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Furanoside thioether–phosphinite ligands for Pd-catalyzed asymmetric allylic substitution reactions: Scope and limitations

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Abstract

A series of readily available thioether–phosphinite ligands has been tested in the Pd-catalyzed allylic substitution reactions of several acyclic and cyclic allylic substrates (**S1**–**S7**). This series of ligands have been designed to uncover their important structural features and to determine the scope of the thioether–phosphinite ligands in these catalytic reactions. Systematic variation of the electronic and steric properties at the thioether moiety provide useful information about the ligand parameters that control the enantiodiscrimination. By carefully selecting the ligand parameters, good enantioselectivities with high activities were obtained for hindered linear substrates **S1** and **S2** (ee's up to 95%) and for unhindered cyclic substrates **S4** and **S5** (ee's up to 91%).

Keywords: Palladium; Asymmetric catalysis; Allylic alkylation; Phosphinite–thioether ligands; Carbohydrate

1. Experimental

1.1. General considerations

All reactions were carried out using standard Schlenk techniques under an atmosphere of argon. Solvents were purified and dried by standard procedures. Thioether–phosphinite ligands **1**–**7** were prepared using previously described methods [1]. Racemic substrates **S1**–**S7** were prepared as previously reported [2–5]. NMR spectra were recorded using a 400 MHz spectrometer. Chemical shifts are relative to that of $SiMe_4$ (^1H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard.

1.2. Typical procedure of allylic alkylation of disubstituted linear substrates *S1–S3*

A degassed solution of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (0.9 mg, 0.0025 mmol) and the corresponding thioether–phosphinite (0.0055 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of substrate (0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and KOAc (5 mg) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3×10 mL) and the extract dried over $MgSO_4$. For substrate **S1**, conversion was measured by ^1H NMR and enantiomeric excess was determined by HPLC (Chiralcel-OD, 0.5% 2-propanol/hexane, flow 0.5 mL/min). For substrate **S2**, conversion was measured by ^1H NMR and enantiomeric excess was determined by ^1H NMR using $Eu(hfc)_3$ as resolving agent. For substrate **S3**, conversion and enantiomeric excess were determined by GC.

1.3. Typical procedure of allylic alkylation of cyclic substrates *S4* and *S5*

A degassed solution of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (0.9 mg, 0.0025 mmol) and the corresponding thioether–phosphinite ligand (0.0055 mmol) in dichloromethane (0.5 mL)

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was stirred for 30 min. Subsequently, a solution of substrate (0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and KOAc (5 mg) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3×10 mL) and the extract dried over $MgSO_4$. For substrate **S4**, conversion and enantiomeric excess were determined by GC using a FS-Cyclodex β-I/P 25 m column, internal diameter 0.2 mm, film thickness 0.33 mm, carrier gas: 100 kPa He, F.I.D. detector. For substrate **S5**, conversion was determined by GC and enantiomeric excess was determined by ^1H NMR using $Eu(hfc)_3$.

*1.4. Typical procedure of allylic alkylation of monosubstituted linear substrates **S6** and **S7***

A degassed solution of $[Pd(\pi\text{-}C_3H_5)Cl]_2$ (1.8 mg, 0.005 mmol) and the corresponding thioether–phosphinite ligand (0.011 mmol) in dichloromethane (0.5 mL) was stirred for 30 min. Subsequently, a solution of substrate (0.5 mmol) in dichloromethane (1.5 mL), dimethyl malonate (171 μL, 1.5 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (370 μL, 1.5 mmol) and KOAc (5 mg) were added. The reaction mixture was stirred at room temperature. After the desired reaction time, the reaction mixture was diluted with Et_2O (5 mL) and a saturated NH_4Cl (aq) (25 mL) was added. The mixture was extracted with Et_2O (3×10 mL) and the extract dried over $MgSO_4$. Solvent was removed and conversion and regioselectivity were measured by ^1H NMR. To determine the ee by HPLC (Chiralcel-OJ, 3% 2-propanol/hexane, flow 0.7 mL/min), a sample was filtered over basic alumina using dichloromethane as the eluent.

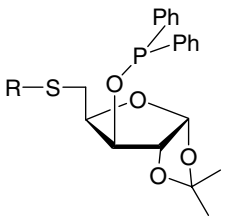
2. Introduction

Palladium-catalyzed allylic substitution is a useful synthetic method for the formation of carbon–carbon and carbon–heteroatom bonds [6]. Most of the chiral ligands developed for asymmetric allylic substitution are mixed bidentate donor ligands (such as P–N, P–S and N–S) [6]. The efficiency of this type of hard–soft heterodonor ligands has been mainly attributed to the different electronic effects of the donor atoms. Mixed phosphorus–nitrogen ligands have played a dominant role among the heterodonor ligands. To a lesser extent, phosphorus–thioether ligands have also demonstrated their potential utility in Pd-catalyzed asymmetric allylic substitution [7,8]. In this context only two families of thioether–phosphinite ligands have been developed for this process [1a,8]. Evans and coworkers have therefore designed the first family of thioether–phosphinite ligands that proved to be effective [8]. Their results indicated a remarkable steric effect of the thioether moiety on enantioselectivity. More recently, we have reported the first carbohydrate-based thioether–phosphinite ligands for the Pd-catalyzed asymmetric allylic alkylation reactions (ligands **1**–**3**, Fig. 1) [1a]. Results were only satisfactory for the allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene (ee's up to 93%) while enantioselectivities were low for the cyclic substrate *rac*-3-acetoxycyclohexene (ee's up to 51%) [1a]. Furthermore, in contrast to Evans' work an unclear effect of the thioether substituents on enantioselectivity were observed. In light of this, in this paper we expand the previous study to other furanoside thioether–phosphinite ligands (Fig. 1, ligands **4**–**7** [9]) in which the steric and electronic properties of the thioether moiety were systematically varied. This allowed us to investigate the possibility of an steric and/or electronic effect of the sulfur substituent in enantioselectivity. Therefore, with ligands **1**–**4** and **7** we mainly investigated the steric effect on enantioselectivity, while with ligands **1**, **5** and **6** we studied how the electronic properties affected enantioselectivity. This study will therefore provide more information about the parameters that control enantioselectivity and, at the same time, may help us to increase the efficiency of our catalytic system. We also extended the study to other types of substrates with different steric properties (**S1**–**S7**) to determine the scope of this type of ligands.

3. Results and discussion

3.1. Allylic alkylation of disubstituted linear substrates

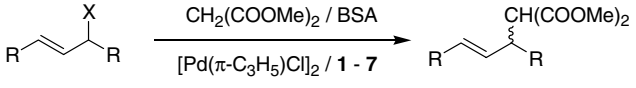
In this section, we report the use of the chiral thioether–phosphinite ligands **1**–**7** in the Pd-catalyzed allylic alkylation (Eq. (1)) of three linear substrates with different steric properties: *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** (widely used as a model substrate), *rac*-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate **S2** and *rac*-1,3-dimethyl-3-acetoxyprop-1-ene **S3**. In all the cases, the catalysts were



1 R = Ph **5** R = 4-Me-C_6H_4
2 R = Me **6** R = 4-CF_3-C_6H_4
3 R = ^{i}Pr **7** R = 2,6-di-Me-C_6H_3
4 R = ^{t}Bu

Fig. 1. Thioether–phosphinite ligands **1**–**7**.

generated in situ from π-allyl-palladium chloride dimer $[Pd(\pi\text{-}C_3H_5)Cl]_2$ and the corresponding ligand. The nucleophile was generated from dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)-acetamide (BSA).



S1 R= Ph; X= OAc
S2 R = ^{i}Pr; X= OCOOEt
S3 R= Me; X= OAc

8 R= Ph
9 R= ^{i}Pr
10 R= Me

(1)

3.1.1. Allylic alkylation of rac-1,3-diphenyl-3-acetoxyprop-1-ene *S1* (Eq. (1))

We first investigated the Pd-catalyzed allylic substitution of *rac*-1,3-diphenyl-3-acetoxyprop-1-ene **S1** with dimethyl malonate using the chiral thioether–phosphinite ligands **1**–**7** (Eq. (1)).

Preliminary investigations into the solvent effect, ligand-to-palladium ratio and source of base with the new ligand **4** provided the same trends as those with the previously tested ligands **1**–**3** [1a] in substrate **S1** (Table 1). The trade-off between enantioselectivities and reaction rates was therefore optimum with dichloromethane, a ligand-to-palladium ratio of 1.1 and KOAc as base.

The results of using the rest of the furanoside thioether–phosphinite ligands (**1**–**7**) under the optimized conditions are showed in Table 2. Our results show that the enantiomeric excesses are dependent on both the electronic and steric properties of the substituents in the thioether moiety. This behavior contrasts with the results obtained with the Evans' thioether–phosphinite ligands, for which enantioselectivities were only affected by the steric properties of the thioether moiety [8b].

Table 1
Effect of the solvent, ligand-to-palladium ratio and source of base in the Pd-catalyzed allylic alkylation of **S1** using ligand **4**[a]

Entry	Solvent	Base	% Conv. (min)[b]	% ee[c]
1	CH_2Cl_2	KOAc	100 (15)	87 (*S*)
2	DMF	KOAc	100 (5)	78 (*S*)
3	THF	KOAc	55 (30)	83 (*S*)
4	Toluene	KOAc	29 (30)	87 (*S*)
5	CH_2Cl_2	K_2CO_3	72 (20)	86 (*S*)
6	CH_2Cl_2	NaOAc	96 (15)	84 (*S*)
7	CH_2Cl_2	Li_2CO_3	92 (30)	82 (*S*)
8[d]	CH_2Cl_2	KOAc	98 (15)	79 (*S*)
9[e]	CH_2Cl_2	KOAc	100 (20)	86 (*S*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), 5 mg of the corresponding base, room temperature.
[b] Measured by ^{1}H NMR. Reaction time in minutes shown in parentheses.
[c] Determined by HPLC (Chiralcel OD). Absolute configuration drawn in parentheses.
[d] L/Pd = 2.
[e] L/Pd = 0.9.

Table 2
Pd-catalyzed allylic alkylation of **S1** with ligands **1**–**7**[a]

Entry	Ligand	% Conv. (min)[b]	% ee[c]
1	**1**	90 (30)	47 (*S*)
2	**2**	91 (5)	61 (*S*)
3	**3**	100 (30)	86 (*S*)
4	**4**	100 (15)	87 (*S*)
5	**5**	100 (30)	59 (*S*)
6	**6**	100 (30)	39 (*S*)
7	**7**	100 (30)	68 (*S*)
8[d]	**4**	48 (120)	95 (*S*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), KOAc (5 mg), room temperature and CH_2Cl_2 as solvent.
[b] Measured by ^{1}H NMR. Reaction time in minutes shown in parentheses.
[c] Determined by HPLC (Chiralcel OD). Absolute configuration drawn in parentheses.
[d] Reaction carried out at −5 °C.

Using ligands **1**, **5** and **6**, with different substituents at the *para* positions of the thiophenyl group, we studied how the electronic properties of the ligand affects enantioselectivity. The results indicated that enantioselectivity was best when electron-donating thioether substituents were present. The use of ligand **5** with a methyl substituent in the *para* position of the phenyl thioether moiety therefore provided **8** in 59% ee (entry 5), while ligand **6** with an electron-withdrawing group yielded **8** in only 39% ee (entry 6).

With ligands **1**–**4** and **7** we mainly studied how the steric properties of the ligand affects the product outcome. If we compare the results obtained with these ligands we can conclude that enantioselectivities were best when bulky thioether substituents were present (entries 1–4 and 7). Thus, the best enantioselectivities were obtained with ligands **3** and **4** that contains bulky isopropyl and *tert*-butyl groups in the thioether moiety. The fact that ligand **2**, with a small methyl substituent, provided higher enantioselectivity than ligand **1**, with a phenyl substituent, can be explained by the electronic effect previously mentioned.

To sum up, the best enantioselectivities were obtained with the previously tested ligand **3** [1a] and the new ligand **4**, that contain electron-donating and bulky substituents at the thioether moiety.

We also studied how the temperature affected the outcome of the reaction using ligand **4**. Lowering the reaction temperature to −5 °C, enantioselectivity increased to up to 95% (*S*) (entries 8 vs. 4).

3.1.2. Allylic alkylation of rac-(*E*)-ethyl-2,5-dimethyl-3-hex-4-enylcarbonate *S2* (Eq. (1))

We also evaluated the thioether–phosphinite ligands **1**–**7** in the allylic substitution process of **S2** using dimethyl malonate as nucleophile (Eq. (1)). This substrate is more sterically demanding than the previously used substrate **S1** [6,8b]. The most remarkable results are shown in Table 3. In general, they follow the same trends as for the allylic alkylation of **S1**. However, the enantiomeric excesses were

Table 3
Pd-catalyzed allylic alkylation of **S2** with ligands **1**–**7**[a]

Entry	Ligand	% Conv. (h)[b]	% ee[c]
1	**1**	100 (18)	52 (*R*)
2	**2**	100 (18)	65 (*R*)
3	**3**	100 (18)	88 (*R*)
4	**4**	100 (18)	90 (*R*)
5	**5**	100 (18)	63 (*R*)
6	**6**	94 (18)	45 (*R*)
7	**7**	100 (18)	68 (*R*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), KOAc (5 mg), room temperature and CH_2Cl_2 as solvent.
[b] Measured by ^1H NMR. Reaction time in hours shown in parentheses.
[c] Enantiomeric excesses determined by ^1H NMR using $Eu(hfc)_3$. Absolute configuration drawn in parentheses.

slightly higher (ee's up to 90% at room temperature). As expected, the activities were lower than in the alkylation reaction of **S1** [6,8b]. Again, the catalyst precursor containing the thioether–phosphinite ligands **3** and **4** provided the best enantioselectivity (entries 3 and 4). The stereoselectivity of the alkylation of **S2** was the same as for the alkylation reaction of **S1**, though the CIP descriptor was inverted due to the change in priority of the groups.

3.1.3. Allylic alkylation of rac-1,3-dimethyl-3-acetoxyprop-1-ene *S3* (Eq. (1))

We also screened ligands **1**–**7** in the allylic alkylation of the linear substrate **S3** (Eq. (1)). This substrate is less sterically demanding than the previously used substrates **S1** and **S2**. Enantioselectivity for **S3** is therefore more difficult to control than with hindered substrates such as **S1** and **S2** [6]. The results of using the thioether–phosphinite ligands under the optimized conditions are summarized in Table 4. The general trends that controlled enantioselectivity were different from those that controlled **S1** and **S2**, being the steric effect more predominantly. Therefore, the best enantioselectivity was obtained with ligand **4**. Unfortunately, as observed with the Evans' thioether–phosphinite ligands [8b], our ligand systems also proved to be inadequate in terms of enantioselectivities. So, further modifications directed to increase the steric bulk of the ligand could provided better results.

Table 4
Pd-catalyzed allylic alkylation of **S3** with ligands **1**–**7**[a]

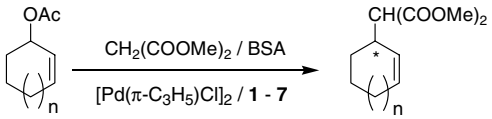
Entry	Ligand	% Conv. (min)[b]	% ee[c]
1	**1**	100 (30)	7 (*R*)
2	**2**	100 (15)	4 (*R*)
3	**3**	100 (15)	18 (*R*)
4	**4**	100 (15)	33 (*R*)
5	**5**	100 (30)	9 (*R*)
6	**6**	100 (30)	5 (*R*)
7	**7**	100 (30)	13 (*R*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), KOAc (5 mg), room temperature and CH_2Cl_2 as solvent.
[b] Measured by GC. Reaction time in minutes shown in parentheses.
[c] Enantiomeric excesses determined by GC. Absolute configuration drawn in parentheses.

3.2. Allylic alkylation of cyclic substrates

As for the unhindered substrate **S3**, enantioselectivity in cyclic substrates is difficult to control, mainly because of the presence of less sterically *syn* substituents. These *syn* substituents are thought to play a crucial role in the enantioselection observed with acyclic substrates in the corresponding Pd-allyl intermediate [6]. To obtain high ee's, the ligand must create a small chiral pocket (the chiral cavity where the allyl is embedded) around the metal center [6].

In this section, we report the use of the chiral thioether–phosphinite ligands **1**–**7** in the Pd-catalyzed allylic alkylation of two cyclic substrates (Eq. (2)): *rac*-3-acetoxycyclohexene **S4** (which is widely used as a model substrate) and *rac*-3-acetoxycycloheptene **S5**.



(2)

S4 n=1
S5 n=2

11 n=1
12 n=2

We initially studied the allylic alkylation of *rac*-3-acetoxycyclohexene **S4** using ligands **1**–**7**. Preliminary investigations into the solvent effect, ligand-to-palladium ratio and source of base provided the same trends as those with the previously tested linear substrate **S1**. The trade-off between enantioselectivities and reaction rates was therefore optimum with dichloromethane, a ligand-to-palladium ratio of 1.1 and KOAc as base. The results of using the thioether–phosphinite ligands **1**–**7** under the optimized conditions are showed Table 5.

Table 5
Pd-catalyzed allylic alkylation of **S4** and **S5** with ligands **1**–**7**[a]

Entry	Substrate	Ligand	% Conv. (min)[b]	% ee[c]
1	**S4**	**1**	98 (30)	4 (*R*)
2	**S4**	**2**	100 (30)	21 (*R*)
3	**S4**	**3**	100 (30)	41 (*R*)
4	**S4**	**4**	50 (30)	75 (*S*)
5	**S4**	**5**	32 (30)	28 (*R*)
6	**S4**	**6**	8 (60)	2 (*R*)
7	**S4**	**7**	12 (30)	24 (*R*)
8[d]	**S4**	**3**	98 (90)	51 (*R*)
9[e]	**S4**	**4**	12 (360)	89 (*S*)
10	**S5**	**4**	98 (60)	79 (*S*)
11[e]	**S5**	**4**	10 (360)	91 (*S*)

[a] 0.5 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 1.1 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), KOAc (5 mg), room temperature and CH_2Cl_2 as solvent.
[b] Measured by GC. Reaction time in minutes shown in parentheses.
[c] Enantiomeric excesses determined by GC. Absolute configuration drawn in parentheses.
[d] Reaction carried out at 0 °C.
[e] Reaction carried out at −20 °C.

As observed for substrates **S1** and **S2**, enantioselectivities were affected by the electronic and steric properties of the substituents at the thioether moiety. However, the effect of these parameters was different. Enantioselectivity was therefore best only with ligand **4**, containing a bulky *tert*-butyl thioether substituent. It is interesting to note that ligand **4** affords the opposite sense of induction to the rest of ligands tested (entries 4 vs. 1–3 and 5–7). Therefore with the new ligand **4**, we were able to increase enantioselectivity from the previously reported 51% [1a] ee to 89% ee (entries 8 vs. 9). This result is amongst the best reported for cyclic substrates [6,8b].

Ligand **4** were also effective (ee's up to 91%) in the allylic alkylation of the seven-membered ring substrate **S5** (entries 10 and 11).

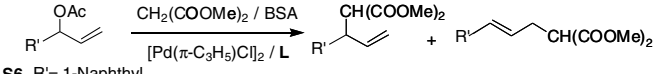
3.3. Allylic substitution of monosubstituted linear substrates

Finally, we also examined the regio- and stereoselective allylic alkylation of 1-(1-naphthyl)allyl acetate **S6** and 1-phenylallyl acetate **S7** with dimethyl malonate. For both substrates, the development of highly regio- and enantioselective Pd-catalysts is still a challenge [10]. The results obtained with the furanoside thioether–phosphinite ligands **1**–**7** are summarized in Table 6. Unfortunately, the regioselectivity for the branched products was not high. However, good enantioselectivities can be obtained (ee's up to 79% for substrate **S6** and 74% for substrate **S7**).

From the results presented in Table 6, we can conclude that enantioselectivity was affected on both electronic and steric properties of the substituents at the thioether moiety. Enantioselectivities were therefore best when bulky *tert*-butyl groups in the thioether moiety (ligand **4**) were present (entries 4 and 8). In addition, an electronic effect on the sense of enantioselectivity was also observed. Thus, ligands containing electron-withdrawing thioether groups favor the (*S*) enantiomer (entries 1, 6 and 7), while ligands containing electron-donor groups favor the formation of the (*R*) enantiomer (entries 2–5).

In contrast, regioselectivity was mainly dependent on the electronic properties of the thioether moiety and the size of the substrate substituent (R′). Electron-withdrawing substituents in the thioether moiety of the ligand [11] (entry 6 vs. 5) along with bulky R′ substituents in the substrate (entry 4 vs. 8) therefore favored the formation of the desired branched product.

Table 6
Selected results for the Pd-catalyzed allylic alkylation of **S6** and **S7**[a]



S6 R'= 1-Naphthyl
S7 R'= Phenyl

b **l**

Entry	Substrate	Ligand	% Conv. (t/h)[b]	**b/l**[b]	% ee[c]
1	**S6**	**1**	100 (2)	50/50	4 (*R*)
2	**S6**	**2**	100 (2)	34/66	11 (*S*)
3	**S6**	**3**	100 (2)	31/69	34 (*S*)
4	**S6**	**4**	100 (2)	30/70	79 (*S*)
5	**S6**	**5**	100 (2)	30/70	4 (*S*)
6	**S6**	**6**	100 (2)	60/40	8 (*R*)
7	**S6**	**7**	100 (2)	50/50	8 (*S*)
8	**S7**	**4**	100 (2)	7/93	74 (*S*)

[a] 1 mol% $[Pd(\pi\text{-}C_3H_5)Cl]_2$, 2.2 mol% ligand, room temperature, 30 min; 3 equiv of $CH_2(COOMe)_2$ and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), KOAc (5 mg), room temperature and CH_2Cl_2 as solvent.

[b] Conversion percentage and linear-to-branched ratio determined by ^1H NMR.

[c] Enantiomeric excesses determined by HPLC on a Chiralcel-OJ column. Absolute configuration drawn in parentheses.

4. Conclusions

A series of readily available thioether–phosphinite ligands has been tested in the Pd-catalyzed allylic substitution reactions of several acyclic and cyclic allylic substrates (**S1**–**S7**). This series of ligands have been designed to uncover their important structural features and to determine the scope of the thioether–phosphinite ligands in these catalytic reactions. Systematic variation of the electronic and steric properties at the thioether moiety provide useful information about the ligand parameters that control the enantiodiscrimination. Particularly, for the hindered disubstituted acyclic substrates **S1** and **S2**, we found that enantioselectivities depended on the steric and electronic properties of the substituent of the thioether moiety. Good enantioselectivies with high activities were obtained with ligands **3** and **4**, containing bulky and electron-donating isopropyl and *tert*-butyl substituents, respectively (ee's up to 95%). For the unhindered linear substrate **S3**, enantioselectivities were mainly affected by the steric properties of the thioether moiety. Enantioselectivity was therefore best using ligand **4** that contains the more bulky sulfur substituent (ee's up to 33%). For the unhindered cyclic substrates **S4** and **S5**, enantioselectivites followed similar trends as those for the alkylation of substrates **S1** and **S2**, but an interesting steric effect on the sense of enantioselectivity was observed. Therefore, with the new ligand **4** we were able to increase enantioselectivities until 89% ee and 91% ee for substrates **S4** and **S5**, respectively. For the monosubstituted acyclic substrates, these ligands proved to be inadequate in terms of regioselectivities. However, we obtained good enantioselectivty by carefully selecting the electronic and steric properties of the thioether moiety (ee's up to 79%).

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