Synthesis of Novel Highly Active Thiophene and Benzothiophene Containing Diphosphine Ligands and their Use in the Asymmetric Allylation of Catechol

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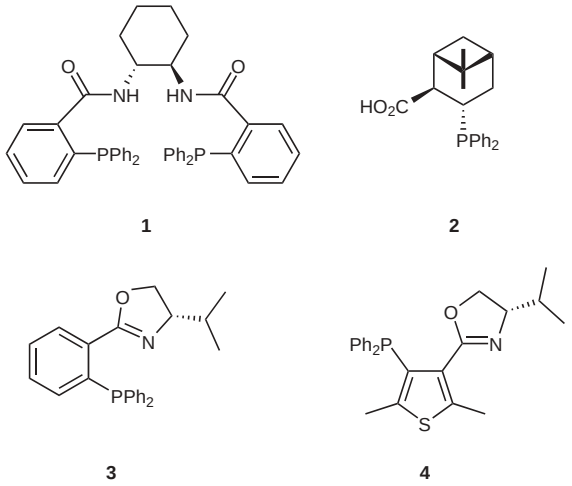
Abstract: Novel thiophene and benzothiophene containing diphosphine ligands **5**–**8** with a chiral cyclohexyl diamine backbone have been prepared and used in the asymmetric allylation of catechol. The advantage of these new ligands is their high reactivity and excellent selectivity. The best results were obtained using ligand **7** to give the allylated catechol **24b** from **23b** in 90% ee and 91% yield within 4 hours.

Key words: allylation, asymmetric catalysis, catechol, palladium, phosphines, thiophenes

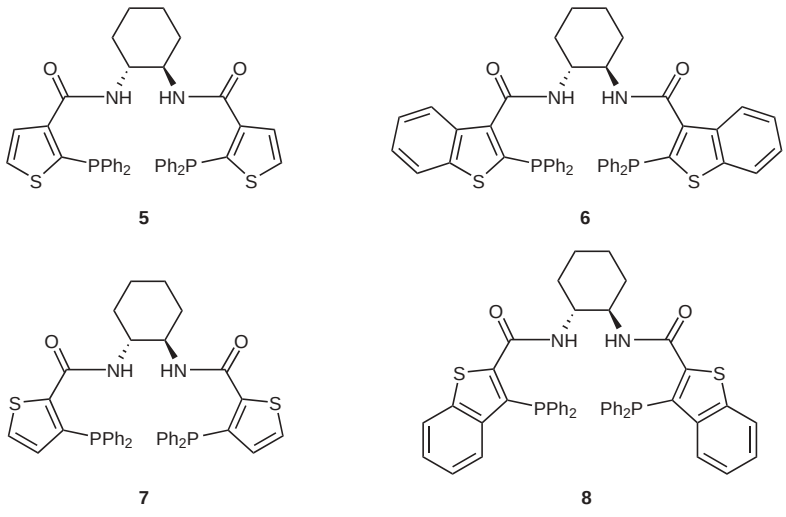
Among the enantioselective Pd-catalyzed processes[1] the asymmetric allylic substitution[2] is one of the most versatile and efficient methods to generate chiral compounds and the methodology has been used in numerous total syntheses of natural products.[2a,b] Chiral ligands (Scheme 1) have been prepared and applied in this transformation.[3] However, none of these is of universal use therefore, there is still a considerable need for new, highly reactive and selective ligands.

Recently, we have shown that thiophene containing ligands can increase selectivity as well as reactivity in inter- and intramolecular Heck reactions.[4] In addition, we synthesized a number of chiral thiophene phosphine oxazoline ligands like **4**, which are not only easily accessible but also showed an excellent selectivity and reactivity in the asymmetric allylation of malonate.[5]



1 2 3 4

Scheme 1 Chiral ligands **1**–**4** for the Pd-catalyzed nucleophilic allylation.



5 6 7 8

Scheme 2 Novel thiophene containing diphosphine ligands **5**–**8**.

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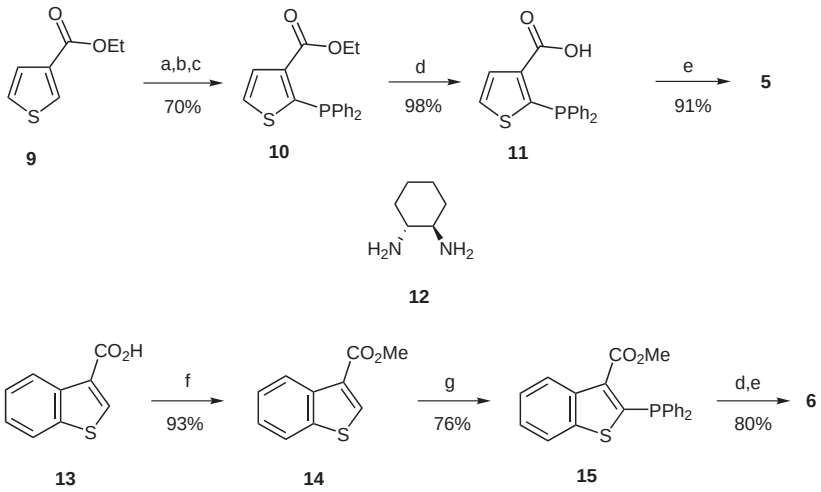
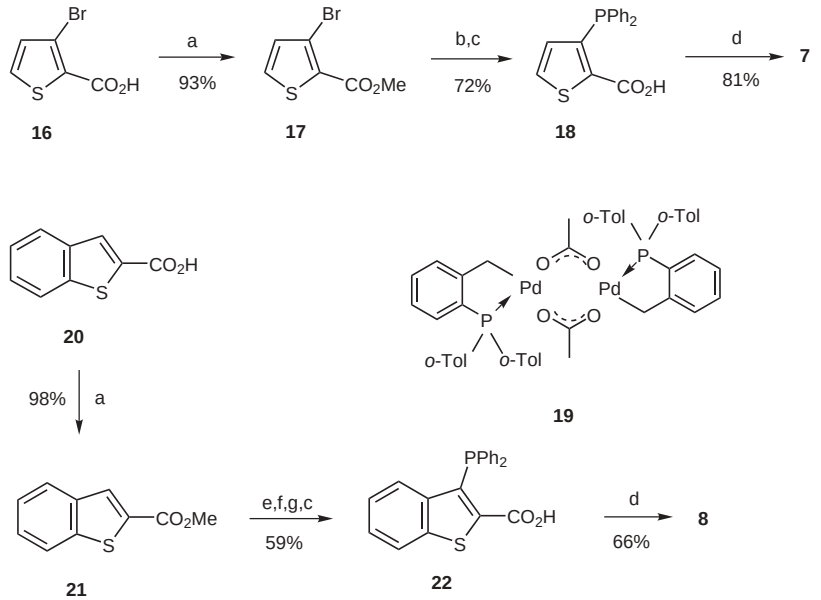


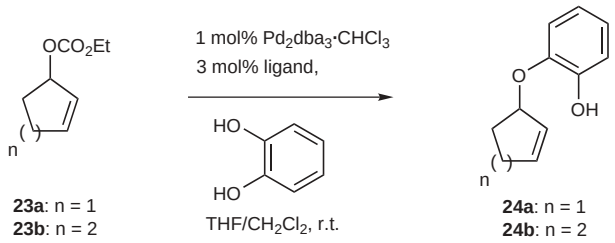
Scheme 3 Synthesis of chiral ligands **5** and **6**.
Reagents and conditions: (a) BuMgCl, *i*-Pr_2NH, THF, 25 °C, 24 h; (b) **9**, 0 °C, 10 min; (c) $ClPPh_2$, THF, 1 h; (d) $LiOH·H_2O$, THF/MeOH/H_2O; (e) EDC·HCl, HOBt, DMF, **12**; (f) MeOH, Me_3SiCl; (g) LTMP, THF, $ClPPh_2$.

Here we describe the synthesis of the novel chiral thiophene ligands **5**–**8** containing a 1,2-diaminocyclohexane backbone and their application in the asymmetric allylation of catechol with **23a** and **23b** (Scheme 2). The advantage of these compounds is their improved reactivity and selectivity compared to the known ligand **1**, furthermore they can be synthesized in a simple way starting from the inexpensive commercially available thiophene derivatives **9**, **13**, **16** and **20** in 4–6 steps (Scheme 3 and Scheme 4). The diphenylphosphino group in **5** to **8** is either introduced by direct metallation[6] of the thiophene/benzothiophene core or by a palladium catalyzed phosphorylation[7] of the corresponding bromothiophene. The coupling of the corresponding carboxylic acids with (*R*,*R*)-1,2-diaminocyclohexane to give the ligands **5** to **8** was performed using EDC and HOBt in good to excellent yields.

The thiophene containing ligands **5**–**8** were used in the asymmetric allylation of catechol with cyclopentenyl carbonate **24a** and cyclohexenyl carbonate **24b** (Scheme 5). In all transformations the palladium complexes generated from the novel ligands showed a faster conversion than using the known ligand **1**. A selectivity of 90% ee and a yield of 91% was achieved when catechol was allylated with cyclohexenyl carbonate **24b** within 4 hours using



Scheme 4 Synthesis of chiral ligands **7** and **8**
Reagents and conditions: (a) MeOH, Me_3SiCl; (b) $HPPh_2$, NaOAc, cat. **19**, DMF, 100 °C; (c) $LiOH·H_2O$, THF/MeOH/H_2O; (d) EDC·HCl, HOBt, DMF, **12**; (e) BuMgCl, HN*i*-Pr_2, THF, 25 °C, 24 h; (f) **21**, 0 °C, 10 min; (g) $ClPPh_2$, THF, 1 h.



23a: n = 1
23b: n = 2

24a: n = 1
24b: n = 2

Entry	n	Ligand	Time (h)	Yield (%)	ee[a] (%)
1	2	**5**	6	82	79
2	2	**6**	8	87	85
3	2	**7**	4	91	90
4	2	**8**	10	88	82
5	2	**1**	14	76	89
6	1	**5**	6	83	58
7	1	**6**	8	83	82
8	1	**7**	4	79	56
9	1	**8**	3	85	81
10	1	**1**	14	81	28

[a] Determined by chiral HPLC using a chiracel OD-column with hexane:isopropanol 99:1 as eluent.

Scheme 5 Enantioselective allylation of catechol with cyclopentenyl and cyclohexenyl carbonate **23a** and **23b** using ligands **1** and **5**–**8**

ligand **7**[8] (entry 3), which was slightly better than with ligand **1** giving 89% ee and 76% yield within 12 hours (entry 5). With ligands **5**, **6** and **8** a slightly decreased enantioselectivity was found compared to ligand **1**, but the yields were still higher and the reaction time reduced. However, in the allylation of catechol with cyclopentenyl carbonate the new ligands showed an astounding superiority over ligand **1**. Thus, using ligand **1** an enantioselectivity of only 28% ee was obtained (entry 10), whereas with the thiophene ligands **5** and **7** an asymmetric induction of 58% and 56% ee, respectively was observed. (entries 6 and 8). A still much better selectivity of 81% and 82% ee, respectively was found for the reaction using the benzothiophene containing ligands **6** and **8** (entries 7 and 9).

The improved selectivity and reactivity of the new ligands **5** → **8** might be due to the different bond angles and the different electronic properties of the phosphine moiety in the thiophene compounds as compared to **1**. We are now in the process to investigate the new ligands in the allylation using different nucleophiles and allylic substrates.

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(8) **Synthesis of Ligand 7:** A mixture of 3-bromo-thiophene-2-carboxylic acid (**16**, 9.44 g, 46 mmol) and Me_3SiCl (92 mmol, 2.0 equiv) in MeOH was refluxed for 24 h. After cooling, the crude product was adsorbed on silica gel (20 g) and purified by column chromatography (*n*-pentane/EtOAc, 10:1). The methyl ester **17** (9.50 g, 43.0 mmol, 93%) was obtained as a white solid. A solution of this ester (7.1 g, 32.1 mmol), dry NaOAc (5.47 g, 66.7 mmol, 2.1 equiv) and catalyst **19** (620 mg, 2 mol%) was degassed and diphenylphosphine (7.5 mL, 8.03 g, 43.1 mmol, 1.3 equiv) was added via syringe. The solution was heated under argon to 100 °C for 5 h. After cooling, H_2O (200 mL) was added. Extraction with EtOAc (3 × 200 mL) gave the crude product, which was purified via column chromatography (*n*-pentane: EtOAc, 10:1). The ester (6.90 g, 21.1 mmol) was dissolved in THF/MeOH/H_2O (5:5:1, 100 mL) and LiOH·H_2O (105 mmol, 5.0 equiv) was added. After 24 h 1 N HCl (200 mL) was added and the solution was extracted with EtOAc (3 × 150 mL). The product was purified by chromatography (*n*-pentane:EtOAc, 10:1, 1% HOAc) and the acid **18** (6.25 g, 20.0 mmol, 95%) was obtained as a white solid. The acid (1.12 g, 3.6 mmol) was dissolved in DMF (50 mL) and HOBt (3.6 mmol) and EDC·HCl (3.6 mmol) were added at r.t. After 30 min, cyclohexanediamine (1.8 mmol) was added and the reaction mixture was stirred for 24 h. 1 N HCl (100 mL) was added add the resulting mixture was extracted thrice with EtOAc (100 mL). After purification by column chromatography ligand **7** was obtained as a white foam. $[\alpha]_D^{20}$ –110.8 (*c* 0.3, $CHCl_3$); R_f (*n*-pentane:EtOAc = 4:1, 1% Et_3N) = 0.41. IR (KBr): ν = 3281, 3014, 2932, 2051, 1638, 1526 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.26 (m_c, 2 H, 3′-H), 1.68 (m_c, 1 H, 2′-H_a), 2.04 (m_c, 1 H, 2′-H_b), 3.87

(m_c, 1 H, 1′-H), 6.52 (dd, *J* = 5.0, 1.0 Hz, 1 H, 5-H), 7.23–7.33 (m, 11 H, Ph-H, N-H), 7.64 (dd, *J* = 8.0, 5.0 Hz, 1 H, 4-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.44 (C-3′), 31.99 (C-2′), 54.12 (C-1′), 128.21 (d, *J* = 2.5 Hz, C-5), 128.61 (d, *J* = 7.0 Hz, Ph-C-3), 128.88 (d, *J* = 6.5 Hz, C-4), 133.23, 133.27 (d, *J* = 19.5 Hz, Ph-C-2), 133.34, 133.37 (Ph-C-4), 136.21, 136.43 (d, *J* = 8.0 Hz, Ph-C-1), 137.87 (d, *J* = 21.0 Hz, C-2), 142.73 (d, *J* = 24.5 Hz, C-3), 162.30 (d, *J* = 2.5 Hz, C=O). ^{31}P NMR (80 MHz, $CDCl_3$): δ = –22.70. MS (EI): *m/z* = 702 (M^+), 310. Anal. Calcd for $C_{40}H_{36}N_2O_2P_2S_2$: 702.1694. Found: 702.1694 (HRMS).