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TADDOL-based *P*,*S*-bidentate diastereomeric ligands in asymmetric allylation and hydrogenation reactions

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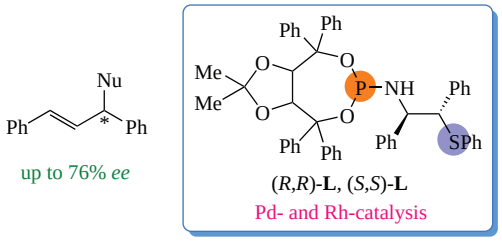
Diastereomeric *P*,*S*-bidentate phosphoramidite ligands with TADDOL core and (1*R*,2*S*)-1,2-diphenyl-2-(phenylthio)-ethan-1-amine residue were synthesized. These ligands provided up to 76% *ee* in the Pd-catalyzed alkylation of (*E*)-1,3-diphenylallyl acetate with dimethyl malonate, up to 70% *ee* in the amination of this substrate with pyrrolidine, and 89–95% *ee* in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate and methyl (*Z*)-2-acetamido-3-arylacrylates. The different contributions of diastereomeric chiral inducers to the catalytic outcome are discussed.

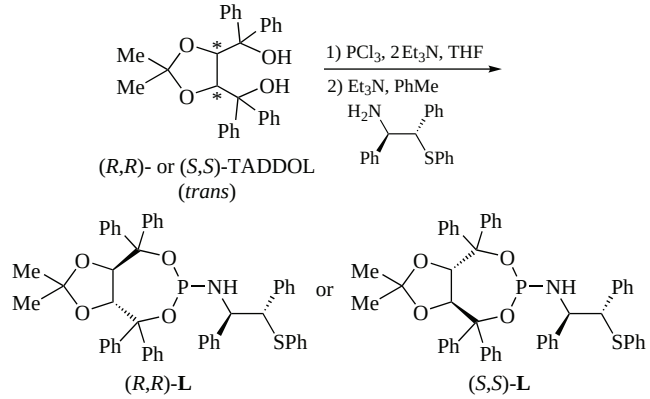


Keywords: asymmetric catalysis, allylic substitution, palladium, hydrogenation, rhodium, phosphoramidites, *P*,*S*-ligands.

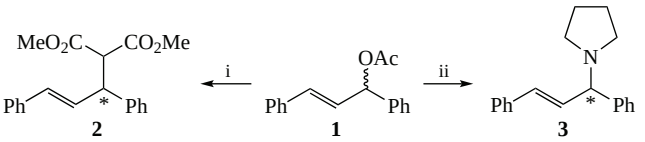
TADDOL-based phosphoramidites are cheap, readily available, and easily tunable so-called 'privileged' ligands due to their ability to promote a wide range of highly enantioselective metal-catalyzed transformations.[1] Here we describe the synthesis and catalytic applications of the pioneer phosphoramidite-thioethers with a TADDOL core. Mixed phosphorus/sulfur ligands attract special attention because of the electronic and steric differences between the two donor atoms: sulfur has a lower σ-donor and π-acceptor ability than phosphorus, besides divalent sulfur with two substituents creates a less hindered environment than trivalent phosphorus. These compounds have an additional important advantage over other hetero donor ligands, since a new stereogenic center is formed on sulfur upon coordination with a metal. The variation of substituents at sulfur and phosphorus atoms along with the backbone can provide very efficient structures in terms of activity and enantioselectivity in catalytic reactions.[2] In this article, we demonstrate the importance of the proper combination of the chiral TADDOL-derived phosphoramidite core with the additional chiral centers in the backbone chain between two donor atoms.

The condensation of (*R*,*R*)- or (*S*,*S*)-TADDOLs with PCl_3 in the presence of Et_3N followed by reaction with (1*R*,2*S*)-1,2-diphenyl-2-(phenylthio)ethan-1-amine afforded diastereomeric *P*,*S*-bidentate phosphoramidites (*R*,*R*)-**L** and (*S*,*S*)-**L** (Scheme 1). The structures of these ligands were confirmed by elemental analysis and ^1H, $^{13}C\{^1H\}$, and $^{31}P\{^1H\}$ NMR spectroscopy. The assignment of ^1H and $^{13}C\{^1H\}$ resonances (excluding aromatic ones) was done using ^1H–^1H COSY and ^{13}C–^1H HSQC NMR techniques (see Online Supplementary Materials, Figures S1 and S2). Compounds (*R*,*R*)-**L** and (*S*,*S*)-**L** are stable enough to be purified by flash chromatography, they are stored and handled with ease.

The ligands were tested in Pd-catalyzed enantioselective allylic substitution reactions, which are known to be tolerant to various functional groups in substrates and proceed with a wide range of C-, N-, O-, S- and P-nucleophiles under mild conditions.[3] The classic reaction between (*E*)-1,3-diphenylallyl acetate **1** as the electrophile and dimethyl malonate as the C-nucleophile was performed according to the standard procedure using



Scheme 1



Scheme 2 *Reagents and conditions*: i, $CH_2(CO_2Me)_2$ (1.8 equiv.), $[Pd(\pi\text{-allyl})Cl]_2$ (1 mol%), ligand (2 or 4 mol%), BSA (1.8 equiv.), KOAc (8 mol%), solvent, room temperature, 24 h; ii, pyrrolidine (3 equiv.), $[Pd(\pi\text{-allyl})Cl]_2$ (1 mol%), ligand (2 or 4 mol%), solvent, room temperature, 24 h.

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

Entry	Ligand	Molar ratio L : Pd	Solvent	Conversion (%)	*ee* (%)[a]
1	(*R*,*R*)-**L**	1 : 1	THF	100	75 (*R*)
2	(*R*,*R*)-**L**	2 : 1	THF	89	76 (*R*)
3	(*R*,*R*)-**L**	1 : 1	CH_2Cl_2	98	73 (*R*)
4	(*R*,*R*)-**L**	2 : 1	CH_2Cl_2	38	71 (*R*)
5	(*S*,*S*)-**L**	1 : 1	THF	90	56 (*S*)
6	(*S*,*S*)-**L**	2 : 1	THF	66	55 (*S*)
7	(*S*,*S*)-**L**	1 : 1	CH_2Cl_2	93	61 (*S*)
8	(*S*,*S*)-**L**	2 : 1	CH_2Cl_2	32	60 (*S*)

[a] The conversion of substrate **1** and enantiomeric excess of **2** were determined by HPLC (Kromasil 5-CelluCoat, C_6H_{14}/Pr^iOH = 99 : 1, 0.6 ml min^{-1}, 254 nm, *t*(*R*) = 21.4 min, *t*(*S*) = 23.2 min). The absolute configurations of **2** were assigned by comparison with the literature[4] HPLC retention times.

$[Pd(\pi\text{-allyl})Cl]_2$ as the palladium source and a combined base of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) with a catalytic amount of KOAc (Scheme 2). Ligand (*R*,*R*)-**L** provided the formation of product (*R*)-**2** with 71–76% *ee* and good to quantitative conversion of the starting substrate **1** in most cases (Table 1, entries 1–4). As a solvent, THF was slightly preferable to dichloromethane. Ligand (*S*,*S*)-**L** exhibited lower catalytic activity and selectivity and afforded product (*S*)-**2** with enantiomeric excess of only up to 61% (entries 5–8). The chirality of phosphoramidite moiety seems to be the major factor in controlling the enantioselectivity. For both diastereomeric ligands the asymmetric induction was insensitive to the L/Pd molar ratio.

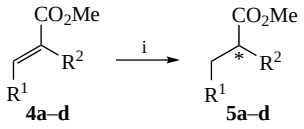
As for the Pd-catalyzed allylic amination of **1** using pyrrolidine as the N-nucleophile (see Scheme 2, Table 2), all experiments were carried out in CH_2Cl_2 (no conversion of **1** was observed when the reaction was carried out in THF). Phosphoramidites (*R*,*R*)-**L** and (*S*,*S*)-**L** gave almost equal enantioselectivity (up to 67 and 70% *ee*, respectively), but the catalytic activity was higher in the former case. Similarly to the allylic alkylation, the application of diastereomers of **L** led to the formation of enantiomeric products **3**, and the L/Pd molar ratio had no noticeable effect on the asymmetric induction.

To expand the range of possible applications of the novel ligands, we examined the Rh-catalyzed enantioselective

Table 2 Pd-catalyzed allylic amination of substrate **1** with pyrrolidine.

Entry	Ligand	Molar ratio L : Pd	Solvent	Conversion (%)	*ee* (%)[a]
1	(*R*,*R*)-**L**	1 : 1	CH_2Cl_2	45	67 (*S*)
2	(*R*,*R*)-**L**	2 : 1	CH_2Cl_2	100	66 (*S*)
3	(*S*,*S*)-**L**	1 : 1	CH_2Cl_2	7	65 (*R*)
4	(*S*,*S*)-**L**	2 : 1	CH_2Cl_2	12	70 (*R*)

[a] The conversion of substrate **1** and enantiomeric excess of **3** were determined by HPLC (Daicel Chiralcel OD-H, C_6H_{14}/Pr^iOH = 95 : 5, 0.4 ml min^{-1}, 254 nm, *t*(*R*) = 9.7 min, *t*(*S*) = 10.2 min). The absolute configurations of **3** were assigned by comparison with the literature[5] HPLC retention times.



a R^1 = H, R^2 = CH_2CO_2Me
b R^1 = Ph, R^2 = NHAc
c R^1 = 4-FC_6H_4, R^2 = NHAc
d R^1 = 2-naphthyl, R^2 = NHAc

Scheme 3 *Reagents and conditions*: i, H_2 (6 atm), $[Rh(Cod)_2]BF_4$ (1 mol%), ligand (1 mol%), CH_2Cl_2, room temperature, 24 h.

Table 3 Rh-catalyzed asymmetric hydrogenation of substrates **4a**–**d**.

Entry	Ligand	Substrate	Conversion (%)	*ee* (%)[a]
1	(*R*,*R*)-**L**	**4a**	100	91 (*S*)
2	(*R*,*R*)-**L**	**4b**	100	89 (*R*)
3	(*R*,*R*)-**L**	**4c**	100	94 (*R*)
4	(*R*,*R*)-**L**	**4d**	100	95 (*R*)
5	(*S*,*S*)-**L**	**4a**	0	–
6	(*S*,*S*)-**L**	**4b**	100	7 (*R*)
7	(*S*,*S*)-**L**	**4c**	95	1 (*S*)
8	(*S*,*S*)-**L**	**4d**	98	8 (*S*)

[a] The conversion of substrates **4a**–**d** and enantiomeric excesses of **5a**–**d** were determined by HPLC (**5a**, Daicel Chiralcel OD-H, C_6H_{14}/Pr^iOH = 98 : 2, 0.8 ml min^{-1}, 215 nm, *t*(*R*) = 9.2 min, *t*(*S*) = 16.1 min; **5b**, Daicel Chiralcel OD-H, C_6H_{14}/Pr^iOH = 4 : 1, 0.6 ml min^{-1}, 215 nm, *t*(*R*) = 10.0 min, *t*(*S*) = 12.4 min; **5c**, Daicel Chiralcel OD-H, C_6H_{14}/Pr^iOH = 9 : 1, 1.0 ml min^{-1}, 219 nm, *t*(*R*) = 10.4 min, *t*(*S*) = 14.2 min and **5d**, Daicel Chiralcel OD-H, C_6H_{14}/Pr^iOH = 9 : 1, 0.8 ml min^{-1}, 215 nm, *t*(*R*) = 9.0 min, *t*(*S*) = 11.8 min). The absolute configurations of **5a**–**d** were assigned by comparison with the HPLC retention times reported [refs. 4(*a*),6].

hydrogenation of prochiral unsaturated esters **4a**–**d** (Scheme 3). Like the allylic substitution reactions mentioned above, Rh-catalyzed hydrogenation is widely used to produce a large number of enantio-enriched (enantiopure) synthetic precursors of valuable natural and unnatural compounds.[3] The cationic rhodium catalysts were prepared *in situ* by treating $[Rh(Cod)_2]BF_4$ with 1 equiv. of the corresponding ligand in CH_2Cl_2. The dramatic difference between the diastereomers of **L** was observed. The usage of (*R*,*R*)-**L** resulted in the quantitative conversion of dimethyl itaconate **4a** or methyl (*Z*)-2-acetamido-3-arylacrylates **4b**–**d** and good asymmetric induction: products (*S*)-**5a** and (*R*)-**5b**–**d** were formed with 89–95% *ee* (Table 3, entries 1–5). The diastereomeric ligand (*S*,*S*)-**L** demonstrated a pronounced mismatch effect and either showed a poor enantiocontrol (no more than 8% *ee*, entries 6–8), or turned out to be completely inactive (entry 5).

In summary, the obtained *P*,*S*-bidentate phosphoramidites with TADDOL framework (*R*,*R*)-**L** and (*S*,*S*)-**L** are promising chirality inducers exhibiting notable results in asymmetric Pd-catalyzed allylic substitution and Rh-catalyzed hydrogenation. Additional studies highlighting the potential of these and similar ligands in other enantioselective reactions are now in progress in our laboratories.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.012.

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