Catalysis Communications 115 (2018) 49–54

Contents lists available at ScienceDirect

Catalysis Communications

journal homepage: www.elsevier.com/locate/catcom

Short communication

[N,P]-pyrrole-phosphine ligand: An efficient and robust ligand for Ru-catalyzed transfer hydrogenation microwave-assisted reactions

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ARTICLE INFO

Key-words:
[N,P]-ligand
Ruthenium
Transfer-hydrogenation
Microwave

ABSTRACT

A pyrrolyl-containing [N-P]-ligand (**L1**) and [Ru] were evaluated as catalytic system in transfer hydrogenation reaction of ketones. A comparison between microwave irradiation vs conventional heating conditions indicates that MW can be successfully used as energy source, improving the reaction time. The **L1**/Ru(II) proved to be an active, efficient and robust catalytic system. The scope of this catalytic system was evaluated using a diversity of substrates that include electron-withdrawing and electron-donor groups achieving a range of 65 to 95% conversion. Moreover, the catalytic system showed good activity even with highly sterically hindered ketones.

1. Introduction

Transition-metal-catalyzed transfer hydrogenation reactions have been considered in terms of ease, efficiency, and commercial viability, as the most attractive procedure for reduction of unsaturated C=O and C=N bonds. [1–6] In this process, a variety of transition metals, ligands, hydrogen sources, bases, reaction media, supports, and unsaturated compounds have been used. The hydrogen donor source is generally an alcohol such as 2-propanol, glycerol or a formate in combination with a base as co-catalyst. [1,7] Notably, this is a valuable alternative reduction procedure of ketones to useful secondary alcohols, in the context of high demand of the petrochemical, pharmaceutical, and food industries. [8–10]

Among the transition metal complexes, Ru complexes with various combinations of ligands are by far the most widely used catalysts to mediate this reaction. [1,11–14] Hemilabile ligands, especially mixed [N,P]-chelate ligands [15–17], have been particularly used to assist metals in transfer hydrogenation, where it is necessary that a ligand fragment dissociates to allow the coordination of the organic substrate that will undergo the transformation. For example, half-sandwich Ru-catalysts containing [N,P]-ligands remarkably promoted transfer hydrogenation of a broad scope of ketones. [18–20]

Our group is involved in the design of a new class of [N,P]-pyrrole-phosphine ligands based on pyrrole with a dimethylamino group and a phosphine moiety as hard and soft donors, respectively. Recently, we have demonstrated that their palladium complexes efficiently promote Heck coupling reactions [21] and intramolecular arylations. [22] In addition, we have successfully employed microwave irradiation to accelerate these metal-catalyzed reactions(Fig. 1). [23,24]

As part of our ongoing work, we decided to explore the potential of these [N,P]-ligands in ruthenium-catalyzed transfer hydrogenation reactions using microwave irradiation as a heating source, since the reaction rates involves polar components, it can be accelerated under these heating conditions. Although, microwave enhanced Ru-catalyzed transfer hydrogenation of ketones could be considered an ecofriendly approach, only some examples have been reported using this approach. [25–28] Herein, we report the transfer hydrogenation of various ketones catalyzed by a [N,P]-ligand/Ru system. No inert atmosphere was necessary, neither active catalyst previous formation. To establish the greenest and most efficient catalytic protocol, we have also performed the reactions under microwave conditions, and the results were compared with those obtained by the conventional oil-bath heating procedure.

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https://doi.org/10.1016/j.catcom.2018.07.009
Received 30 May 2018; Received in revised form 7 July 2018; Accepted 9 July 2018
Available online 11 July 2018

2. Experimental section

2.1. General considerations

All reagents and solvents were obtained from commercial suppliers and used without further purification. Melting points were obtained on a Melt-Temp II apparatus and are uncorrected. All compounds were characterized by NMR spectra measured with a Bruker Avance III at 300 MHz for ^{1}H and 75 MHz for ^{13}C using $CDCl_3$ as a solvent. Chemical shifts are in ppm (δ), relative to TMS.

The calculated conversion was corroborated by gas chromatography analyses using an Agilent 6890 system, equipped with a Cyclosilb column (solvent: isopropanol; 30 m × 0.32 mm 0.25 μm). The GC parameters were as follows: initial temperature, 100 °C; temperature ramp: 5 °C/min 150 °C (0 min), 10 °C/min; final temperature, 230 °C; final time, 23 min; injector port temperature, 240 °C; detector temperature, 240 °C; injection volume,1.0 μL.

Microwave irradiation experiments were performed using a Monowave 300 single-mode microwave reactor. The reaction temperature is monitored by an internal fiber-optic (FO) temperature probe (ruby thermometer) protected by a borosilicate immersion well inserted directly into the reaction mixture. Reaction times refer to the hold time at the desired set temperature and not to the total irradiation time. Pressure sensing is achieved by a hydraulic sensor integrated in the swiveling cover of the instrument. The reusable 10 mL Pyrex vial is sealed with PEEK snap caps and standard PTFE coated silicone septa. Reaction cooling is performed by compressed air automatically after the heating period has elapsed.

The X-ray diffraction (XRD) patterns were recorded using a Bruker Advanced D8-FOCUS diffractometer with Cu-*kα* radiation (λ = 1.54 Å) at a scanning speed of 0.02° (2θ) min^{-1} in the range of 10–100°. The morphology of selected samples was examined by scanning electron microscopy (SEM) on a JSM-6701F JEOL microscope.

The pyrrole-containing [N,P]-ligands **L1** and **L2** were synthetized according to the methodology previously described [21]. NMR data of all secondary alcohols **2a-l** and **4a-d** agreed with the literature (See, SI).

2.2. General procedure for transfer hydrogenation

2.2.1. Procedure under traditional oil-bath heating

The catalytic species was prepared under nitrogen atmosphere by dissolving ligand **L1**, $[RuCl_2(PPh_3)_3]$ and KOH (25 mol%) in 2-propanol (3 mL). The system was heated at 82 °C for 3 h, observing the formation of a deep red solution, this is the pre-activation time. Then, acetophenone (1 equiv) was added. After magnetic stirring for 15 h, the reaction mixture was cooled and filtered through a celite-alumina pad to remove any catalyst.

2.2.2. Procedure under microwave heating with catalyst pre-activation

The catalytic species was prepared in a 30 mL microwave-transparent process vial by dissolving ligand **L1** (0.5 mol%), $[RuCl_2(PPh_3)_3]$ (0.5 mol%) and KOH (5% mol) in 2-propanol (3 mL). The system was heated at 100 °C for 5 min, observing the formation of a deep red solution. Then, acetophenone (1 equiv) was added. After 60 min, the reaction mixture was cooled and filtered through a celite-alumina pad to remove any catalyst.

2.2.3. General procedure under microwave irradiation without catalyst pre-activation

In a 30 mL microwave-transparent process vial were added the corresponding ligand, $[RuCl_2(PPh_3)_3]$, KOH (5 mol%) and ketone in 2-propanol (3 mL). The mixture was heated at 100 °C during the required reaction time. Then, the reaction mixture was cooled and filtered through a celite-alumina pad to remove any catalyst.

2.2.4. Product analysis

For all three catalytic methods, products were analyzed according to the following procedure: After the reaction time, the reaction mixture was evaporated under reduced pressure and analyzed by ^{1}H NMR to determine the conversion in reference with residual starting material. The calculated conversion was corroborated by gas chromatography. The catalytic reactions were done in duplicates to ensure the reproducibility of the results.

Note: The entire flasks used in each hydrogen transfer experiment were meticulously cleaned with aqua regia to avoid the presence of unseen ruthenium catalyst.

3. Results and discussion

Initially, the ligands *N,N*-dimethyl-1*H*-pyrrol-1-amine-2-diarylphosphine **L1** and **L2** were prepared in good yields by the selective lithiation of 1-(*N,N*-dimethylamino)pyrrole and the subsequent anion trapping with chlorodiphenylphosphine (**L1**) or chloro-di(*o*-tolyl)phosphine (**L2**), as we have previously reported. [21] For comparison purposes, we have also included a [P,P]-ligand as (*rac*)-BINAP, usually employed in this kind of catalytic applications.

Preliminary experiments using the ligand **L1** in the catalytic transfer hydrogenation of acetophenone as a model substrate were conducted using KOH as base (25 mol%), 2-propanol as solvent and hydrogen source, **L1** (1.2 mol%) and $[Ru(PPh_3)_3Cl_2]$ (1 mol%) under different heating conditions (Table 1). We have compared the effect of using conventional heating versus microwave irradiation. The percentage conversions were determined by ^{1}H NMR spectroscopy by comparing the integration of the methyl signal of acetophenone (s, δ 2.59) and methyl signal of 1-phenylethanol (d, δ 1.49) of the crude products. These results were also confirmed by gas chromatography technique.

Under conventional oil-bath heating, the reaction was conducted at 2-propanol reflux (82 °C) for reaction time of 18 h, including 3 h of the catalytic species formation. According with the mechanism accepted for the transfer hydrogenation, [29] the active catalytic species $[RuH_2L_2PPh_3]$ is formed in the pre-activation step, and then when the substrate is added, the reaction starts (Table 1, entry 1). During the pre-activation step, we observe a color change of the solution before the addition of substrate, which could indicate the coordination of the [N,P]-ligand. Likewise a screening by thin layer chromatography showed the total consumption of [N,P]-ligand and the presence of PPh_3 in solution. Thus, we conducted a coordination experiment using the ligand **L1** and the ruthenium precursor in anhydrous THF at room temperature. Unfortunately, despite efforts to isolate the new ruthenium complex, we could not isolate or identify this compound, obtaining in all cases an insoluble solid in the common solvents used for spectroscopic characterization. For this reason, we decided to generate this species in situ.

The product (**2a**) was yielded in 97%, after chromatography purification (Table 1, entry 3). Under the same conditions, using the half of the catalytic system load (entry 4), the calculated conversion was 88%. When the reaction was conducted without the pre-activation step, no conversion was obtained (entry 2), which indicates that this step is crucial under conventional heating.

When, this reaction was assisted by microwave heating at 100 °C for 60 min, we observe that pre-activation step was not necessary, obtaining practically the same conversion in both cases, 91 and 90%, respectively (Table 1, entries 6 and 7). At this temperature, the microwave reactor reaches a pressure of 5 bars. The conversion obtained under these conditions shows that the microwave method is comparable to that performed under conventional reflux heating. However, the reaction time is drastically reduced from 18 to 1 h and the pre-activation step is not required to form the catalytically active species. Likewise, to demonstrate the influence of the [N,P]-ligand, two control experiments were performed (Table 1, entries 1 and 5), these reactions afforded modest conversions.