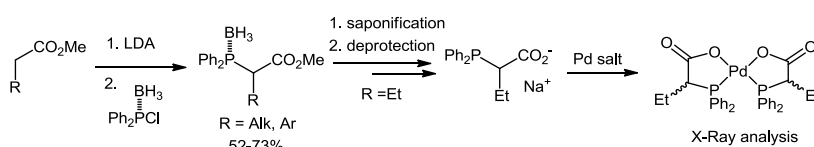# Synthesis of α-substituted diphenylphosphinocarboxylic acids and their palladium complexes

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Abstract A general and efficient synthesis of α-substituted phosphinoacetic acids using simple esters and diphenylchlorophosphine-borane as readily available starting materials is here described. The formation and structure of the corresponding palladium complex derived from 2-ethyl diphenylphosphinoacetic acid is also reported.

Key words phosphine, carboxylic acids, P,O-ligands, palladium, homogeneous catalysis

Phosphine are considered a privileged class of ligands for their versatility to effect a wide range of transformations in organic synthesis.[1] In particular, bidentate phosphinocarboxylic acid ligands (P,O-ligands) (Figure 1) play an important role in catalytic processes such as the Shell higher olefin process (SHOP).[2] The synthesis of some of these ligands involves either nucleophilic phosphanylation (e.g. **A**, **B** and **C**, Figure 1)[3] or Pd-catalyzed cross coupling reactions of arylhalides with phosphanes (e.g. B, Figure 1).[4]

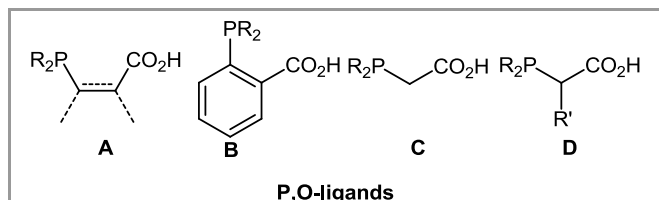**Figure 1** Different classes of P,O-ligands

However, a general synthesis of α-substituted phosphinoacetic acids (D, Figure 1) has not been reported so far, which might explain why this type of ligands have not been applied in homogeneous catalysis yet. The catalytic activity of metal complexes derived from α-substituted phosphinoacetic acids **D** is expected to be significantly different than the one observed

for the phosphinoacetic acids **C**, and might open new possibilities in catalytic processes.

Few methods for the synthesis of α-substituted phosphinoacetic acids have been reported to date (Scheme 1).[5] However, these methods lack from generality, as a seminal work from Shell Research Laboratories concludes: 'it is impossible to prepare a large diversity of functionalized aliphatic phosphinocarboxylic acids by one generally applicable synthetic method'.[5a] The reaction of metal phosphide with halocarboxylic acids or esters (route a, Scheme 1) is, at present, the most straightforward route for the synthesis of α-substituted phosphinoacetic acids. Unfortunately, using this strategy, only the 2-methyl diphenylphosphinoacetic acid derivative can be obtained in good yield. In addition, halocarboxylic acids are not readily available, which limits the broad applicability of this strategy. The second approach to the synthesis of α-substituted phosphinoacetic acids is the carbonation of metallated alkyldiarylphosphines substrates, which again, are not ready available either (route b, Scheme 1). Moreover, this method also lacks from generality and only allows the preparation of very few α-substituted phosphinoacetic acids. Therefore, the development of a general synthetic method for the synthesis of α-substituted phosphinoacetic acids **D** using readily available starting materials is highly desired. Herein, we report an efficient method for the synthesis of α-substituted phosphinoacetic acids, using simple esters and diphenylchlorophosphine as starting materials (Scheme 1), both commercial and readily available substrates. The synthesis of O-methyl 2-ethyl diphenylphosphinoacetohydroxamic acid and the palladium complexes derived from 2-ethyl diphenylphosphinoacetic acid are also described.

Scheme 1 Methods for synthesizing α-substituted phosphinoacetic acids
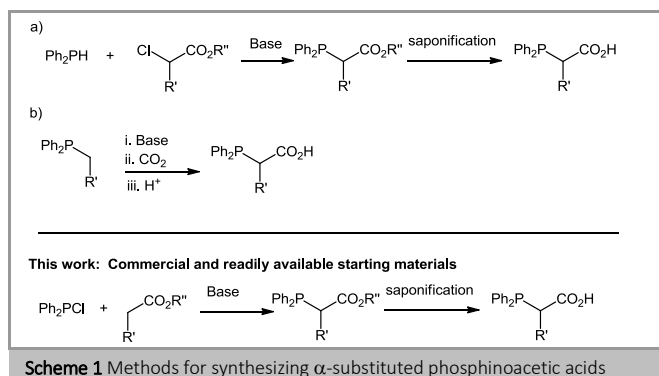
The interest of our research group in the development of metal-catalyzed reactions drove our attention to the urgent need of new, general and reliable methods for the synthesis of α-substituted phosphinoacetic acids, an unexplored class of ligand in homogeneous catalysis. Our proposal towards the synthesis of these valuable targets was based on the phosphonylation of lithium enolates (Scheme 2). In this context, it has been reported that the reaction of lithium 2-lithiopropionate with diphenylchlorophosphine does not provide the desired phosphonylated product;[5a] this might be the reason why this simple approach has not been explored to date. Our first approach using 1.2 equiv of LDA, methyl butyrate and diphenylchlorophosphine, showed the formation of the corresponding phosphine oxide. Therefore, we decided to perform the reaction using diphenylchlorophosphine-borane as starting material, which can be easily synthesized *in situ*.[6] Using this phosphine complex as the phosphonylation agent, and after certain optimization of the reaction conditions, the desired methyl 2-ethyl diphenylphosphinoacetate-borane (**1**) was obtained in 73% isolated yield (Scheme 2). With the optimal reaction conditions in hand, the synthesis of different methyl α-substituted diphenylphosphinoacetates-boranes complexes was explored. The reaction with the hindered methyl 3-methylbutanoate provided the desired product **2** in good yield (52%, Scheme2), while methyl 3-phenylpropionate furnished the corresponding methyl 2-benzyl diphenylphosphinoacetate-borane (**3**) in 72% isolated yield. Moreover, we successfully applied this protocol to the synthesis of methyl 2-aryl diphenylphosphinoacetates. Thus, the reaction of methyl phenylacetate led to the formation of the desired methyl 2-phenyl diphenylphosphinoacetate-borane (**4**) in good yield (56%, Scheme 2).

Scheme 2 Synthesis of methyl α-substituted diphenylphosphinoacetates
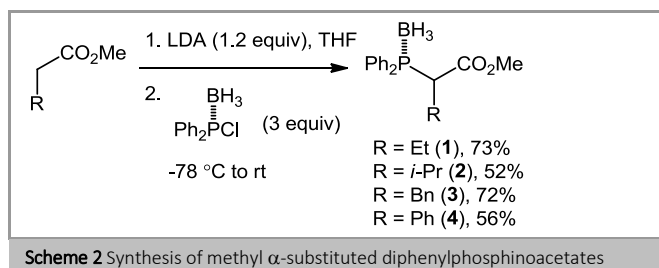
Next, the hydrolysis of the ester moiety and the phosphine deprotection in the model substrate methyl 2-ethyl diphenylphosphinoacetate-borane (**1**) were evaluated.

The hydrolysis of ester **1** was carried out under usual reaction condition using NaOH in THF:MeOH:H$_2$O at room temperature.
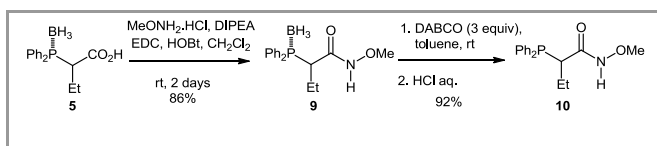
After 18 h, 2-ethyl diphenylphosphinoacetic acid borane (**5**) was obtained in 74% isolated yield (Scheme 3).[7]

Scheme 3 Hydrolysis and deprotection of methyl 2-ethyl diphenylphosphinoacetate (**1**)
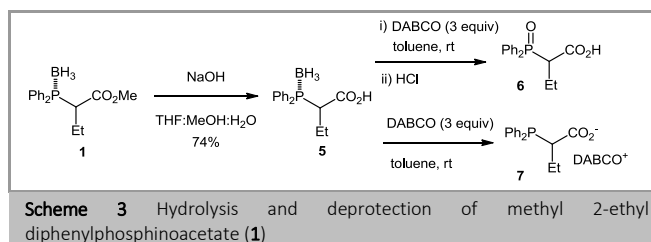
Diphenylphosphinoacetic acid borane **5** was subsequently subjected to several deprotection methods to liberate the phosphine from the borane ligand. The deprotection with HNEt$_2$,[6] morpholine,[8] TFA[9] or HBF$_4$[10] was tested, however, no clean formation of the desired product was observed in any case. The reaction using DABCO[11] in toluene at room temperature cleanly furnished, after acidic workup, the 2-ethyl diphenylphosphorylacetic acid (**6**) (Scheme 3). During this experiment, we noticed that the corresponding DABCO salt of 2-ethyl diphenylphosphinoacetic acid (**7**) is relatively stable towards oxidation, while the 2-ethyl diphenylphosphinoacetic acid is extremely sensitive to oxidation. With this in mind, we hypothesized that the corresponding sodium 2-ethyl diphenylphosphinoacetate (**8**) could be more stable to oxidation than the 2-ethyl diphenylphosphinoacetic acid. Therefore, we performed the acidic workup of the DABCO salt **7** under inert atmosphere, followed by the addition of 1 equiv of NaOH, to obtain the corresponding sodium 2-ethyl diphenylphosphinoacetate (**8**) in 54% yield, which is indeed relatively stable towards oxidation (Scheme 4).


Scheme 4 Synthesis of sodium 2-ethyl diphenylphosphinoacetate (**8**)
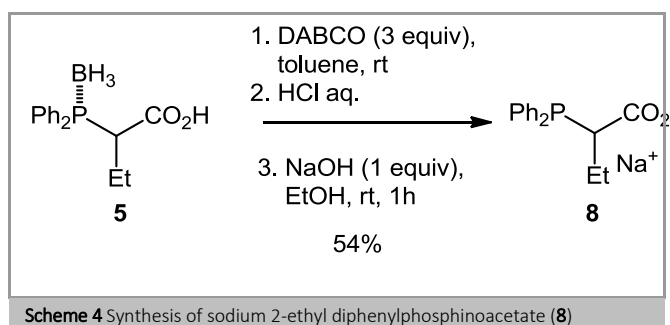
After establishing a general protocol for the synthesis of α-substituted diphenylphosphinoacetic acids, we decided to synthesize the corresponding 2-ethyl diphenylphosphinoacetohydroxamic acid (**10**), which could be a potential ligand for homogeneous catalysis.[12] Thus, the reaction of 2-ethyl diphenylphosphinoacetic acid borane (**5**) in the presence of methoxyamine under standard coupling reaction conditions provided *O*-methyl ethyl diphenylphosphinoacetohydroxamic acid-borane (**9**) in 86% yield (Scheme 5). The deprotection of the phosphine using DABCO followed by acidic workup afforded the desired *O*-methyl 2-ethyl diphenylphosphinoacetohydroxamic acid (**10**), which is relatively stable to oxidation, in excellent yield (92%).

Scheme 5 Synthesis of 2-ethyl diphenylphosphinoacetohydroxamic acid (**10**)

Finally, we concentrated our efforts towards the synthesis and isolation of the corresponding P,O-palladium complex derived from ligand **8**. The stoichiometric reaction of 2-ethyl diphenylphosphinoacetate (**8**) with $PdCl_2$ showed the formation of two complexes **11** and **12** by NMR (Scheme 6). Complex **11** was unequivocally identified by X-Ray analysis,[13] possesses two molecules of ligands with different stereochemistry attached (i.e. *R,S*) in a *cis* geometry. The small differences observed in NMR between complexes **11** and **12** suggest that complex **12** is the diastereoisomer of **11** (i.e. *R,R*). The unusual *cis* P-P, square-planar geometry obtained in **11** and **12**, has been previously reported on Pd and Pt complexes derivatives from phosphinoacetic acid.[14]
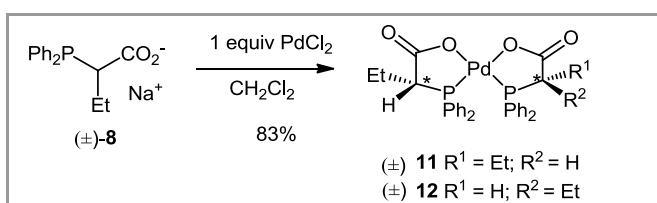
Scheme 6 Synthesis of palladium complexes

In conclusion, we have developed a general and efficient method for the synthesis of α-substituted phosphinoacetic acids using simple esters and diphenylchlorophosphine-borane as starting materials. The phosphonylation of lithium enolates furnished the corresponding methyl α-substituted diphenylphosphinoacetates-boranes in good yields for both aromatic and aliphatic substrates. To prove the viability of the overall sequence, the saponification and deprotection of methyl 2-ethyl diphenylphosphinoacetate-borane was carried out under standard reaction conditions, to furnish the desired sodium 2-ethyl diphenylphosphinoacetate. We observed that the 2-ethyl diphenylphosphinoacetic acid is more sensitive towards P-oxidation than its corresponding sodium salt. As an application for the methodology, *O*-methyl 2-ethyl diphenylphosphinoacetohydroxamic acid was successfully synthesized. Last, two palladium complexes derived from 2-ethyl diphenylphosphinoacetic acid were prepared and one of them isolated and characterized by X-Ray analysis.

Acknowledgment

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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