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Chiral inducers with (1*R*,2*R*)-1,2-diaminocyclohexane core for organo- and metallocatalysis

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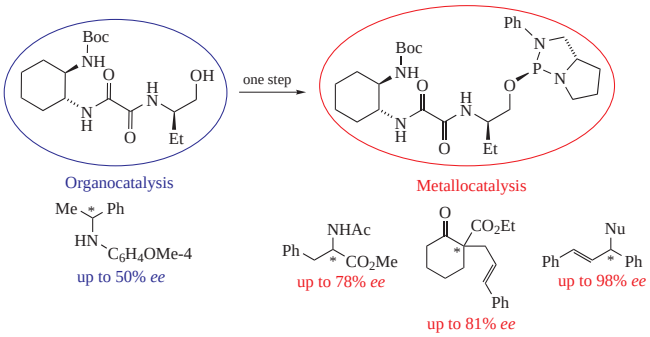
A P*-chiral diamidophosphite ligand of the 1,3,2-diazaphospholidine series was obtained by direct phosphorylation of *N*-[(1*R*,2*R*)-2-(*tert*-butoxycarbonylaminocyclohexyl)]-*N'*-[(1*R*)-1-(hydroxymethyl)propyl]oxalamide. The use of this ligand made it possible to reach 98% *ee* in the Pd-catalyzed allylation involving (*E*)-1,3-diphenylallyl acetate, 81% *ee* in the allylation of ethyl 2-oxocyclohexane-1-carboxylate with cinnamyl acetate, 78% *ee* in the Rh-catalyzed hydrogenation of methyl (*Z*)-2-acetamido-3-phenylacrylate, and 32% *ee* in the Rh- and Ir-catalyzed hydrosilylation of (*E*)-*N*-(4-methoxyphenyl)-1-phenylethan-1-imine with diphenylsilane. The above mentioned oxalamide provides up to 50% *ee* in the organocatalytic reduction of the same imine.

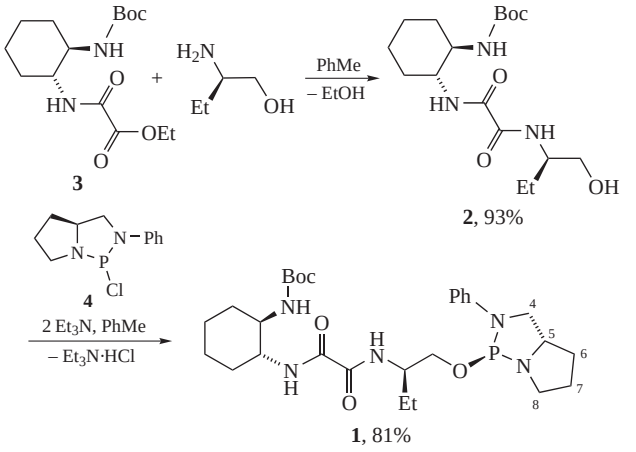


Asymmetric metal complex catalysis is an efficient tool for the synthesis of enantioenriched and, in particular, enantiopure compounds. Such products are used in the preparation of pharmaceuticals, crop protection chemical agents, synthetic aromas, ferroelectric liquid crystals, chiral polymers with nonlinear optical properties, *etc*.[1]

Phosphite-type asymmetric inducers constitute an effective class of chiral phosphorus-containing ligands which can be conveniently prepared in high yields by simple condensation involving readily available enantiopure precursors without preliminary modification. Therefore, large ligand libraries can be produced by single-step phosphorylation using parallel and solid-phase synthesis techniques. Moreover, phosphite derivatives can boast a good resistance towards oxidation due to the absence of P–C bonds, good solubility of their metal complexes in a broad range of media useful for catalytic reactions (common organic solvents, ionic liquids, and supercritical carbon dioxide), and low cost. High π-acidity of phosphite ligand centers helps to stabilize low oxidation states of metals at the same time increasing their electrophilicity.[2]

Phosphite derivatives of hydroxyl-containing amides (Figure S1, Online Supplementary Materials) is an interesting ligand group, which has found application in the asymmetric Rh- and Ir-catalyzed hydrogenation, as well as the Cu-catalyzed conjugate addition.[3] It seems necessary to further expand the range of these promising chiral inducers. For this purpose, in the present work we describe the preparation of P*-chiral diamidophosphite ligand **1** based on the hydroxyl-containing amide **2** comprising (1*R*,2*R*)-1,2-diaminocyclohexane residue, and its application in the enantioselective catalysis (Scheme 1). The variation of substituents at the phosphorus and/or nitrogen atoms in diamidophosphites allows one to tune their steric and electronic parameters.[4] The presence of the asymmetric electron-donating phosphorus atom can favour an efficient chirality transfer in the catalytic cycle.[5]

Enantiopure hydroxyl-containing oxalic acid diamide **2** was obtained by condensation of chiral oxalic derivative **3** with (*R*)-2-aminobutan-1-ol in refluxing toluene (see Scheme 1). Its



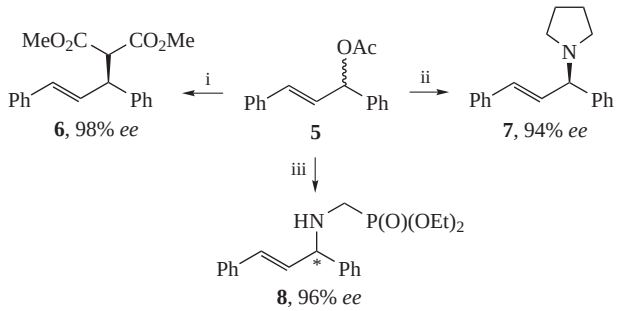
Scheme 1

subsequent reaction with the phosphorylating agent **4** in toluene in the presence of excess of Et_3N as base afforded a new diamidophosphite **1**. It is well soluble in common organic solvents, can be easily purified by flash chromatography, is stable if stored under dry atmosphere. The preparation is scalable to multigram amounts.

The structure of diamidophosphite **1** was confirmed by elemental analysis and NMR spectroscopy, including 2D ^{1}H-^{1}H COSY and ^{1}H-^{13}C HSQC techniques, which provided complete assignment of all signals in the ^{1}H and ^{13}C NMR spectra (Figure S2). Ligand **1** is stereoindividual, which is confirmed by the single narrow singlet at δ_P 122.8 ppm in the ^{31}P{^{1}H} NMR spectrum. The P*-stereocenter has the (*R*) configuration, which is supported by the value of $^2J_{C^8,P}$ 39.1 Hz suggesting that the lone pair of the phosphorus atom and the C^8 atom of the pyrrolidine $(CH_2)_3$ fragment are in *syn* arrangement relative to the 1,3,2-diazaphospholidine ring plane (Figure S3).[6]

The enantio-discriminating ability of diamidophosphite **1** was tested in enantioselective Pd-catalyzed allylic substitution, as well as in enantioselective Rh-catalyzed hydrogenation and hydrosilylation. These reactions are used as models to estimate the efficacy of new chiral inducers, as well as in asymmetric synthesis of valuable organic and natural compounds.[2(*c*),5,7]

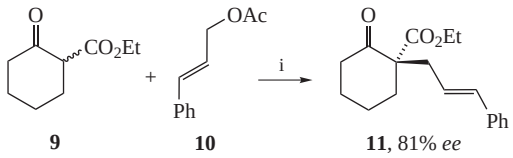
Ligand **1** demonstrated high stereo-differentiating ability in the Pd-catalyzed allylic substitution involving (*E*)-1,3-diphenylallyl acetate **5** (Scheme 2, Tables S1–S3). For example, reaction with dimethyl malonate (C-nucleophile) using $[Pd(allyl)Cl]_2$ as a precatalyst (**1**:Pd molar ratio of 2:1) in CH_2Cl_2 brought about (*S*)-enantiomer of product **6** with 98% *ee* and quantitative conversion (see Table S1, entry 4). In the reaction with pyrrolidine (N-nucleophile), higher asymmetric induction was observed in THF, while **1**:Pd molar ratio had almost no effect on the process outcome. Enantiopurity of (*R*)-enantiomer of product **7** reached 94% *ee* (see Table S2, entries 1, 2).



Scheme 2 *Reagents and conditions*: i, $CH_2(CO_2Me)_2$, $[Pd(allyl)Cl]_2$, **1**, BSA, KOAc, CH_2Cl_2; ii, $(CH_2)_4NH$, $[Pd(allyl)Cl]_2$, **1**, THF; iii, $(EtO)_2P(O)CH_2NH_2$, $[Pd(allyl)Cl]_2$, **1**, CH_2Cl_2.

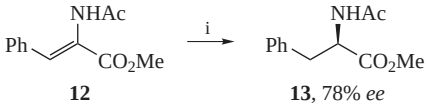
When another N-nucleophile, diethyl (aminomethyl)phosphonate, was used, α-amino phosphonate **8** was obtained with enantiomeric purity of up to 96% *ee* (see Table S3). Dichloromethane was found to be the optimum solvent, with the highest conversion being achieved for **1**:Pd molar ratio of 2:1. Note that this reaction opens new possibilities for the synthesis of valuable nonracemic α-amino phosphonates.[8,9]

In addition, diamidophosphite **1** was tested in palladium-catalyzed allylation of ethyl 2-oxocyclohexane-1-caroboxylate **9** with cinnamyl acetate **10** (Scheme 3). In this case, the quaternary chiral center emerges at the carbon atom belonging to the nucleophile. For **1**:Pd molar ratio of 2:1, enantioselectivity of the (*S*)-enantiomer of product **11** was 81% *ee* upon conversion being quantitative (Table S4, entry 2). The asymmetric catalytic synthesis of compounds containing quaternary C* stereocenters is one of the important topics in organic synthetic chemistry.[6(*a*),7(*h*),10]



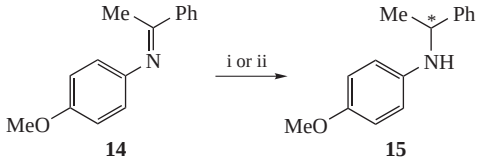
Scheme 3 *Reagents and conditions*: i, $[Pd(allyl)Cl]_2$, **1**, BSA, $Zn(OAc)_2$, PhMe.

Ligand **1** was also tested in the Rh-catalyzed asymmetric hydrogenation of methyl (*Z*)-2-acetamido-3-phenylacrylate **12**; $[Rh(COD)_2]X$ (X = BF_4, $B[C_6H_3(CF_3)_2\text{-}3,5]_4$) and CH_2Cl_2 were chosen as precatalyst and solvent, respectively (Scheme 4, Table S5). In all experiments, quantitative conversion of substrate **12** was observed and the resulting phenylalanine derivative **13** had (*R*) configuration. Higher enantioselectivity (78% *ee*) was achieved using $[Rh(COD)_2]B[C_6H_3(CF_3)_2\text{-}3,5]_4$ at **1**:Rh molar ratio of 1:1 (see Table S5, entry 3).



Scheme 4 *Reagents and conditions*: i, H_2, $[Rh(COD)_2]B[C_6H_3(CF_3)_2\text{-}3,5]_4$, **1**, CH_2Cl_2.

The use of diamidophosphite **4** in the Rh-catalyzed hydrosilylation of (*E*)-*N*-(4-methoxyphenyl)-1-phenylethan-1-imine **14** with diphenylsilane was less successful (Scheme 5, Table S6). The asymmetric induction did not exceed 32% *ee* in chemical yield of 55%. Note that the resulting amine **15** had (*R*)-configuration. The attempt to use the iridium catalysis in this case was far less successful.



Scheme 5 *Reagents and conditions*: i, H_2SiPh_2, $[Rh(COD)Cl]_2$, **1**, PhMe; ii, $HSiCl_3$, **2**, $CHCl_3$.

Further, we applied an alternative approach to reduce imine **14** with trichlorosilane using chiral oxalamide **2** as organocatalyst (Scheme 5, Table S7, entry 1), which allowed us to increase the chemical yield and to raise the enantiomeric excess of amine **15** up to 90% and 50% *ee*, respectively, with predominant formation of the (*S*)-enantiomer of product **15**. Note that monoamides derived from (1*R*,2*R*)-1,2-diaminocyclohexane as well as chiral hydroxy amides are rather efficient organocatalysts for asymmetric Michael and Biginelli reactions, respectively.[11]

In conclusion, diamidophosphite **1** and diamide **2** can be regarded as promising chiral inducers. Further studies focused on the synthesis and catalytic application of diastereomeric analogues of these compounds should provide a clear insight into the mechanistic aspects and the role of each stereogenic center in chiral induction including possible match-mismatch effects. These investigations are under exploration and will be reported in due course.

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alkylation of substrates **5** and **10** and the hydrogenation of substrate **12**).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.010.

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