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Mendeleev Commun., 2020, **30**, 31–33

Mendeleev Communications

First P*,S-bidentate diamidophosphite ligand in Pd-catalyzed asymmetric reactions

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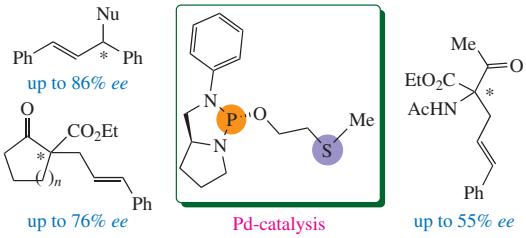
DOI: 10.1016/j.mencom.2020.01.010

A novel P*,S-bidentate diamidophosphite ligand with a 1,3,2-diazaphospholidine core and an exocyclic thioether fragment provided up to 86% *ee* in the Pd-catalyzed alkylation of *rac*-(*E*)-1,3-diphenylallyl acetate with dimethyl malonate, as well as up to 73 and 75% *ee* in the amination of this substrate with pyrrolidine and diethyl (aminomethyl)phosphonate, respectively. For the Pd-catalyzed alkylation of cinnamyl acetate with β-keto esters, *ee* values up to 76% were achieved.



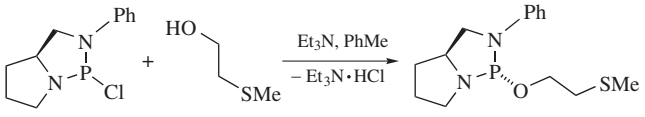
Keywords: chiral diamidophosphites, chiral P,S-ligands, palladium-catalyzed asymmetric reactions.

Diamidophosphites (with characteristic unit PON_2) constitute a very promising group of asymmetric inducers with significant differences from more common phosphites (PO_3) and phosphoramidites (PO_2N). In particular, the replacement of bivalent oxygen atoms in the first coordination sphere of the phosphorus atom for the trivalent nitrogen atoms bearing certain substituents increases the electron density and steric hindrances on phosphorus. The modular structure of diamidophosphites allows one to vary substituents at the phosphorus and/or nitrogen atoms (thereby finely tuning the steric and electronic parameters of a ligand), as well as the configuration of P*- and C*-stereocenters. The presence of asymmetric phosphorus atom can significantly favor a successful chirality transfer in a catalytic cycle. Incorporation of the phosphorus and nitrogen atoms into the 1,3,2-diazaphospholidine ring leads to a higher degree of rigidity and resistance to oxidation and hydrolysis. Therefore, known P*-monodentate, P*,N- and P*,P-bidentate diamidophosphite ligands have found a successful application in the asymmetric Pd-catalyzed allylation and cycloaddition, Rh-catalyzed hydrogenation and hydroformylation, as well as in the Ni-catalyzed hydrovinylation.[1] There are no data on the synthesis of P*,S-bidentate diamidophosphites and their use in asymmetric catalysis, while P*,S-bidentate phosphites and phosphoramidites are well-known.[2]

Herein we report on the synthesis of the first P*,S-bidentate diamidophosphite ligand bearing an asymmetric phosphorus atom in the 1,3,2-diazaphospholidine ring and its application in the Pd-mediated asymmetric allylic substitution processes such as alkylation and amination. These catalytic transformations are reliable methods to evaluate the efficiency of new chiral ligands.[1(d),2(e),3] The products of alkylation using dimethyl malonate are convenient precursors of enantioenriched unsaturated carboxylic acids derivatives,[4] and allylic amines are important starting compounds for many natural products and drugs.[5] The Pd-catalyzed enantioselective synthesis of a quaternary carbon center is highly challenging and provides access to practically significant building blocks.[6] Note that in the case of Pd–π-allyl catalytic intermediates based on P*,S-ligands, the nucleophilic attack occurs *trans* to P-atom, thus sulfide donor center can serve as an important stereocontrolling element, primarily when S-atom becomes a stereogenic center if coordinated to a metal.[2(c)–(e),3(b),7]

As illustrated in Scheme 1, novel P*,S-bidentate diamidophosphite ligand, *viz.*, (2*R*,5*S*)-2-(2-methylthioethoxy)-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane, **1** was efficiently prepared by the reaction of 2-(methylthio)ethan-1-ol with (5*S*)-2-chloro-3-phenyl-1,3-diaza-2-phosphabicyclo[3.3.0]octane in toluene in the presence of excess Et_3N as the hydrochloride scavenger. After vacuum distillation, compound **1** was obtained as clear oil, quite stable for manipulations in air and storage under dry conditions at room temperature for several months with negligible degradation.

The structure of compound **1** was confirmed by elemental analysis and ^1H, ^{13}C, and ^{31}P NMR spectroscopy. The complete assignment of ^1H and ^{13}C chemical shifts was performed by 2D NMR techniques, including ^1H-^1H COSY, ^1H-^1H NOESY, ^1H-^{13}C HSQC and ^1H-^{13}C HMBC spectra (see Figure S1, Online Supplementary Materials). The $^{31}P\{^1H\}$ spectrum featured a



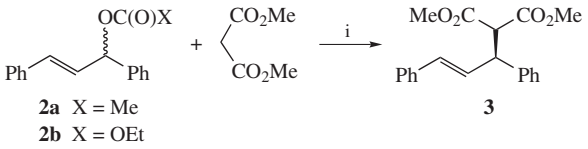
1

Scheme 1

single sharp singlet at δ_P 123.1 ppm indicating that ligand **1** is stereoindividual. Its P*-stereocenter has (*R*) absolute configuration, which is supported by a large value $^2J_{C(8),P}$ of 38.1 Hz suggesting that the lone pair of the phosphorus atom and the C(8) atom of the pyrrolidine –$(CH_2)_3$– fragment are located in the *syn*-orientation relative to the 1,3,2-diazaphospholidine ring plane (Figure S2).[1(*a*),(*b*),(*m*),(*o*),(*p*),8]

Initially the efficiency of ligand **1** was examined in the allylic alkylation of *rac*-(*E*)-1,3-diphenylallyl acetate **2a** with dimethyl malonate as the C-nucleophile using $[Pd(\pi\text{-allyl})Cl]_2$ as the pre-catalyst with a combined base of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of KOAc (Scheme 2). Representative results of the optimization study are highlighted in Table 1, demonstrating high catalytic activity of ligand **1**; irrespective of the experimental conditions applied, quantitative conversions were observed in all cases. In all cases, the (*S*)-enantiomer of the reaction product **3** was predominant. However, the value of the enantioselectivity strongly depended on the solvent and the ratio of ligand to palladium (entries 1–4). The best *ee* of 84% was achieved using CH_2Cl_2 as the solvent and **1**:Pd molar ratio of 2:1 (entry 4). The catalyst loading can be reduced to 0.2 or 0.1 mol% without any loss in activity or selectivity (entries 5, 6). Running the reaction at –20 °C provided 86% *ee* (entry 7). The replacement of KOAc with weaker Lewis basic LiOAc (entries 8, 9), the use of Cs_2CO_3 as the base (entry 10), $NaB[C_6H_3(CF_3)_2\text{-}3,5]_4$ as a noncoordinating counterion source (entry 11) or ethyl carbonate derivative **2b** as the electrophile (entry 12) did not cause any improvement. Nevertheless, it should be pointed out that new heterodonor P*,S-ligand **1** provided superior or comparable efficiency to P*-mono, P*,P- and P*,N-bidentate 1,3,2-diazaphospholidine-based ligands reported to date (see Table S1).[1(*a*),(*b*),(*i*),(*l*)]

We further tested ligand **1** in Pd-catalyzed allylic amination reactions (Scheme 3). In the case of pyrrolidine as the N-nucleophile, ligand **1** provided high catalytic activity, the corresponding product **4** being obtained with 73% *ee* (*R*). In contrast to the allylic alkylation, THF was the solvent of choice and the **1**:Pd molar ratio of 1:1 was preferable (see Table S2).

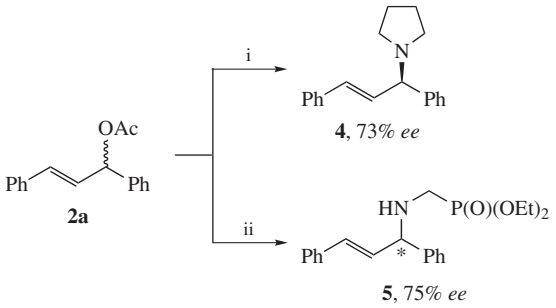


Scheme 2 *Reagents and conditions*: i, $[Pd(\pi\text{-allyl})Cl]_2$ (2.0 mol%), **1** (4.0 or 8.0 mol%), **2** (0.25 mmol), dimethyl malonate (1.8 equiv.), BSA (1.8 equiv.), KOAc (8 mol%), solvent (1.5 ml), room temperature, 48 h.

Table 1 Pd-catalyzed allylic alkylation of substrates **2** with dimethyl malonate.

Entry	Substrate	Molar ratio **1**:Pd	Solvent	Conversion of **2** (%)	*ee* of **3** (%)[a]
1	**2a**	1:1	THF	100	66 (*S*)
2	**2a**	2:1	THF	100	76 (*S*)
3	**2a**	1:1	CH_2Cl_2	100	43 (*S*)
4	**2a**	2:1	CH_2Cl_2	100	84 (*S*)
5	**2a**	2:1	CH_2Cl_2	100	85 (*S*)[b]
6	**2a**	2:1	CH_2Cl_2	100	85 (*S*)[c]
7	**2a**	2:1	CH_2Cl_2	100	86 (*S*)[d]
8	**2a**	1:1	CH_2Cl_2	100	79 (*S*)[e]
9	**2a**	2:1	CH_2Cl_2	100	83 (*S*)[e]
10	**2a**	2:1	CH_2Cl_2	100	82 (*S*)[f]
11	**2a**	2:1	CH_2Cl_2	100	85 (*S*)[g]
12	**2b**	2:1	CH_2Cl_2	99	83 (*S*)

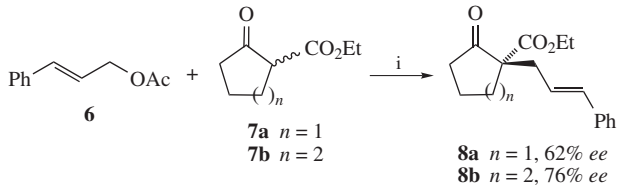
[a] The conversion of **2** and *ee* values of **3** were determined by HPLC analysis. The absolute configuration was assigned by comparison of the HPLC retention times [Kromasil 5-CelluCoat, C_6H_{14}/Pr^iOH = 99:1, 0.6 ml min^{-1}, 254 nm, $t(R)$ = = 18.8 min, $t(S)$ = 20.2 min] with reported data.[1(*p*),9] [b] 0.2 mol% $[Pd(\pi\text{-allyl})Cl]_2$. [c] 0.1 mol% $[Pd(\pi\text{-allyl})Cl]_2$. [d] Performed at –20 °C. [e] With LiOAc instead of KOAc. [f] With Cs_2CO_3 (2 equiv.) as the base. [g] $NaB[C_6H_3(CF_3)_2\text{-}3,5]_4$ (5 mol%) was used as the additive.



Scheme 3 *Reagents and conditions*: i, pyrrolidine, $[Pd(\pi\text{-allyl})Cl]_2$, **1**, THF; ii, $(EtO)_2P(O)CH_2NH_2$, $[Pd(\pi\text{-allyl})Cl]_2$, **1**, CH_2Cl_2.

When a more challenging N-nucleophile, diethyl (aminomethyl)-phosphonate, was used, the conversion of substrate **2a** and the enantioselectivity were higher in CH_2Cl_2 as the reaction medium and with the **1**:Pd molar ratio of 2:1 (see Table S3). α-Amino phosphonate **5** was obtained with 75% *ee*, but its absolute configuration has not yet been ascertained. Note that this reaction offers an additional scope for the synthesis of nonracemic α-amino phosphonates.[10]

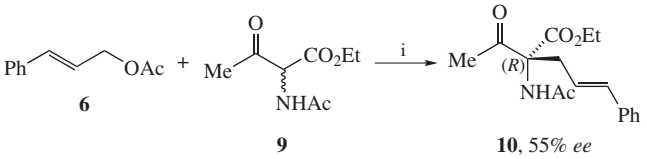
The next step was an attempt to use ligand **1** in the Pd-catalyzed allylic alkylation of non-symmetric cinnamyl acetate **6** with β-keto esters **7a** and **7b** (Scheme 4). In this process, a quaternary C*-stereocenter is formed at the carbon atom belonging to the nucleophile. To the best of our knowledge, there are only three examples for the synthesis of the enantioenriched compound **8a**.[6(*g*),11] When ligand **1** was used, the reactions proceeded with the quantitative conversion providing (*S*)-isomers of the desired products **8a**,**b** with 62 and 76% *ee*, respectively (see Tables S4 and S5). For both the reactions, **1**:Pd molar ratio of 2:1 was optimal.



Scheme 4 *Reagents and conditions*: i, $[Pd(\pi\text{-allyl})Cl]_2$, **1**, BSA, $Zn(OAc)_2$, PhMe.

We also examined the Pd-catalyzed asymmetric allylic substitution using β-keto ester **9** with acetamido group at the α-carbon as the prochiral nucleophile (Scheme 5). This is one of the most straightforward approaches to chiral quaternary α-amino acid derivatives.[12] Product (*R*)-**10** was obtained with 55% *ee* and quantitative conversion of substrate **6** (see Table S6).

In summary, P*,S-bidentate diamidophosphite ligand **1** turned to be a promising chiral inducer being rather sensitive to the nature of nucleophile and reaction conditions. This ligand exhibits noticeable advantages over P*-mono, P*,P- and P*,N-bidentate



Scheme 5 *Reagents and conditions*: i, $[Pd(\pi\text{-allyl})Cl]_2$, **1**, BSA, KOAc or BSA, $Zn(OAc)_2$, PhMe.

diamidophosphites. Further studies using a structurally optimized P-chirogenic diamidophosphites bearing an additional sulfide donor centre are in progress.

This work was supported by the Russian Science Foundation (project no. 19-13-00197).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2020.01.010.

References

1 (*a*) J. M. Brunel, T. Constantieux and G. Buono, *J. Org. Chem.*, 1999, **64**, 8940; (*b*) V. N. Tsarev, S. E. Lyubimov, A. A. Shiryaev, S. V. Zheglov, O. G. Bondarev, V. A. Davankov, A. A. Kabro, S. K. Moiseev, V. N. Kalinin and K. N. Gavrilov, *Eur. J. Org. Chem.*, 2004, 2214; (*c*) C. Markert, P. Rösel and A. Pfaltz, *J. Am. Chem. Soc.*, 2008, **130**, 3234; (*d*) *Privileged Chiral Ligands and Catalysts*, ed. Q.-L. Zhou, Wiley-VCH, Weinheim, 2011; (*e*) A. Grabulosa, *P-Stereogenic Ligands in Enantioselective Catalysis*, RSC, Cambridge, 2011; (*f*) B. M. Trost and A. Maruniak, *Angew. Chem., Int. Ed.*, 2013, **52**, 6262; (*g*) M. J. Bravo, R. M. Ceder, G. Muller and M. Rocamora, *Organometallics*, 2013, **32**, 2632; (*h*) M. Schmitkamp, W, Leitner and G. Francio, *Catal. Sci. Technol.*, 2013, **3**, 589; (*i*) K. N. Gavrilov, A. A. Shiryaev, S. V. Zheglov, V. K. Gavrilov, N. N. Groshkin, M. G. Maksimova, A. N. Volov and I. A. Zamilatskov, *Tetrahedron*, 2014, **70**, 616; (*j*) C. Schmitz, W. Leitner and G. Francio, *Eur. J. Org. Chem*., 2015, 6205; (*k*) M. J. Bravo, R. M. Ceder, A. Grabulosa, G. Muller, M. Rocamora, J. C. Bayón and D. Peral, *Organometallics*, 2015, **34**, 3799; (*l*) K. N. Gavrilov, S. V. Zheglov, I. M. Novikov, V. K. Gavrilov, I. A. Zamilatskov and I. S. Mikhel, *Russ. Chem. Bull., Int. Ed*., 2016, **65**, 2278 (*Izv. Akad. Nauk, Ser. Khim.*, 2016, 2278); (*m*) K. N. Gavrilov, S. V. Zheglov, V. K. Gavrilov, M. G. Maksimova, V. A. Tafeenko, V. V. Chernyshev, K. P. Birin and I. S. Mikhel, *Tetrahedron*, 2017, **73**, 461; (*n*) K. N. Gavrilov, S. V. Zheglov, V. K. Gavrilov, I. D. Firsin and M. G. Maksimova, *Russ. Chem. Bull., Int. Ed*., 2019, **68**, 1376 (*Izv. Akad. Nauk, Ser. Khim.*, 2019, 1376); (*o*) V. K. Gavrilov, I. V. Chuchelkin, S. V. Zheglov, I. D. Firsin, A. A. Shiryaev, K. N. Gavrilov, A. V. Maximychev, A. M. Perepukhov, N. S. Goulioukina and I. P. Beletskaya, *Mendeleev Commun*., 2019, **29**, 35; (*p*) K. N. Gavrilov, I. S. Mikhel, S. V. Zheglov, V. K. Gavrilov, I. V. Chuchelkin, I. D. Firsin, K. P. Birin, I. S. Pytskii, K. A. Paseshnichenko, V. A. Tafeenko, V. V. Chernyshev and A. A. Shiryaev, *Org. Chem. Front*., 2019, **6**, 1637.

2 (*a*) K. Selvakumar, M. Valentini, P. S. Pregosin and A. Albinati, *Organometallics*, 1999, **18**, 4591; (*b*) T. Kanayama, K. Yoshida, H. Miyabe and Y. Takemoto, *Angew. Chem., Int. Ed*., 2003, **42**, 2054; (*c*) M. Coll, O. Pàmies and M. Diéguez, *Org. Lett.*, 2014, **16**, 1892; (*d*) J. Margalef, M. Coll, P. O. Norrby, O. Pàmies and M. Diéguez, *Organometallics*, 2016, **35**, 3323; (*e*) M. Biosca, J. Margalef, X. Caldentey, M. Besora, C. Rodriguez-Escrich, J. Saltó, X. C. Cambeiro, F. Maseras, O. Pàmies, M. Diéguez and M. A. Pericàs, *ACS Catal*., 2018, **8**, 3587; (*f*) J. Margalef, C. Borràs, S. Alegre, E. Alberico, O. Pàmies and M. Diéguez, *ChemCatChem*, 2019, **11**, 2142; (*g*) B. Feng, X.-Y. Pu, Z.-C. Liu, W.-J. Xiao and J.-R. Chen, *Org. Chem. Front.*, 2016, **3**, 1246; (*h*) B. Feng, L.-Q. Lu, J.-R. Chen, G. Feng, B.-Q. He, B. Lu and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2018, **57**, 5888.

3 (*a*) Z. Lu and S. Ma, *Angew. Chem., Int. Ed.*, 2008, **47**, 258; (*b*) F. L. Lam, F. Y. Kwong and A. S. C. Chan, *Chem. Commun.*, 2010, **46**, 4649; (*c*) J. F. Teichert and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2010, **49**, 2486; (*d*) M. Diéguez and O. Pàmies, *Acc. Chem. Res.*, 2010, **43**, 312; (*e*) T. Nemoto and Y. Hamada, *Tetrahedron*, 2011, **67**, 667; (*f*) H. Fernández-Pérez, P. Etayo, A. Panossian and A. Vidal-Ferran, *Chem. Rev.*, 2011, **111**, 2119; (*g*) *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*, ed. U. Kazmaier, Springer, Berlin, Heidelberg, 2012.

4 D. Lafrance, P. Bowles, K. Leeman and R. Rafka, *Org. Lett.*, 2011, **13**, 2322.

5 (*a*) S. Nag and S. Batra, *Tetrahedron*, 2011, **67**, 8959; (*b*) S. P. Chavan, L. B. Khairnar and P. N. Chavan, *Tetrahedron Lett.*, 2014, **55**, 5905; (*c*) R. L. Grange, E. A. Clizbe and P. A. Evans, *Synthesis*, 2016, **48**, 2911.

6 (*a*) T. Nemoto, T. Matsumoto, T. Masuda, T. Hitomi, K. Hatano and Y. Hamada, *J. Am. Chem. Soc*., 2004, **126**, 3690; (*b*) T. Nemoto, T. Masuda, T. Matsumoto and Y. Hamada, *J. Org. Chem.*, 2005, **70**, 7172; (*c*) T. Nemoto, T. Fukuda, T. Matsumoto, T. Hitomi and Y. Hamada, *Adv. Synth. Catal*., 2005, **347**, 1504; (*d*) C. Hawner and A. Alexakis, *Chem. Commun*., 2010, **46**, 7295; (*e*) T. Punirun, K. Peewasan, C. Kuhakarn, D. Soorukram, P. Tuchinda, V. Reutrakul, P. Kongsaeree, S. Prabpai and M. Pohmakotr, *Org. Lett*., 2012, **14**, 1820; (*f*) Y. Liu, S.-J. Han, W.-B. Liu and B. M. Stoltz, *Acc. Chem. Res.*, 2015, **48**, 740; (*g*) Y. Kita, R. D. Kavthe, H. Oda and K. Mashima, *Angew. Chem., Int. Ed*., 2016, **55**, 1098.

7 D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael and M. R. Gagné, *J. Am. Chem. Soc.*, 2000, **122**, 7905.

8 (*a*) K Barta, M. Hölscher, G. Franciò and W. Leitner, *Eur. J. Org. Chem*., 2009, 4102; (*b*) M. Kimura and Y. Uozumi, *J. Org. Chem.*, 2007, **72**, 707.

9 (*a*) E. B. Benetskiy and C. Bolm, *Tetrahedron: Asymmetry*, 2011, **22**, 373; (*b*) K. E. Thiesen, K. Maitra, M. M. Olmstead and S. Attar, *Organometallics*, 2010, **29**, 6334; (*c*) M. Ramillien, N. Vanthuyne, M. Jean, D. Gherase, M. Giorgi, J.-V. Naubron, P. Piras and C. Roussel, *J. Chromatogr. A*, 2012, **1269**, 82.

10 (*a*) K. N. Gavrilov, I. S. Mikhel, I. V. Chuchelkin, S. V. Zheglov, V. K. Gavrilov, K. P. Birin, V. A. Tafeenko, V. V. Chernyshev, N. S. Goulioukina and I. P. Beletskaya, *ChemistrySelect*, 2016, **1**, 4173; (*b*) M. Brzezinska-Rodak, M. Klimek-Ochab, E. Zymanczyk-Duda and P. Kafarski, *Molecules*, 2011, **16**, 5896; (*c*) T. K. Olszewski, *Synthesis*, 2014, **46**, 403; (*d*) D. Kowalczyk and L. Albrecht, *Chem. Commun.*, 2015, **51**, 3981; (*e*) Z. Yan, B. Wu, X. Gao, M.-W. Chen and Y.-G. Zhou, *Org. Lett*., 2016, **18**, 692.

11 (*a*) M. Yoshida, *J. Org. Chem.*, 2017, **82**, 12821; (*b*) A. A. Zagidullin, E. S. Oshchepkova, I. V. Chuchelkin, S. A. Kondrashova, V. A. Miluykov, Sh. K. Latypov, K. N. Gavrilov and E. Hey-Hawkins, *Dalton Trans.*, 2019, **48**, 4677.

12 T. Nemoto, T. Harada, T. Matsumoto and Y. Hamada, *Tetrahedron Lett.*, 2007, **48**, 6304.

Received: 23rd July 2019; Com. 19/5992