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

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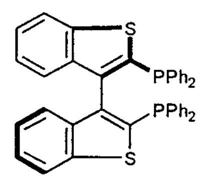
The Heck reaction of dihydrofuran 3 with aryl triflates 4 and 6a–d and alkenyl triflate 8 in the presence of the chiral ligand (*R*)-BITIANP 1 provides the 2-substituted 2,3-dihydrofurans 5a, 7a–d and 9, respectively, with complete regioselectivity, high enantioselectivity (86–96% ee) and good yields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



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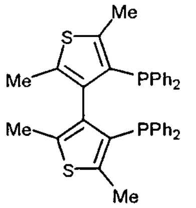

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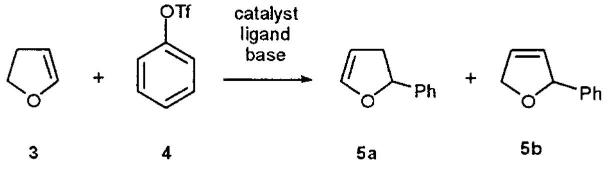
To allow a comparison with other chiral ligands we investigated the Heck reactions of dihydrofuran **3** with the triflates **4**, **6a–d** and **8**. In principle, the Heck reaction of dihydrofuran **3** with phenyl triflate **4** leads to the two isomers **5a** and **5b** (Scheme 1). Using BINAP[7] 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$_2$dba$_3$·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$^i_2$NEt 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

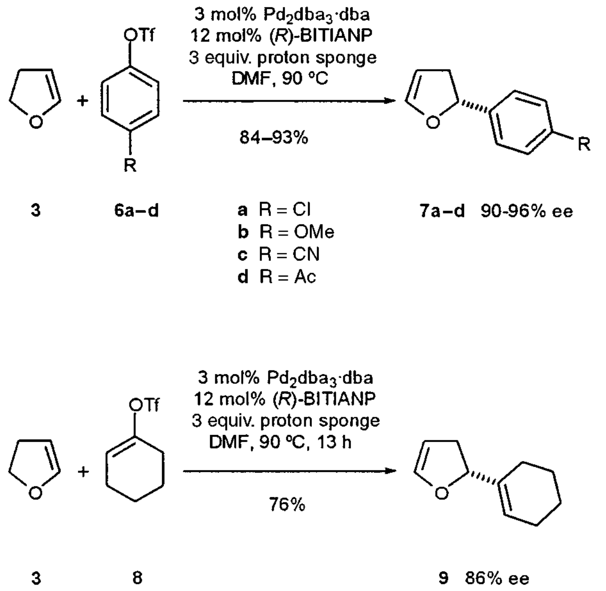


Scheme 1

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

	Pd$_2$dba$_3$·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$^i_2$NEt (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$^i_2$NEt (3).	DMF	90	3 d	< 1:100	1:2	27	58	4	2
6	5	TMBTP **2** (10)	Pr$^i_2$NEt (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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