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Modular Synthesis of Chiral Phosphine-Phosphite-Ligands from Phenolic Precursors: A New Approach to Bidentate Chelate Ligands Exploiting a P–O to P–C Migration Rearrangement

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Abstract: An efficient and modular approach to bidentate phosphine-phosphite ligands formally derived from a 6-alkyl-2-phosphanylphenol, a chiral diol and phosphorus trichloride has been developed. In a key step, a borane-protected phosphinite, prepared from an *o*-bromophenol by *O*-phosphanylation, is reacted with *n*-butyllithium to afford the corresponding *ortho*-phosphanylphenol (as the stable borane adduct) through bromine-lithium exchange and anionic migration rearrangement. Treatment with phosphorus trichloride in the presence of a base and subsequent reaction of the *in situ* formed dichlorophosphite with a chiral diol (such as TADDOL or BINOL) affords the target P,P ligands in good overall yield (up to 60% over 4 steps). In contrast to an earlier approach, the new methodology is very general and tolerates bulky *ortho*-substituents. The reliability of the operationally convenient protocol was demonstrated in the synthesis of a library of 16 new phosphine-phosphite ligands, starting from different *ortho*-alkylphenols. The modular concept opens a rapid access to a broad variety of ligands and might be useful in the search for and structural optimization of suitable ligands for specific chirogenic transition metal-catalyzed transformations.

Keywords: chirality; diversity-oriented synthesis; ligand design; lithiation; metal catalysis; phosphite ligands

Introduction

During the last decades, transition metal-catalyzed reactions have evolved as most powerful tools in asymmetric organic synthesis and many classes of chiral ligands were discovered which provide impressively efficient solutions for a growing number of chirogenic transformations.[1] However, the identification of suitable ligands for a specific metal-catalyzed process still remains a challenge, as even potent catalysts often show low activities for demanding substrates. Furthermore, certain types of transformations cannot even be performed in a satisfying asymmetric manner at all. As rational ligand design is usually not possible based on our existing state of knowledge and theory, the discovery of new potent structures is still a rather empirical enterprise. A successful approach is the screening of ligand libraries obtained by modular (diversity-oriented) synthesis based on "privileged" ligand architectures.[2] Prominent classes of (bidentate) modular chiral ligands are, for instance, oxazoline-derived ligands[3] and ligands with a ferrocenyl[4] or a biaryl[5] backbone.

As our own contribution to the field, we had previously disclosed a modular synthetic approach towards structurally diverse bidentate phenol-derived ligands.[6] By screening a small library of these P,P, P,S-, and P,N ligands in the Rh-catalyzed hydroboration of styrene, the phosphine-phosphite ligand **1** was identified to be particularly selective (91% *ee*).[7] In fact, chiral phosphine-phosphite ligands[8] seem to possess a significant (albeit little explored) potential for asymmetric transition metal catalysis. For example, ligands **2** (BINAPHOS), **3** and **4** (Figure 1) have been successfully applied in Rh-catalyzed hydrogenation[9] and hydroformylation[10] reactions as well as in Cu-catalyzed asymmetric conjugate additions.[11]

In the course of our previous work (see above),[7] it became apparent that a substituent (R′) in the *ortho*-position to the phosphite moiety in P,P ligands of type

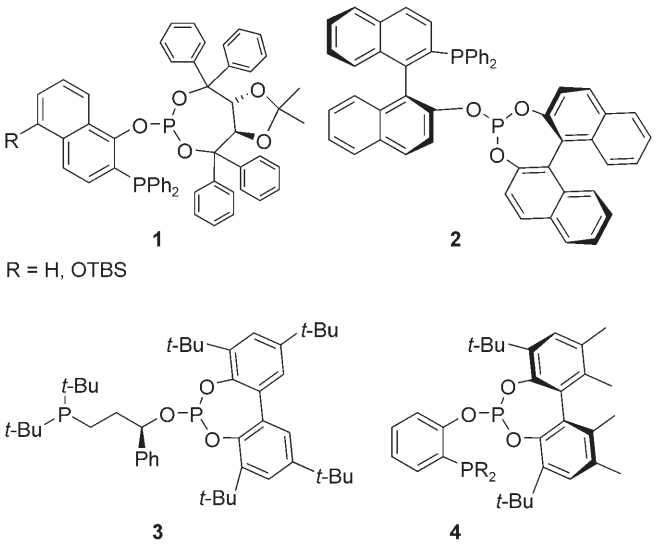
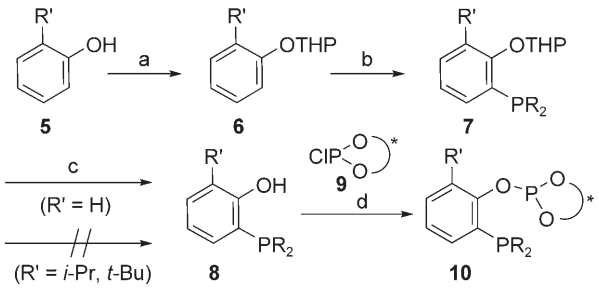


Figure 1. Selected chiral phosphine-phosphite ligands.

10 seems to exhibit a positive influence on the performance of such ligands. However, in our initial attempts to synthesize ligands of type **10** with $R' \neq H$ following the original approach (Scheme 1) we faced some unexpected problems. While the lithiation/phosphanylation of the THP-protected phenols (**6**) proceeded smoothly as before, the deprotection (THP ether cleavage) of the resulting products (**7**) was not achievable even under rather harsh conditions (e.g., 1 equiv. *p*-TsOH, MeOH, reflux, 17 h). Also considering the highly air-sensitive nature of the expected *ortho*-phosphanylphenol intermediates of type **8**,[6,7,12] we decided not to further pursue the original strategy. We herein report a new synthetic protocol which overcomes the above-mentioned problems and opens a reliable, general and still highly modular access to chiral phosphine-phosphite ligands of type **10**, requiring only 4 steps starting from simple substituted phenols.

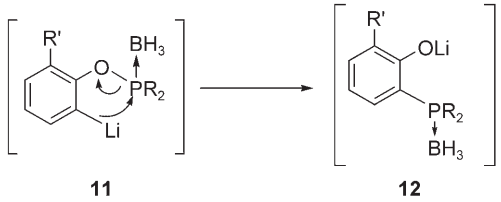


Scheme 1. Original approach towards ligands of type **10**; (a) DHP, cat. PPTS, CH_2Cl_2, r.t.; (b) *n*-BuLi, THF, −78 °C to r.t., then $ClPR_2$, −78 °C to r.t.; (c) *p*-TsOH, MeOH, r.t.; (d) THF, Et_3N, $ClP(OR)_2$.

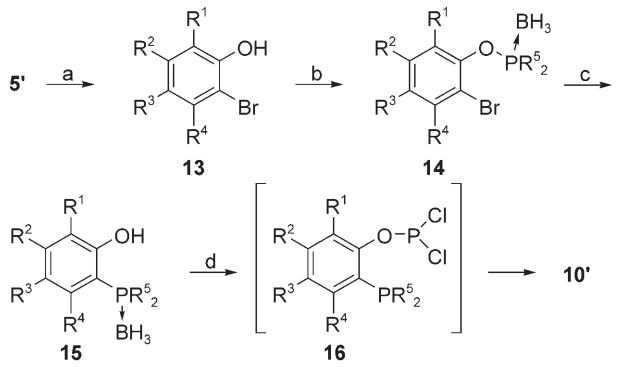
Results and Discussion

Inspired by the work of Heinicke[12] and, in particular, Jugé,[13] we envisioned exploiting a P–O to P–C migration rearrangement to introduce the phosphanyl substituent in the *ortho*-position without the requirement to protect the phenol functionality (Scheme 2). In such a process, an *ortho*-lithiated and borane-protected aryl phosphinite (**11**) would be supposed to rearrange to a more stable *ortho*-phosphanylphenolate of type **12**[13] from which the intermediates of type **8** would be obtained after work-up in a still borane-protected (thus easier to handle) form.

Much to our satisfaction, this consideration was found to work out successfully. The overall synthetic scheme, which finally allowed us to synthesize various new ligands of type **10**, even with bulky substituents R′ (e.g., *t*-Bu, *i*-Pr, Ph), is summarized in Scheme 3 and Table 1. Starting from differently substituted phenols (**5′**), *ortho*-bromination was routinely achieved using NBS (cat. $i\text{-Pr}_2NH$, DCM, reflux),[14] a method which proved superior to others especially on a multi 10 g scale. To suppress the formation of dibrominated by-products and to circumvent the low solubility of NBS in dichloromethane, a Soxhlet apparatus was used to extract the NBS bit by bit from the thimble



Scheme 2. Rearrangement of an *ortho*-lithiated and borane-protected aryl phosphinite (**11**) to an *ortho*-phosphanylphenolate of type **12**.



Scheme 3. Improved and general synthesis of ligands of type **10**. (a) NBS, cat. $i\text{-Pr}_2NH$, CH_2Cl_2, reflux; (b) $ClP(R^5)_2$, DABCO (1.1 equiv.), CH_2Cl_2, 0–25 °C, 2 h, then BH_3·THF, 0 °C to r.t.; (c) *n*-BuLi (1.5 equiv.), THF, 0 °C; (d) PCl_3 (1.0 equiv.), DABCO (10 equiv.), CH_2Cl_2, 3 h, rt, then chiral diol (1.5 equiv.), 16 h, r.t.

Table 1. Synthesis of various ligands of type **10** according to Scheme 3.

Entry	R^1	R^2	R^3	R^4	Intermediate **13** (yield [%])[a]	R^5	Intermediate **15** (yield [%])[a]	Chiral Diol	Final Ligand (yield [%])[a]
1	Me	H	H	H	**13a** (98)	Ph	**15a** (92)	TADDOL	**10a** (79)
2	Me	Me	H	H	**13b** (98)	Ph	**15b** (71)	TADDOL	**10b** (79)
3	Me	H	H	Me	**13c** (61)	Ph	**15c** (83)	TADDOL	**10c** (68)
4	*i*-Pr	H	H	H	**13d** (97)	Ph	**15d** (85)	TADDOL	**10d** (75)
5	*t*-Bu	H	H	H	**13e** (95)	Ph	**15e** (91)	TADDOL	**10e** (86)
6	*t*-Bu	H	*t*-Bu	H	**13f** (66)	Ph	**15f** (81)	TADDOL	**10f** (94)
7	-$(CH)_4$-		H	H	**13g** (97)	Ph	**15g** (91)	TADDOL	**10g** (74)
8	Ph	H	H	H	**13h** (96)	Ph	**15h** (91)	TADDOL	**10h** (79)
9	Ph	H	H	H	**13h**	*i*-Pr	**15i** (70)	TADDOL	**10i** (35)[b]
10	Me	Me	H	H	**13b**	Ph	**15b**	BINOL	**10j** (88)
11	*t*-Bu	H	*t*-Bu	H	**13f**	Ph	**15f**	BINOL	**10k** (78)
12	Ph	H	H	H	**13h**	Ph	**15h**	BINOL	**10l** (80)
13	Ph	H	H	H	**13h**	Ph	**15h**	2-naphthyl-TADDOL	**10m** (35)
14	*i*-Pr	H	H	H	**13b**	Ph	**15b**	2-naphthyl-TADDOL	**10n** (66)
15	*t*-Bu	H	H	H	**13e**	Ph	**15e**	2-naphthyl-TADDOL	**10o** (49)
16	*t*-Bu	H	*t*-Bu	H	**13f**	Ph	**15f**	2-naphthyl-TADDOL	**10p** (61)

[a] Isolated yield.
[b] DIPEA was used instead of DABCO in the final step.

into the reaction mixture. The bromophenols **13** were then converted into the *O*-phosphanylated and borane-protected derivatives **14** by reaction with a chlorophosphine in the presence of DABCO in dichloromethane and subsequent addition of BH_3 in THF. Alternatively, the reaction could be performed with equal success in THF using sodium hydride as a base. Without purification, the resulting phosphinites of type **14**, usually obtained as colourless solids, were directly subjected to the key rearrangement (Scheme 2) by treatment of a solution in THF at with an excess (1.5 equiv.) of *n*-BuLi to smoothly afford the corresponding (still BH_3-protected) phosphines **15** in good yields (Table 1). It is worthy of note that *n*-BuLi (even at 0 °C) could be used instead of *t*-BuLi at −78 °C (as described in the original protocol).[13] Moreover, even if the starting material (**14**) was contaminated to some extent with the dibrominated species, the reaction product (**15**) was obtained in very pure form, as a result of a process of "self-purification" under the reaction conditions (due to non-productive Br/Li exchange followed by protonation during work-up). Both the borane-protected phosphinites (**14**) and the corresponding rearranged phosphines (**15**) proved to be air-stable and, in most cases, nicely crystalline compounds. The structures of selected compounds (**14h**, **14f**, **15b, 15e**, **15f** and **15i**) were determined by X-ray crystallography (Figure 2) to unambiguously probe the correct structural assignments.

With the desired BH_3-protected 6-alkyl-2-phosphanylphenols of type **15** in our hands, we next investigated the final introduction of the (chiral) phosphite unit. Initial attempts to achieve this goal as before (compare Scheme 1)[6,7] *via* base-mediated reaction of the phenol with a chiral chlorophosphite (accessible in one step from PCl_3 and a chiral diol) resulted in low yields. Obviously, the increased steric hindrance caused by the substituents R^1 seems to impede the reaction with the bulky chlorophosphites derived from chiral diols such as TADDOL[15] and BINOL.[16] Challenged by these circumstances, we devised a new "one-pot" procedure in which the phosphanylphenol (**15**) is first reacted with 1 equiv. of PCl_3 in dichloromethane at room temperature in the presence of an excess of DABCO as a base. The resulting dichlorophosphite intermediate **16** is then converted to the corresponding phosphite by addition of the chiral diol (Scheme 3). Using this method, various TADDOL- and BINOL-derived ligands of type **10** were reliably obtained in good yields (Table 1). With DABCO as a base, complete deprotection (removal of the BH_3 group) occurred under the reaction conditions. In the case of the more sensitive diisopropylphosphanyl ligand **10i** the less nucleophilic Hünig's base (DIPEA) was used and the still protected product was isolated. Only moderate yields were observed when the more bulky naphthyl-TADDOL[15a] was employed. The structures of the various chiral phosphine-phosphite ligands of type **10** synthesized in the course of this study are shown in Figure 3.

Conclusions

Based on our earlier discovery that chiral phosphine-phosphite ligands of type **10** possess a promising potential for enantioselective transition metal catalysis,[7] the goal of the present study was to develop a general

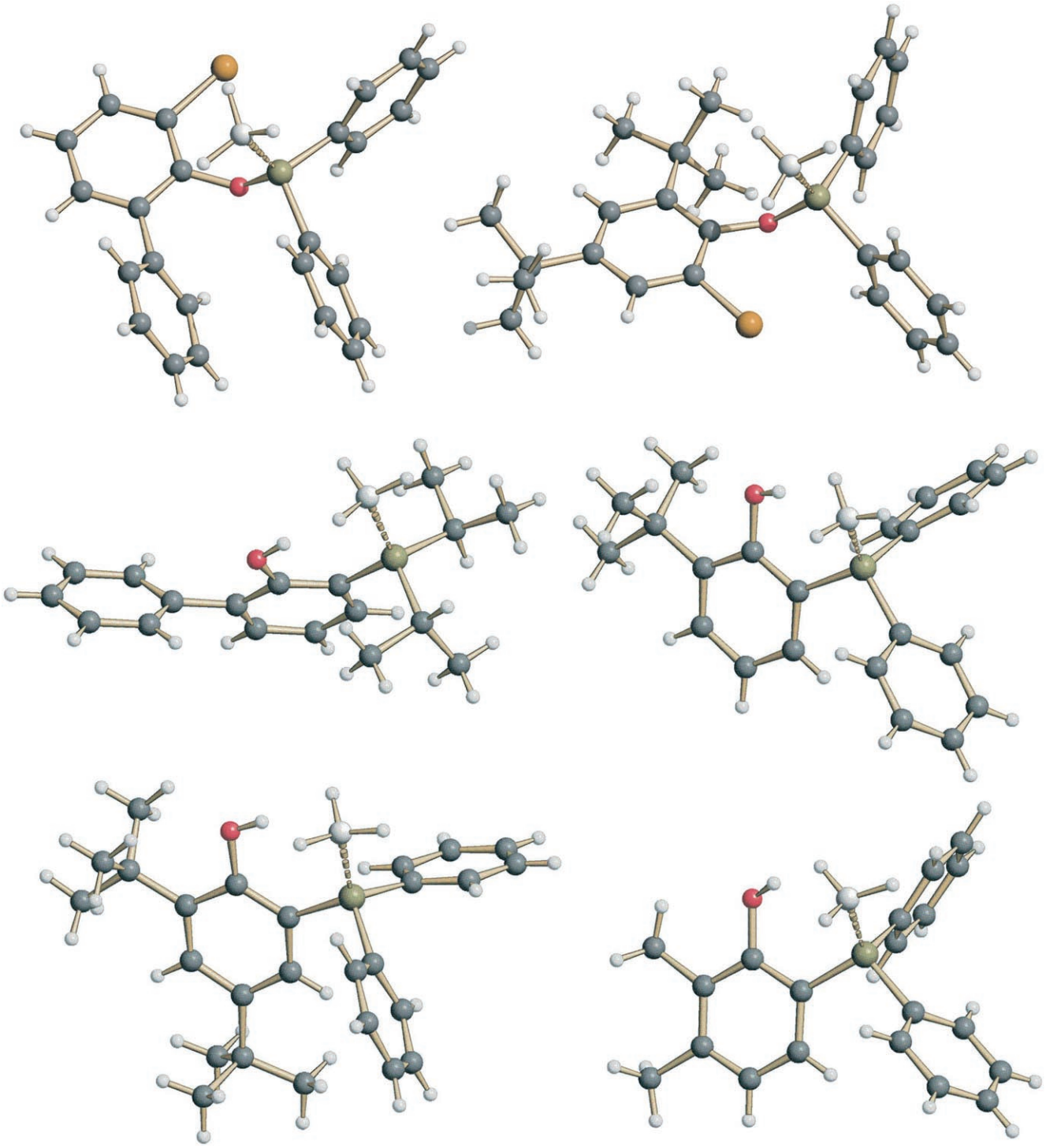


Figure 2. Structures of the borane-protected *ortho*-bromoarylphosphinites **14h** and **14f** (*upper row*) and of the borane-protected *ortho*-hydroxyarylphosphines **15i**, **15e**, **15f** and **15b** (*middle and lower rows*) in the crystalline state. Selected P–B bond lengths: 1.897 Å (**14h**), 1.907 Å (**14f**), 1.937 Å (**15i**), 1.931 Å (**15e**), 1.927 Å (**15f**), 1.926 Å (**15b**).

synthetic access to a broader variety of such compounds. In particular, ligands with a sterically demanding substituent ($R^1 \neq H$) in the *ortho* position to the phosphite moiety were not available through our previous synthesis. Exploiting an anionic P–O to P–C migration rearrangement as a key step, this goal was achieved. The new protocol disclosed herein indeed opens an efficient and reliable entry to the targeted ligand class in a diversity-oriented manner and has the following advantages: (1) circumvention of a pro-

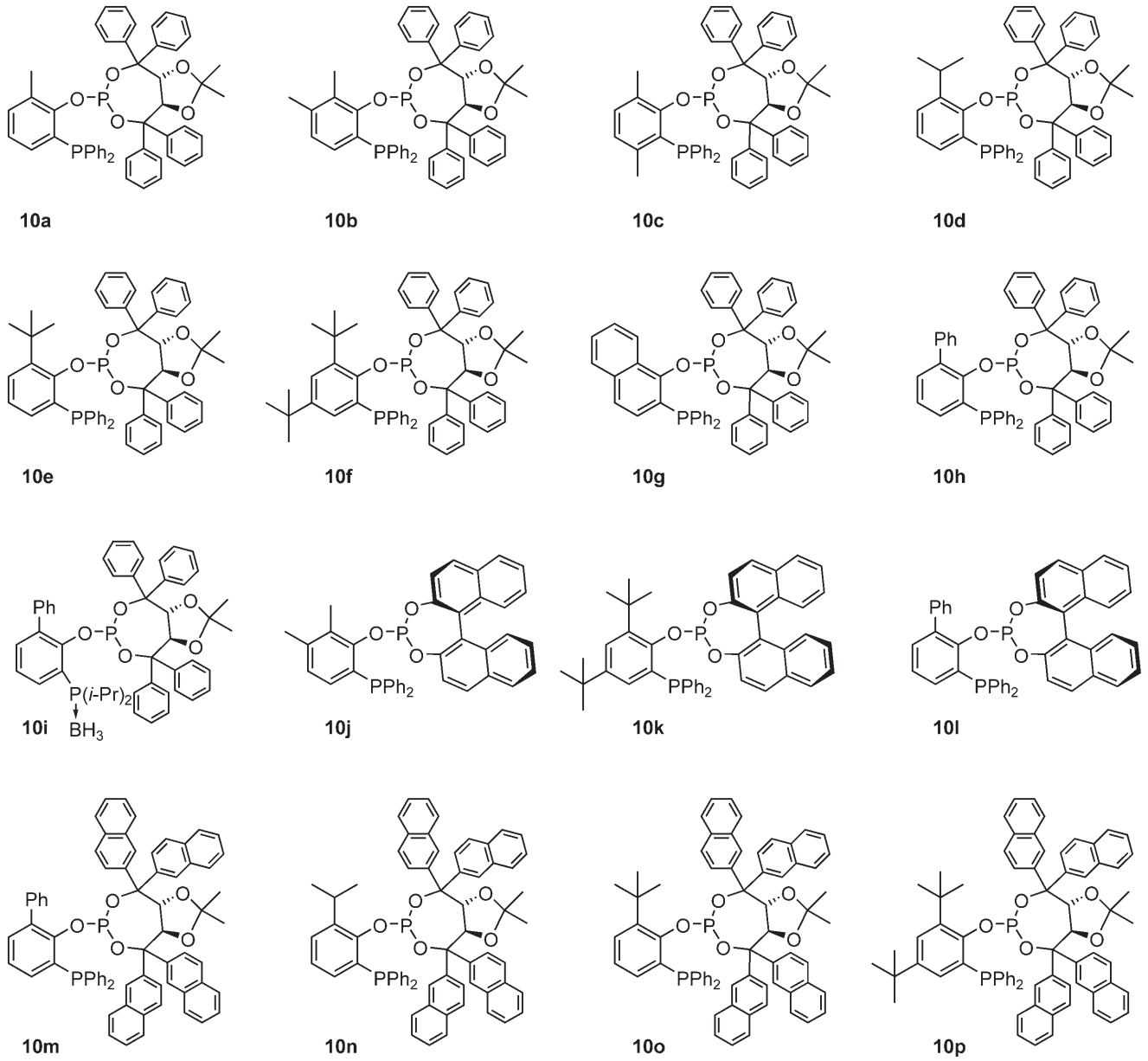
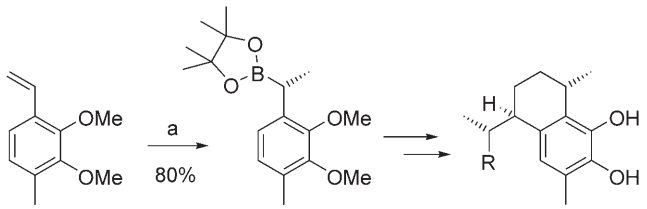


Figure 3. Chiral phosphine-phosphite ligands of type **10** synthesized in the course of the present study.

tecting group for the phenol function (shortening the overall sequence to four steps starting from simple substituted phenols); (2) enhanced operational simplicity through avoidance of sensitive intermediates (using BH_3 adducts), and (3) toleration of bulky *ortho*-substituents (e.g., *tert*-butyl). The practicability of the modular scheme was exemplified in the synthesis of a library of sixteen well-characterized ligands using different phenol building blocks, chlorophosphanes and chiral diols (Figure 3).

As a first probe of its value, we recently screened this library in the Rh-catalyzed hydroboration[17] of the substituted styrene derivative **17**, that is, the chirogenic step in our synthesis of dihydroxycalamenenes and other natural products (marine diterpenes) showing a substructure of type **19** (Scheme 4).[18] Noteworthy is the circumstance that **17** represents a rather demanding substrate which, in contrast to the parent unsubstituted styrene, only gave unsatisfying enantioselectivities ($\leq$75 *ee*) under standard conditions when BINAP or our first generation ligand **1** was employed. We observed a pronounced effect of the substitution pattern at the ligand backbone and identified **10b** as the most effective ligand so far, giving intermediate **18** with at least 93% *ee*.[18] Exploiting the efficient diversity-oriented synthetic scheme, further variation (optimization) of the ligand structure should be possible without unreasonable expenditure.

We are optimistic that by screening of libraries of modular compounds of type **10** new useful ligands



Scheme 4. Application of ligand **10b** in the enantioselective synthesis of compounds of type **19**. (a) 2 mol% $[Rh(COD)_2]BF_4$, 2.2 mol% **10b**, 1.2 equiv. catecholborane, DME, −45 °C; then pinacol (2.3 equiv.).

will be identified also for other types of enantioselective transition metal-catalyzed transformations. Corresponding investigations are currently performed in our laboratories and the results will be reported in due course.

Experimental Section

For detailled (individual) procedures and characterization of compounds, see the Supporting Information.

General Procedure I: *ortho*-Bromination to Bromides 13a–h

In a flame-dried flask equipped with a Soxhlet apparatus and flushed with argon the substituted phenols **1a–h** (1 equiv.) and diisopropylamine (0.1 equiv.) were dissolved in absolute CH_2Cl_2. The thimble was filled with NBS (1 equiv.) and the system was heated to reflux for 16 h. During this time, the NBS was slowly consumed. After cooling to room temperature the resulting mixture was treated with 2 M sulfuric acid. The layers were separated and the aqueous layer was extracted with *tert*-butyl methyl ether. The combined organic layers were washed with water and brine, and dried ($MgSO_4$). The solvent was removed and the crude product was purified by flash chromatography.

General Procedure II: Synthesis of BH_3-Protected Phosphinites (14a–i)

A flame-dried Schlenk flask was charged under argon with a substituted 2-bromophenol (**13a–h**, 1 equiv.) and DABCO (1.1 equiv.) and dissolved in CH_2Cl_2. This solution was stirred for 5 min at room temperature then cooled to 0 °C and the chlorophosphine (1.1 equiv.) was added dropwise *via* syringe. The resulting suspension was stirred 10 min at this temperature, warmed to room temperatuere and stirred for another 2 h. The reaction mixture was then cooled to 0 °C and a solution of BH_3 in THF (2 equiv.) was added. This resulting solution was stirred 15 min at 0 °C and 1 h at room temperature before it was quenched with H_2O (***caution! strong H_2 gas formation***) and extracted with *tert*-butyl methyl ether. The ethereal phase was washed with brine and dried ($MgSO_4$). The solvent was evaporated to give the crude product (**14a–i**) which was used without further purification.

General Procedure III: Rearrangement of BH_3-Protected Phosphinites to 2-Boranatodiphenylphosphanylphenols (15a–h)

In a flame-dried Schlenk flask under argon a solution of a BH_3-protected phosphinite (**14a–i**, 1 equiv.) in THF was cooled to 0 °C and treated with *n*-BuLi (1.5 equiv.). The mixture was stirred for 2 h at this temperature, then quenched with H_2O, extracted with *tert*-butyl methyl ether and washed with NH_4Cl solution. The organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product which was purified by flash chromatography to provide the phosphines **15a–h** as white solids.

General Procedure IV: Synthesis of Chiral Phosphine-Phosphite Ligands (10a–p)

A flame-dried Schlenk flask was put under argon and the phosphine (**15a–h**; 1.0 equiv.) and DABCO (20 equiv.) were dissolved in absolute CH_2Cl_2. The resulting solution was stirred for 10 min at room temperature, then cooled to 0 °C and a solution of PCl_3 in CH_2Cl_2 (1.0 equiv,) was added dropwise *via* syringe. The reaction mixture was stirred for 30 min at this temperature, warmed to room temperature and stirred for 3 h. The milky suspension was cooled to 0 °C and a solution of the chiral diol (1.5 equiv.) in CH_2Cl_2 was added. After 30 min the resulting solution was allowed to warm to room temperature and stirring was continued for another 20 h. The solvent was evaporated to give the crude product, which was purified by flash chromatography to afford ligands **10a–p** as white foams.

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