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Noyori-Ikariya Catalyst Supported on Tetra-arylphosphonium Salt for Asymmetric Transfer Hydrogenation in Water

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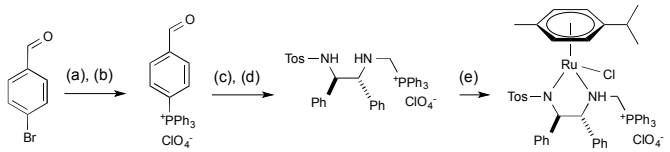
A straightforward synthesis of a tetraarylphosphonium (TAP)-supported Noyori-Ikariya catalyst is described. The TAP-supported ruthenium precatalyst provided good conversions and high enantioselectivities for the asymmetric transfer hydrogenation of ketones in water. In addition the catalyst was easily recovered and used in multiple catalytic cycles.

Asymmetric transfer hydrogenation (ATH) is a safe, operationally simple and "green chemistry-compatible" alternative to hydrogenation processes.[1-6] An important breakthrough in the field of ATH was achieved by Noyori, Ikariya, Hashiguchi and co-workers with the discovery of the Ru-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (Ru-TsDPEN) catalyst.[7-9] Since then, TsDPEN coordinated Ru(II) complexes have been particularly successful in reducing a wide range of aromatic ketones, using either propan-2-ol, azeotropic mixtures of HCOOH-Et_3N or HCOONa as hydrogen sources.[10-16] Hence, Ru-TsDPEN complexes are highly effective in asymmetric catalyses under green chemical processes, and are particularly suitable for ATH in water.[4, 12, 17-19] However, the high monetary cost of such complexes due to the rarity of the metal and its chiral environment brings forth a need for minimizing the amount consumed throughout a reaction and the subsequent purification steps. Therefore, strategies to recycle the metal catalysts have attracted considerable interest, and great efforts have been devoted to develop recoverable and reusable complexes.[20, 21] A popular method to support TsDPEN-based catalysts is their covalent binding *via* immobilization on solid supports. For instance, heterogeneous catalysts were designed using amorphous silica gel[22] and silica mesopores of MCM-41 and SBA-15.[23, 24] A nanocage to encapsulate Ru-TsDPEN was also envisioned.[25] In other cases, dendritic catalysts were successfully employed in ATH.[26-28] Surprisingly, TsDPEN ligands could also be linked to imidazolium ionic liquids (ILs) to provide recyclable catalysts.[29-31] However, polymers proved to be one of the best supports used to graft TsDPEN ligands, particularly polyethylene glycol (PEG) chains.[32-36] One of the most efficient ligands for ATH in water was created by Xiao *et al.*, who prepared a ruthenium catalyst bearing a PEG-supported TsDPEN.[37, 38] Despite the great success achieved, the latter immobilization methods usually suffer from several drawbacks: (i) heterogeneous catalysts are generally accompanied with a substantial decrease in catalytic activity and selectivity; (ii) most immobilization supports are of high molecular weight and expensive (*e.g.* dendrimers or polyethylene glycol derivatives), and generally require troublesome multistep synthesis; (iii) only few have been demonstrated to be both effective and recyclable; moreover, none appears to be more active than TsDPEN itself.

Phosphonium salts have found various applications in different fields of chemistry, ranging from medicinal chemistry, organic synthesis and material sciences.[39-46] Our group has been interested in phosphorus chemistry, and has reported the use of tetraarylphosphonium salts (TAP) as solubility-control groups (SCGs) for reagents, ligands and catalysts. Various reagents were successfully grafted on TAP, *e.g.* triphenylphosphine, diethyl azodicarboxylate,[47] dialkylcarbodiimide[48] or TEMPO.[49] This technology has also been applied for the synthesis of small molecules and in the challenging field of solid-phase peptide synthesis.[50]

With the attractive properties of TAP in mind, we set to prepare a recyclable and reusable Noyori-Ikariya catalyst, whilst aiming at simple procedures to prepare TAP-supported catalysts. For that purpose, we envisioned linking our support through the non-alkylated amine of the catalyst. Herein, we report the

straightforward synthesis of TAP-Ru-TsDPEN and its uses for enantioselective ketone reduction in water. The synthetic route to prepare TAP-TsDPEN is described in Scheme 1. First, commercially available bromobenzaldehyde was reacted with PPh_3 in the presence of a nickel catalyst to yield TAP-benzaldehyde. The latter intermediate was reductively aminated with (*R*,*R*)-TsDPEN using $NaBH_4$ as reductive agent to afford TAP-supported ligand.



Scheme 1 Synthesis of Ru-TAP-TsDPEN. Reaction conditions: (a) PPh_3, $NiBr_2$ in ethylene glycol, 180 °C, 4 h; (b) aq. $LiClO_4$, 75%; (c) (*R*,*R*)-TsDPEN, $AcOH_{gla}$, MeOH, RT, 24 h; (d) $NaBH_4$, 2 h, RT, 80%; (e) precatalyst formed *in situ* before catalysis with 0.6 equiv. $[Ru(p\text{-cymene})Cl_2]_2$ in water (0.25 mL) at 40 °C for 1 h.

We then examined the influence of solvent and hydrogen sources in ATH with TAP-Ru-TSDPEN (Table 1). Reduction of acetophenone (Acp) was selected as a model reaction and the precatalyst was preformed as indicated in Scheme 1. After 1 h, HCOOH and Et_3N were added (total volume of 0.25 mL). The reaction was initiated by addition of Acp (0.5 mmol).

Table 1 ATH of acetophenone using TAP-Ru-TsDPEN[a]

Entry	Temp (°C)	Time (h)	Solvent/H source	Conv (%)[b]	*ee* (%)[c]
1	40	16	FA/TEA[d]	-	-
2	35	16	FA/TEA[e]	24	87.1 (*R*)
3	40	16	aq. HCOONa[f]	>99	93.8 (*R*)
4	40	24	FA/TEA[g]	83	94.4 (*R*)
5	40	16	aq. FA/TEA[h]	>99	95.7 (*R*)

[a] Reactions were performed for the temperature and times indicated, see ESI for details. [b] Determined by NMR. [c] Determined by SFC. [d] FA/TEA (5/2 molar ratio). [e] Reaction performed in CH_2Cl_2. [f] HCOONa (5M). [g] FA/TEA (0.2/1 molar ratio). [h] FA/TEA (1.2/1 molar ratio).

The ATH of ketones using the Noyori-Ikariya catalyst has been carried out in the past, with varying reported success according to solvents and hydrogen source.[4, 7, 12] For example, Ogo *et al*. demonstrated a strong pH dependence in the reaction rate of the reduction of ketones by HCOONa.[14] Similarly, Xiao reported that ATH of aromatic ketones, performed in aqueous-phase by formic acid using the same catalyst as Ogo, can be modulated by pH.[51] Later on, he demonstrated that in neat azeotropic mixtures of HCOOH (FA) and Et_3N (TEA), the optimum ratio was 0.2/1.[52] Thence, different conditions were compared using TAP supported catalyst (Table 1). The results clearly indicated that the highest *ee* and conversion were obtained with aqueous azeotropic mixtures of FA and TEA in a molar ratio of 1.2/1 (Table 1, entry 4). This is in accordance with the results reported by Xiao that established optimized conditions for ATH of ketones in water.[51] Having determined the best reaction conditions, we proceeded to study the influence of pH on the reduction of acetophenone with TAP-Ru-TsDPEN (Figure 1). Results demonstrated that FA/TEA ratio affected the performance of this catalyst. Reduction of Acp was slowed down under basic conditions and required a ratio of 1.2/1 to achieve full conversion. This observation suggests that the reduction is intimately related to the concentration of formate. In contrast, enantioselection was little affected by changing FA/TEA ratio. Thus, the reduction of Acp follows the concerted mechanism proposed by Noyori *et al*.[53-56] From all observations aforementioned, we selected 1.2/1 as the optimum FA/TEA ratio for further studies.

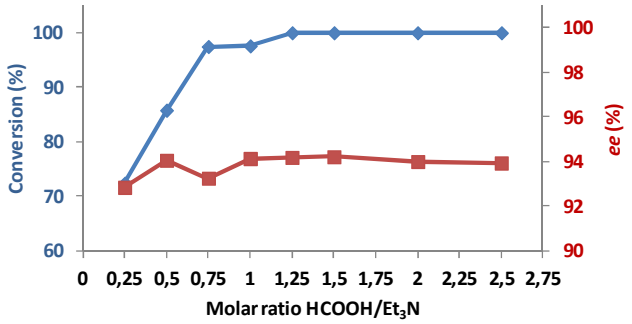


Fig.1 Conversion and *ee* vs. FA/TEA mixtures (0.25 mL total volume; see ESI for details) for ATH of Acp (0.5 mmol), S/C = 100 in water (0.25 mL) using TAP-Ru-TsDPEN, at 40 °C for 16 h.

The behavior of the supported catalyst, in terms of activity and selectivity, was thus studied over time (Figure 2). Complete transformation of acetophenone (Acp) was reached within 5 h (Figure 2). It is noteworthy that enantioselectivity remained remarkably constant over time.

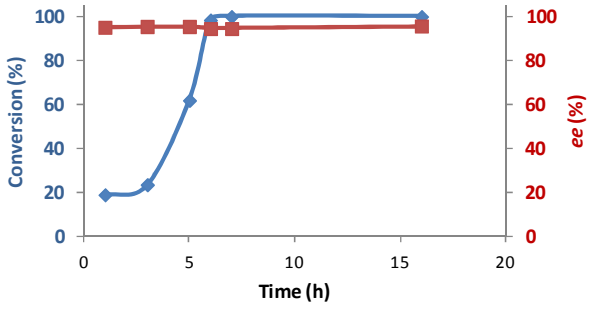


Fig. 2 Conversion and *ee* vs. time for ATH of Acp (0.5 mmol), S/C= 100 in water (0,25 mL) with FA/TEA (1.2/1 molar ratio; 0.25 mL total volume) using TAP-Ru-TsDPEN at 40 °C.

In order to accelerate the reaction, the temperature was increased to 60 °C. As a result, TAP-Ru-TsDPEN achieved complete conversion of Acp in 3 h. However, a decreased

enantioselectivity was observed (from 95.7% down to 94.3%). The maximum activity of the catalyst was determined by performing the reaction with a substrate/catalyst (S/C) ratio of 1000 at 60 °C, using the reaction conditions described in Figure 2. The catalyst afforded 55% of the reduced form of Acp after 48 h and a slight erosion on enantioselectivity was observed (93.3%). These results demonstrate that attaching TAP on the free amine was not without consequence in the ATH of ketones. The lower activities exhibited by TAP-Ru-TsDPEN can be due to several factors related to the presence of a bulky TAP moiety, *i.e.* slow formation of the Ru-H species or slow transfer of the hydride from the Ru-H species to the substrate.[32, 52, 57-59] Since different conditions are employed in ATH of ketones, it is difficult to compare the efficiency of supported catalysts. However, two kind of comparison can be done: (i) with the classical Noyori-Ikariya catalyst and (ii) with catalysts bearing their support on the free amine. (i) Comparing with the classical Noyori-Ikariya catalyst, both activity and selectivity were found to be lower with TAP-Ru-TsDPEN. Using the same reaction conditions, full conversion and 97% *ee* were obtained after 1.5h.[51] (ii) Comparing with catalysts bearing their support on free amine. In this context, Wills *et al*. prepared triazole-functionalized TsDPEN derivatives on a soluble polymer support.[59] The best catalyst of the series reduced Acp in 24 h at 40 °C with 94% *ee*. Similarly, Li *et al*. explored a nitrogen joined *N*-PEG-TsDPEN ligand in ATH of ketone,[32] reporting that *N*-PEG400-TsDPEN provided full conversion and 94.8% *ee* after 15h, for the production of 1-phenylethanol. These results confirmed that such *N*-alkylated catalysts have slightly slower rate but conserve similar enantioselectivities than other versions of TsDPEN-supported catalysts. Concerning TAP-Ru-TsDPEN, both activity and enantioselectivity were found to be higher than Wills' and Li's catalysts: complete conversion of Acp and 95.7% *ee* was obtained after only 3h reaction time at 40°C.

Encouraged by these results, the TAP-supported ruthenium catalyst was tested for the reduction of different aromatic ketones (Table 2).

Table 2 ATH of ketones using TAP-Ru-TsDPEN in aqueous FA/TEA[a]

Entry	Ketone[b]	Time (h)	Conv (%)[b]	*ee* (%)[c]
1	2'-chloro-acp	14	>99	89.6 (*R*)
2	4'-chloro-acp	4	>99	91.1 (*R*)
3	2'-bromo-acp	7	>99	89.9 (*R*)
4	4'-bromo-acp	5	>99	91.7 (*R*)
5	4'-MeO-acp	14	>99	95.5 (*R*)
6	acetylfurane	14	>99	95.8 (*R*)
7	2'-acetylthiophene	14	>99	95.5 (*R*)
8	tetralone	7	>99	98.1 (*R*)
9	1'-indanone	5	>99	96.8 (*R*)
10	2'-acetonaphtene	7	>99	93.7 (*R*)

[a] Reactions were performed at 40 °C, for a certain period of time, using 0.5 mmol of ketone and FA/TEA (1.2/1 molar ratio; 0.25 mL total volume); S/C = 100 in 0.25 mL of water. [b] Determined by NMR. [c] Determined by SFC.

Various ketones, including 2-substituted, electron-rich, and electron-poor substrates, were reduced with good to excellent enantioselection (Table 2). The electronic effect of the substrates was important towards the enantioselectivity of the reaction. Electron-poor aromatic ring bearing halogenated substituents provided the lowest enantioselectivities (Table 2, entries 1-4). Furthermore, *o*-chloroacetophenone required an increased reaction time. In contrast, methoxyacetophenone was reduced in good *ee* (95.5%). Interestingly, 1'-indanone, acethylthiophene and tetralone provided the best enantioselectivities with 96.8%, 97.2% and 98.1%, respectively. These results indicated that steric hindrance plays a key role in ketone reduction with our catalyst. This trend was also observed by Li and coworkers with *N*-PEG400-TsDPEN ligand,[32] although, TAP-TsDPEN demonstrated better capacities, both in terms of activity and enantioselectivity.

The recycling abilities of the present catalytic system were evaluated with Acp and an aqueous FA/TEA mixture as hydrogen source. After full conversion of Acp (followed by TLC), addition of hexane allowed the extraction of the product; the residue containing the catalyst was reused by adding fresh FA/TEA mixture to regenerate the hydrogen source for the next cycle. TAP-Ru-TsDPEN was reused in four cycles without any significant loss of actitity (Table 3). These results are in accordance with the limit of catalyst performances of 550 TON. However, in the 4th and 5th run, longer reaction times were necessary to yield the reported conversions (Table 3, entries 4 and 5).

Table 3 Conversion/*ee* vs. number of run for ATH of Acp[a]

Run	Time (h)	Conv. (%)[b]	*ee* (%)[c]
1	7	>99	94.7
2	7	>99	95.0
3	7	>99	95.2
4	16	>99	94.9
5	36	75	92.1

[a] Reactions were performed at 40 °C, for a certain period of time, using Acp (2 mmol; S/C = 100) in aqueous Et_3N-HCOOH (1.2/1 molar ratio) with TAP-Ru-TsDPEN. [b] Determined by NMR. [c] Determined by SFC.

An attractive feature of supported catalyst lies on the possibility to separate the catalyst from the products. In order to confirm that TAP-Ru-TsDPEN can be readily removed from the reaction mixture, precipitation experiments were conducted. A first catalysis was performed in the same reaction conditions as described in Table 3, except that temperature was increased to 60 C. At the end of the reaction, addition of an excess of Et_2O allowed the precipitation and easy recovery of the catalyst. Two consecutive catalytic runs were performed by adding fresh

FA/TEA mixture, water and Acp (see ESI). From these consecutive runs, the following conversions and *ee*'s were obtained: 1st run (in 3h), >99% conversion, 93.1% *ee*; 2nd run (in 6h), 92% conversion, 93.1% *ee*; and 3rd run (in 24h), 60% conversion, 93.5% *ee*. The decrease in catalytic activity can be attributed to catalyst loss during solvent extraction, *i.e.* ruthenium leaching into the organic phase. Since enantioselectivities remained intact, it appears that the catalyst did not decompose, even after three precipitations. We conclude from these results that TAP-Ru-TsDPEN is a remarkably stable supported catalyst.

Conclusions

In conclusion, a straightforward synthesis to prepare Noyori-Ikariya TAP-supported catalyst has been described. The resulting supported catalyst proved to be highly effective and easily separable in asymmetric transfer hydrogenation of simple ketones in water with HCOOH-Et_3N as the hydrogen source. In addition, the supported catalyst can be extracted from the reaction and be reused several times whilst maintaining its good performance.

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Notes and references

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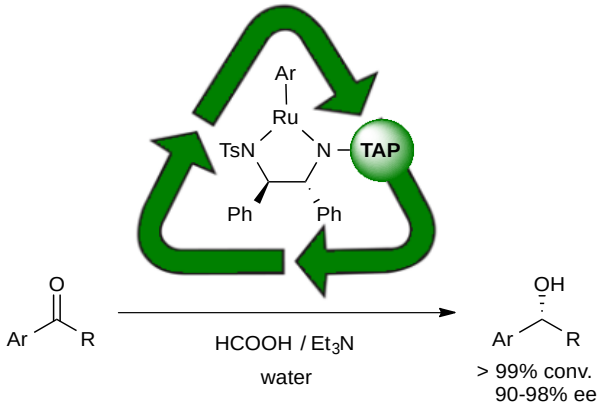

An easily prepared, low molecular weight supported Noyori-Ikariya catalyst is described. The tetraarylphosphonium-supported ruthenium precatalyst provides excellent conversions and high enantioselectivities for the asymmetric transfer hydrogenations of ketones in water. The catalyst can be recycled and reused up to four times without any significant loss of activity.