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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of allylic sulfides via palladium-mediated allylation of thiols

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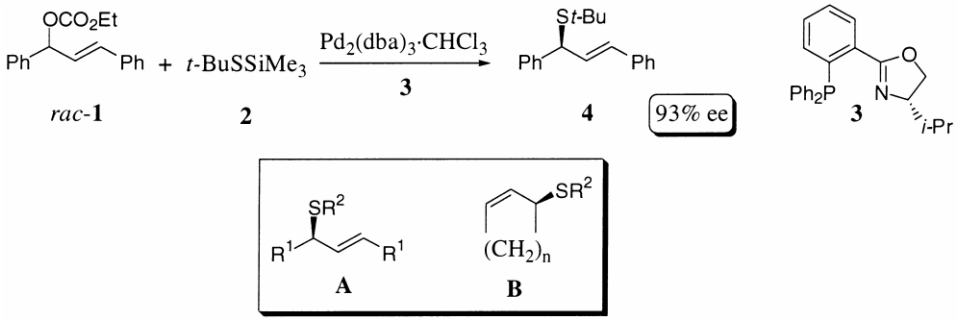
Abstract

Cyclic and acyclic allylic *S*-*p*-chlorophenyl, *S*-2-pyridyl and *S*-2-pyrimidyl sulfides of 50–96% ee have been obtained in 24–87% yield through reaction of the corresponding racemic carbonates with *p*-chlorothiophenol, 2-mercaptopyridine and 2-mercaptopyrimidine, respectively, mediated by a complex generated in situ from $Pd_2(dba)_3 \cdot CHCl_3$ and the Trost ligand.

We recently reported on the palladium-mediated enantioselective formation of sulfide **4** from carbonate *rac*-**1** and the silyl sulfide **2** in the presence of the Helmchen–Pfaltz–Williams ligand **3** (Scheme 1).[1]



Scheme 1.

This observation suggested an asymmetric synthesis of allylic sulfides of type **A** and **B** by a palladium-mediated reaction of the corresponding racemic allylic carbonates or acetates with thiols or silylated thiols[2] in the presence of a chiral phosphino ligand.[3] Enantiomerically enriched allylic sulfides should be interesting synthetic building blocks. For example, utilization of **A** and **B** as educts in the allylic alkylation with organocopper reagents,[4] the synthesis of chiral lithiosulfides[5,6] and the ketene–Claisen

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Table 1
Synthesis of acyclic allylic sulfides[a]

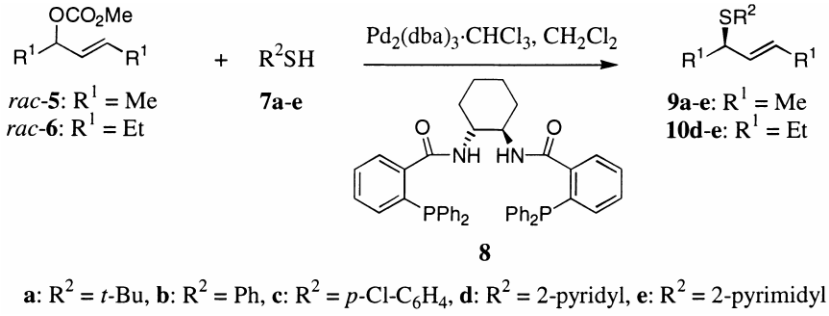
entry	substrate	R^2SH	Pd (mol%)	ligand (mol%)	t (d)	T (°C)	solvent	sulfide (*E*:*Z*)	yield (%)[b]	ee (%)[c]
1	*rac*-**5**	**2**	5	**3** (6.25)	5	20	CH_2Cl_2	**9a**	0	-
2	*rac*-**5**	**7a**	10	**8** (10)	1	20	CH_2Cl_2	**9a**	0	-
3	*rac*-**5**	**7b**	10	**8** (10)	1	20	CH_2Cl_2	**9b**	traces	-
4	*rac*-**5**	**7c**	10	**8** (13)	2	0→20	CH_2Cl_2	**9c** (10:1)	73	90
5	*rac*-**5**	**7c**	10	**8** (12.5)	7	0→20	CH_2Cl_2/H_2O[d]	**9c** (9:1)	41	93
6	*rac*-**5**	**7d**	10	**8** (11)	2	0→20	CH_2Cl_2	**9d** (15:1)	87	68
7	*rac*-**5**	**7d**	10	**8** (11)	1	0→20	CH_2Cl_2/H_2O[e]	**9d** (14:1)	64	64
8	*rac*-**5**	**7d**	5	**8** (5.5)	6	0→20	CH_2Cl_2	**9d** (15:1)	65	67
9	*rac*-**5**	**7d**	1	**8** (1.1)	6	0→20	CH_2Cl_2	**9d**	4.5[f]	-[g]
10	*rac*-**5**	**7e**	10	**8** (10)	2	0→20	CH_2Cl_2	**9e** (29:1)	72	89
11	*rac*-**6**	**7d**	10	**8** (10)	3	0→20	CH_2Cl_2	**10d** (16:1)	24	50
12	*rac*-**6**	**7e**	10	**8** (11)	6	20	CH_2Cl_2	**10e** (≥99:1)	64	91[h]

[a] Reactions were run under argon on a 1 mmol scale (entries 1-7, 10-12) and on a 2 mmol scale (entries 8 and 9) by using $Pd_2(dba)_3 \cdot CHCl_3$ as precatalyst [b] Yields refer to isolated compounds. [c] Determined by capillary GC analysis on a octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin column (Macherey-Nagel) (entries 4, 5, 10 and 11) or a octakis(3-*O*-butyryl-2,6-di-*O*-pentyl)-γ-cyclodextrin column (Macherey-Nagel) (entries 6, 7, 8 and 9). [d] In the presence of 1.5 mol% *n*-Bu_4NBr. [e] In the presence of 10 mol% of *n*-Bu_4NF. [f] Conversion. [g] Not determined. [h] Determined by HPLC analysis on a Chiralcel OD-H column (Baker/Daicel) (*n*-hexane/*i*-PrOH, 95:5).

rearrangement[7] can be envisioned. We report herein on the asymmetric synthesis of allylic sulfides mediated by a complex generated in situ from $Pd_2(dba)_3 \cdot CHCl_3$ and the Trost ligand **8**.[8]

Attempts to prepare sulfide **9a** by a palladium-mediated reaction of carbonate *rac*-**5** with **2** in the presence of **3**[9–11] were met with no success (Table 1, entry 1) (Scheme 2).[12] Only the precipitation of the catalyst from the reaction solution,[2b] perhaps because of the formation of a palladium thiolate complex,[13,14] was observed. Because of the high enantioselectivity recorded in the corresponding reaction of *rac*-**5** with sulfinates by using ligand **8**,[1,15] synthesis of **9a** in the presence of this ligand was attempted. However, formation of **9a** upon treatment of *rac*-**5** with **2** or *tert*-butylthiol **7a**, $Pd_2(dba)_3 \cdot CHCl_3$ and **8** could not be detected (entry 2).[16] While the analogous treatment of *rac*-**5** with thiophenol **7b** in the presence of **8** gave traces of sulfide **9b** (entry 3),[16] the use of *p*-chlorothiophenol **7c** saw a significant increase in the conversion of *rac*-**5**. Sulfide **9c**[17] of 90% ee could be isolated in 73% yield (entry 4). Under two-phase conditions in CH_2Cl_2/H_2O the reaction of *rac*-**5** with **7c** was slower but the enantioselectivity was almost the same (entry 5). Because of the high reactivity of heteroaromatic allylic sulfides towards copper reagents,[4] the reactions of carbonates *rac*-**5** and *rac*-**6** with 2-mercaptopyridine **7d** and 2-mercaptopyrimidine **7e** were studied. Treatment of *rac*-**5** with **7d**, $Pd_2(dba)_3 \cdot CHCl_3$ and **8** resulted in isolation of sulfide **9d**[17] of 68% ee in 87% yield (entry 6). Under two-phase conditions in CH_2Cl_2/H_2O, **9d** was obtained with a somewhat lower ee-value in a reduced yield (entry 7). Rather large amounts of palladium and ligand were employed in the above described substitutions. While the reduction of the amounts of palladium and ligand in the reaction of *rac*-**5** with **7d** from 10 mol% to 5 mol% gave still acceptable results (entry 8), the further reduction to 1 mol% resulted in only a minor conversion of the allylic substrate (entry 9). Reaction of *rac*-**5** with **7e** proceeded with a significantly higher enantioselectivity than with **7d** and afforded sulfide **9e**[17] of 89% ee in 72% yield (entry 10).

Monitoring the reaction of *rac*-**5** with **7e** by GC revealed ratios of *rac*-**5** and **9e** of 66:1, 40:33 and 5:72 after 1 h, 18 h and 42 h, respectively. Due to the low solubility of **7e** in CH_2Cl_2 the reaction mixture was heterogeneous at the beginning and became homogeneous only towards the end of the reaction. However, the ee-value of **9e** remained constant during the course of the substitution.



a: R^2 = *t*-Bu, **b**: R^2 = Ph, **c**: R^2 = *p*-Cl-C_6H_4, **d**: R^2 = 2-pyridyl, **e**: R^2 = 2-pyrimidyl

Scheme 2.

Not only did the reactions of the pentenyl carbonate *rac*-**5** with **7d** and **7e** proceed with different enantioselectivities but also those of the heptenyl carbonate *rac*-**6** (entries 11 and 12). Sulfides **10d**[17] and **10e**[17] of 50% ee and 91% ee, respectively, were obtained in 24% and 64% yield, respectively. While all other acyclic sulfides described above were obtained as *E*/*Z* mixtures in ratios ranging from 9:1 to 29:1, sulfide **10e** was not contaminated by its *Z* isomer according to GC analysis. The structures of **9c**–**e**, **10d** and **10e** were secured by NMR spectroscopy in combination with MS and elemental analyses. The ^{13}C NMR data of **9d**, **9e**, **10d** and **10e** in comparison with those of *N*-alkyl-thiopyridones/thiopyrimidones and the corresponding 2-(alkylthio)-pyridines/pyrimidines,[18] especially, allowed for their unequivocal assignment as *S*-allylic derivatives.

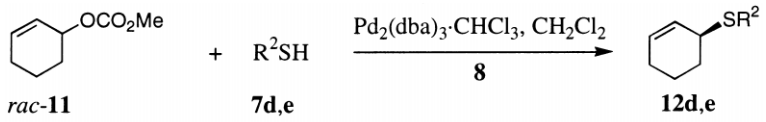
Extension of the palladium-mediated allylic substitution to the cyclic substrate *rac*-**11** posed no problems. Reaction of *rac*-**11** with **7d** in the presence of **8** gave sulfide **12d**[17,2e,h] of 55% ee in 64% yield (Table 2, entry 1) (Scheme 3). The corresponding reaction of *rac*-**11** with **7e** afforded sulfide **12e**[17] in a similar yield but with a much higher ee-value of 96% (entry 2). While the reduction of the amounts of catalyst and ligand in the reaction of *rac*-**11** with **7e** from 10 mol% to 2 mol% led to a significant increase in the reaction time, the enantioselectivity remained unchanged (entry 3). It is interesting to note that substitutions with 2-mercaptopyrimidine, which is only sparingly soluble in CH_2Cl_2, proceeded with significantly higher enantioselectivities than those with 2-mercaptopyridine which is readily soluble in CH_2Cl_2.

The absolute configuration of **9e** was established by chemical correlation (Scheme 4). Alcohol **13**,[19]

Table 2
Synthesis of cyclic allylic sulfides[a]

entry	substrate	R^2SH	Pd (mol%)	ligand (mol%)	t (h)	T (°C)	product	yield (%)[b]	ee (%)[c]
1	*rac*-**11**	**7d**	10	**8** (11)	27	0→20	**12d**	64	55
2	*rac*-**11**	**7e**	10	**8** (11)	24	20	**12e**	63	96
3	*rac*-**11**	**7e**	2	**8** (2.2)	96	20	**12e**	58	95

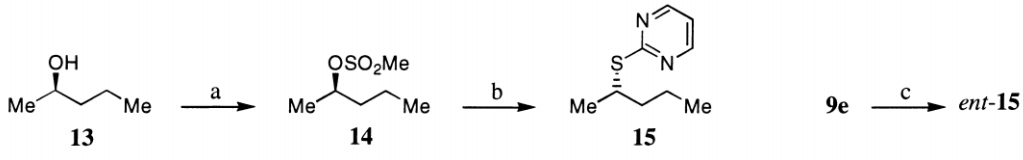
[a] Reactions were run in CH_2Cl_2 under argon on a 1 mmol scale (entries 1 and 2) and on a 5 mmol scale (entry 3) by using $Pd_2(dba)_3{\cdot}CHCl_3$ as precatalyst. [b] Yields refer to isolated compounds. [c] Determined by capillary GC analysis on a heptakis(per-methyl)-ß-cyclodextrin (Chrompack) column.



d: R^2 = 2-pyridyl, **e**: R^2 = 2-pyrimidyl

Scheme 3.

having the *R* configuration and an ee-value of 96% ee (by GC on an octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin column), was converted to mesylate **14** which upon reaction with the sodium salt of **7e** afforded sulfide **15** of 95% ee (by GC on an octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin column). Reduction of **9e** of 84% ee with diimide yielded *ent*-**15**. Thus, sulfide **9e** has the *R* configuration and sulfides **9c**, **9d**, **10d** and **10e** most likely also have the *R* configuration. Because of this result, we assume that **12d** and **12e** have the *S* configuration.[1,15b,20] Hence, the substitutions of *rac*-**5**, *rac*-**6** and *rac*-**11** with sulfinates and thiols mediated by a complex derived in situ from $Pd_2(dba)_3$ and **8** take a similar stereochemical course. Interestingly, reaction of *rac*-**11** (11 mmol) with **7e** (10.4 mmol) at 20°C in CH_2Cl_2 in the presence of $Pd_2(dba)\cdot CHCl_3$ (5 mol%) and **8** (5.5 mol%) proceeded under kinetic resolution of the substrate. Workup after a period of 24 h, at which time conversion of the substrate came to a complete halt, gave *R*-**11** of ≥99% ee in 23% yield and *S*-**12e** of ≥99% ee in 70% yield. Thus, we note that not only the palladium-mediated reaction of *rac*-**1** with sulfinate in the presence of **3**,[1] but also that of *rac*-**11** with thiolate in the presence of **8**, proceeds under kinetic resolution, and that in both cases the faster reacting substrate and the faster formed product have the same absolute configuration.



Reagents and conditions: (a) $MeSO_2Cl$, pyridine, 0 °C→20 °C, 69%; (b) sodium 2-pyrimidyl thiolate, DMF, 20 °C, 16%; (c) KO_2C-N=N-CO_2K, AcOH, dioxane, 47%.

Scheme 4.

Acknowledgements

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16. Treatment of *rac*-**5** with **7a** (THF, 50°C, 18 h) and **7b** (THF, 50°C, 24 h) by using $Pd_2(dba)_3 \cdot CHCl_3$ (2 mol%) and DIOP (8 mol%) gave **9a** (*E*:*Z*=24:1, 16% ee, 68% yield) and **9b** (*E*:*Z* ≥99:1, 3% ee, 95% yield), respectively.
17. **9c**: $[\alpha]_D^{22}$ +35.7 (*c* 1.45, $CHCl_3$) (90% ee); **9d**: $[\alpha]_D^{22}$ +100.0 (*c* 2.52, $CHCl_3$) (68% ee); **9e**: $[\alpha]_D^{22}$ +155.2 (*c* 2.02, $CHCl_3$) (89% ee); **10d**: $[\alpha]_D^{22}$ +88.8 (*c* 1.27, $CHCl_3$) (50% ee); **10e**: $[\alpha]_D^{22}$ +210.9 (*c* 0.98, $CHCl_3$) (91% ee); **12d**: $[\alpha]_D^{22}$ −60.9 (*c* 1.83, $CHCl_3$) (55% ee); **12e**: $[\alpha]_D^{22}$ −118.0 (*c* 1.11, $CHCl_3$) (96% ee).
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