Further insight into the mechanism of Heck oxyarylation in the presence of chiral ligands

Loránd Kiss,[a] Tibor Kurtán,[a] Sándor Antus,[a] Henri Brunner[b]

[a]Department of Organic Chemistry, University of Debrecen, P.O.Box 20, H-4010 Debrecen, Hungary
[b]Institut für Anorganische Chemie, Universitat Regensburg, 93040 Regensburg, Germany
E-mail: antuss@tigris.klte.hu

Dedicated to Professor Gábor Bernáth on his 70th birthday

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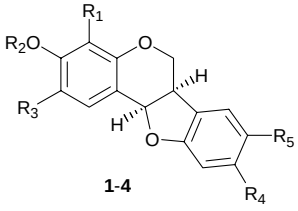
Abstract

The Heck oxyarylation reaction to 3-benzyloxypterocarpan (**15**) has been studied in the presence of chiral phosphine ligands, a chiral ionic liquid and (+)-α-pinene. The observed small selectivities suggest that this reaction takes place through parallel pathways and the main pathway involves an achiral intermediate **11** where the chirality introduced by the chiral ligands is lost. Although practical asymmetric Heck oxyarylation to chiral pterocarpans could not be achieved, a convenient Heck-oxyarylation synthesis of *rac*-**15** with (+)-α-pinene as ligand gave the highest yield reported to this type of reactions.

Keywords: Pterocarpan, asymmetric Heck oxyarylation, ionic liquid, chiral ligand

Introduction

Pterocarpans, carrying a *cis*-fused benzofuranyl-benzopyran skeleton, form the second largest group of naturally occuring isoflavonoids. Many of their derivatives exhibit remarkable pharmacological activity such as antifungal, antibacterial[1] and anti-HIV effects.[2] Nakanishi and co-workers[3] also demonstrated that two representatives of these natural products, cabenegrin A-(I) (**1**) and cabenegrin A-(II) (**2**), showed activity against snake and spider venom but their mode of action is still to be explored.



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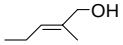
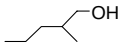
	R_1	R_2	R_3	R_4	R_5
1		H	H	-OCH_2O-	
2	H	H		-OCH_2O-	
3	H	H	H	-OCH_2O-	
4	H	Bn	H	-OCH_2O-	

Although we have published[4] the total synthesis of (-)-6a*R*,11a*R*-1 *via* (-)-6a*R*,11a*R*-maackiain [(-)-**3**], the synthesis of (-)-**3** suffered from limitations such as (i) the need of equimolar amounts of palladium(II) salt in the Heck-oxyarylation reaction of 7-benzyloxy-2*H*-chromene (**13**) and 2-chloromercury-3,4-methylenedioxyphenol resulting in the racemic precursor **4** in 53% yield and (ii) the low yield in the resolution of *rac*-maackiain (**3**). Recently, a convenient modification of this Heck-oxyarylation step has also been described[5,6] by the replacement of the toxic chloromercury-phenol derivatives with 2-iodophenols which allowed to considerably decrease the amount of the expensive palladium(II) salt (from 100 mol % to 10 mol %) in the presence of triphenylphosphine and silver carbonate in acetone or in ionic liquids such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]).

Although intermolecular Heck oxyarylation is widely used in the synthesis of racemic pterocarpans[7-10], in contrast to the conventional Heck reaction[11-14], its mechanism is not fully understood. It presumably proceeds also *via* the generation of active Pd(0), oxidative addition of the aryl iodide to Pd(0), followed by regioselective *syn*-addition of **6** to **7** and palladium displacement by the phenolic oxygen whose details are not known (Figure 1).

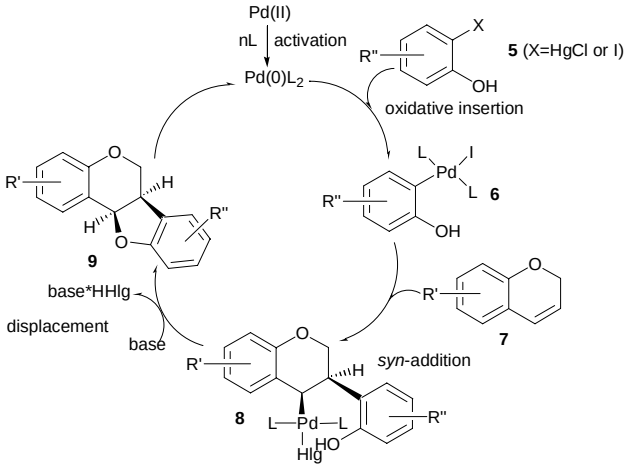


Figure 1. Proposed sequence of Pd catalyzed oxyarylation.

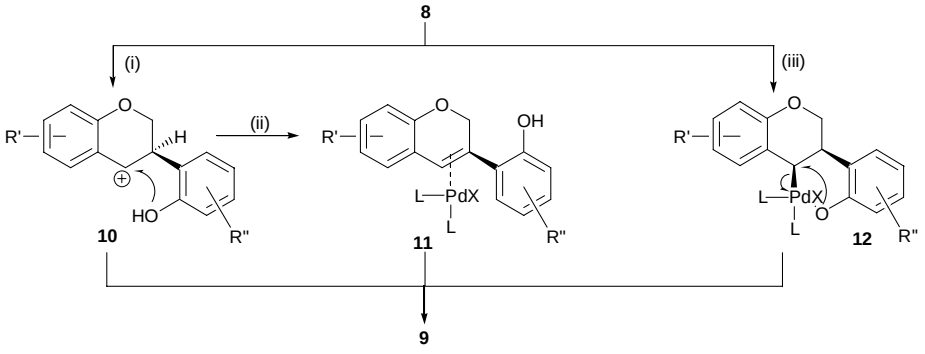
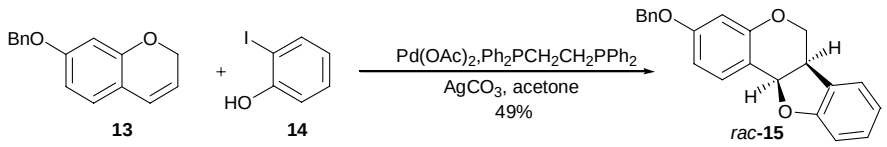


Figure 2. Possible pathways of the displacement step.

On the basis of the data published in the literature,[15] the displacement step may take place *via* (i) cationic (**10**), (ii) neutral (**11**) or a palladium containing cyclic intermediate (**12**) as shown in Figure 2. In order to investigate the mechanism of this step (8→9), we envisaged the study of this process in the presence of chiral ligands. Thus, if this step is carried out through the pathway (i) (**8→10→9**) or pathway (iii) (**8→12→9**) an asymmetric Heck-oxyarylation synthesis of pterocarpans 9 will be achieved.

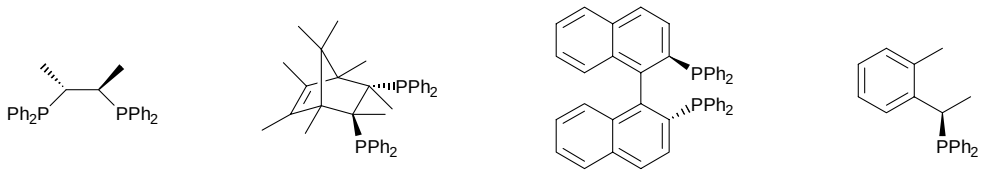
Results and Discussion

Since the Heck oxyarylation reaction of 7-benzyloxy-2*H*-chromene (**13**) and 2-iodophenol (**14**) has been already performed by two of us using 1,2-bis(diphenylphosphino)ethane (dppe) as ligand and Ag_2CO_3 as base[5] (Scheme 1) it could be expected that the change of 1,2-bis(diphenylphosphino)ethane to optically active phosphine ligands could result in optically active **15**.



Scheme 1

Three chiral bidentate phosphine ligands; 2*R*,3*R*(+)-bis(diphenylphosphino)butane (CHIRAPHOS) (**16**)[16], *trans*-2*S*,3*S*-bis(diphenylphosphino) bicyclo[2.2.1]hept-5-ene (NORPHOS) (**17**)[17], *R*(+)-bis(diphenylphosphino)binaphthyl [(*R*)-BINAP] (**18**)[18] and a monodendate phosphine ligand, namely, *R*-1-[2'-diphenylphosphino]phenyl-methoxyethane (**19**)[19] were selected for testing, based on literature data. It is noteworthy that asymmetric Heck reactions (AHRs) were usually accomplished by active palladium species generated *in situ* with chiral phosphine ligands which could often provide ee's more than 90%.



(2R,3R)-(+)-**16**
CHIRAPHOS

(2S,3S)-(+)-**17**
NORPHOS

(R)-(+)-**18**
(R)-BINAP

(R)-(+)-**19**
TRIPHOS

Regarding the stereoselectivity, the *syn*-addition step is considered to be the key one in the AHRs. This step can follow either a cationic or a neutral pathway and the former one is reported[20] to give better enantiomeric excesses. All the oxyarylation reactions were carried out with 3 equivalents of halophilic Ag_2CO_3 in order to sequester the iodide from the intermediate **8** and thus promote the favored cationic pathway. The enantiomeric purity of the obtained pterocarpan **15** was determined using chiral HPLC and the configurations of the baseline-

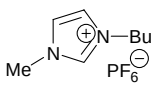
separated peaks were assigned on the basis of their elution order using our chiral recognition model.[21]

In contrast to the acceptable 49% yield of entry 1 (Table 1) when the achiral dppe was used as ligand, the reactions with chiral phosphine ligands gave very low yields (Table 1, entry 2-6) and very small selectivities (5-10%). It was found that the (*R*)-BINAP slightly favored the formation of (6a*R*,11a*R*)-15, while the CHIRAPHOS, NORPHOS and TRIPHOS slightly preferred the formation of the 6a*S*,11a*S* isomer. It was surprising that the commercially available chiral palladium complex Pd[(*R*)-BINAP]Cl_2 showed no selectivity at all and lead to racemic **15**.

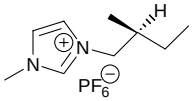
Table 1. Conditions used and results obtained in the transformation of 7-benzyloxychromene (**13**) and 2-iodophenol (**14**) to pterocarpan **15**

Entry	Catalyst	Ligand	Solvent	Reaction time (h)	Temp. (°C)	Yield (%)	ee (%)	Config. 6a,11a
1[5]	$Pd(OAc)_2$	dppe	A	22	56	49	-	-
2	$Pd(C_6H_5CN)_2Cl_2$	CHIRAPHOS	C	23	100	5	8	S,S
3	$Pd(OAc)_2$	NORPHOS	C	3	100	5	10	S,S
4	$Pd(OAc)_2$	R-BINAP	B	28	60	7	6	R,R
5	Pd[(R)-BINAP]Cl_2	-	B	46	60	9	-	-
6	$Pd(OAc)_2$	TRIPHOS	C	3	100	7	5	S,S
7[6]	$PdCl_2$	-	C	18	100	28	-	-
8	$Pd(OAc)_2$	-	D	4	100	13	5	R,R
9	$PdCl_2$	-	D	18	100	28	4	R,R
10	$Pd(OAc)_2$	PPh_3	D	2	100	45	-	-
11[6]	$Pd(C_6H_5CN)_2Cl_2$	PPh_3	C	4	100	45	-	-
12	$Pd(C_6H_5CN)_2Cl_2$	α(+)-pinene	A	24	56	40	-	-
13	$Pd(C_6H_5CN)_2Cl_2$	α(+)-pinene	C	2	56	71	-	-

A = acetone, B = THF, C= [bmim][PF_6], D = [bmim*][PF_6],

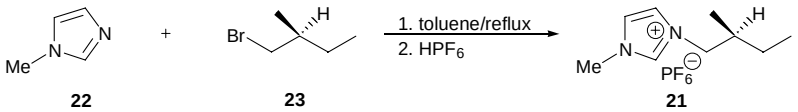


[bmim][PF6]
20



[bmim*][PF6]
21

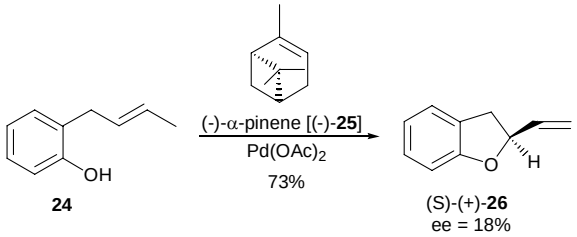
It was found earlier[22,23] that besides being a suitable solvent for Heck reactions, ionic liquids like [bmim][PF_6] could form a carbene-palladium complex, which turned out to be an active catalyst. Thus, in the presence of ionic liquids, the Heck oxyarylation could be achieved without phosphine ligands (entry 7). Therefore, it was expected that the use of a chiral ionic liquid may afford selectivity in the Heck oxyarylation. The chiral ionic liquid **21** was prepared from N-methylimidazole (**22**) and *S*(+)-1-bromo-2-methylpropane (**23**) (Scheme 2) and used as both chiral ligand and solvent in the synthesis of **15**.



Scheme 2

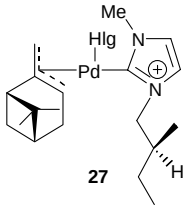
Although the yield of the transformation did not decrease drastically in entry **8** and **9** compared to entry **7**, the selectivities remained very low (see entry **8** and **9**). When triphenylphosphine was added (entry **9**) the yield increased significantly but the chiral induction was completely lost. This indicated that the chiral inductor **21** was completely exchanged by triphenylphospine in the palladium complex and the solvation of the chiral ionic liquid had no effect on the selectivity.

It was also reported by Hosokawa *et al*.[24] that the enantioselective ring closure of the phenol derivative **24** could be achieved with high yield when the complex of palladium acetate and (-)-α-pinene (**25**) was used as chiral catalyst.



Scheme 3

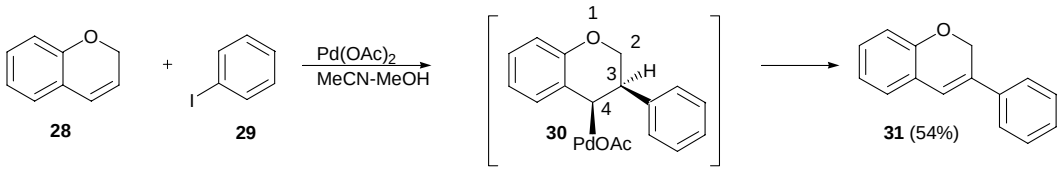
Thus, (+)-α-pinene was also tested as chiral ligand in our asymmetric Heck oxyarylation reaction with both acetone and the achiral ionic liquid [bmim][PF_6] as solvent (entry **12** and **13**). Although the reactions with (+)-α-pinene led to *rac*-**15**, these conditions provided the highest yield (71%) of *rac*-**15** obtained ever for the Heck oxyarylation reactions to pterocarpans.[5,7,8-10]



Comparing the yield of entry **12** with that of entry **13** it may be assumed that the (+)-α-pinene [(+)-**25**] and the palladium-acetate formed a π-allyl-palladium complex **27** which has better stability and solubility in the applied condition and proved a suitable catalyst system for the Heck-oxyarylation reaction with high turn-over number.

On the basis of the very small or the lack of selectivity obtained during our asymmetric Heck oxyarylations to levo- or dextrorotatory pterocarpans [(6a*R*,11a*R*)-**9** or (6a*S*,11a*S*)-**9**] the pathways (**8→10→9**) and (**8→12→9**) could be ruled out as main pathways. Therefore, one may suggest that the σ-benzylpalladium intermediate 8 (see Figure 1) is first transformed to the carbocation **8** and then the chirality introduced by the *syn*-addition step (**7+6→8**) is lost during

its transformation to the π-benzylpalladium complex **11** by the removal of 3-H that results in *rac*-pterocarpan **9**. The formation of a similar compound (**31**) was already reported[24] in the Heck reaction of 2H-chromene (**28**) and iodobenzene (**29**) where the ring closure of the corresponding σ-benzylpalladium intermediate (**30**) was not possible due to the lack of hydroxy group at C-2'.



Scheme 4

Our results strongly support that the formation of pterocarpan **9** mostly takes place through an achiral intermediate, which may be the intermediate **11**, and this is the reason for the unexpected small selectivities.

Experimental Section

General Procedures. All reagents and organic compounds used were purchased from Sigma-Aldrich. 7-benzyloxy-2*H*-chromene (**13**) and 1-butyl-3-methylimidazolium hexafluorophosphate (**20**) were prepared according to the known procedures.[26,27] 200 MHz ^{1}H-NMR spectra were recorded with a Bruker WP 200 SY instrument with TMS as internal standard. Precoated silica gel plates (Kieselgel 60 F 254, 0.25 mm Merck) were applied for analytical and preparative TLC. The yields imply the isolated amount of the product after separation by preparative TLC. The HPLC analysis was performed using a chiralpack OT (+) column and hexane: isopropanol 9:1 as eluent which condition gave baseline separation for the enantiomers of 3-benzyloxypterocarpan (**15**). The optical rotation (α_D) was determined by a Perkin Elmer 341 polarimeter and the concentrations were given in g /100 mL.

General procedures for the Heck-oxyarylation reaction

A. (entries 1, 4, 5 and 12) To a stirred solution of 7-benzyloxy-2*H*-chromene (**13**) in acetone or tetrahydrofuran 2-iodophenol (**14**) (1 equivalent), silver-carbonate (3 equivalents), the ligand (20 mol %) and the palladium catalyst (10 mol %) were added. The reaction mixture was refluxed for the time indicated in Table 1. Then the mixture was poured into brine, extracted with dichloromethane, dried and concentrated. The crude product was purified by means of preparative TLC (dichloromethane: n-hexane = 2:1) giving the 3-benzyloxypterocarpan (**15**); m.p. = 145-147 °C (lit[5] m.p. = 146-148 °C).

B. (entries 2, 3, 6, 10, 11 and 13) The palladium catalyst (10 mol %) and the ligand (20 mol %) were stirred in the ionic liquid [bmim][PF_6] at 80 °C for 5 min. Then the 7-benzyloxy-2*H*-chromene (**13**), 2-iodophenol (**14**) (1 equivalent) and silver carbonate (3 equivalents) were added. Stirring was continued at 100 °C for the time indicated in Table 1. and then the mixture was cooled, extracted with toluene and concentrated. The crude product was purified as described above.

C. (entries 7-9) The palladium catalyst (10 mol %) was stirred in the ionic liquid at 80 °C for 2 h. Then the above mentioned amounts of 7-benzyloxy-2*H*-chromene (**13**), 2-iodophenol (**14**) and silver-carbonate were added. After stirring at 100 °C for the time indicated in Table 1. the reaction mixture was worked up as described above.

(+)*S*-1-(2'-Methyl)-butyl-3-methylimidazolium hexafluorophosphate (**21**)**.**The N-methylimidazole (**22**) (24.4 mmoles) and *S*(+)-1-bromo-2-methylbutane (**23**) (25.6 mmoles) were stirred in 15 mL toluene at reflux for 20 h while two phases were formed. The lower phase was washed four times with 10 mL toluene, then it was dissolved in 20 mL water and hexafluorophosphoric acid (29.3 mmoles) was added. The mixture was then stirred at room temperature for 15 h while the ionic liquid was formed. The separated liquid was washed 10 times with 10 mL water and was dried giving the room temperature ionic liquid **21** in 49 % yield. $[\alpha]_D^{24}$ = +1.32 (c = 0.63, $CHCl_3$). NMR data: δ_H($CDCl_3$) 0.7-0.85(3H, -CH_3, ^3J = 12.5 Hz), 0.85-0.95(3H, 2'-CH_3, ^2J = 10 Hz), 0.95-1.35(m, 2H, -CH_2), 1.7-1.9(m, 1H, -CH), 3.7-3.8(s, 3H, N-CH_3), 3.8-4(m, 2H, N-CH_2), 7.15-7.25(m, 3H, -N-CH).

Acknowledgments

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