FULL PAPER

Transfer Hydrogenation of Flavanones and *ortho*-Hydroxychalcones to 1,3-Diarylpropanols Catalyzed by CNN Pincer Ruthenium Complexes

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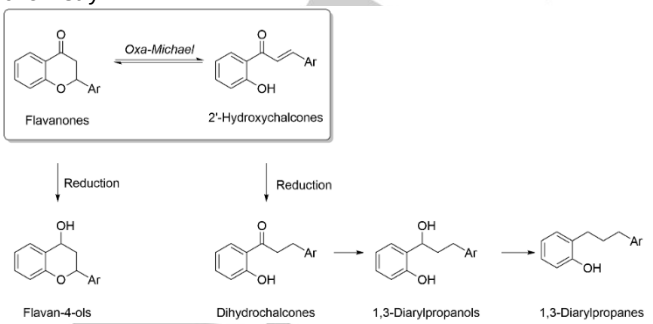
Abstract: The transfer hydrogenation of flavanones and ortho-hydroxychalcones catalyzed by ruthenium pincer complexes RuCl(CNNPh)(disphosphine) has allowed the synthesis of *ortho*-hydroxy 1,3-diarypropanols in 80-88 % yield, under mild reaction conditions and short reaction times (1 h) in 2-propanol. The amount of the co-catalyst NaOiPr has been found crucial for the selective reduction of flavanones to *ortho*-hydroxy 1,3-diarypropanols vs. flavan-4-ols. Preliminary results show that with pincer catalysts bearing (*S*,*R*)-Josiphos, flavanone is reduced to the corresponding (*S*)-alcohol in moderate conversion (36 %) and up to 92 % *ee*.

Introduction

Flavonoids are polyphenolic compounds displaying broad biological activities in plants and animals and have been investigated as drugs in the treatment of several disorders, such as diabetes, inflammatory processes, malaria and cancer.[1] Among the flavonoid derivatives, flavanones and ortho-hydroxychalcones, which are in a pH dependent equilibrium (oxa-Michael reaction),[2] are relevant precursors in the biosynthesis of a large number of biologically active products. For this reason, the chalcone scaffold is considered a privileged structure in medicinal chemistry.[3]



Scheme 1. Reduction of flavanones and ortho-hydroxychalcones

Flavanones can be reduced at the C=O group affording flavan-4-ols (Scheme 1, left), whereas ortho-hydroxychalcones are hydrogenated to dihydrochalcones, 1,3-diarylpropanols and 1,3-diarylpropanes (Scheme 1, right), which are compounds of high biological relevance.[4] While the syntheses of flavan-4-ols,[5] dihydrochalcones[6] and 1,3-diarylpropanes[7-9] have been widely described in the literature, the preparation of ortho-hydroxy 1,3-diarylpropanols has not been properly covered yet. Interestingly, compounds containing this motif have shown to display inhibitory properties in the transcription factor NF-κB,[10] anti-cholinesterase,[11] anti-inflammatory activity[12] and P-glycoprotein-inhibitory effects (GP-88)[13](Figure 1).

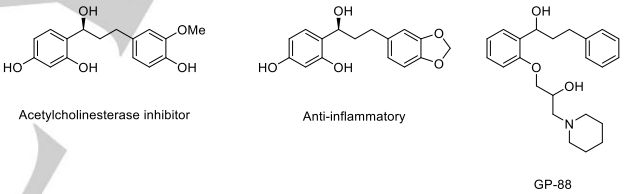


Figure 1. Structure of biologically relevant compounds containing the 1,3-diarylpropanol motif.

Among the reported methods for the synthesis of *ortho*-hydroxy 1,3-diarylpropanols, the model compound 2-(1-hydroxy-3-arylpropyl)phenol entails the C=C reduction of chalcones via hydrogenation under pressure using Pd/C followed by C=O reduction with $NaBH_4$, affording the product in low yield.[10] Katagi and co-workers described the reduction of flavone using $NaAlH_2(OCH_2CH_2OCH_3)_2$ to afford the desired product in 33% yield,[14] with concomitant formation of a functionalized indane from a rearrangement-side reaction. More recently, Zheng and Hall reported the synthesis of 2-(1-hydroxy-3-phenypropyl)phenol in moderate yield via zirconium-catalyzed condensation between 3,5-bis(trifluoromethyl)phenylboronic acid, phenol and 2-phenylpropanal followed by hydrolytic oxidation of the corresponding dioxaborin intermediate with H_2O_2.[15] Recently, our research group published a stereodivergent methodology for the hydrogenation of 2'-hydroxychalcones to generate their reduction products, but the preparation to 1,3-diarylpropanols was no general and difficult to achieve due to overreduction problems.[7]

The lack of general and efficient methods for the preparation of *ortho*-hydroxy 1,3-diarylpropanols, prompted us to develop an alternative procedure via catalytic reduction of flavanones and *ortho*-hydroxychalcones, which are accessible from natural sources or can be easily synthesized following diverse approaches, including aldol condensation between ortho-hydroxyacetophenones and benzaldehydes in basic media and further cyclation[16,17] and arylation of chromanones with arylboronic acids in the presence of a palladium catalyst.[18]

Employment of well-defined homogeneous catalysts has been demonstrated crucial for achieving high selectivity in several organic transformations,[19] reducing the formation of by-products and waste.[20] The transfer hydrogenation (TH)[21-25] of carbonyl compounds catalyzed by ruthenium(II) complexes[26] is a well-established way for the preparations of (chiral) alcohols by using 2-propanol as hydrogen donor. This protocol avoids the employment of reducing agents such as $NaBH_4$ or $LiAlH_4$, facilitating the work-up and decreasing the amount of side-reaction products.[27] It is worth pointing out that the derivatives cis-$RuCl_2$(ampy)(PP)[28-30] and the related pincer complexes RuCl(CNN)(PP)[31-33] (PP = diphosphine) containing the 2-(aminomethyl)pyridine (ampy) motif[34] are among the most active catalysts for the TH of carbonyl compounds with 2-propanol. Particularly challenging is the TH of substrates containing additional functional groups (i.e. phenols) which can coordinate to the metal center resulting in catalyst deactivation.

Herein, we describe a straightforward synthesis of *ortho*-hydroxy 1,3-diarylpropanols from flavanones and *ortho*-hydroxychalcones via TH in 2-propanol, employing the pincer ruthenium catalyst RuCl(CNN)(PP) in basic media, including preliminary results on the asymmetric TH version.

Results and Discussion

The reduction of the commercially available flavanone **1a** has been performed via TH using the ampy[34] and benzo-[*h*]quinoline[32] pincer ruthenium complexes **A-D** in 2-propanol and in the presence of an alkaline base (Figure 2).[28, 29, 35,36]

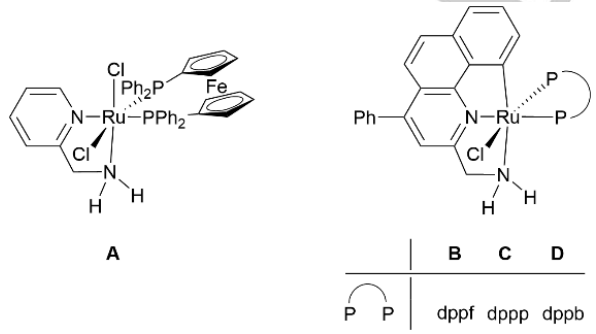


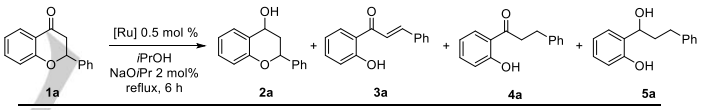
Figure 2. Ampy and benzo-[*h*]quinoline pincer ruthenium catalysts **A-D**.

Compound **1a** (0.1 M) with 0.5 mol % $RuCl_2$(ampy)(dppf) **A** and NaO*i*Pr (2 mol %) in 2-propanol at 82 °C was poorly converted (49 %), after 6 h, affording a mixture of the cyclic alcohol flavan-4-ol **2a** (19 %), *ortho*-hydroxychalcone **3a** (8 %) and the hydrogenated products dihydrochalcone **4a** (3%) and 2-(1-hydroxy-3-phenyl)phenol **5a** (19 %) (entry 1, Table 1). Employment of the more robust pincer complexes RuCl(CNNPh)(PP)[32] (PP = dppf **B**, dppp **C** and dppb **D**)[37] resulted in a higher conversion (93-99%, entries 2-4, Table 1). The type of diphosphine slightly affects the selectivity, the cyclic alcohol **2a** and 1,3-diarylpropanol **5a** being the main products. With catalyst **B** containing the dppf diphosphine, **2a** (*cis:trans* = 9:1 relative ratio) is formed in 59 %, whereas with **D**, bearing dppb, **2a** is obtained in 46 % (entries 2 and 4). Conversely, the use of **D** resulted in a higher yield for **5a** (41 %, entry 4), compared to **C** and **B** (38 and 33%, entries 2 and 3). In all these cases the formation of compounds **3a** and **4a** was lower than 8 % (entries 2-4), while no TH occurred without ruthenium catalyst and in the presence of NaO*i*Pr, affording only **3a** (13 %) via the flavanone ring opening (entry 5). In addition, a very small amount of the allyl alcohol (E)-2-(1-hydroxy-3-phenylallyl)phenol (< 2%) was also detected during the TH of **1a** (see ESI).

By employment of $RuCl_3$ hydrate and [Ru(*p*-cymene)Cl_2]$_2$ (0.5 mol%) **1a** under these catalytic conditions affords a mixture of **1a** and **3a** (7:1 molar ratio), according to the Michael reaction, without formation of the reduction products

These results show that with catalysts **A-D**, flavan-4-ol **2a** is formed from **1a** by reduction at the C=O bond, while the other derivatives entail a retro oxa-Michael reaction. Although the reduction of flavanones towards flavan-4-ols has been described,[5,38] no reports on the synthesis of 1,3-diarylpropanols *via* TH from flavanones or *ortho*-hydroxychalcones has been reported.

Table 1. TH of flavanone **1a** (0.1 M) with the ruthenium catalysts **A**-**D** (0.5 mol %) in 2-propanol at reflux after 6 h.



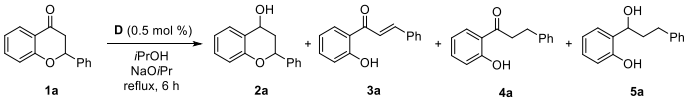
Entry	Catalyst	Conv. (%)[a]	**2a** (%)[b]	**3a** (%)[b]	**4a** (%)[b]	**5a**(%)[b]
1	**A**	49	19	8	3	19
2	**B**	99	59	0	7	33
3	**C**	93	47	0	8	38
4	**D**	98	46	3	8	41
5	-	13	0	13	0	0

a) The conversion was determined by ^{1}H-NMR measurements. b) The percentages of **2a**, **3a**, **4a** and **5a** were determined by ^{1}H-NMR analysis on the crude reaction products.

Since the Michael reaction is base dependant,[2] the role of NaO*i*Pr was explored to improve the selectivity of the flavanone TH (Table 2). Reaction of **1a** with catalyst **D** (0.5 mol%), in absence of NaO*i*Pr, gives **2a** as main product (75 %), whereas **5a** is obtained in low amount (22 %) in 6 h (entry 1, Table 2). Increasing the amount of NaO*i*Pr from 2 to 150 mol % resulted in a progressive enhancement of the formation of desired **5a** (38 to 85 %, entries 2-7), whereas the amount of **2a** decreased from 47 to 6 %. It is worth pointing out that with 100 mol % of base at 0.1 M and at 0.05 M of **1a** no significant change of the distribution products has been observed, indicating that the substrate concentration has a

slight effect on the selectivity (entries 5 and 6). At 150 mol %of base, the TH was performed at 0.05 M concentration of substrate **1a** due to the poor solubility of the chalcone phenoxide in 2-propanol. Control experiments show that *ortho*-hydroxychalcone **3a** with **D** (0.5 mol %) and NaO*i*Pr (2 mol %) is easily converted into a mixture of **2a**, **4a**, and **5a** in 47, 9, 42 %, respectively, whereas with 150 mol % of NaO*i*Pr **5a** is formed in 85 % yield indicating that the base has strong influence on the selectivity for **5a**. The similar results obtained for **1a** and **3a** are in agreement with a fast pre-equilibrium between **1a** and **3a**, under these catalytic conditions.

Table 2. Effect of the NaO*i*Pr on the selectivity of the TH of **1a** (0.1 M) with catalyst **D** (0.5 mol%) in 2-propanol at reflux after 6 h.

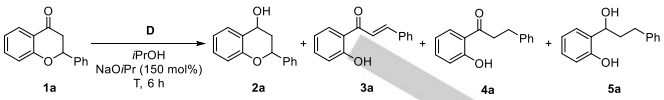


Entry	NaO*i*Pr (%)	Conv. (%)[a]	**2a** (%)[b]	**3a** (%)[b]	**4a** (%)[b]	**5a**(%)[b]
1	0	99	75	0	2	22
2	2	93	47	0	8	38
3	5	91	40	0	0	51
4	40	94	36	0	0	58
5	100	98	23	0	0	75
6[c]	100	97	21	0	0	76
6[c]	150	99	6	0	8	85

[a] The conversion was determined by ^{1}H-NMR measurements. [b] The percentages of **2a**, **3a**, **4a** and **5a** were determined by ^{1}H-NMR analysis on the crude reaction products. [c] **1a** 0.05M.

The influence of the temperature and the amount of catalyst on the selectivity of the TH of **1a** was also investigated and the data are summarized in Table 3. At 50 °C with **D** (0.5 mol%), complete conversion is achieved in 6 h, affording **5a** in 36% yield, while at 60 and 82 °C, **5a** is formed in 52 to 74 % yield, respectively (entries 1-3). Rising the amount of **D** to 1 mol % at 50, 60 and 82 °C, conducts to a increase in the amount of **5a**, which is obtained in 79-92 % yield, whereas at 1.5 mol% of **D** no significant improvements were observed in the obtention of **5a** (entries 4-7).

Table 3. Effect of temperature and loading of D in theTH of **1a** (0.05 M) with the in 2-propanol in the presence of NaO*i*Pr (150 mol%) after 6 h.



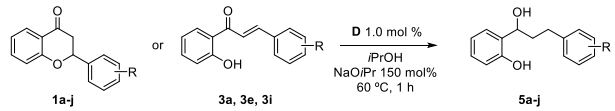
Entry	[**D**] (%)	T (°C)	Conv. (%)[a]	**2a** (%)[b]	**3a** (%)[b]	**4a** (%)[b]	**5a**(%)[b]
1	0.5	50	99	0	1	52	36
2	0.5	60	99	0	1	46	52
3	0.5	82	99	7	1	17	74
4	1.0	50	99	0	0	20	79
5	1.0	60	99	0	0	7	92
6	1.0	82	99	4	0	3	92
7	1.5	60	99	0	0	8	91

[a] The conversion was determined by ^{1}H-NMR measurements. [b] The percentages of **2a**, **3a**, **4a** and **5a** were determined by ^{1}H-NMR analysis on the crude reaction products.

The best selectivity for **5a** is achieved at 60 °C with 1 mol% of **D**, also observing that complete conversion is attained in 1 h.

In order to broaden the scope of this reaction, the reduction of flavanones[16] and *ortho*-hydroxychalcones bearing different substituents on the phenyl ring was carried out using **D** (1.0 mol%) with NaO*i*Pr (150 mol%) at 60 °C in 1 h. Thus, **1a** and the flavanones **1b-e** bearing electron donating groups (Me, OMe) and **1f-j** containing electron withdrawing groups (F, Cl, Br) are reduced to *ortho*-hydroxy 1,3-propanols **5a-j** and isolated in 80-88 % yield (entries 1-13, Table 4). In addition, the TH of *ortho*-hydroxychalcones **3a**, **3e** and **3i** lead to **5a**, **5e** and **5i** (84-85 %, entries 2, 7, 12), showing similar reactivity of the corresponding flavanones. These results indicate that the nature and position of the aryl substituent do not significantly affect the selectivity of the TH, showing a broad substrate scope for this reaction. To show the practical potential of this methodology, 1.84 g of 1,3-diarylpropanol **5a** (81% yield) were obtained from 2.24 g (10 mmol) of flavanone **1a** in 1 h at 60 °C, using 1.0 mol% of complex **D** in 2-propanol.

Table 4. Synthesis of 1,3-diarylpropanols **5a-j** from flavanones **1a-j** and *ortho*-hydroxychalcones **3a**,**3e**, **3i** (0.05M) via TH.



Entry	Substrate	R	Product	Yield (%)[a]
1	**1a**	H	**5a**	87
2	**3a**	H	**5a**	85
3	**1b**	4-Me	**5b**	86
4	**1c**	2-OMe	**5c**	82
5	**1d**	3-OMe	**5d**	83
6	**1e**	4-OMe	**5e**	86
7	**3e**	4-OMe	**5e**	84
8	**1f**	2-F	**5f**	83
9	**1g**	3-F	**5g**	82
10	**1h**	4-F	**5h**	88
11	**1i**	4-Cl	**5i**	80
12	**3i**	4-Cl	**5i**	84
13	**1j**	4-Br	**5j**	84

[a] Isolated yield after flash column chromatography.

Finally, the asymmetric TH version was envisaged for the preparation of chiral 1,3-diarylpropanols, so the reduction of **1a** was carried out using the chiral pincer ruthenium complexes **E**[31] and **F**,[39] under the optimized catalytic conditions (catalyst 1.0 mol %, NaO*i*Pr 150 mol%, 60 °C and 1 h) (Figure 3).

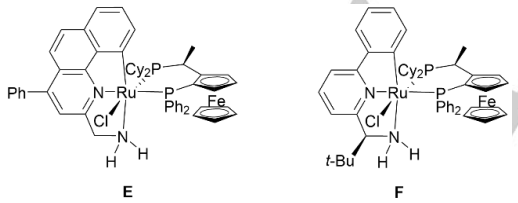
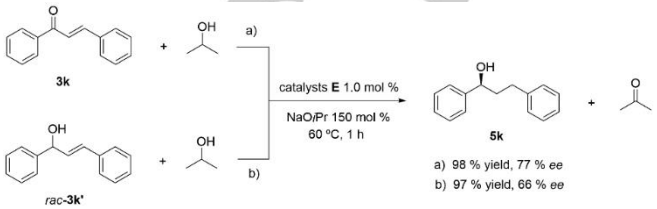


Figure 3. Chiral pincer ruthenium catalysts **E** and **F.**

Preliminary results show that complexes **E** and **F** containing the (*S*,*R*)-Josiphos[37] diphosphine, which are highly efficient catalysts for the asymmetric TH of aryl-alkyl ketones to (*S*)-alcohols,[39-41] are able to reduce **1a** to a mixture of **4a** (69 and 64 %) and (*S*)-**5a** (31 and 36 %) with 70 and 92 % *ee*, respectively.

Control experiments show that the TH of the model chalcone **3k** with catalyst **E**, under the same catalytic conditions, gives the corresponding (*S*)-1,3-diphenylpropan-1-ol **5k** with 77 % *ee*, as confirmed by NMR and HPLC measurements (Scheme 2).[42,43]



Scheme 2. Asymmetric TH of chalcone **3k** and the allyl alcohol *rac*-**3k'** to enantioenriched alcohol **5k** with catalyst **E**.

This reaction gives the saturated alcohol with an *ee* value close to that found in the reduction of the flavanone **1a** to (*S*)-**5a** and in agreement with the data observed for the TH of the aryl-alkyl ketones with **E**, affording (*S*)-alcohols.[32] Interestingly, the TH of the racemic allylic alcohol **3k'** affords (*S*)-**5k** with 66 % *ee*. Since **E** catalyzes efficiently the asymmetric TH at the C=O bond, while it displays poor activity for the C=C reduction, it is likely that the reaction occurs through a ruthenium-catalyzed allylic alcohol isomerization[28] of *rac*-**3k'** to the corresponding saturated ketone, (i.e. 1,3-diphenylpropanone), which is finally enantioselectively reduced to (*S*)-**5k**.

Accordingly, it is likely that the ruthenium catalyzed conversion of flavanones to 1,3-diarylpropanols in basic 2-propanol entails a retro oxa-Michael reaction to hydroxychalcones, followed by a TH at the C=O bond affording the corresponding allylic alcohols. Subsequent isomerization[28, 44] gives the dihydrochalcones which are reduced to 1,3-diarylpropanols via (asymmetric) TH.

In the TH the catalytically active ruthenium hydride is formed by substitution of the chloride with the isopropoxide followed by a β-H elimination. Nucleophilic attack of the hydride to the ketone substrate gives a Ru-alkoxide which is protonated by 2-propanol, affording the alcohol product and Ru-O*i*Pr which closes the catalytic cycle. The presence of the N-H functionality strongly accelerates the catalytic process via proton shuttling involving the N-H group, 2-propanol and the ketone substrate.[45,46] The use of robust pincer catalysts appears crucial with these substrates, since the chalcones and their reduced products are present as phenoxides under basic catalytic conditions and therefore are apt to coordinate to the metal center, hindering the catalytic activity.

Conclusions

In summary, we have reported that flavanones and ortho-hydroxychalcones can been easily and selectively reduced to ortho-hydroxy 1,3-diarylpropanols in a one-pot reaction using robust pincer ruthenium complexes RuCl(CNNPh)(disphosphine) with 2-propanol and in the presence of NaO*i*Pr. This general and straightforward procedure has allowed the synthesis of 1,3-diarylpropanols containing electron donating and withdrawing

substituents at the phenyl ring under mild reaction conditions. Interestingly, the use of pincer ruthenium catalysts bearing (*S*,*R*)-Josiphos diphosphine allowed the conversion of flavanone to the (*S*)-alcohol (36 % conversion) with up to 92 % *ee*. Further studies are underway to broaden the scope of pincer ruthenium catalysts in organic transformations.

Experimental Section

General Experimental Information

All reactions were carried out under an argon atmosphere using standard Schlenk techniques. The solvent 2-propanol used in TH has been carefully dried with sodium and distilled under argon before use.. Flavanones **1b-j** and chalcones **3a**, **3e**, **3i** were prepared following the literature procedures,[16] while **1a** was purchased from Alfa Aesar. The ampy and CNN pincer ruthenium complexes $RuCl_2$(ampy)(dppf) **A**[34], RuCl(CNNPh)(PP)[31-33] (PP = dppf **B**, dppp **C**, dppb **D**, (*S,R*)-Josiphos **E**)[31] RuCl(CNNBu)[(*S,R*)-Josiphos] (**F**)[39] were prepared according to literature procedures, whereas all other chemicals were purchased from Aldrich and used without further purification. NMR measurements were recorded on Bruker Avance III HD NMR 400 spectrometers. Chemical shifts (ppm) are relative to TMS for ^{1}H and ^{13}C. High performance liquid chromatography (HPLC) analyses were carried out in a Hewlett Packard 1100 chromatograph equipped with a VIS-UV detector.

Synthesis of *ortho*-hydroxy 1,3-diarylpropanols 5a-j from flavanones 1a-j or chalcones 3a, 3e and 3i

The ruthenium catalyst solution used for TH was prepared by dissolving the ruthenium complex (2.0 μmol) in 0.5 mL of 2-propanol. The catalyst solution (250 μL, 1.0 μmol) and NaO*i*Pr (1.5 mL, 0.15 mmol, 0.1 M in 2-propanol) were added to a 0.4 M flavanone **1a-j** or chalcone **3a**, **3e**, **3i** solution (250 μL, 0.1 mmol) in 2-propanol (final volume 2 mL) and the resulting mixture was kept at the defined temperature (60 °C) for 1 h. Reaction was quenched by addition of an aqueous 0.1M solution of HCl (5.0 mL) and the resulting mixture was extracted with dichloromethane (3 x 5.0 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Final alcohols **5a-j** were obtained in 82-87% yield after column chromatography (silica gel) using hexane:ethyl acetate 5:1 as eluent. The addition of the base was considered as the start time of the reaction. The S/C molar ratio was 100/1, whereas the base concentration was 150 mol% respect to the substrate (0.05 M).

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Keywords: alcohols • flavonoid • transfer hydrogenation • ketones • ruthenium

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[37] ampy = 2-(aminomethyl)pyridine; HCNNPh = 4-phenyl-2-aminomethylbenzo[h]quinoline; HCNNBu = 2,2-dimethyl-1-(6-phenylpyridin-2-yl)propan-1-amine; dppf = 1,1'-bis(diphenylphosphanyl) ferrocene; dppp = 1,3-bis(diphenylphosphino)propane; dppb = 1,4-bis(diphenylphosphino)butane; (*S,R*)-Josiphos = (*S*)-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine).
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Transfer Hydrogenation of Flavanones and *ortho*-Hydroxychalcones to 1,3-Diarylpropanols Catalyzed by CNN Pincer Ruthenium Complexes

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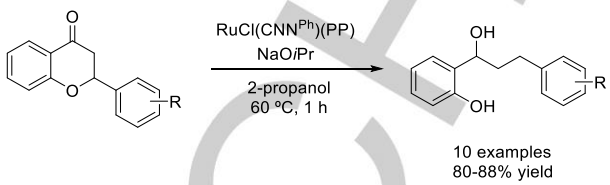

Efficient reduction of flavanones and 2'-hydroxychalcones to 1,3-diarylpropanols has been achieved with the pincer ruthenium catalysts RuCl(CNN)(diphosphine) with NaO*i*Pr in 2-propanol via transfer hydrogenation. The amount of base has been found to be a crucial parameter for the control of the oxa-Michael reaction that determines the selectivity of the reaction. Preliminary results show that this reaction can be performed with chiral pincer catalysts reaching an *ee* of 92%