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Short communication

Synthesis of atropisomeric chiral MeOBIPHEP analogues via Pd-catalyzed P–C coupling — applications to asymmetric Rh-catalyzed C–C bond formations in water

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ABSTRACT

The preparation and catalytic applications of water-soluble MeOBIPHEP-based atropisomeric chiral congener ligands are described. The optimization of the catalytic system to promote the key P–C coupling revealed the superiority of palladium catalysts versus nickel or copper. Spectroscopic studies of the Pd-catalyzed reaction medium showed the presence of phosphorylated intermediates. The asymmetric Rh-catalyzed 1,4-addition of boronic acids to enones in water was described in the presence of water-soluble MeOBIPHEP derivatives. The 4-CO_2Na-, 3-CO_2Na- and 3,5-$(CO_2Na)_2$-substituted MeOBIPHEP analogues showed high and complementary reactivities and enantioselectivities, considering either the enone or the boronic acid.

1. Introduction

The demand for efficient synthetic methodologies proceeding with atom economy has been increasing constantly along with the need of optically active compounds from the chemical industry [1]. In this field, chiral ligands, and more specifically atropisomeric ligands since the discovery of atropisomeric binaphthyl BINAP, have proven to be outstanding chiral inducers [2,3]. The main strategies for their synthesis involved a Grignard addition to a phosphane intermediate [4], a Pd- or Ni-catalyzed phosphorus–carbon bond formation starting from bistriflate derivatives [5,6] or a chiral phosphonate and an aryl Grignard reagent [7,8]. These three strategies have been highly successful and have led to the development of an important number of new ligands. However, drawbacks such as resolution of racemate and reduction of phosphane oxide often cannot be avoided. Our ongoing research program on asymmetric metal-catalyzed reactions [9,10] prompted us to develop a novel synthesis of atropisomeric ligands starting from simple chiral primary bisphosphonate derivative [11,12]. Whereas a flurry of chiral ligands has been developed by original methods, the development of chiral hydrophilic ligands has been less studied, most probably because it generally relied on complicated multistep syntheses [13,14]. On the other hand, due to its obvious economic and environmental advantages, the use of water as a reaction medium is still challenging in modern chemistry [15–17]. Chiral diphosphanes bearing sulfonated water-soluble moieties [18,19], in particular MeOBIPHEP analogues developed at Roche [7] have for example been used in aqueous media hydrogenation reactions. We wish to report therein that our study on the optimization of the catalytic system enables to promote the synthesis of water-soluble MeOBIPHEP analogues and their catalytic activities towards asymmetric metal-catalyzed carbon–carbon bond formation reactions in water.

2. Results and discussion

The primary phosphane (***R***)-**1** was available on a 20 gram scale, via a quantitative reduction of the Roche industrially prepared bisphosphonate [12]. Table 1 compiles the attempts for Ni-, Cu- and Pd-catalyzed P–C couplings of (***R***)-**1**, the reactions being followed by ^{31}P NMR (see supplementary material for selected spectra). The first attempt for the phosphorus–carbon coupling using a Ni catalyst [20] in the presence of (***R***)-**1** and 4-methylphenyltriflate gave poor results as only traces of the desired product was detected (entry 1). Considering the high temperature for such coupling, we turned our attention to copper catalysts [21,22]. Under the reported reaction conditions for the

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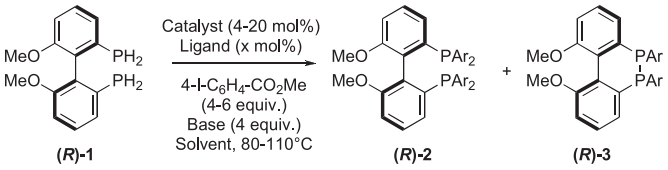
Table 1
Metal-catalyzed P–C coupling.



Entry	Catalyst (mol%)	Ligand (mol%)	Solvent	Base	2/3 (%)[a]	Yield of 2[b]
1[c]	$NiCl_2$(dppe) (10)	/	DMF	DABCO	/	/
2	CuI (20)	DMEDA (40)	Toluene	Cs_2CO_3	100/0	8
3[d]	CuI (20)	DMEDA (40)	Toluene	/	0/100	/
4[d]	CuI (20)	DMEDA (40)	Toluene	Cs_2CO_3	100/0	15
5	CuI (20)	DMEDA (20)	Toluene	Cs_2CO_3	100/0	18
6	CuI (20)	/	Toluene	Cs_2CO_3	100/0	15
7	$Pd(OAc)_2$ (4)	/	DMF	Et_3N	13/87	/
8	$Pd(OAc)_2$ (4)	/	Toluene	Et_3N	60/40	/
9	$Pd(OAc)_2$ (4)	/	DMA	Et_3N	85/15	30
10	$Pd(OAc)_2$ (4)	/	CH_3CN	Et_3N	97/3	31
11	$Pd(PPh_3)_4$ (4)	/	DMF	Et_3N	33/67	5
12	$Pd(PPh_3)_4$ (4)	/	Toluene	Et_3N	100/0	24
13	$Pd(PPh_3)_4$ (4)	/	CH_3CN	Et_3N	73/27	17
14	$Pd(OAc)_2$ (4)	/	CH_3CN	n-Bu_3N	68/32	/
15	$Pd(OAc)_2$ (4)	/	CH_3CN	i-Pr_2NEt	85/15	41
16	$Pd(OAc)_2$ (4)	PPh_3 (12)	CH_3CN	Et_3N	95/5	31
17	$Pd(OAc)_2$ (4)	P(t-Bu)$_3$HBF$_4$ (12)	CH_3CN	Et_3N	0/100	/
18	$Pd(OAc)_2$ (4)	dppe (8)	CH_3CN	Et_3N	47/53	/
19	$Pd(OAc)_2$ (4)	dppf (8)	CH_3CN	Et_3N	81/19	40
20	$Pd(OAc)_2$ (4)	dppf (8)	CH_3CN	i-Pr_2NEt	90/10	61
21	$Pd(OAc)_2$ (4)	dppf (4)	CH_3CN	i-Pr_2NEt	60/40	/
22	$Pd(OAc)_2$ (4)	dppf (12)	CH_3CN	i-Pr_2NEt	40/60	/
23[d]	$Pd(OAc)_2$ (4)	dppf (8)	CH_3CN	i-Pr_2NEt	100/0	57
24[e]	$Pd(OAc)_2$ (4)	dppf (8)	CH_3CN	i-Pr_2NEt	94/6	83

[a] Determined by ^{31}P NMR.
[b] Isolated yield.
[c] 4-Me-C_6H_4OTf was used instead of ArI, 130 °C.
[d] 6 equivalents of ArI.
[e] Slow addition of ArI.

synthesis of monophosphanes, we observed the disappearance of starting material but the desired product was isolated only in a low 8% yield (entry 2). The presence of the base was crucial as the reaction led to the formation of another product, biarylphosphine (***R***)-**3** (9% isolated yield), instead of the desired derivative (***R***)-**2** in the absence of Cs_2CO_3 (entry 3). Modifying the reaction conditions, such as the number of equivalents of aryl iodide or DMEDA ligand led to similar results (entries 4–6). The formation of the desired product was observed in concomitance with several non-identified species, such that (***R***)-**2** could be isolated in 15% to 18% yield. We therefore turned our attention to palladium-catalyzed P–C couplings [23–25]. The use of palladium diacetate in the presence of triethylamine afforded a mixture of the desired product (***R***)-**2** and the compound (***R***)-**3** in various ratios depending on the solvent (DMF, toluene, DMA or acetonitrile) (entries 7–10). The best results were obtained in DMA and acetonitrile, giving the highest **2**/**3** ratio, but leading to several by-products and disappointingly low isolated yields. The use of $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ did not give better results (entries 11–13). Other bases such as tri-*n*-butylamine and di-isopropylethylamine were also tested in lieu of triethylamine and an encouraging 41% isolated yield was obtained in the latter case (entries 14–15). The addition of triphenylphosphane or hindered tri-*tert*-butylphosphine (entries 16–17) did not lead to better results. The use of a bidentate ligand such as diphenylphosphinoethane afforded approximately a 1/1 mixture of phosphanes (***R***)-**2** and (***R***)-**3** (entry 18), whereas the use of diphenylphosphino ferrocene had a consistent positive influence on the reaction outcome (entry 19).

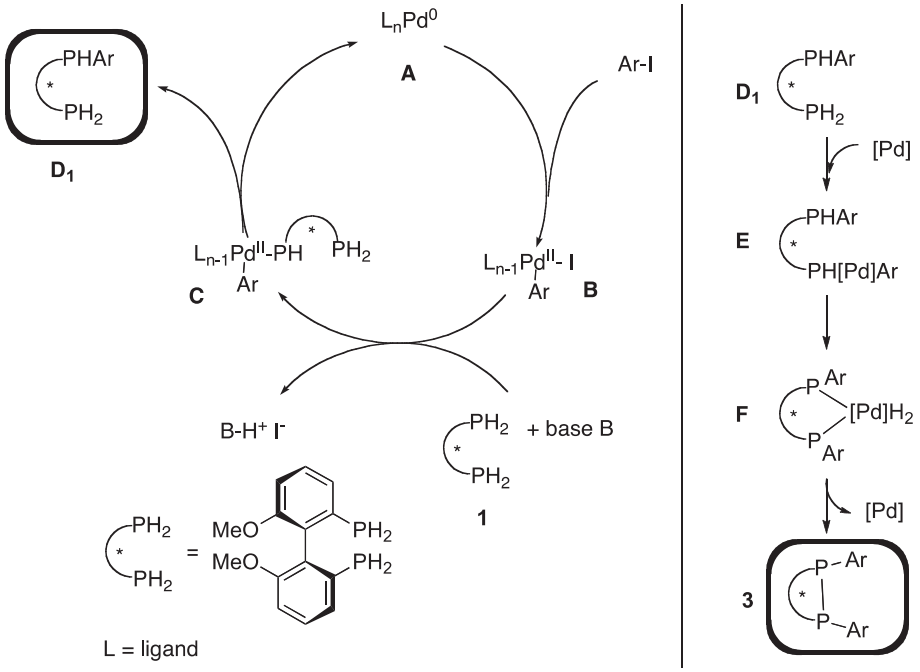
The use of di-isopropylethylamine was beneficial to the (***R***)-**2**/(***R***)-**3** ratio and the desired product was isolated in 61% yield (entry 20). The catalytic amount of the ligand was optimized, the best result being observed using 8 mol% of diphenylphosphino ferrocene, 4 equivalents of di-isopropylethylamine, and 4 equivalents of methyl 4-iodobenzoate (entries 20–22). Increasing the amount of aryliodide did not give much better results (entry 23), whereas slow addition of the iodide partner allowed the formation of the desired ligand in 83% isolated yield and an excellent selectivity (entry 24). These observations and the results reported in the literature [23–25] led us to postulate the mechanism described in Scheme 1. The active Pd(0) species would be generated by analogy to the $Pd(OAc)_2$/PPh_3 system [26], where an excess of reductant (amine or phosphane) present in the reaction media would enable the transformation of Pd(II) into Pd(0). The oxidative addition of the aryl iodide would lead to the intermediate **B** that would then undergo a ligand exchange. The nucleophilic assistance of the base would allow the iodide ligand to be exchanged with a phosphido group from the primary phosphane **1** to generate the intermediate **C**. A reductive elimination step would free the ligand $\mathbf{D_1}$ and regenerate the active Pd(0) specie **A**. The repetition of this process would allow the insertion of four aromatic rings on the phosphorus atoms to give ligand **2**. Noteworthy that the intermediate species containing only 1–3 aryl substituents on phosphorus do not have to de-coordinate to continue in the catalytic cycle but could well remain coordinated.

The formation of the side product **3** could be explained by a dehydro-coupling step, observed in the literature on simpler phosphanes [27]. Based on the results described in the literature, the dehydro-coupling step between the two phosphorus atoms would occur after the insertion of an aromatic ring on $\mathbf{D_1}$ intermediate leading to complex **E**, which would evolve towards the bis-phosphido species **F**. The steric vicinity between the phosphorus atoms on intermediate **F** would then enable the dehydro-coupling leading to **3**.

Facing these encouraging results, we determined the optical purity of ligand **2** and, disappointingly, observed that starting from an enantiopure (*ee* > 95%) phosphonate total racemization had occurred leading to the formation of *rac*-**2**. The racemization process seemed more likely to occur during the P–C coupling step at 80 °C than during the reduction step of the bisphosphonate into (***R***)-**1** at −78 °C. The Pd-catalyzed coupling was monitored by ^{31}P NMR (see supplementary material for details) revealed, as anticipated, the presence of several intermediates. A slow and progressive addition of (***R***)-**1** to the reaction media allowed its rapid consumption with no racemization process. We selected *para*- and *meta*-ester substituted aryl iodides for the preparation of water-soluble ligands (Scheme 2). Under the optimized reaction conditions, ligands (***R***)-**4**, (***R***)-**5**, and (***R***)-**6** were isolated in good to excellent yields (76–88%) along with excellent enantioselectivities (>98% *ee*) [11].

In the presence of trifluoroacetic acid, the *tert*-butyl esters of ligands (***R***)-**4**–**6** were quantitatively transformed into carboxylic acids [12]. The corresponding salts were obtained by the addition of sodium hydride allowing the synthesis of water-soluble ligands (***R***)-**7a–c** in high overall yields. In order to evaluate the influence of the sodium carboxylate water-soluble groups, we also prepared the corresponding alcohols and sodium alcoholates (***R***)-**8a–c** via a reduction/deprotonation sequence.

There are still few examples of asymmetric metal-catalyzed carbon–carbon bond formation reactions in water [12–19], which encouraged us to test the prepared water-soluble ligands in the Rh-catalyzed addition of phenylboronic acid to enones (cyclopentenone, cyclohexenone and cycloheptenone, Table 2) [28,29]. The choice of this Rh-catalyzed reaction was also motivated by the fact that both organoaqueous and aqueous conditions were compatible with several atropisomeric ligands [30,31]. Most of the chiral MeOBIPHEP analogues led to similar results under classic conditions compared to BINAP ligand [32]. We selected some conditions involving Na_2CO_3 in water as we and others have shown that it can accelerate the reaction kinetic [33–35]. We screened

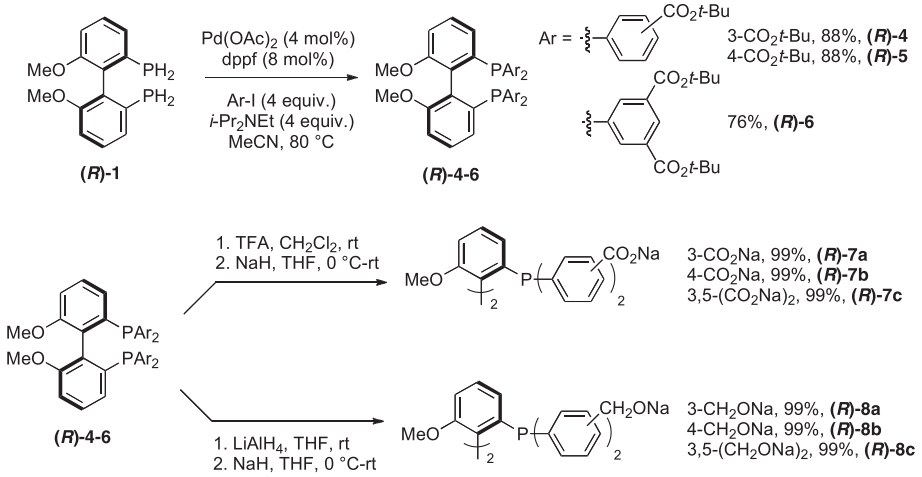


Scheme 1. Reaction mechanism proposal.

the efficiency of ligands (***R***)-**7a–c** and (***R***)-**8a–c** to evaluate the influence of the water-soluble groups and their position relative to the aromatic ring of the phosphorus ligand.

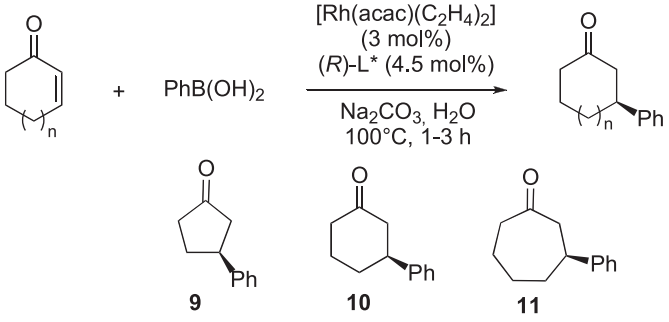
The 1,4-addition of phenylboronic acid to enones proved to be very substrate- and ligand-dependent. In all cases, the higher efficiency of the ligands bearing a carboxylated group such as (***R***)-**7a–c**, was demonstrated comparing to those bearing an alcoholate moiety (***R***)-**8a–c** (entry 1 versus 2, entry 2 versus 3 and entry 5 versus 6). In the case of cyclopentenone, the *para*-substituted ligand (***R***)-**7b** was found to be the best water-soluble ligand as the corresponding ketone was isolated in 99% yield and 90% *ee* (entry 3, compound **9**). Increasing the hindrance on the aromatic ring of the phosphorus atoms afforded a slow decrease of the enantiomeric excess (entries 1 and 5, compound **9**). The reaction of cyclohexenone was less surprising and followed the expected tendency: the highest enantiomeric excess was obtained in the presence of the 3,5-disubstituted ligand (***R***)-**7c**. The corresponding arylated ketone **10** was isolated in 96% enantiomeric excess (entry 5). In the case of cycloheptenone, we performed the addition of the phenylboronic acid to the enone with all the three carboxylated ligands and observed that the best ligand was this time the mono-*meta*-substituted one (***R***)-**7a** (entry 1, compound **11**). The 7-membered ring ketone **11** was isolated in 96% enantiomeric excess instead of 90% in the presence of (***R***)-**7c** (entry 5). Pleasingly, each of the three carboxylated-substituted ligands could therefore be valorized for Rh-catalyzed arylation of 5-membered to 7-membered ring enones.

We then studied the influence of the aryl boronic acid in the Rh-catalyzed arylation in water and more specifically the influence of the electronic and steric effects for the cyclohexenone (Scheme 3). Boronic acids bearing electron-donating or withdrawing groups (MeO, Cl and CF_3) reacted smoothly under the same conditions with cyclohexenone



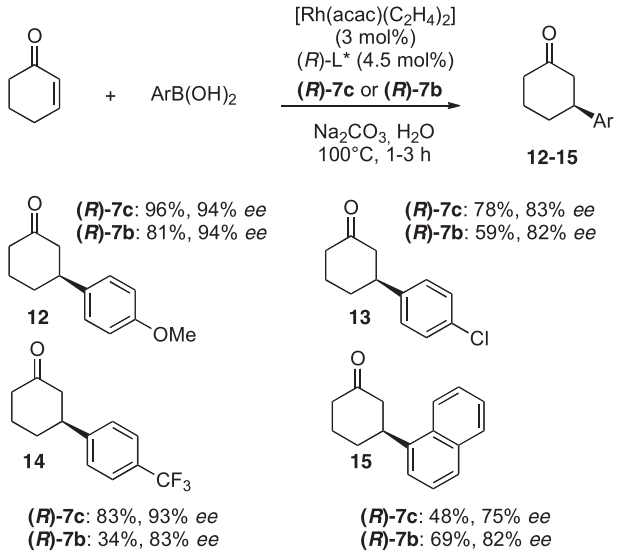
Scheme 2. Synthesis of water-soluble ligands.

Table 2
Rh-catalyzed addition of phenylboronic acid to enones.



Entry	(*R*)-L*	9 (% yield, % *ee*)	10 (% yield, % *ee*)	11 (% yield, % *ee*)
1	CO_2Na (***R***)-**7a**	89, 88	99, 95	83, 96
2	CH_2ONa (***R***)-**8a**	95, 76	99, 64	78, 54
3	CO_2Na (***R***)-**7b**	99, 90	99, 93	86, 75
4	CH_2ONa (***R***)-**8b**	97, 60	99, 68	85, 38
5	CO_2Na (***R***)-**7c**	99, 82	99, 96	99, 90
6	CH_2ONa (***R***)-**8c**	97, 80	99, 84	91, 80

substrate in the presence of ligand (***R***)-**7c** and led to the corresponding ketones **12**–**15** with enantiomeric excesses superior to 80%, the best result being observed in the case of the methoxy- and trifluoromethyl-substituted boronic acid (94% and 93% *ee* respectively). Either lower enantiomeric excesses or lower yields were observed in the presence of the *para*-carboxylated ligand (***R***)-**7b** except in the case of a hindered boronic acids such as the 1-naphthylboronic acid. The use of the hindered ligand (***R***)-**7c** afforded the corresponding ketone **15** in 75% *ee* whereas the use of the *para*-substituted ligand (***R***)-**7b** gave higher yield and enantiomeric excess, 69% and 82% respectively.



Scheme 3. Influence of the arylboronic acid.

3. Conclusion

We have extended the methodology developed for the preparation of MeOBIPHEP-based atropisomeric chiral congener ligands. The optimization of the catalytic system to promote the key P–C coupling revealed the superiority of palladium catalysts versus nickel or copper. During the study of the asymmetric Rh-catalyzed 1,4-addition of boronic acids to enones in water, the best ligands were found to be the carboxylated-substituted ones. The 4-CO_2Na-, 3-CO_2Na- and 3,5-$(CO_2Na)_2$-substituted MeOBIPHEP analogues showed high and complementary reactivities and enantioselectivities, regarding either the enone or the boronic acid. Further studies will be dedicated to the study of other catalytic applications of substituted ligands based on the MeOBIPHEP skeleton.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2015.06.005.

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