# Regio- and enantio-selective Heck reactions of aryl and alkenyl triflates with the new chiral ligand (*R*)-BITIANP

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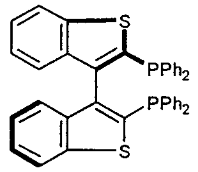
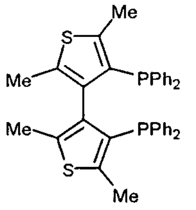
**The Heck reaction of dihydrofuran 3 with aryl triflates 4 and 6a–d and alkenyl triflate 8 in the presence of the chiral ligand (*R*)-BITIANP 1 provides the 2-substituted 2,3-dihydrofurans 5a, 7a–d and 9, respectively, with complete regioselectivity, high enantioselectivity (86–96% ee) and good yields (76–93%).**

One of the main objectives in modern synthetic organic chemistry is the catalytic enantioselective formation of C–C bonds. In this respect, the Heck reaction[1]—the Pd$^0$ catalyzed coupling of an aryl or alkenyl halide or triflate with an alkene—is a highly versatile procedure since it tolerates several functional groups. In the years since the first enantioselective Heck reactions in 1989, published by Shibasaki[2] and Overman,[3] several novel chiral ligands have been developed which give high enantioselectivities and which have been used in natural product syntheses.[4] However, one of the problems encountered in the use of chiral ligands, especially in intermolecular Heck reactions, is the often low reactivity of the formed Pd complexes.[5] Therefore it is important to develop novel ligands and show their applicability in C–C bond formation. Here we report on the use of the new chiral ligands (*R*)-(+)-2,2′-bis(diphenylphosphino)-3,3′-bi(benzo[*b*]thiophene) [(*R*)-BITIANP] **1** and (+)-4,4′-bis(diphenylphosphino)-2,2′,5,5′-tetramethyl-3,3′-bithiophene [(+)-TMBTP] **2** in Heck reactions; ligand **1** has been employed with great success in the hydrogenation of C–C and C–O bonds,[6] whereas ligand **2** has not been used so far for enantioselective transformations.



**1**



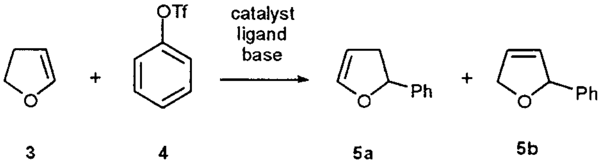
**2**

To allow a comparison with other chiral ligands we investigated the Heck reactions of dihydrofuran **3** with the triflates **4**, **6a–d** and **8**. In principle, the Heck reaction of dihydrofuran **3** with phenyl triflate **4** leads to the two isomers **5a** and **5b** (Scheme 1). Using BINAP[7] the regioselectivity is rather low, whereas with a substituted MeO-BIPHEP[8] ligand a 22 : 1 ratio of **5a** and **5b** was obtained, and with chiral phosphino-oxazolines[9] only **5b** is obtained.[10]

We have now shown that the Heck reaction of **3** and **4** in DMF at 90 °C using $Pd_2dba_3{\cdot}dba$ and the new chiral ligand **1** employing a Pd ligand ratio of 1 : 2 and 1,8-bis(dimethylamino)-naphthalene (proton sponge) as the base affords **5a** exclusively in 84% yield and 91% ee within 18 h (Table 1, entry 1).† Similar results were obtained using $Pr^i_2NEt$ as base (entry 2); however, with THF as solvent at 70 °C the transformation was less selective and much slower. Even after 7 days the reaction was not complete (entry 3). Interestingly, (*R*)-BINAP as chiral ligand using the best conditions found for the transformation with **1** gave **5a** with a 3 : 1 regioselectivity and only 42% ee (entry 4). The use of the second new ligand (+)-TMBTP **2** was only marginally successful. Here the regioisomer **5b** was obtained preferentially, but with very poor ee values (entries 5–7).

In the presence of the ligand (*R*)-BITIANP **1**, other phenyl triflates **6a–d** containing either an electron-withdrawing or an electron-donating group also reacted with high regio- and enantio-selectivities (Scheme 2, Table 2). In addition alkenyl triflates could be transformed successfully; thus, the Pd catalyzed reaction of cyclohex-1-enyl triflate **8** with dihydrofuran **3** provides exclusively the dihydrofuran derivative **9** within 13 h with good yield and high enantioselectivity.

The described Heck reactions with the new chiral ligand (*R*)-BITIANP **1** have shown that this ligand has an excellent potency and may serve as a useful alternative to the ligands

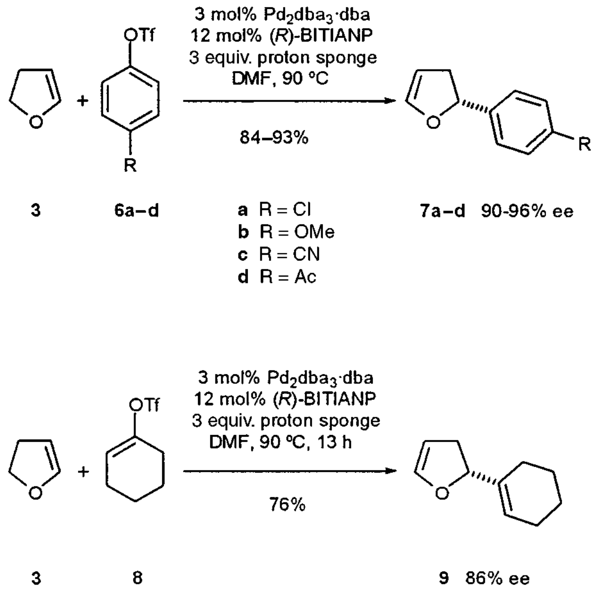


**Scheme 1**

**Table 1** Enantioselective Heck reactions of **3** and **4** providing **5a** and **5b**

| | $Pd_2dba_3{\cdot}dba$/ mol% | Ligand (mol%) | Base (equiv.) | Solvent | *T*/°C | *t* | Conversion[a] (**4** : **5a** + **5b**) | Ratio[a] **5a** : **5b** | Yield (%) **5a** | Yield (%) **5b** | Ee (%)[b] **5a** | Ee (%)[b] **5b** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3 | BITIANP **1** (12) | PS (3)[c] | DMF | 90 | 18 h | < 1 : 100 | 100 : < 1 | 84 | — | 91 | |
| 2 | 3 | BITIANP **1** (12) | $Pr^i_2$ NEt (3) | DMF | 90 | 20 h | < 1 : 100 | 100 : < 1 | 90 | — | 90 | |
| 3 | 5 | BITIANP **1** (10) | $Pr^i_2NEt$ (3) | THF | 70 | 7 d | 16 : 84 | 7 : 1 | 62 | — | 80 | |
| 4 | 3 | BINAP (12) | PS (3)[c] | DMF | 90 | 18 h | < 1 : 100 | 3 : 1 | 58 | 20 | 42 | 33 |
| 5 | 5 | TMBTP **2** (10) | $Pr^i_2NEt$ (3). | DMF | 90 | 3 d | < 1 : 100 | 1 : 2 | 27 | 58 | 4 | 2 |
| 6 | 5 | TMBTP **2** (10) | $Pr^i_2NEt$ (3) | THF | 70 | 4 d | 1 : 22 | 3 : 1 | 54 | 19 | 14 | 10 |
| 7 | 5 | TMBTP **2** (10 | PS (3)[c] | $C_6H_6$ | 70 | 4 d | 1 : 26 | 6 : 1 | 73 | 12 | 4 | 0 |

[a] Determined by GC. [b] Determined by chiral GC. [c] PS = Proton sponge = 1,8-bis(dimethylamino)naphthalene.



**Scheme 2**

**Table 2** Enantioselective Heck reaction with the aryl triflates **4**, **6a–d** and the alkenyl triflate **8**

| Entry | R | Substrate | Product | t/h | Yield (%) | Ee (%)[a] |
|---|---|---|---|---|---|---|
| 1 | H | **4** | **5a** | 18 | 84 | 91 |
| 2 | Cl | **6a** | **7a** | 18 | 87 | 94 |
| 3 | MeO | **6b** | **7b** | 18 | 84 | 90 |
| 4 | CN | **6c** | **7c** | 24 | 91 | 96 |
| 5 | MeCO | **6d** | **7d** | 24 | 93 | 95 |
| 6 | — | **8** | **9** | 13 | 76 | 86 |

[a] Determined by chiral GC.

described by Hayashi,[7] Pfaltz,[9] Pregosin[8] and Shibasaki[5] with the special advantage of high reactivity.

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## Notes and references

† Typical experimental procedure: A mixture of $Pd_2dba_3$·dba (7.6 mg, 6.63 μmol, 3 mol%), (*R*)-BITIANP **1** (16.8 mg, 26.5 μmol, 12 mol%) and 1,8-bis(dimethylamino)naphthalene (142.1 mg, 0.663 mmol, 3 equiv.) in dry and degassed DMF (5 ml) was stirred for 0.5 h at 40 °C until an orange solution was formed. Then **4** (50.0 mg, 0.221 mmol) and **3** (77.5 mg, 1.105 mmol, 5 equiv.) were added and the mixture was stirred for 18 h at 90 °C until the reaction was complete [GC analysis; SGE BPX-5% phenyl (equiv.) polysilphenylene-siloxane, 50 m, 60–160 °C, 5 °C $min^{-1}$, 50 kPa: $t_R$ = 8.8 min (**4**), $t_R$ = 15.1 min (**5a**)]. The red solution was filtered through a batch of silica gel, eluted with $Et_2O$ (100 ml), concentrated, diluted with the same volume of water and extracted with $Et_2O$ (3 × 30 ml). The organic layers were combined, washed with water and brine and dried over $Na_2SO_4$. Removal of the solvent *in vacuo* and purification of the residue by column chromatography (silica gel, 2 × 25 cm, light petroleum–$CH_2Cl_2$ 3:1) gave (*R*)-(−)-**5a** (27.0 mg, 84%) as a colourless oil, $[\alpha]_D$ −61.5 (*c* 2.30, $CHCl_3$, 20 °C, 91% ee according to GC). GC [octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin (50% in OV 1701 w/w), 25 m, 70–100 °C, 1 °C $min^{-1}$, 50 kPa]: 13.1 min (*S*)-**5a**, 14.4 min (*R*)-**5a**.

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