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Palladium-Catalyzed Asymmetric Allylic Sulfonylation

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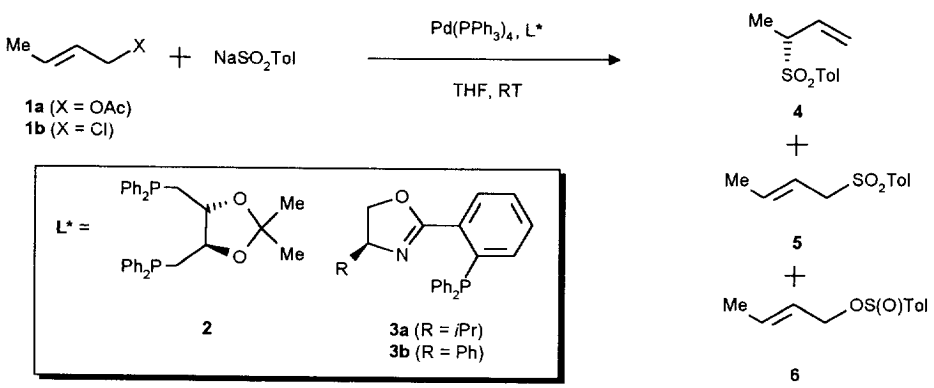
Abstract: *The palladium-catalyzed asymmetric sulfonylation of allylic substrates rac-**7a,b** and rac-**8a,b** in the presence of the chiral phosphino-oxazoline ligand **3a** gave the allylic sulfones **9a** and **9b** with ee-values of 59% and 88%, respectively, in high yield. In the presence of ligand ent-**3b** the enantiomeric allylic sulfones ent-**9a** and ent-**9b** were obtained with ee-values of 57% and 93% in high yield.*

We have recently shown that chiral, non-racemic lithiosulfones, which are configurationally stable at low temperatures, are accessible by deprotonation/lithiation of the corresponding chiral, non-racemic sulfones.[1] For the synthetic utilization of such chiral lithiosulfones a method for the asymmetric synthesis of sulfones via C-S bond formation[2] would be desirable. In 1986 Hiroi et al. reported on the Pd-catalyzed asymmetric sulfonylation of allylic acetate **1a** with sodium *p*-toluenesulfinate and $Pd(PPh_3)_4$[3] in the presence of the chiral bisphosphino ligand **2** which led to the isolation of the allylic sulfone (*R*)-(-)-**4** with an *ee*-value of 88% in 73% yield (Scheme 1).[2a,b]

Scheme 1



However, besides **4** the isomeric sulfone **5** was isolated in 24% yield. Since the substitution of unsymmetrical allylic substrates such as **1** is faced with the regioselectivity problem a Pd-catalyzed asymmetric sulfonylation of racemic allylic substrates of the symmetrical type[4] (Scheme 2) would be synthetically more attractive. In recent years a number of chiral phosphine ligands have been devised for the highly selective

asymmetric Pd-catalyzed substitution of allylic substrates with C- and N-nucleophiles.[5,6] The chiral phosphino-oxazoline ligands **3a,b** developed by Helmchen et al.,[7] Pfaltz et al.,[8] and Williams et al.[9] are especially interesting.[10]

Here we report on the Pd-catalyzed asymmetric sulfonylation of allylic substrates of the symmetrical type in the presence of the Helmchen-Pfaltz-Williams ligands **3a** and *ent*-**3b**. We began our investigations, however, with the allylic substrates **1a,b** and by using **2** as ligand (Table 1).

Table 1. Palladium-Catalyzed Asymmetric Sulfonylation of the Allylic Substrates **1a,b**.[a]

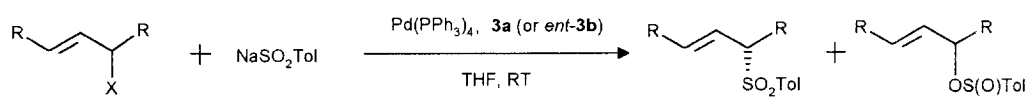
entry	substrate	equiv of $Pd(PPh_3)_4$	chiral ligand, equiv.	time (h)	yield (%)[b] of **4**, **5** and **6**[c]	*ee*-value (%)[d] of **4** or *ent*-**4**[e]
1	**1a**	0.15	—	6	99	0
2	**1a**	0.15	**2**, 0.60	6	98	14 (–)
3	**1a**	0.01	—	22	75	0
4	**1a**	0.01	**3a**, 0.02	22	53	14 (+)
5	**1a**	0.01	*ent*-**3b**, 0.02	22	51	17 (–)
6	**1b**	0.01	—	22	77	0
7	**1b**	0.01	**2**, 0.60	22	70	15 (–)
8	**1b**	0.01	**3a**, 0.02	22	50	11 (+)
9	**1b**	0.01	*ent*-**3b**, 0.02	22	47	21 (–)

[a] **1a,b** (0.5 mmole) were reacted with $TolSO_2Na$ (1 mmole) in the presence of $Pd(PPh_3)_4$ and **2**, **3a** or *ent*-**3b** at room temperature in THF (5 mL). [b] After purification by flash-chromatography. [c] The ratio of **4**:**5**:**6**, which was in all cases 73:24:3, was determined by ^1H NMR spectroscopy and by GC on DB5 column. [d] Determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ (100 mol%) in $CDCl_3$ or by GC on a 2,3-di-O-pentyl-6-O-methyl-γ-cyclodextrin column. [e] In parenthesis, the sign of the optical rotation of the mixture of **4**, **5** and **6** in ethanol is given.

Experiments with PPh_3 as ligand served to establish the reactivity of the allylic substrates and to secure the racemic allylic sulfones for analytical purposes (Table 1, entries 1, 3 and 6). The substitution of **1a,b** in the presence of **2** under the conditions reported[2a,b] gave a mixture of the allylic sulfones **4** and **5** besides the sulfinic ester **6** in a ratio of 73:24:3 (Table 1, entries 2 and 7). The sulfone **4**, however, had an *ee*-value of only 14% (15%). The *ee*-determination was done by NMR spectroscopy in the presence of $Eu(hfc)_3$ taking the signal of the α-methyl group ($\Delta\Delta\delta = 0.12$ ppm), and by GC analysis on a 2,3-di-O-pentyl-6-O-methyl-γ-cyclodextrin column with *rac*-**4** as standard in both cases. Even by using the ligands **3a** and *ent*-**3b** for this substitution the *ee*-values of *ent*-**4** and **4** did not exceed 14% and 21%, respectively (Table 1, entries 4, 5, 8 and 9). It is interesting to note that with **2** as ligand the enantioselectivity of the Pd-catalyzed substitution of **1a** with sodium *p*-toluenesulfinate is almost the same as with sodium dimethylmalonate.[11]

Further studies were therefore conducted with *rac*-**7a,b** and *rac*-**8a,b** as allylic substrates and **3a** as well as *ent*-**3b** as chiral ligands (Scheme 2). Here too experiments in the presence of PPh_3 were run to establish the reactivity and to obtain racemic samples as analytical standards (Table 2, entries 1, 5, 8 and 11). Reaction of dimethyl-substituted substrates *rac*-**7a,b** with sodium *p*-toluenesulfinate and $Pd(PPh_3)_4$ in the presence of **3a** at room temperature in THF gave sulfone **9a**[12a] and sulfinic acid ester **10a**[12b] in ratios varying from 10:1 to 15:1 as an inseparable mixture (Table 2, entries 2 and 6). The sulfone **9a** had *ee*-values ranging from 52 to 59%.[13] With *ent*-**3b** as ligand the sulfone *ent*-**9a** was obtained with *ee*-values in the range of 50 to 57% (Table 2, entries 4 and 7).

Scheme 2



rac-**7a,b** (R = Me, X = OAc,Cl)
rac-**8a,b** (R = Ph, X = OAc,Cl)

9a (R = Me)
9b (R = Ph)

10a (R = Me)
10b (R = Ph)

Table 2. Palladium-Catalyzed Asymmetric Sulfonylation of the Allylic Substrates *rac*-**7a,b** and *rac*-**8a,b**.[a]

entry	substrate	chiral Ligand	time (h)	yield (%)[b] of **9** or *ent*-**9** and **10**	ratio of **9**:**10**[c]	*ee*-value (%)[d] of **9** or *ent*-**9**[e]
1	**7a**	—	22	52	5 : 1	0
2	**7a**	**3a**	22	42	15 : 1	59 (–)
3[f]	**7a**	**3a**	72	83	10 : 1	55 (–)
4	**7a**	*ent*-**3b**	21	40	12 : 1	57 (+)
5	**7b**	—	20	59	8 : 1	0
6	**7b**	**3a**	20	55	15 : 1	52 (–)
7	**7b**	*ent*-**3b**	19	51	10 : 1	50 (+)
8	**8a**	—	4	98	100 : 0	0
9	**8a**	**3a**	4	88	100 : 0	78 (–)
10	**8a**	*ent*-**3b**	4	77	100 : 0	91 (+)
11	**8b**	—	4	93	100 : 0	0
12	**8b**	**3a**	4	91	100 : 0	86 (–)
13[g]	**8b**	**3a**	4	97	100 : 0	88 (–)
14	**8b**	*ent*-**3b**	4	87	100 : 0	93 (+)

[a] **7a,b** and **8a,b** (0.5 mmole) were reacted with $TolSO_2Na$ (2 equiv) in the presence of $Pd(PPh_3)_4$ (0.01 equiv) and **3a** or *ent*-**3b** (0.022 equiv) at room temperature in THF (5 mL). [b] After purification by flash-chromatography. [c] Determined by ^1H NMR spectroscopy and by chiral GC on a 2,3-di-O-pentyl-6-O-methyl-γ-cyclodextrin column. [d] Determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ (140 mol%) (**9a**: $\Delta\Delta\delta(\alpha\text{-Me}) = 0.09$ ppm; **9b**: $\Delta\Delta\delta(\gamma\text{-H}) = 0.06$ ppm) or by GC on a 2,3-di-O-pentyl-6-O-methyl-γ-cyclodextrin column (only **9a**). [e] In parenthesis, the sign of the optical rotation in ethanol is given. [f] 10 mmole of **7a**, 2 equiv of $TolSO_2Na$, 0.05 equiv of $Pd(PPh_3)_4$ and 0.11 equiv of **3a**. [g] 10 mmole of **8b**, 2 equiv of $TolSO_2Na$, 0.005 equiv of $Pd(PPh_3)_4$ and 0.011 equiv of **3a**.

Under similar reaction conditions substitution of the diphenyl-substituted substrates *rac*-**8a,b** gave in the presence of **3a** the sulfone **9b**[13c] with *ee*-values ranging from 78% to 88%. Here, formation of the sulfinic ester **10b** could not be detected (Table 2, entries 9 and 12). By using *ent*-**3b** as ligand the sulfone *ent*-**9b** was obtained with somewhat higher *ee*-values in the range of 91% to 93% (Table 2, entries 11 and 14. Similar enantioselectivities were found in the Pd-catalyzed substitution of *rac*-**7** and *rac*-**8** with C- and N-nucleophiles in the presence of **3a** or *ent*-**3b**.[5-10] For the determination of the absolute configuration (-)-**9b** was reduced with diimine[14] to (+)-1-(1,3-diphenylpropyl)-*p*-toluenesulfone[12d] to whom we assign the *R*-configuration since the absolute configuration of (+)-1-phenylethyl phenyl sulfone as a structurally closely related sulfone is known to be *R*.[15] This leads to the assignment of the *R*-configuration to the allylic sulfone (-)-**9b**. Thus Pd-catalyzed substitutions of *rac*-**8a** with C-, N- and S-nucleophiles in the presence of **3a** as chiral ligand proceed with the same sense and a similar degree of asymmetric induction. A mechanistic scheme for the rationalization of the sense of asymmetric induction in the substitution of **8a** with nucleophiles in the presence of **3a** based on X-ray crystal structure analysis and NMR spectroscopic studies has been proposed by Helmchen et al.[7b,16] The syntheses of the sulfones **9a,b** were run on a 10 mmol scale with similar results (Table 2, entry 3 and 13). The reaction of *rac*-**8b** in the presence of 0.005 equiv of $Pd(PPh_3)_4$ and 0.011 equiv of **3** took 4 h for completion and gave (-)-**9b** in 97 % yield with 88% *ee*. Recrystallisation from diethyl ether afforded enantiomerically pure (-)-**9b**.

In summary, with ligands **3a** and *ent*-**3b** the Pd-catalyzed allylic substitution of racemic diphenyl-substituted allylic substrates gives a synthetically useful access to chiral allylic sulfones. We are currently studying other racemic dialkyl-substituted allylic substrates as well as other sulfinates.

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12. (a) **9a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (d, J = 7.1 Hz, 3H), 1.66 (d, J = 6.1 Hz, 3H), 2.45 (s, 3H), 3.62 (quint, J = 7.1 Hz, 1H), 5.35-5.55 (m, 2H), 7.30-7.37 (2H), 7.67-7.78 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6 (CH_3), 18.1 (CH_3), 21.6 (CH_3), 63.7 (CH), 124.0 (CH), 129.27 (CH), 129.33 (CH), 133.4 (CH), 134.1 (C), 144.4 (C). (b) **10a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, J = 6.8 Hz, 3H), 1.44 (d, J = 7.1 Hz, 3H), 2.45 (s, 3H), 3.98 (m, 1H), 5.23 (m, 1H), 5.68 (m, 1H), 7.30-7.37 8 (m; 2H), 7.67-7.78 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.0 (CH_3), 18.5 (CH_3), 21.6 (CH_3), 58.6 (CH), 120.5 (CH), 129.3 (CH),129.4 (CH), 31.7 (CH), 144.4 (C). (c) **9b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 4.81 (dd, J = 0.67, J = 7.38 Hz, 1H), 6.52 (dd, J = 0.67, J = 15.44 Hz, 1H), 6.59 (dd, J = 15.44, J = 7.38 Hz, 1H), 7.20 (m, 2H), 7.24-7.38 (m, 10H), 7.53 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.6 (CH_3), 75.4 (CH), 120.3 (CH), 126.8 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 128.9 (CH), 129.3 (CH), 129.4 (CH), 129.7 (CH), 132.5 (C), 134.5 (C), 136.0 (C), 138.0 (CH), 144.6 (C); $[\alpha]_D^{20}$ –6.0 (*c* 0.17, ethanol) (>98% *ee*).(d) (+)-1-(1,3-Diphenylpropyl)-*p*-toluenesulfone: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.40-2.52 (m, 2H), 2.56-2.80 (m, 2H), 3.99 (m, 1H), 7.01-7.37 (m, 14H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.6 (CH_3), 28.9 (CH_2), 32.5 (CH_2), 70.6 (CH), 126.3 (CH), 128.4 (CH), 128.48 (CH), 128.52 (CH), 128.8 (CH), 129.0 (CH), 129.2 (CH), 130.0 (CH), 132.1 (C), 134.3 (C), 140.0 (C), 144.3 (C); $[\alpha]_D^{20}$ +18.5 (*c* 2.3, ethanol).
13. According to ^{1}H NMR spectroscopy and GC on a 2,3-di-O-pentyl-6-O-methyl-γ-cyclodextrin column **10a** was a 1:1 mixture of diastereomers which were both racemic.
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