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Practical Synthesis of SimplePhos Ligands: Further Development of Alkyl-Substituted Phosphanamines

Daniel Müller,[a] Laure Guénée,[b] and Alexandre Alexakis*[a]

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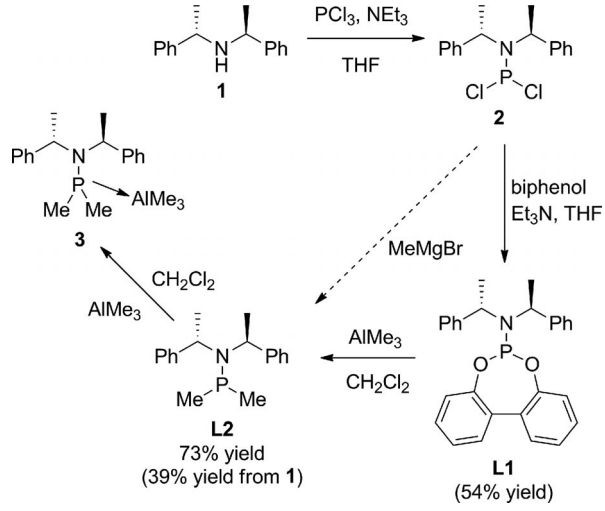
Herein we disclose a rapid and easy synthetic procedure to access aryl- and alkyl-substituted phosphanamines (SimplePhos ligands). During the synthesis of a library of diverse aryl-substituted phosphanamine ligands we also found that alkyl-substituted phosphanamines can be synthesized and handled easily. This was unexpected as a previous report described them as highly air-sensitive compounds. Subsequently, we created a library of alkyl-substituted phosphanamines and found some to be highly efficient ligands in copper-catalyzed reactions such as the Cu-catalyzed asymmetric conjugate addition and propargylic alkylation reactions. Moreover, our efforts towards the synthesis of SimplePhos ligands led to the development of an easy and practical synthesis of diaryl(chloro)phosphanes, which is also presented in this paper.

Introduction

In 2006, chiral monodentate phosphanamine ligands were prepared for the first time rather by accident than intentionally. Alexakis and Micouin observed that phosphoramidite ligands such as **L1** when exposed to Me_3Al in noncoordinating solvents like toluene or CH_2Cl_2 exchanged the diol moiety for methyl substituents affording the corresponding phosphanamine **L2** (Scheme 1).[1] This reaction does not occur in the presence of strongly coordinating solvents such as THF or with less oxophilic organozinc reagents. Several chiral dimethylphosphanamine ligands were synthesized by cleavage of the corresponding phosphoramidites with Me_3Al and tested for their ability to desymmetrize polycyclic hydrazines (Scheme 2). The preparation of methyl-substituted phosphanamine ligands **L2** by treatment of dichlorophosphoramine **2** with methylmagnesium bromide failed as the ligands were contaminated with amine **1** (Scheme 1). Hence, alkyl-substituted ligands such as **L2** had to be accessed by cleavage of **L1** with moderate total yields (<39% from the amine). Interestingly, ligand **L2** is able to coordinate strong Lewis acids through the lone pair of the phosphorus atom. This was observed by ^{31}P NMR spectroscopy when ligand **L2** was exposed to an excess of Me_3Al in noncoordinating solvents.



Scheme 1. First synthetic route to alkyl-substituted SimplePhos ligands, as exemplified for ligand **L2**.

The air-sensitivity of methyl-substituted SimplePhos ligands such as **L2** required rapid use of these compounds in asymmetric catalysis as storage was prevented by quick oxidation. These shortcomings in combination with the moderate enantioselectivities obtained for the desymmetrization of polycyclic hydrazines initially discouraged further use of alkyl-substituted phosphanamines in asymmetric synthesis. One year later, in 2007, another generation of phosphanamine ligands bearing aryl substituents on the phosphorus was reported by the same authors.[2] The basic idea for this substitution pattern was that the amine backbone would directly influence the helicity of the aryl substituents on phosphorus and thus create a chiral environment around the phosphorus atom (Figure 1).

[a] Département de Chimie Organique, Université de Genève,
30 quai Ernest-Ansermet, 1211 Genève 4, Switzerland
E-mail: alexandre.alexakis@unige.ch
Homepage: http://www.unige.ch/sciences/chiorg/alexakis/group/
[b] Laboratory of crystallography, Ecole de Physique Université de Genève,
30 quai Ernest-Ansermet, 1211 Genève 4, Switzerland
E-mail: laure.guenee@unige.ch

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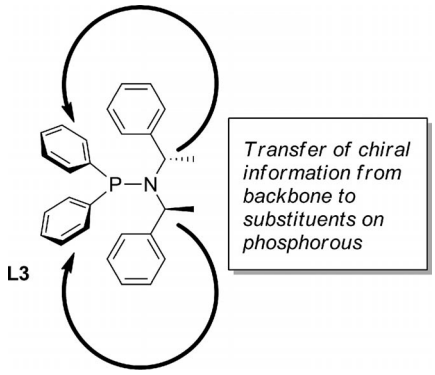
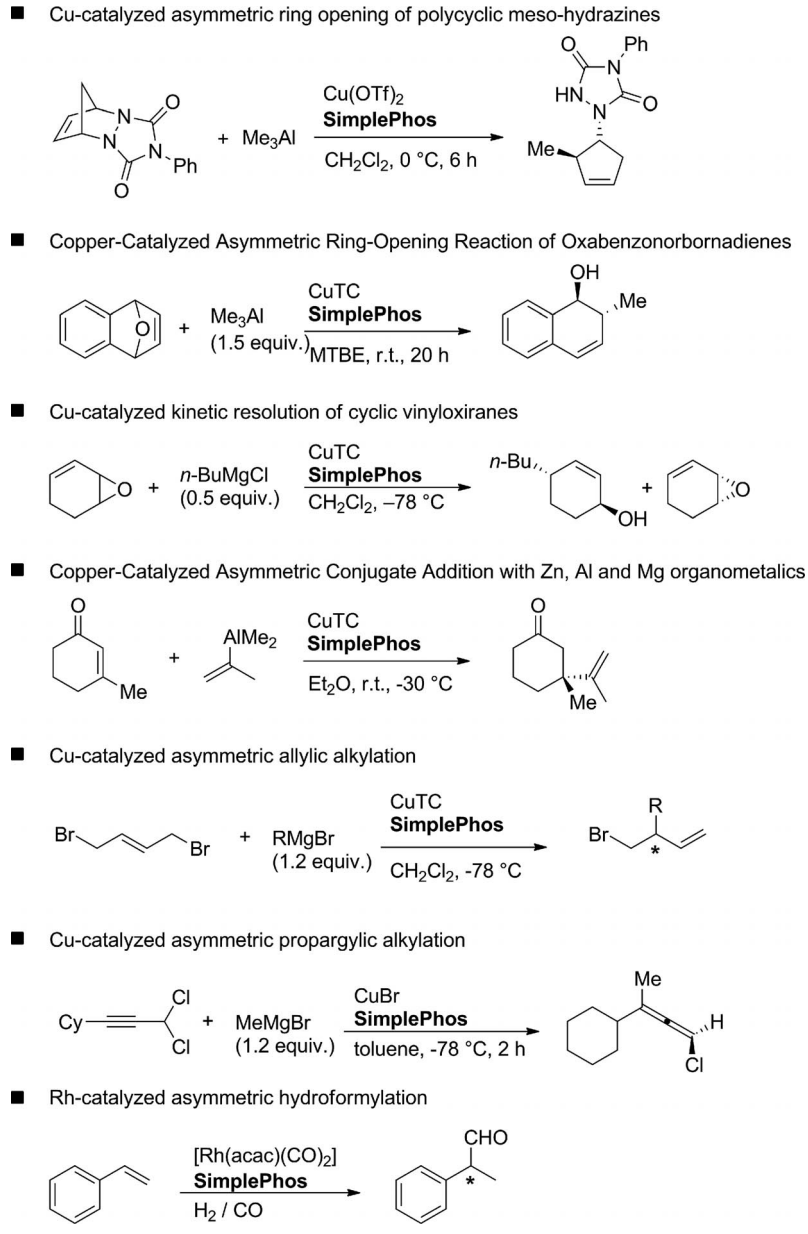
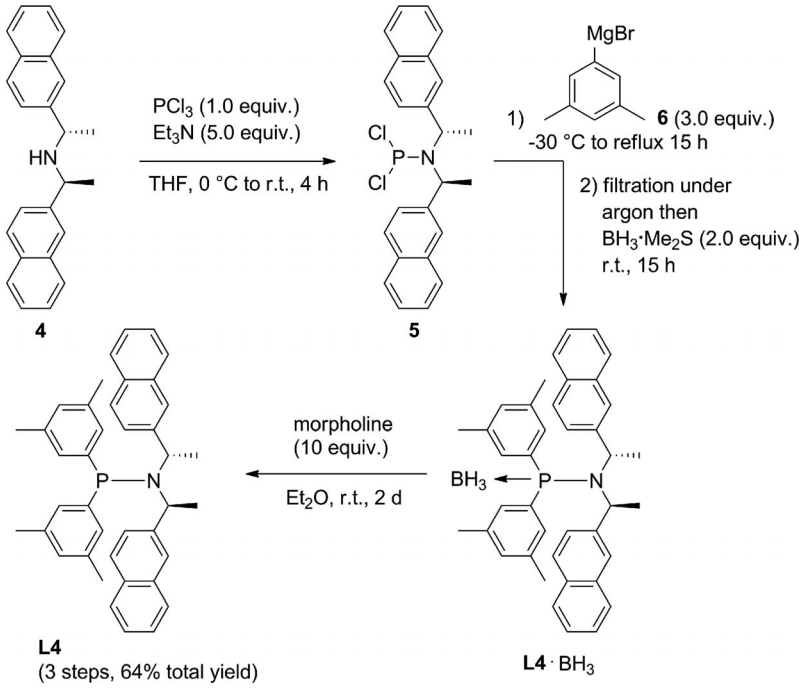


Figure 1. Chiral amine-induced helicity of the aryl substituents on phosphorus.

The change from alkyl to aryl substituents also rendered these ligands less sensitive to air. Hence aryl-substituted SimplePhos ligands can be conveniently handled without the use of a glovebox or other precautions and were used in a manifold of asymmetric transformations (Scheme 2). For example, aryl-substituted ligands were found to be efficient ligands for the Cu-catalyzed ring-opening of polycyclic *meso*-hydrazines[1–3] and oxabenzonorbornadienes,[4] the kinetic resolution of cyclic vinyloxiranes,[5] the Cu-catalyzed asymmetric conjugate addition with diorganozinc,[2,6] triorganoaluminium,[2,7] and Grignard reagents[8] as well as for Cu-catalyzed allylic alkylations.[3,6] Moreover, aryl-substituted SimplePhos ligands have been used for Rh-catalyzed asymmetric hydroformylation reactions.[9] However, the enantioselectivities obtained were poor in this case.



Scheme 2. Application of SimplePhos ligands in Cu- and Rh-catalyzed asymmetric catalysis; display of selected examples (references are given in the text).



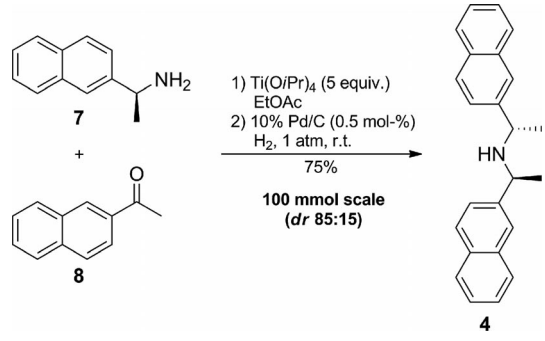
Scheme 3. First synthetic route towards aryl-substituted SimplePhos ligands, ilustrated for ligand **L4**.

Although aryl-substituted SimplePhos ligands are air-stable in the solid state, they are slightly air-sensitive in solution and therefore Alexakis and co-workers decided to transform them into air-stable borane–phosphane complexes before chromatographic purification of the crude ligand (Scheme 3).[2] It is important to note that the presence of magnesium salts impeded the formation of the borane complex of the SimplePhos ligands and hence had to be removed by filtration through neutral alumina under an inert atmosphere. Deprotection of the borane-protected ligands afforded the desired ligands in satisfactory yields (Scheme 3).

In conclusion, SimplePhos ligands, which were first considered to be too air-sensitive to be of practical use, quickly gained importance with the emergence of air-stable aryl-substituted ligands and their usefulness for a large number of asymmetric transformations has been demonstrated (Scheme 2).

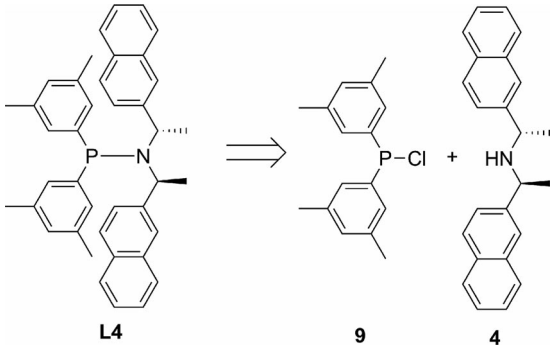
Results and Discussion

Recently, we discovered the high efficiency of SimplePhos ligands, in particular **L4**, for Cu-catalyzed asymmetric conjugate addition (ACA) reactions with aryl- and alkenylaluminium reagents.[7] The phosphanamine ligands outperformed even the best phosphoramidite ligands that had previously been reported for the highly enantioselective conjugate addition reactions with trialkylaluminiums.[10] Unfortunately, the ligand loading for such reactions was relatively high (between 11 and 22 mol-%), which necessitated an efficient and large-scale synthesis of **L4** in particular.[7] The reported protocol for the synthesis of SimplePhos ligands involved multiple steps and was limited in its scalability as it required filtration under argon (Scheme 3).[2,6] Moreover, the time efficiency of the synthetic procedure was low as the entire ligand synthesis, including protection and deprotection steps, took several days. Therefore we considered alternative procedures to achieve a more feasible and less time-consuming synthesis of phosphanamine ligand **L4**. First, we developed a reliable method for the large-scale synthesis of amine **4** bearing the 2-naphthyl motif (Scheme 4), which was essential for obtaining high enantioselectivities in Cu-catalyzed ACA reactions.[6,7,10] It was found that trituration in hot acetone easily removed ketone **8** impurities and the undesired diastereomer of amine **4**.[11] This finding was crucial for the synthesis on a large scale, typically 100 mmol in good overall yield (Scheme 4).



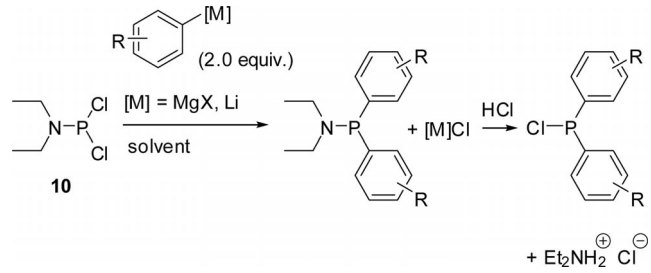
Scheme 4. Large-scale synthesis of amine **4**.

With large amounts of amine **4** in hand, we considered an alternative synthesis of ligand **L4** by combining amine **4** with the corresponding diaryl(chloro)phosphane **9**, as depicted in Scheme 5.



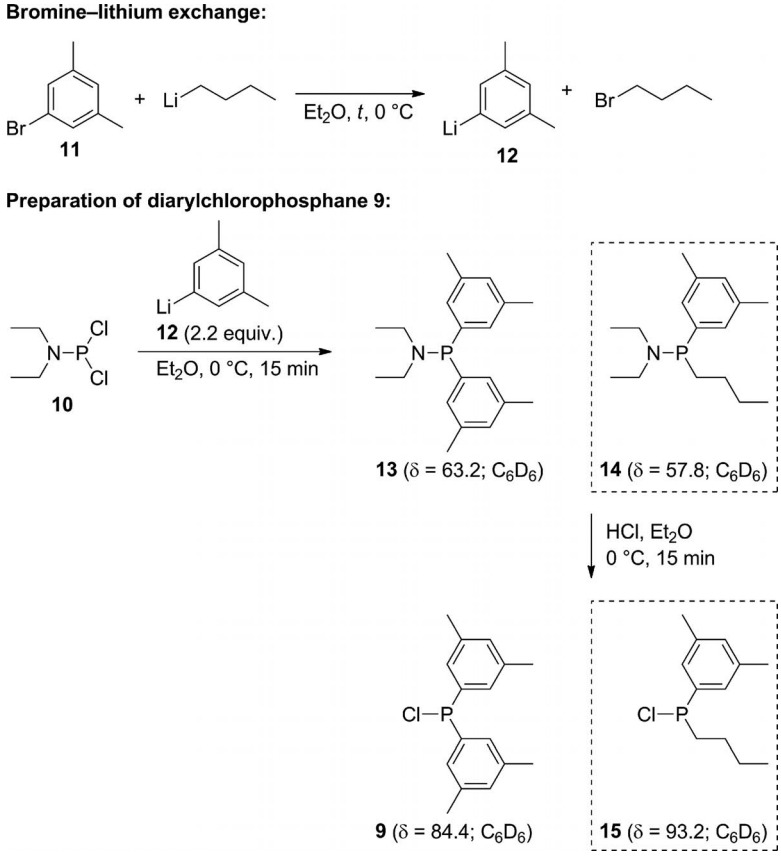
Scheme 5. Alternative synthesis of **L4**.

Although chlorobis(3,5-dimethylphenyl)phosphane (**9**) is commercially available, it is relatively expensive and we envisaged synthesizing it.[12] Unfortunately, standard procedures are relatively complicated and require preparation of the aryl-Grignard reagent in THF, reaction with dichloride **10**, and subsequent cleavage of the P–N bond with dry HCl gas (Scheme 6).[13] The major practical problem is the removal of the magnesium salts, which are soluble in THF or form a gluey residue when the solvents are evaporated and the salts filtered off.[14] Reports in the literature describe the addition of cyclohexane to the crude solution and careful removal of THF by co-evaporation with cyclohexane.[13] In contrast, Manners[15] and Le Drian[16] and their co-workers reported the use of aryllithium reagents instead of Grignard reagents, which were prepared by bromine/lithium exchange in diethyl ether or hexanes. Note that Manners only reported one exchange with *n*BuLi for an electron-poor aryl bromide whereas Le Drian used 2 equiv. of *t*BuLi for the Br/Li exchange of aryl bromides in hexanes at 0 °C.



Scheme 6. Typical synthesis of diaryl(chloro)phosphanes.

In comparison to THF, the use of diethyl ether or hydrocarbons as solvent are advantageous for the preparation of diaryl(chloro)phosphanes as they poorly dissolve lithium or diethylammonium salts and hence allow their clean precipitation, which can then be easily removed by filtration. Therefore we chose to prepare aryllithium **12** by bromine/

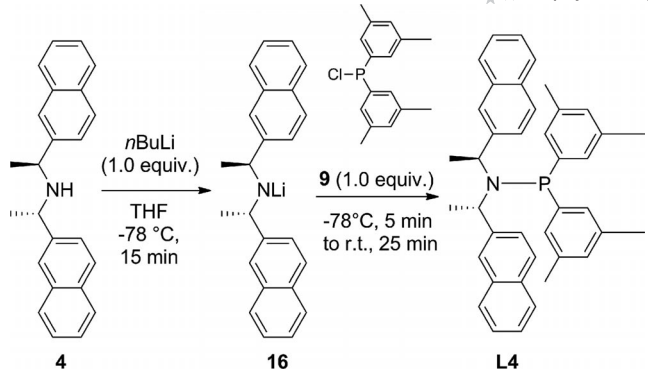


Scheme 7. Preparation of diaryl(chloro)phosphane **9**.

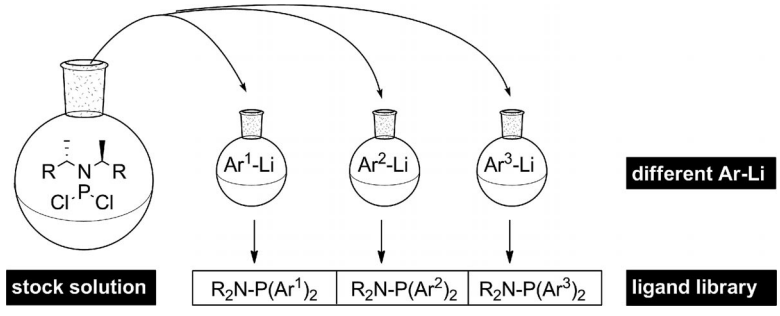
lithium exchange of **11** with *n*BuLi in diethyl ether at 0 °C and then added dichloride **10** after 1.5 h (Scheme 7). Two signals were observed in the ^{31}P NMR spectrum (δ = 63.2 and 58.0 ppm in C_6D_6), which were attributed to the phosphanamines **13** and **14**. Incomplete bromine/lithium exchange led to the formation of phosphanamine **14**, which was subsequently converted into **15** after treatment with dry HCl. To avoid the byproducts **14** and **15**, we decided to increase the reaction time for the Br/Li exchange. After 4 h, one peak in the ^{31}P NMR spectrum was observed corresponding to phosphanamine **13**, and subsequent quenching with a solution of HCl in Et_2O cleanly afforded diaryl(chloro)phosphane **9**. Dry solutions of HCl in diethyl ether are commercially available or can be easily prepared by bubbling dry HCl gas into diethyl ether at 0 °C.

Removal of the salts by filtration and evaporation of the solvents under reduced pressure and then under high vacuum (0.5 mbar) at room temperature afforded compound **9** in approximately 90% purity (Scheme 7). All operations were carried out without the use of Schlenk techniques and only the careful drying of glassware was required. The biaryl-coupling byproduct and traces of hydrolyzed compound **9** were obtained as impurities The procedure is operationally simple and only necessitated one quick filtration. Hence compound **9** was typically obtained in >95% yield and could be used immediately for the preparation of ligand **L4** (Scheme 8). Deprotonation of amine **4** with 1 equiv. of *n*BuLi and treatment of lithium amide **16** with diaryl(chloro)phosphane **9** afforded ligand **L4** in 57% yield after column chromatographic purification over triethylamine-treated silica gel.

This reaction sequence has advantages over the strategy shown in Scheme 3 as the reaction can be easily scaled-up and is experimentally relatively simple. Diaryl(chloro)phosphanes are stable compounds when stored under an inert atmosphere at –20 °C; even after 2 months there was no evidence of oxidation or hydrolysis. Moreover, the reaction was relatively clean as it involves the combination of only two molecules, thus limiting the number of possible byproducts. Importantly, we noted that ligand **L4** could be isolated in satisfactory yield without borane protection when we gradually increased the polarity of the solvent for column chromatographic purification over triethylamine-treated silica gel. This clearly shows that prolonged exposure of ligand **L4** to silica gel leads to decomposition of the compound. In general, prolonged exposure of phosphanamine ligands to materials with a high surface area such as aluminium oxide and silica gel should be avoided to obtain good yields. Unfortunately, when we tried to prepare electron-rich diaryl(chloro)phosphanes such as chlorobis(4-methoxyphenyl)phosphane for the synthesis of **L5**, we noticed that the bromine/lithium exchange in diethyl ether did not proceed to completion even when the reaction time was increased to 9 h. After several unsuccessful attempts to increase the ligand scope using the synthesis shown in Scheme 8, we revisited the synthetic procedure shown in Scheme 3 and implemented several changes. 1) We envisaged preparing the aminophosphane dichloride by deprotonation of the amine with *n*BuLi and then quenching the amide with PCl_3. This strategy is advantageous as the two reactions take less than 15 min and avoid the formation of the ammonium salt, which would then have to be deprotonated by a third equivalent of the aryl-Grignard reagent, which can be expensive. Note that the corresponding lithium amide **16** is very bulky and hence reacts with only one molecule of PCl_3 to cleanly give dichloride **5**. 2) Grignard reagents were replaced by aryllithiums. Aryl-Grignard reagents do not react at room temperature with the sterically encumbered aminophosphane dichloride **5** and heating at reflux overnight is required to bring the reaction to completion. Aryllithiums, in contrast, react within a few minutes at 0 °C with aminophosphane dichloride **5** and can be easily prepared by bromine/lithium exchange from commercially available aryl bromides and *n*BuLi. 3) Protection and deprotection steps for ligand **L4** could be circumvented by



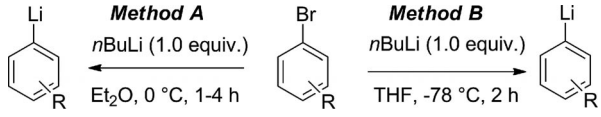
Scheme 8. Alternative synthetic approach towards ligand **L4**.



Scheme 9. Rapid synthesis of a SimplePhos ligand library.

gradually increasing the polarity of the solvent mixture used for column chromatography. 4) The clean synthesis of a stable solution of aminophosphane dichloride allowed the parallel synthesis of phosphanamine ligands by reaction of the parent dichloride solution with several aryllithiums (Scheme 9).

In the course of our investigations we developed two protocols for the bromine/lithium exchange depending on the electronic properties of the aryl bromide. For strongly electron-rich aryl bromides, the exchange was carried out at –78 °C in THF for 2 h, whereas for electron-poor to slightly electron-rich aryl bromides, the exchange was performed at 0 °C in Et_2O (Scheme 10).



Scheme 10. Preparation of aryllithium reagents by bromine/lithium exchange in diethyl ether or THF.

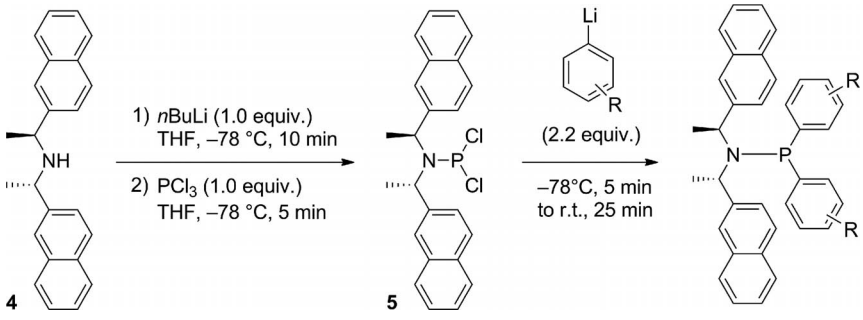
Under the optimized elution conditions, similar yields were afforded for the highly efficient ligand **L4** compared with the former protocol involving protection and deprotection steps (Table 1 and Scheme 3; 64 vs. 65%). The greater time-efficiency (approximately 5 h instead of 1 week) and the versatility of the improved protocol made it ideal for the rapid generation of a ligand library (Table 1). Note that the corresponding Grignard reagents for the preparation of **L8**–**L10** are not easy to prepare and the bromine/lithium exchange represents a cleaner alternative to accessing such aryl nucleophiles.[17] Ligands **L4**–**L11** only contain *meta* and *para* substituents because we knew from previous studies with trialkylaluminium reagents that ligands containing *ortho* substituents are not efficient for Cu-catalyzed conjugate addition reactions.[6]

The yields of ligands **L6**–**L12** were poor to moderate (20–50%), which is simply due to non-optimized elution in their purification by column chromatography (Table 1, entries 3–9). Ligand **L4** gave similar low yields (33% yield) when the column chromatography was carried out without a constant increase of the solvent polarity. Only the elution conditions for ligand **L4** were optimized because all other ligands **L5**–**L12** were less or equally efficient in Cu-catalyzed ACA reactions.[19] Pure **L5** was obtained by trituration of the crude product, thus affording better yields compared with purification by column chromatography.

Further Development of the Alkyl-Substituted SimplePhos Ligands

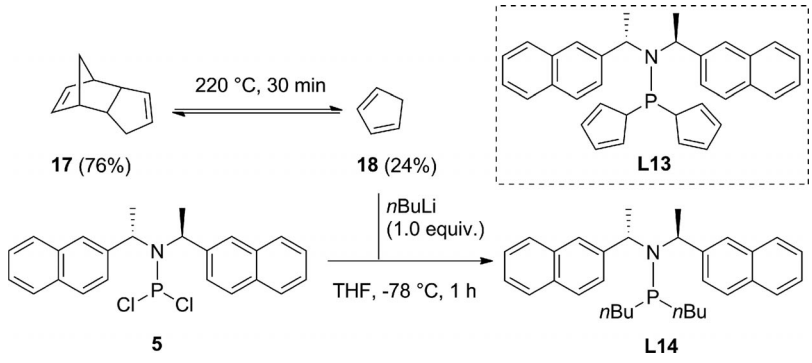
We were interested in further extending the library to alkyl-substituted phosphanamine ligands. The first report by Alexakis and Micouin on the cleavage of phosphoramidite ligands by Me_3Al discouraged the synthesis of alkyl-substituted ligands. They noted in their Supporting Information: "Dimethylaminophosphanes are air sensitive reagents that readily oxidize, and must be used rapidly after isolation".[1] We envisaged the synthesis of a phosphanamine with an alkyl substituent, which would be sterically more demanding but not offer too much flexibility and hence be possibly as air-stable as aryl-substituted ligands and provide similar efficiency in Cu-catalyzed ACA reac-

Table 1. Synthesis of a ligand library **L4**–**L12**.[a]



Entry	Method for Br/Li exchange/time for exchange [h][b]	Ligand	R	Yield [%][c]
1[d]	A/4	**L4**	3,5-Me	65
2	B/2	**L5**	4-MeO	71[e]
3	A/3.5	**L6**	4-*t*Bu	29[f]
4	A/1.5	**L7**	4-F	25[f]
5	B/2	**L8**	3,5-MeO	22[f]
6	B/2	**L9**	3,5-Me-4-MeO	46[f]
7	B/1.5	**L10**	3,5-*t*Bu	45[f]
8	A/1.0	**L11**	3,5-CF_3	18[f]
9	–[g]	**L12**	1-Furyl	23[f]

[a] For all ligands, the ^{31}P NMR spectra of the crude product indicated a >90% purity of the ligand. [b] Methods A and B are as depicted in Scheme 10. [c] Yields of pure ligands after column chromatography on triethylamine-treated silica gel. [d] Reaction was carried out on a 13.5 mmol scale; optimized conditions for column chromatography. [e] Purification by trituration in pentane. [f] Elution conditions for column chromatographic purification non-optimized. [g] The lithium reagent was generated by deprotonation of furan with 1.0 equiv. of *n*BuLi at 0 °C in THF.



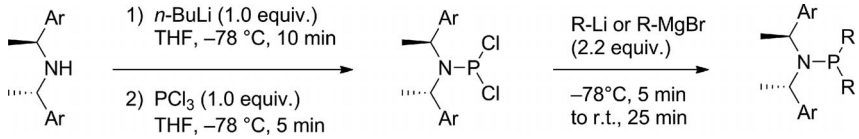
Scheme 11. Unanticipated synthesis of ligand **L14**.

tions. A cyclopentadienyl substituent seemed to be the ideal choice because the corresponding lithium reagent can be easily synthesized by deprotonation of cyclopentadiene and the dienic ring structure would grant some rigidity. Therefore we carried out thermal cracking of dicyclopentadiene **17**,[20] immediately deprotonated the generated cyclopentadiene with *n*BuLi, and added the lithiumorganyl to aminophosphane dichloride **5** (Scheme 11). Note that once prepared, cyclopentadiene (**18**) needs to be used immediately due to rapid dimerization at room temperature.[21] Only one major peak was observed in the ^{31}P NMR spectrum, which we at first assumed to be compound **L13**. However, ^{1}H NMR analysis showed that only alkene protons from cyclopentadiene were present and subsequent NMR analysis showed that the supposedly "pure" cyclopentadiene was indeed a mixture of 76% of the dimer and 24% of the monomer. Next we heated the crude ligand for 20 min at 200 °C at 1 mbar, which led to the total disappearance of the alkene protons in the ^{1}H NMR spectrum, whereas the major phosphorus peak at δ = 30.8 ppm (C_6D_6) remained. It was clear that instead of the desired ligand **L13**, *n*Bu-substituted ligand **L14** was obtained. This was confirmed by complete analysis of the pure ligand and direct synthesis of the ligand from **5** with 2 equiv. of *n*BuLi.

To our surprise we found that ligand **L14** is highly air- and temperature-stable. This observation was unexpected as a previous report[1] by our group and Micouin described methyl-substituted phosphanamines as being highly sensitive to oxidation. It is also known that trialkylphosphanes such as P(*n*Bu)$_3$ even show pyrophoric behavior.[22] We reasoned that the stability of the ligands towards oxidation is mainly due to the steric shielding of the phosphorus by the adjacent bulky amine moiety and its alkyl substituents. The scope of alkyl-substituted phosphanamines was further explored by the reaction of a large number of alkyllithium and alkyl-Grignard reagents with the corresponding aminophosphane dichlorides (Table 2). Partial results for the synthesis of the isolated ligands displayed in Table 2 have been published elsewhere.[7c]

In general, ligands containing a smaller amine moiety (**L2**, **L15**, and **L16**) are slightly more sensitive to oxidation than related ligands (**L29**, **L30**, and **L14**) bearing an amine with the 2-naphthyl motif. In particular, methyl-substituted phosphanamine ligand **L2** proved to be difficult to purify by standard laboratory techniques as the ligand is very sensitive to oxidation and contaminated by free amine **1**. Strangely, this purification problem is unique to **L2** as amine impurities were not observed for any of the other ligands. We believe that **L2** is contaminated with amine as a result of the cleavage of the ligand on basic alumina and simultaneous elution of the two compounds. This separation problem has already been reported by Alexakis and Micouin, who chose to synthesize the phosphanamine ligands **L2** and **L29** by cleavage of phosphoramidite ligand **L1** with Me_3Al instead of by direct reaction of the aminophosphane dichlorides with MeMgBr (cf. Scheme 1). Alexakis and Micouin also found that the decomposition could be suppressed by rapid filtration instead of column chromatographic purification.[1] **L29** was much less sensitive to degradation on basic alumina and the pure ligand was purified in 60% yield. This shows that the steric shielding of the amine moiety protects the phosphorus against oxidation and the P–N bond from cleavage. Hence, the bulkier the amine moiety, the more stable is the ligand. In addition to the bulkiness of the amine moiety, the bulkiness of the alkyl group on phosphorus is equally important. For example, **L2** is very sensitive towards oxidation whereas **L15** and **L16** can be stored under air for several months without even a trace of the oxidized product. Many attempts to synthesize styrene-substituted ligand **L19** or branched alkyl-substituted ligands **L20**–**L24** failed probably for steric reasons. Other ligands with linear substituents (**L15**–**L17**, **L29**–**L30** and **L14**) were easily synthesized and are perfectly air-stable. β- and γ-branched ligands **L25**–**L28** were synthesized in good yields (entries 12–15). For **L25** we noticed that the aminophosphane dichloride had to react for 1 h at room temperature with *i*BuMgBr for the reaction to go to completion, whereas for most other alkyl-Grignard and alkyllithium reagents, the reaction times were typically less than 5 min at 0 °C. The yields of alkyl-substituted SimplePhos ligands, especially those made from alkyllithiums, are in general higher than those obtained with aryllithiums. This can be explained by the easy removal of Wurtz-coupling impurities present in the employed alkylorganometallic reagents by evaporation. In contrast, the arylorganolithium, reagents used in this study, contain homocoupling impurities which

Table 2. Synthesis of various alkyl-substituted phosphinamine ligands.



Entry	L	R-M	Ar	R	Yield [%][a]
1	**L2**	R-Li	Ph	Me	–[b]
2	**L15**	R-MgBr	Ph	Et	64
3	**L16**	R-Li	Ph	*n*Bu	85
4	**L17**	R-MgBr	Ph	*n*Hex	43
5	**L18**	R-MgBr	Ph	$CH_2CH{=}CH_2$	51
6[c]	**L19**	R-Li	Ph	CH=CHPh[d]	–
7	**L20**	R-Li	Ph	*n*-1-hexyne[e]	62
8	**L21**	R-MgBr	Ph	*i*Pr	–
9	**L22**	Ph	Ph	isopropenyl[d]	–
10[f]	**L23**	R-Li	Ph	*t*Bu	–
11	**L24**	R-Li	Ph	*s*Bu	–
12	**L25**	R-MgBr	Ph	*i*Bu	50
13	**L26**	R-MgBr	Ph	Bn	59
14	**L27**	R-MgBr	Ph	*i*Am	63
15	**L28**	R-MgBr	Ph	CH_2Bn	60
16	**L29**	R-Li	2-naphthyl	Me	60
17	**L30**	R-MgBr	2-naphthyl	Et	65
18	**L14**	R-Li	2-naphthyl	*n*Bu	90

[a] Isolated yield after column chromatography over basic alumina. [b] Phosphinamine contaminated with 35% of free amine. [c] Supposedly monosubstituted $R_2NPR'Cl$ and non-identified byproducts were observed by ^{31}P NMR spectroscopy. [d] Prepared from the corresponding alkenyl bromide by bromine/lithium exchange with 2 equiv. of *t*BuLi. [e] Prepared by deprotonation of 1-hexyne with *n*BuLi. [f] ^{31}P NMR spectroscopy showed a major peak at δ = 12.7 ppm, but all attempts of isolation of **L23** failed.

are not volatile and hence require column chromatographic separation. Therefore the crude ligands can be purified by quick filtration through basic alumina without a great loss of the compound by decomposition. In contrast, aryl-substituted ligands **L4**–**L12** show contamination by biaryl byproducts, which need to be carefully separated by column chromatography. Many of the alkyl-substituted ligands are viscous oils that turn to crystalline solids or wax-like solids when stored at room temperature or at –30 °C. For example, when stored at room temperature, **L25** crystallized and we were able to determine the X-ray structure of this highly encumbered ligand (Figure 2).[23]

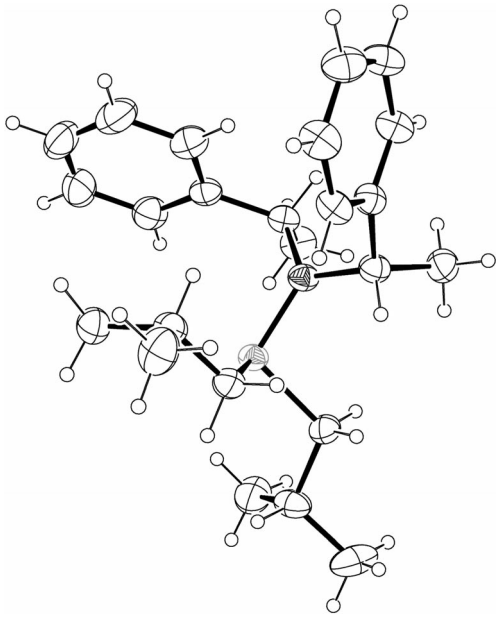


Figure 2. Single-crystal X-ray structure of ligand **L25**. Thermal ellipsoids are shown at the 50% probability level.

Recently we found that chiral copper complexes with alkyl-substituted phosphanamines as ligands show high enantioselectivity in tandem hydroalumination/Cu-catalyzed conjugate addition and Cu-catalyzed asymmetric propargylic substitution reactions (see Scheme 2).[7c,24] We believe that the simple synthesis of this new type of SimplePhos ligands combined with promising results in copper-catalyzed reactions will further promote their use and application in asymmetric catalysis.

Conclusions

The improved protocol for the synthesis of phosphanamine ligands has been crucial for the development of about 20 new aryl- and alkyl-substituted SimplePhos ligands. The new synthetic procedure is very efficient and allows for the generation of a large library of phosphanamine ligands within a very short time. We found that alkyl-substituted phosphanamine ligands, with the exception of **L2**, are air-stable compounds that can be easily handled without any special precautions. Furthermore, ligands **L14** and **L29** were found to be highly efficient for copper-catalyzed asymmetric transformations such as the conjugate addition of alkenylaluminiums and copper-catalyzed propargylic alkylation reactions.

Experimental Section

New Procedure for the Synthesis of SimplePhos Ligands (Exemplified for L4): *n*BuLi (14.1 mL, 22.5 mmol, 1.6 M solution in hexanes, 2.25 equiv.) was added to a solution of 1-bromo-3,5-dimethylbenzene (**11**; 3.14 mL, 4.26 g, 23.0 mmol, 2.4 equiv.) in diethyl ether (25 mL) and stirred for 4 h at 0 °C resulting in a white suspension of aryllithium **13**. In the meantime, *n*BuLi (8.90 mL, 14.2 mmol, 1.05 equiv.) was slowly added to a solution of amine **4** (4.62 g, 14.2 mmol, 1.05 equiv.) in THF (40 mL) at –78 °C and stirred for 10 min, which resulted in a bright-red solution. PCl_3 (1.17 mL, 1.84 g, 13.5 mmol, 1.0 equiv.) was added neat to the amide solution at –78 °C and the solution turned yellow. After 5 min, the complete consumption of PCl_3 was verified by ^{31}P NMR analysis (single peak at 166.5 ppm/C_6D_6), which indicated the complete formation of dichlorophosphanamine **5**. Then a solution of aryllithium reagent **13** (described above) was added at –78 °C to the solution of the dichlorophosphanamine **5**. After immediate removal of the cooling bath, warming to room temp., and stirring for 30 min, ^{31}P NMR analysis showed the formation of the desired ligand **L4** as a single peak (δ =43.8 ppm in C_6D_6). The reaction mixture was quenched with MeOH (0.2 mL) and the solvents were removed under reduced pressure. The residue was diluted with CH_2Cl_2 (50 mL), the lithium salts removed by filtration of the suspension over Celite, rinsing with additional CH_2Cl_2 (100 mL), and evaporation of CH_2Cl_2 under reduced pressure afforded the crude product as a yellow viscous oil. Column chromatography over triethylamine-treated silica gel (pentane/Et_2O = 60:1 to 10:1; R_f = 0.74 in pentane/Et_2O = 10:1), afforded **L4** as a white foam (4.96 g, 8.8 mmol, 65%). The ligand can be stored over several months in air at –40 °C without any evidence of oxidation. The triethylamine-treated silica gel was prepared by addition of NEt_3 (2.0 mL) and pentane (100 mL) to silica gel (100 mL) and then the slurry was filtered and dissolved in the eluent used for column chromatography.

Supporting Information (see footnote on the first page of this article): Experimental procedures and NMR spectra for all compounds.

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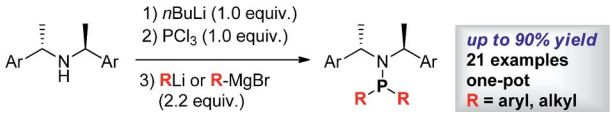
SimplePhos Ligands



An improved synthesis for SimplePhos ligands. A synthetically simple, time efficient, and versatile synthesis of aryl- and alkyl-SimplePhos ligands has been developed. The serendipitous discovery of new alkyl-substituted SimplePhos ligands is very rewarding as they have been found to be highly selective ligands in Cu-catalyzed asymmetric transformations.

Keywords: Synthetic methods / Ligand design / Phosphane ligands

