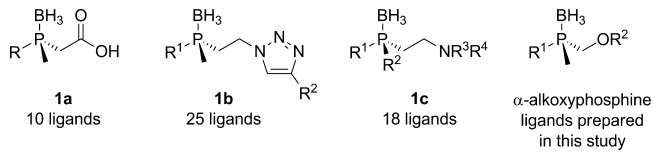


Figure 1. Libraries of P-chiral phosphine ligands (phosphines shown in their borane protected form).[14−16].

RESULTS AND DISCUSSION

To prepare a library of diverse P-chiral *P,O*-type phosphine ligands, the P-chirality was first installed via desymmetrization of a prochiral phosphine substrate, and an adjacent hydroxyl-group was subsequently introduced as a handle for diversification. Prochiral phosphine boranes **2a**–**c** (Scheme 1) were subjected to enantioselective deprotonation using a chiral *sec*-butyl lithium/(−)-sparteine complex, followed by oxidation with molecular oxygen in the presence of triethylphosphite, employing a protocol described by Imamoto.[17] α-Hydrox-

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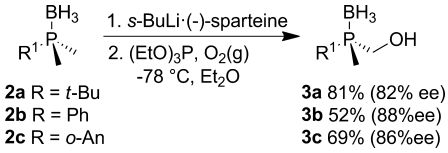
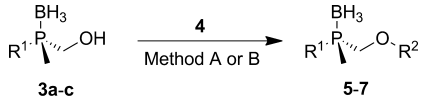
Scheme 1. Preparation of Chiral α-Hydroxyphosphine Boranes Used As Precursors



yphosphine boranes **3a**−**c** were formed in moderate to good yields and with enantioselectivities similar to reported values using this methodology.

Alkylation of the hydroxy-group of **3a**−**c** was then carried out (Scheme 2). For hydroxyphosphines **3a** and **3b**, the

Scheme 2. Alkylation of 3a−c with Chemset 4[a]



[a]Method A: NaH, KI, R^2Br, DMF, r.t., 5 h, then polymer-bound scavenger, 16 h; Method B: Cs_2CO_3, R^2Br, DMF, −20 °C to r.t., 16 h.

reactions were performed at room temperature in parallel in a Quest 210 Manual Synthesizer, using sodium hydride in dimethylformamide (DMF) with catalytic amounts of sodium iodide (Method A). The alkylating agents used were a set of alkyl and benzyl bromides with different electronic properties (Figure 2), including also a heteroaromatic structure (**4**{*10*}).

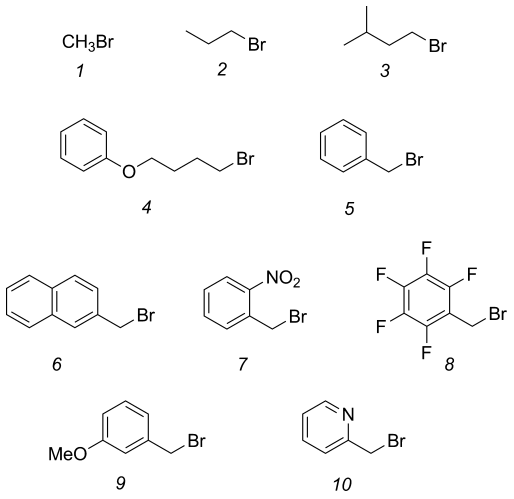


Figure 2. Diversity reagents **4**{1−10} used for the alkylation of **3a**−**c**.

Excess electrophile was subsequently scavenged with PS-thiophenol, and the crude products were isolated and purified by flash chromatography, affording chiral α-alkoxyphosphine ligand chemsets **5** and **6**. In the case of the *tert*-butyl substituted phosphines **5**, the desired products were formed in all cases except one, albeit in rather moderate yields using these conditions (Figure 3 and Table 1). For the phenyl-substituted phosphines **6**, the outcome was somewhat less successful (Table 2, ligand structures shown in Figure 3). Approximately half of the alkylated phosphine ligands were formed, but in significantly lower yields that for the alkyl-substituted ligands **5**.

Upon analysis of other fractions isolated from the flash chromatography, an explanation for the low yields could be found. A second major fraction could be isolated in many cases, which turned out to be phosphines of the type **8** (Scheme 3), where alkylation had taken place directly on the phosphorus atom. Presumably, this occurs via a deformation reaction, forming a secondary phosphine borane which is then directly alkylated by the electrophile. Such deformylation has been reported when using KOH as the base,[17] and can be put to practical use if the secondary phosphine thus formed retains its stereochemical integrity. This was not found to be the case under these reaction conditions, however; analysis of the products **8** showed that these were racemic. Thus an improved synthetic protocol for the aryl-substituted phosphines had to be found.

Switching to a milder base such as cesium carbonate, and performing the initial deprotonation step at −20 °C, before allowing the reaction to warm up to room temperature, turned out to solve the problem of concomitant deformylation. Six reactions using precursor **3a** and seven reactions starting from precursor **3b** were then repeated using this new protocol. Markedly improved yields were obtained in nearly all cases (Table 1 and Table 2), the exception being compound **6**{*10*} which was not formed even under these conditions. The alkylating agent for compound **6**{*10*}, 2-bromomethyl-pyridine is commercially available in the form of its hydrochloride salt, necessitating a liberation step involving polymer supported base (MP-carbonate) prior to reaction. It may be this extra procedure that somehow interferes with the reaction in this case, although the analogous **5**{*10*} was formed without any problem, albeit in a rather moderate yield. The highest yields (86−94%) were obtained for ligands **5**{*6*}, **5**{*7*}, and **6**{*7*}, indicating that the electron-deficient *ortho*-nitrobenzyl bromide is a particularly favorable alkylating agent in this reaction.

To expand the scope of ligands prepared, we also included anisyl-substituted hydroxyphosphine **3c** as a precursor scaffold, employing the new reaction conditions (Method B) for the alkylation. Eight electrophiles from chemset **4** were selected, and the desired alkoxyphosphine products were formed in good to excellent yield in all cases (Figure 3 and Table 3). Particularly the alkyl bromides as well as 2-(bromomethyl)-naphthalene afforded product in over 90% yield. The higher yields when using substrate **3c** may reflect the more electron rich properties of the phosphine, increasing the nucleophilicity of the formed alkoxide.

Although the focus in this investigation was to develop methodology for the modular synthesis of chiral α-alkoxyphosphines, a limited investigation into the capability of the phosphines to act as ligands for asymmetric synthesis was also carried out. We have earlier studied the use of P-chiral α-carboxyphosphine ligands in the asymmetric allylic substitution of 1,3-diphenylpropenyl acetate with dimethyl malonate with up to 91% enantiomeric excess (ee).[14] Imamoto and co-workers have also employed P-chiral phosphine/sulfide hybrid ligands of similar structure in the same allylic substitution, with up to 90% ee,[18] and this therefore seemed a suitable reaction in which to test our *P,O*-type ligands. This reaction also has the advantage that phosphine boranes can be used directly as *pre*-ligands in the reaction, deprotection of the phosphine taking place in situ under the reaction conditions, with concomitant reduction of Pd(II) to Pd(0) as reported by Jugé and co-workers.[19] Six *tert*-butyl-substituted as well as seven aryl-substituted phosphines were selected to study the effect of the substitution pattern (Table 4). In performing the reaction, all selected phosphines afforded the desired substitution product **9**

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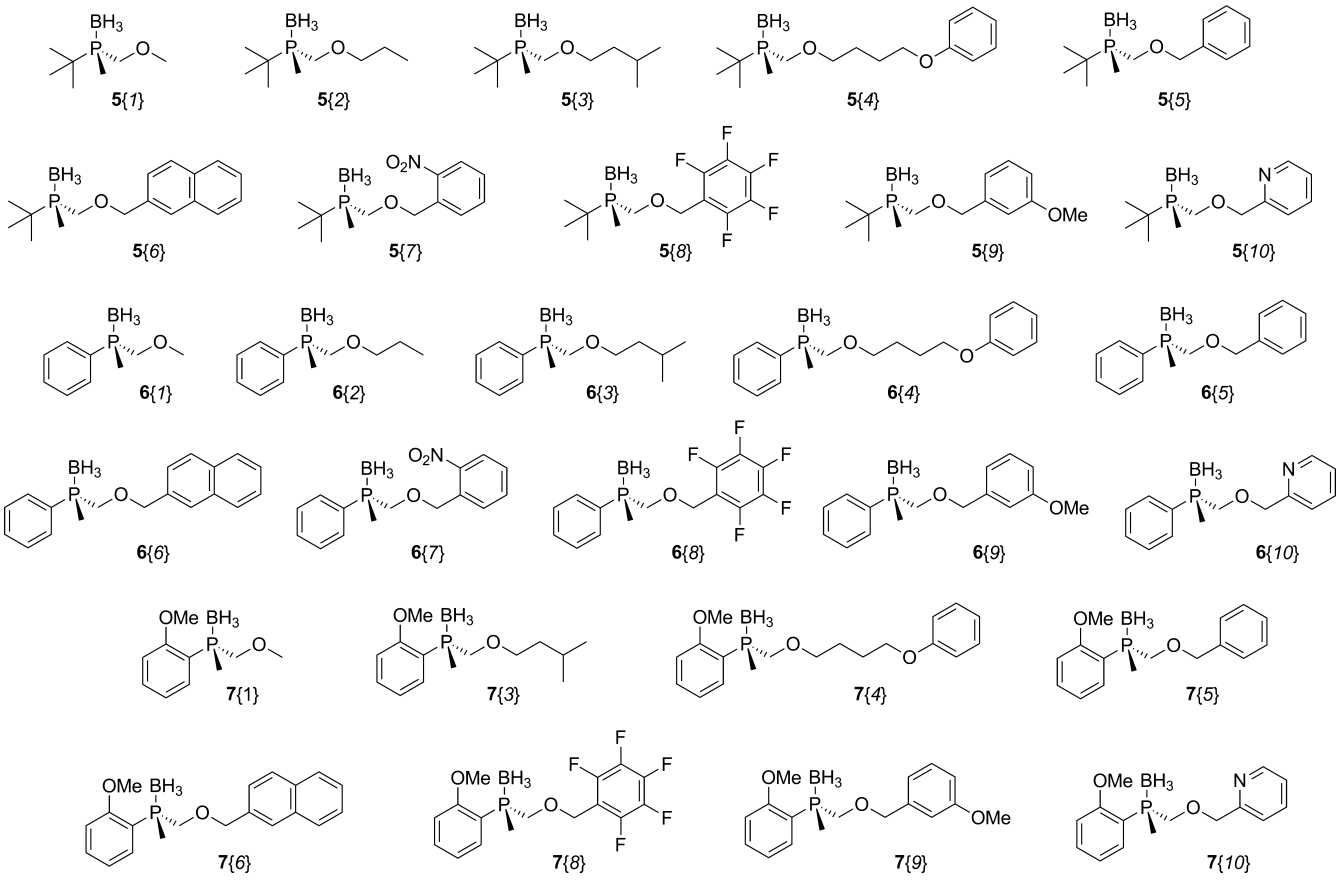

Figure 3. α-Alkoxyphosphines prepared from **3a–c**.

Table 1. Synthesis of α-Alkoxyphosphines 5 from *tert*-Butyl-Substituted Phosphine 3a

entry	ligand[a]	method[b]	yield (%)
1	**5**{*1*}	A	25%
2	**5**{*2*}	A	28%
3		B	50%
4	**5**{*3*}	A	41%
5	**5**{*4*}	A	28%
6		B	52%
7	**5**{*5*}	A	24%
8		B	65%
9	**5**{*6*}	A	29%
10		B	94%
11	**5**{*7*}	A	41%
12		B	93%
13	**5**{*8*}	A	n.r.
14		B	52%
15	**5**{*9*}	A	45%
16	**5**{*10*}	A	45%

[a]Ligand structures shown in Figure 3. [b]See Scheme 2 for method details.

Table 2. Synthesis of α-Alkoxyphosphines 6 from Phenyl-Substituted Phosphine 3b

entry	ligand[a]	method[b]	yield (%)
1	**6**{*1*}	A	n.r.
2	**6**{*2*}	A	19%
3		B	62%
4	**6**{*3*}	A	25%
5	**6**{*4*}	A	6%
6		B	52%
7	**6**{*5*}	A	29%
8	**6**{*6*}	A	n.r.
9		B	65%
10	**6**{*7*}	A	10%
11		B	86%
12	**6**{*8*}	A	n.r.
13		B	50%
14	**6**{*9*}	A	27%
15		B	51%
16	**6**{*10*}	A	n.r.
17		B	n.r.

[a]Ligand structures shown in Figure 3. [b]See Scheme 2 for method details.

when employed as chiral ligands in the reaction, generally in good to excellent yields, with the more electron-rich *tert*-butyl substituted phosphines giving somewhat better results. In terms of the enantioselectivity, the bulk of the *tert*-butyl substituent seems to be important, as here ligands of the type **5** (entries 1–6) clearly performed better than the phenyl- or anisyl-substituted ligands **6** and **7**, the latter affording nearly racemic product (entries 7–12). This is also in line with our earlier

Scheme 3. Deformylation with Concomitant Racemization As a Side Reaction Using Method A

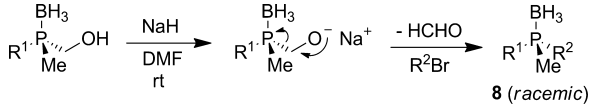

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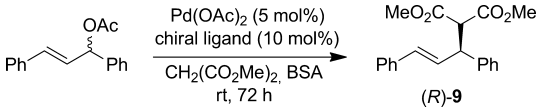
Table 3. Synthesis of α-Alkoxyphosphines 7 from Anisyl-Substituted Phosphine 3c

entry	ligand[a]	method[b]	yield (%)
1	7{*1*}	B	95%
2	7{*3*}	B	91%
3	7{*4*}	B	76%
4	7{*5*}	B	65%
5	7{*6*}	B	93%
6	7{*8*}	B	66%
7	7{*9*}	B	51%
8	7{*10*}	B	49%

[a]Ligand structures shown in Figure 3. [b]See Scheme 2 for method details.

Table 4. Asymmetric Allylic Substitution with Selected α-Alkoxyphosphine Ligands



entry	compound	ee (%)[a]	yield (%)
1	**5**{*2*}	17	93
2	**5**{*6*}	38	97
3	**5**{*7*}	40	77
4	**5**{*8*}	33	96
5	**5**{*9*}	33	63
6	**5**{*10*}	26	99
7	**6**{*4*}	1	47
8	**6**{*6*}	2	77
9	**6**{*7*}	4 (*S*)	99
10	**6**{*8*}	9	60
11	7{*5*}	17	99
12	7{*10*}	3	99

[a]Determined by chiral HPLC, see Supporting Information for details.

results employing α-carboxyphosphine boranes, where ligands carrying sterically hindered groups such as *tert*-butyl, adamantyl or mesityl afforded the best results in terms of stereoselectivity using the same substrate and nucleophile. Looking at the substituents on oxygen, the benzylic functionalities found in electrophiles **4**{6−10} (entries 2−6) gave a better result than phosphine **5**{2} containing a propyl-chain (entry 1). This might simply reflect the larger steric and electronic differences between the three substituents on phosphines **5**{6−10} in comparison with phosphine **5**{2}, which appears to have a beneficial effect on the stereoselectivity. Although the enantioselectivity attained with α-alkoxyphosphine ligands of the type **5** is not as high as that obtained with structurally similar P-chiral α-carboxyphosphine ligands, the results nevertheless show that this class of compounds deserves further study as ligands for asymmetric synthesis, and that the common (*tert*-butyl)(hydroxymethyl)methylphosphine scaffold could be used as a starting point for the design of new ligands of this type.

CONCLUSIONS

In summary, a method for the parallel synthesis of α-alkoxyphosphine boranes, potential ligands in asymmetric organometallic reactions, has been developed via deprotonation of chiral hydroxyphosphine precursors, followed by alkylation with various electrophiles and quenching with a polymer-bound scavenger. The choice of base and temperature was found to be crucial for the alkylation reaction to avoid an undesired side reaction in the form of a deformylation. Using a mild base and low temperature for the initial deprotonation step, *tert*-butyl, phenyl- and anisyl-substituted α-alkoxyphosphine boranes could be formed in good to excellent yields.

ASSOCIATED CONTENT

Supporting Information

Details of experimental procedures and spectroscopic data for synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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