ORGANIC LETTERS

2011
Vol. 13, No. 12
3250–3253

Efficient Route to Atropisomeric Ligands — Application to the Synthesis of MeOBIPHEP Analogues

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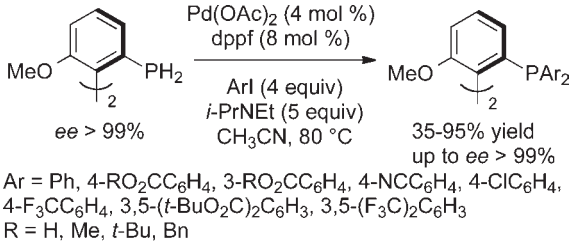
Received May 4, 2011

ABSTRACT



A highly efficient Pd-catalyzed P−C coupling reaction of easily accessible atropisomeric bisphosphane is described in the presence of various electron-poor aromatic iodides. The reactions are conducted in the presence of a Pd(II)/dppf catalyst in acetonitrile at 80 °C. The reaction conditions are compatible with several electron-withdrawing groups such as esters, cyano, chloro, and trifluoromethyl groups and lead to atropisomeric MeOBIPHEP derivatives in good to excellent yields and high enantiomeric purities.

The design of novel chiral ligands has been a field of constant interplay since the discovery of the atropisomeric binaphthyl Binap ligand.[1] Binap has been the leading ligand for asymmetric C−C and C−H bond formations for a long time, and its industrial preparation has been a source of inspiration for organic chemists.[1] Considering some technological and industrial barriers, new atropisomeric ligands appeared in the literature and have been the essential chiral inducers of important breakthroughs on asymmetric catalysis.[2] One general aspect of atropisomeric ligands is their synthesis, which is based on two main general strategies: the first one implies a Pd- or Ni-catalyzed phosphorus−carbon bond formation starting from bistriflate derivatives (Scheme 1, eq 1),[3] whereas the second one involves Grignard addition to phosphane intermediates (Scheme 1, eq 2).[4] Both ways have been highly successful but generally are dependent on either a resolution of racemate and/or a reduction of phosphane oxide. Our ongoing research program on asymmetric metal-

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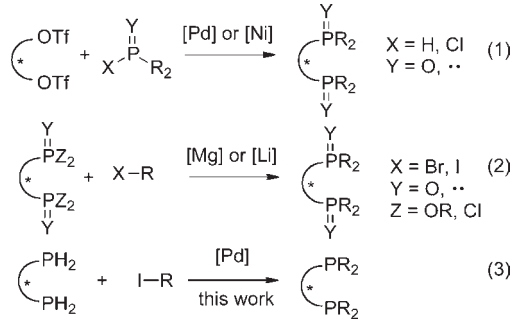
10.1021/ol2011874
Published on Web 05/23/2011

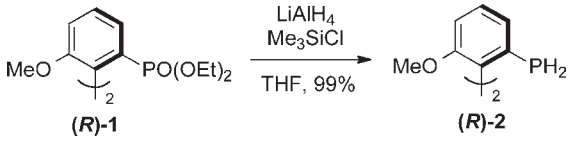
catalyzed reactions[5−7] prompted us to examine the unprecedented possibility to prepare atropisomeric ligands starting from a simple chiral primary bisphosphane derivative (Scheme 1, eq 3). We wish therefore to report our preliminary results on the optimization of a catalytic system able to promote the synthesis of so far unprecedented MeOBIPHEP analogues.[7f]

Scheme 1. General Strategies for the Synthesis of Atropisomeric Ligands



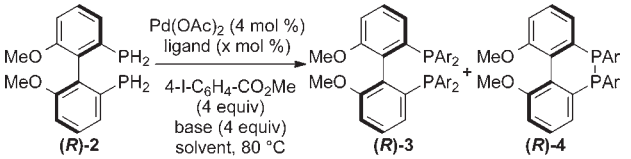
One issue for the success of this reaction has been the accessibility to both (*R*) and (*S*) enantiomers of the primary bisphosphane **2**. Gratifyingly the availability of bisphosphonate **1** on a large scale[7c] allowed us to prepare **2** in up to a 20 g scale by a simple reduction (Scheme 2).[7f,8]

Scheme 2. Synthesis of Phosphane Ligand **2**



We next concentrated our efforts on the preparation of diphosphanes containing electron-poor aromatic rings, whose introduction according to the classic Grignard methodology is delicate, requires a low temperature, and generally is moderate-to-low yielding.[7c] The reactivity of **2** was also particularly tricky as easy racemization occurs at a moderate temperature.

Table 1. Pd-Catalyzed P−C Coupling Reactions[a] (Ar = 4-CO_2Me-C_6H_4)



entry	ligand	*x* (mol %)	base	time (h)	**3**/**4** (%)	yield[b] of **3** (%)
1	/	/	Et_3N	48	97/3	31
2	PPh_3	12	Et_3N	48	95/5	31
3	*t*-Bu_3P[c]	12	Et_3N	20	0/100[d]	/
4	P(4-$CF_3C_6H_4)_3$	12	*i*-Pr_2NEt	20	79/21[d]	37
5	dppe	8	Et_3N	20	47/53[d]	/
6	dppf	8	*i*-Pr_2NEt	18	90/10	67
7	dppf	4	*i*-Pr_2NEt	18	60/40[d]	/
8	dppf	12	*i*-Pr_2NEt	18	40/60[d]	/
9[e]	dppf	8	*i*-Pr_2NEt[f]	3	94/6	83

[a] Determined by ^{31}P NMR. [b] Isolated yield. [c] Used as the HBF_4 salt. [d] Presence of several byproduct. [e] Slow addition of the primary bisphosphane ligand **2**. [f] 5 equiv.

Our initial attempts to couple **(*R*)-2** and methyl 4-iodobenzoate using Ni-, Pd-, or Cu-catalyzed phosphorus−carbon procedures[9] were quite disappointing as only traces of the desired product were detected. The use of palladium diacetate[9a] without additional ligands in solvents such as DMF, toluene, DMA, and CH_3CN afforded the desired phosphane **(*R*)-3** with moderate to good conversion, the best result being observed in acetonitrile in the presence of triethylamine (Table 1, entry 1). We therefore tested various ligands and bases to promote the introduction of four aromatic rings. In all cases, we observed the formation of a novel chiral dibenzo[1,2]diphosphorin derivative **(*R*)-4**, most probably resulting from a dehydrocoupling between the two RPHAr moieties of the reaction

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intermediate. The addition of triphenylphosphane, hindered tri-*tert*-butylphosphane, or electron-poor tri(4-trifluorophenyl) phosphane (entries 2–4) did not lead to better results. The use of bidentate ligands such as (bis)diphenylphosphanoethane (dppe) afforded approximately a 1/1 ratio of **3** and **4** (entry 5). (Bis)diphenylphosphanoferrocene was found to have a consistently positive influence on the reaction outcome (entries 6–9).[10] Finally, a thorough optimization of the amount of dppf and of the reaction conditions (slow addition of **2**) led to the formation of the desired ligand **(*R*)-3** in 83% isolated yield (entry 9), with no racemization (*ee* = 99%, cf. Supporting Information).

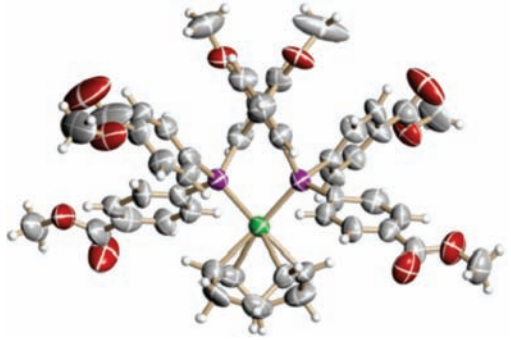


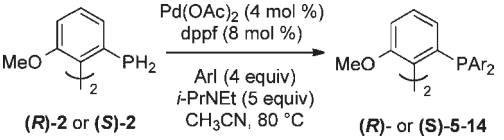
Figure 1. X-ray structure of [Rh((*S*)-**3**)(cod)]BF_4 complex.

The structure of **3** was unambiguously confirmed by reacting **(*S*)-3** with $[Rh(cod)Cl]_2$ and silver tetrafluoroborate in dichloromethane at room temperature. The resulting rhodium complex [Rh((*S*)-**3**)(cod)]BF_4 was analyzed by X-ray spectroscopy (Figure 1 and Supporting Information).

The bisphosphane ligand **2** was then engaged in various Pd-catalyzed coupling reactions in the presence of ester, cyano, carboxylic acid, chloro, and trifluoromethyl substituted aryl iodides (Table 2). Methyl, *tert*-butyl, and benzyl ester functionalized ligands **5**–**8** (either *R* or *S*) (entries 1–5) were isolated in good-to-excellent yields (82–95%) and high enantiomeric purities (>98%). The reaction conditions were compatible with free carboxylic acid moieties, the corresponding tetra acid ligand **(*R*)-9** being isolated in 70% yield (entry 6). Considering the importance for catalysis of the C-3 and C-5 disubstitution on the aromatic ring of the PAr_2 moieties,[11] we attempted the preparation of such ligands according to this methodology.

Gratifyingly, 3,5-disubstituted *tert*-butyl ester and trifluoro-methyl iodobenzenes were found to react extremely well too (entries 10–13), and the corresponding ligands were prepared in high yields and an enantiomeric purity higher than 99%. The ligand **14** had already been prepared

Table 2. Pd-Catalyzed P–C Coupling Reactions

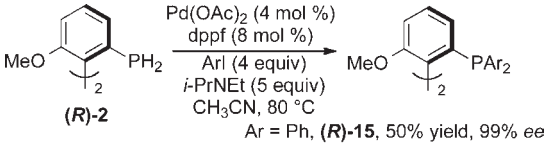


(*R*)-**2** or (*S*)-**2** → (*R*)- or (*S*)-**5-14**

entry	Ar	ligand	yield[a] (%)	*ee*[b] (%)
1	3-MeO_2C-C_6H_4	(*R*)-**5**	94	98
2	4-*t*-BuO_2C-C_6H_4	(*R*)-**6**	88	99
3	4-*t*-BuO_2C-C_6H_4	(*S*)-**6**	82	99
4	3-*t*-BuO_2C-C_6H_4	(*R*)-**7**	95	98
5	4-BnO_2C-C_6H_4	(*R*)-**8**	92	99
6	4-HO_2C-C_6H_4	(*R*)-**9**	70	>99
7	4-NC-C_6H_4	(*R*)-**10**	89	>99
8	4–Cl-C_6H_4	(*R*)-**11**	35	99
9	4-F_3C-C_6H_4	(*R*)-**12**	89	99
10	3,5-(*t*-BuO_2C)$_2$-C_6H_3	(*R*)-**13**	76	>99
11	3,5-(*t*-BuO_2C)$_2$-C_6H_3	(*S*)-**13**	67	>99
12	3,5-(F_3C)$_2$-C_6H_3	(*R*)-**14**	74	99
13	3,5-(F_3C)$_2$-C_6H_3	(*S*)-**14**	74	99

[a] Isolated yield. [b] Determined by HPLC analysis (cf. Supporting Information).

Scheme 3. Synthesis of MeOBIPHEP Analogues



(*R*)-**2** → Ar = Ph, (*R*)-**15**, 50% yield, 99% *ee*; Ar = 3,5-$Me_2C_6H_3$, (*R*)-**16**, 42% yield, 99% *ee*

at Roche according to the Grignard strategy (three-step synthesis) and had been isolated in 20% yield starting from the bisphosphonate **1**.[7c] Using this new route, the (*R*) and (*S*) analogues **14** were obtained in 74% isolated yield (entries 12, 13).

We further challenged our methodology for the preparation of other ligands which do not possess electron-attracting groups on the phenyl substituents at phosphorus such as the parent ligand MeOBIPHEP[7b–d] or its congener 3,5-Me_2-MeOBIPHEP,[7c] whose importance has been recently highlighted in the area of gold catalysis[12,13] (Scheme 3). These ligands were obtained in lower yields (50 and 42%, respectively) compared to the analogues reported in Table 2. This synthetic strategy, however, could probably

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compete with the industrial one in terms of step economy, production of waste, and overall yields.

In conclusion, we have demonstrated that atropisomeric ligands bearing electron-deficient aromatic rings on phosphorus atoms can be prepared under mild catalytic conditions starting from a chiral biphenyl bisphosphonate. The corresponding MeOBIPHEP analogues were isolated in high yields and excellent enantiomeric purities. This methodology opens new perspectives for the design and synthesis of novel chiral ligands. Current studies are dedicated to the applications of these ligands in asymmetric catalysis.

Acknowledgment. L.L. and F.LBH are grateful to the CNRS and F. Hoffmann-La Roche AG for financial support. Helpful discussions with R. Schmid and the analytical support by J.-C. Jordan, M. Althaus, and A. Alker (all F. Hoffmann-La Roche AG, Basel) are kindly acknowledged.

Supporting Information Available. Experimental procedure and full analyses of ligands **3**–**16**. This material is available free of charge via the Internet at http://pubs.acs.org.