

Review

# Green chemistry: C–C coupling and asymmetric reduction by innovative catalysis

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## Abstract

A catalytic method has been developed, which allows aryl halides to couple with various electron-rich olefins to give 1,1'-substituted olefins. The palladium-catalysed coupling in ionic liquid solvent proceeds with high efficiency and remarkable regioselectivity without the need for any costly or toxic halide scavengers. Parallel to this, an environmentally appealing method for the asymmetric reduction of ketones has been established, with which a variety of chiral alcohols can be accessed with high enantioselectivity in water with no need for any organic solvents. The same chemistry has been explored for the reduction of aldehydes, which is shown to be fast and highly chemoselective. These methods add new tools to the armoury of synthetic chemists.

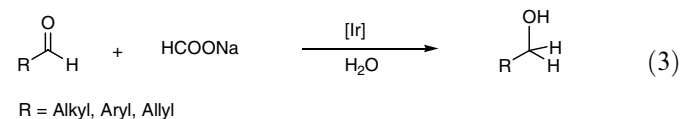
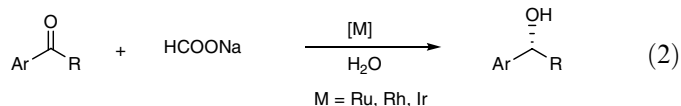
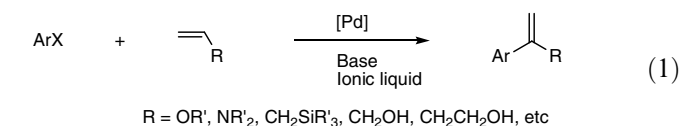
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**Keywords:** Heck reaction; Transfer hydrogenation; Ionic liquid; Water; Green chemistry

## 1. Introduction

Catalysis is the cornerstone of green chemistry, which in turn underpins sustainable development. Novel catalytic methods, such as those that are atom-economic and circumvent the need for hazardous solvents and reagents, contribute particularly to the greening of chemical processes [1]. In our search for green catalytic methods for synthetic organic chemistry, we recently developed a palladium-catalysis method that allows aryl halides to couple with various electron-rich olefins, furnishing 1,1'-substituted olefins in excellent regioselectivities and yields (Eq. (1)) [2–6]. These olefins provide a plethora of molecules that can be used to build more complex compounds and as valuable substrates for new transformations, such as asymmetric oxidation and reduction. At around the same time, we discovered that ketones can be readily reduced by asymmetric transfer

hydrogenation in neat water to give secondary alcohols at fast rates and high enantioselectivities (Eq. (2)) [7–13]. Further studies showed that the same chemistry applies to the reduction of aldehydes (Eq. (3)) [14].



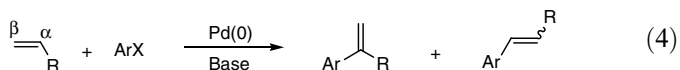
Herein we present a brief account of our effort in developing the palladium-catalysed Heck arylation of electron-rich olefins and the aqueous-phase transfer hydrogenation of

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ketones and aldehydes. These methods are simpler and more practical than currently available approaches, and allow a great number of functionalised small molecules to be readily accessible in a greener manner.

## 2. Heck arylation of electron-rich olefins

Palladium-catalysed arylation and vinylation of olefins by aryl or vinyl halides, that is, the Heck reaction, are now one of the most important tools in synthetic chemistry [15–18]. However, the reaction generally works well only with olefins bearing electron-withdrawing substituents, such as  $\text{CO}_2\text{R}$  and  $\text{CN}$ . With electron-rich olefins such as acyclic enol ethers, silanes, and enol amides, it usually results in a mixture of linear and branched regioisomers, thus limiting the wider applicability of the reaction in synthetic chemistry (Eq. (4)). This is so, because the reaction proceeds via two pathways, one ionic leading to the branched product, and the other neutral giving rise to the linear variant. Scheme 1 shows the key intermediates involved in the two pathways proposed in the literature [18]. The problem of regiocontrol can be addressed by using aryl triflates instead of halides or stoichiometric halide scavengers [Ag(OTf) and Tl(OAc) being most often used] when halides are employed [15,18]. However, triflates are thermally labile and in general not commercially available and the inorganic additives create new problems, i.e. waste salts, toxicity and added cost.

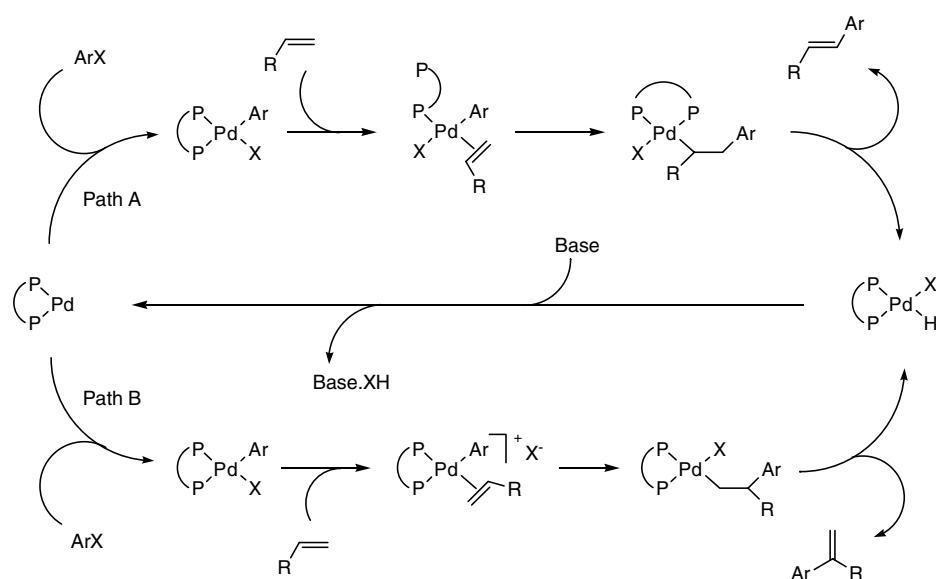


In the course of our investigation into metal-catalysed reactions in imidazolium ionic liquids [2–6,19–27], we discovered that the ionic pathway, and so the production of branched olefins, could be promoted by using ionic liquid

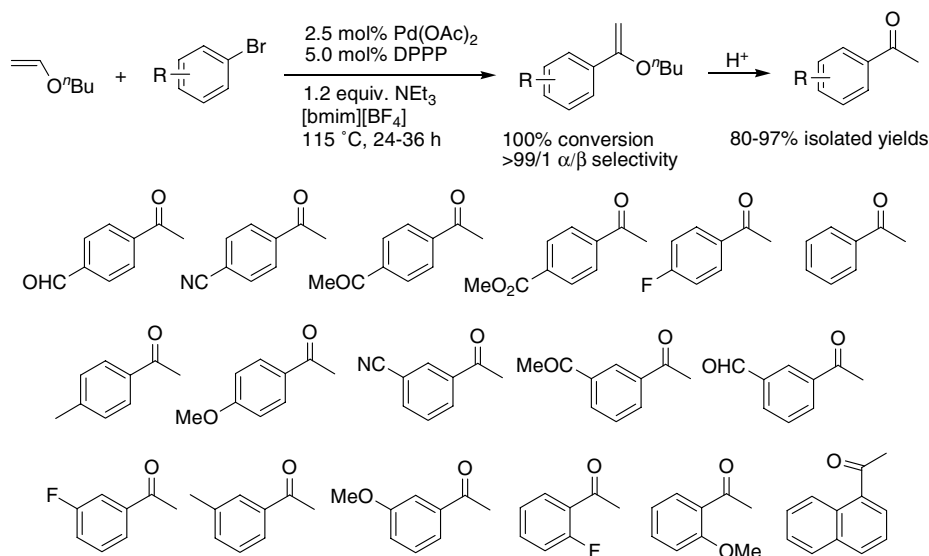
solvents [2–6,19–22]. This may not be surprising. Ionic liquids are entirely composed of ions; hence electrostatic interactions would favour the generation of a Pd–olefin cation and a halide anion from two neutral precursors over that of a neutral Pd–olefin intermediate from the same (Scheme 1). Whilst a great number of catalytic reactions had proved feasible in ionic liquids, with many displaying enhanced reactivities and selectivities [28–39], our results demonstrated the unique capabilities of such media in altering reaction pathways, which had rarely been seen before. Below is a summary of our results obtained in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF<sub>4</sub>]).

### 2.1. Arylation of vinyl ethers

Vinyl ethers are the benchmark electron-rich olefins. Under normal conditions, their regioselective arylation can only be achieved by employing aryl triflates or stoichiometric silver or thallium salts [40–42]. However, when butyl vinyl ether was reacted with an aryl halide in [bmim][BF<sub>4</sub>] in the presence of NEt<sub>3</sub>, Pd(OAc)<sub>2</sub> and 2 equiv. 1,3-bis(diphenylphosphino)propane (DPPP), highly regioselective arylation took place, almost exclusively resulting in the formation of the  $\alpha$ -substituted vinyl ether with no need for halide scavengers. Scheme 2 illustrates the results obtained. The products were isolated as the aryl methyl ketones following hydrolysis of the initially formed branched vinyl ethers. As can be seen, excellent regioselectivities together with high isolated yields for the aryl methyl ketones were obtained in all the reactions in the ionic liquid, regardless of the nature of the substituents on the aryl rings. Thus, bromobenzenes bearing either strongly electron-withdrawing or electron-donating *p*-substituents, such as –CN or –OMe, all furnished good to excellent iso-



Scheme 1. The neutral and ionic pathways of the Heck reaction that lead to linear and branched olefins.

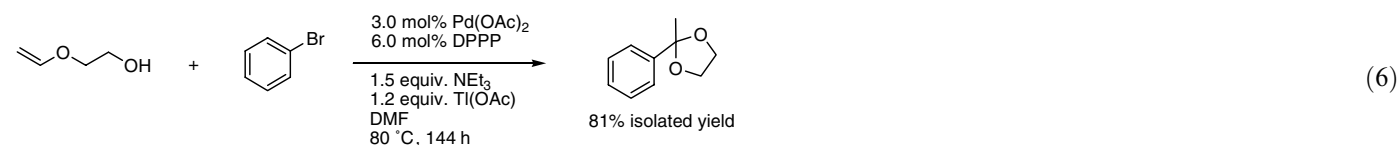
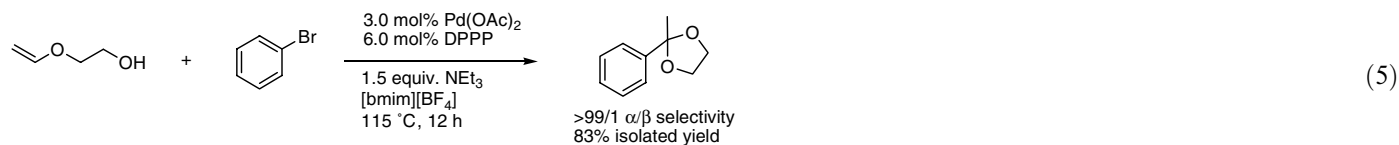
Scheme 2. Regioselective Heck arylation of butyl vinyl ether by aryl bromides in [bmim][BF<sub>4</sub>] and the resulting ketone products.

lated yields with  $\alpha/\beta$  ratios of >99/1. The same reaction can be equally applied to *m*-substituted bromobenzenes having either electron-withdrawing or electron-donating groups. We were pleased that the protocol worked even for some sterically hindered substrates such as the *o*-F and *o*-OMe substituted bromobenzenes, considering that a bulky bidentate ligand is bonded to the palladium centre. However, the sterically more demanding 2-bromo-1,3-dimethylbenzene furnished a conversion of only 9% in a 24-h reaction time. The reactions proceeded smoothly in general, leading to clean products even without chromatographic purification. Under the given conditions, all the reactions shown in the scheme went to completion; but shorter time should be possible, since the reaction time was not optimised for each individual reaction. The remarkable regioselectivities observed in [bmim][BF<sub>4</sub>] suggest that the neutral path A (Scheme 1) is either completely suppressed or its involvement in the arylation in the ionic liquid is insignificant. Being easy to perform and highly regioselective and yielding, the protocol provides a practically useful supplement to the known methodologies for the synthesis of important aromatic ketones [43], and particularly to Friedel-Crafts arylation, which is neither effec-

tive towards electron-deficient arenes nor as regioselective as the current method for the introduction of an acetyl group [44,45].

## 2.2. Arylation of hydroxyvinyl ethers

Hydroxyalkyl vinyl ethers undergo similar reactions and the resulting arylated products can cyclise *in situ* to give cyclic ketals, providing an alternative to the synthesis of protected aryl ketones. This chemistry has been shown to be feasible in molecular solvents such as DMF by Hallberg and coworkers [46]; but it requires the use of either aryl triflates or Ti(OAc) in the case of ArX (X = Br, I), and tends to be slow. In ionic liquids, the arylation with halides took place readily with no need for Ti(OAc), leading to cyclic ketals with >99% regioselectivities and faster rates. A variety of aryl bromides have been demonstrated to undergo the coupling reactions with 2-(vinylloxy)ethanol and 4-(vinylloxy)butan-1-ol, affording five- or seven-membered cyclic ketals in good to excellent yields. An example is given in Eq. (5), alongside one reported by Hallberg for comparison (Eq. (6)) [19].



### 2.3. Arylation of allyltrimethylsilane

To extend the scope of this highly regioselective Heck chemistry, the arylation of allyltrimethylsilane was also examined. The arylated branched allylsilanes are important intermediates in organic synthesis including palladium-catalysed C–C bond formation [47–50]. Unfortunately, under traditional Heck reaction conditions, intermolecular arylation of allyltrimethylsilane with aryl halides affords linear arylated silanes, even in the presence of silver additives [51]. In contrast, when performed in the ionic environment provided by [bmim][BF<sub>4</sub>], the arylation with aryl bromides of diverse electronic properties proceeded regioselectively to give branched allylsilanes in good to excellent yields. Thus, as shown in Scheme 3, the aryl bromides reacted with allyltrimethylsilane, furnishing exclusively the  $\beta$ -arylated allylsilanes in 65%–93% isolated yields in the presence of Pd(OAc)<sub>2</sub> and DPPP in [bmim][BF<sub>4</sub>]. Similar regioselective arylation of allyltrimethylsilane could also be achieved in CH<sub>3</sub>CN; but aryl triflates were necessary, according to Hallberg and coworkers [52]. In addition to relying on triflates, the yields (31%–85%) were generally lower in comparison with the ionic liquid protocol described here. Hallberg suggested that the reaction proceeds via the ionic pathway, the key step being migration of the aryl group to the positively charged  $\beta$  carbon stabilized by the SiMe<sub>3</sub> unit [which could be understood as arising from the olefin acting as a nucleophile attacking the electrophilic palladium (II)]. The excellent selectivities towards the branched products we observed in ionic liquid are in line with this view. Owing to its superior selectivity and yield and functional group compatibility, the present method compares favourably with available methods in the literature for the preparation of  $\beta$ -arylated allylsilanes [52,53].

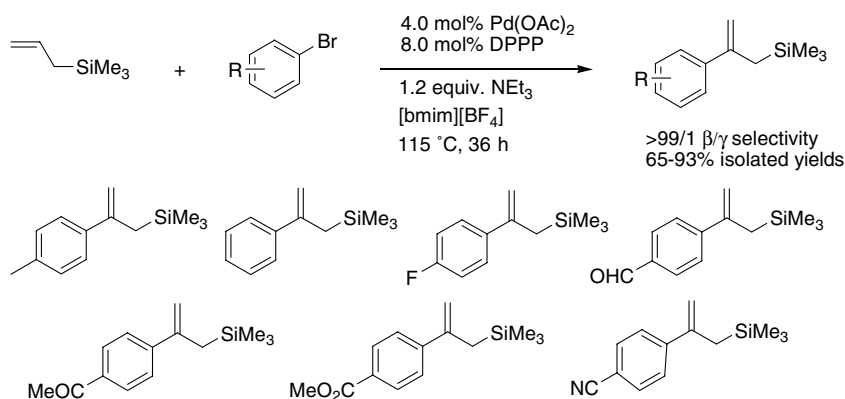
### 2.4. Arylation of enamides

Enamides are another class of electron-rich olefins and their arylation could lead to synthetically and catalytically important  $\alpha$ -arylenamides [54]. Surprisingly, there appeared to be no literature examples in which enamides

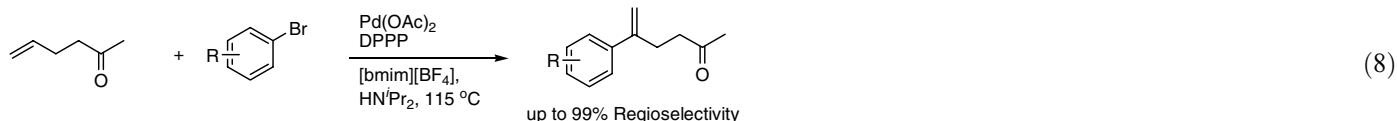
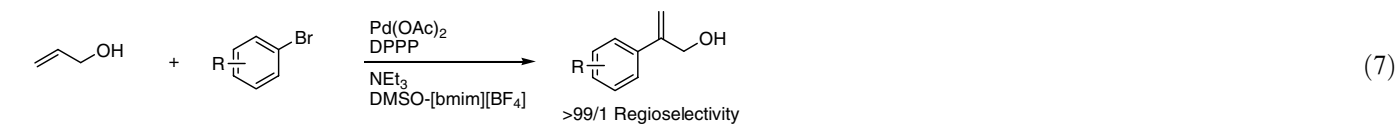
had been  $\alpha$ -arylated with aryl halides, although 1-naphthyl triflate, and recently vinyl triflates, were shown to react with enamides, regioselectively furnishing branched olefins [39,55]. More recently, Larhed and coworkers reported successful regioselective couplings of *N*-methyl-*N*-vinylacetamide with arylboronic acids in 1,4-dioxane, using a phenanthroline ligand for palladium under an atmosphere of oxygen [56]. Applying the conditions established for the vinyl ether, we were disappointed to find that *N*-methyl-*N*-vinylacetamide showed little sign of coupling with the bromoacetophenone in [bmim][BF<sub>4</sub>]. However, when DMSO was introduced as the co-solvent, smooth, regioselective arylation took place. Scheme 4 shows the results obtained with Pd-DPPP in a 1:1 (volume) mixture of [bmim][BF<sub>4</sub>] and DMSO. It should be pointed out that in neat DMSO a mixture of species was formed, in which the olefinic product was the branched one but insignificant. In comparison with Larhed's oxidative coupling using the more costly arylboronic acids [56], our reaction required harsher conditions but afforded in general higher regioselectivities and higher yields. With both methods, aryl substrates bearing the strongly electron-withdrawing -CN group failed to give good conversions, however. The role of DMSO is not entirely clear to us; it may facilitate  $\beta$ -hydrogen elimination by replacing the coordinated amide from palladium. Amine or carbonyl coordination could occur following aryl insertion, impeding the access of  $\beta$ -hydrogen to palladium [57].

### 2.5. Arylation of other electron-rich olefins

Recently, we have also demonstrated that allylic alcohol and 5-hexen-2-one display similar regioselective chemistry with aryl bromides in a mixed solvent made of [bmim][BF<sub>4</sub>]-DMSO or in [bmim][BF<sub>4</sub>] (Eqs. (7) and (8)) [21,22]. The reaction with allyl alcohol is particularly regioselective, furnishing only the internal arylated allylic alcohols, while that with 5-hexen-2-one provides the  $\delta$ -arylated  $\delta,\gamma$ -unsaturated ketones in regioselectivities of up to 99%. These products can serve as valuable synthons in synthesis and as novel substrates for asymmetric transformations.



Scheme 3. Regioselective Heck arylation of allyltrimethylsilane by aryl bromides in [bmim][BF<sub>4</sub>] and the resulting products.



In a significant, more recent development, we discovered that the regioselective arylation reactions in ionic liquids aforementioned can be considerably accelerated by potential hydrogen-bond donating ammonium salts, such as  $[\text{HNEt}_3][\text{BF}_4]$ . Further studies have shown that these salts also enable highly regioselective arylation to take place in common molecular solvents, such as DMF [20].

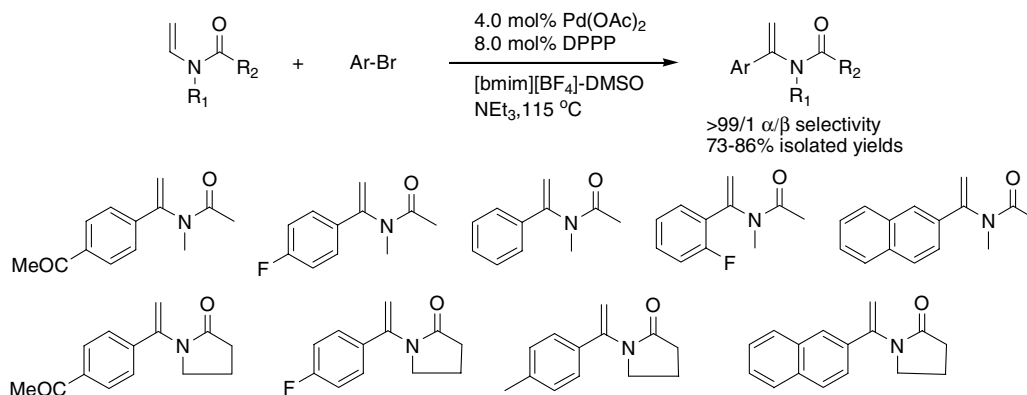
### 3. Asymmetric transfer hydrogenation in water

Asymmetric transfer hydrogenation presents an attractive alternative to asymmetric hydrogenation for the production of chiral alcohols and amines. It requires neither hazardous hydrogen gas, nor pressure vessels, and there are a number of chemicals that are easily available and can be used as hydrogen donors [58–68]. In 1995, Noyori et al. published a seminal paper, reporting a TsDPEN-coordinated Ru(II) complex (Ru-TsDPEN) [TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine] to be an excellent precatalyst for the asymmetric reduction of aromatic ketones, with ee's higher than 99% being obtained [69]. Shortly after, a variety of related catalysts were developed, and new variants are still being reported [70–80]. These catalysts have since been applied to the asymmetric reduction of a wide range of prochiral ketones and imines from academic laboratories to commercial scale [7–14,58–112].

The azeotropic mixture of HCOOH and  $\text{NEt}_3$  (F-T, 2.5 HCOOH/ $\text{NEt}_3$  molar ratio) and 2-propanol are most frequently used as the solvent as well as a hydrogen donor. However, in most cases, the reduction tends to be slow under these conditions. In a DTI MMI (Manufacturing Molecule Initiatives) project aimed at understanding and developing molecular catalysts, we discovered that water acts as an excellent solvent for the asymmetric transfer hydrogenation of ketones by formate with M-diamine catalysts (M = Ru, Rh and Ir) [7–14]. The reduction is easy to conduct, requiring no modification to the common catalysts, no organic solvent, and often no inert gas protection throughout, and uses one of the most easily available and inexpensive hydrogen donors, thus providing a new viable tool for ketone reduction.

#### 3.1. Asymmetric transfer hydrogenation of ketones

Our interest in this area arose from a study of asymmetric transfer hydrogenation with an immobilised Ru-TsDPEN catalyst, where we discovered that water enhances the reduction rates and enantioselectivities [8,81]. This finding prompted us to examine the behaviour of the unmodified Ru-TsDPEN catalyst in ketone reduction by HCOONa in water. Whilst a great number of aqueous-phase catalytic reactions have been described, there were only a few reports on asymmetric transfer hydrogenation



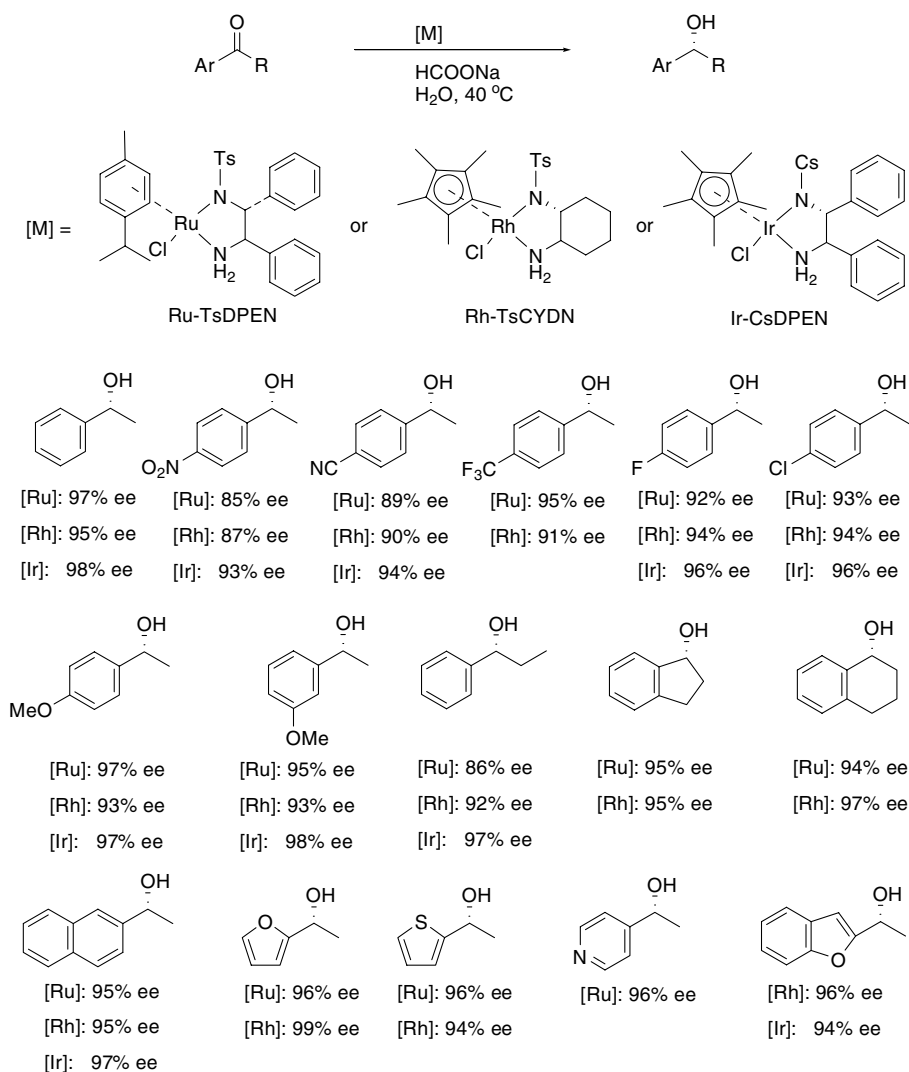
Scheme 4. Regioselective Heck arylation of enamides by aryl bromides in  $[\text{bmim}][\text{BF}_4]$  and the resulting products.

in neat water or using water as co-solvent, none of which concerned catalysis by unmodified M-diamine (diamine = TsDPEN, TsCYDN) catalysts in water prior to 2004 [82–87].

In our initial investigation, acetophenone was chosen as a model substrate to test the feasibility of the aqueous-phase reaction [7]. The precatalyst was generated by reacting TsDPEN with  $[\text{RuCl}_2(p\text{-cymene})_2]$  in water at 40 °C for 1 h. We soon discovered that the aqueous-phase reduction is much faster. Thus, following the addition of 5 equiv.  $\text{HCOONa}$  and acetophenone with a substrate/catalyst (S/C) ratio of 100, the ketone was fully converted into (*R*)-1-phenylethanol in 94% ee in 1 h reaction time. In comparison, the reaction run in the  $\text{HCOOH-NEt}_3$  azeotrope afforded a conversion of less than 2% in 1 h, with full conversion requiring more than 10 h. This initial finding has since been proved to be quite general, that is water enables fast and enantioselective asymmetric reduction of unfunctionalised ketones by  $\text{HCOONa}$  with M-diamine catalysis [7–14,82–102]. Scheme 5 shows some selected examples

obtained by us from catalysis with Ru-TsDPEN, Rh-TsCYDN and Ir-CsDPEN.

These reduction reactions are easy to perform and afford the chiral alcohols with high ee's in a short reaction time. We frequently use a S/C ratio of 100; however, S/C ratios of up to 10,000 have been demonstrated to be feasible [9]. The ketones used are generally water-insoluble; but this does not appear to have any negative bearings on the reaction rates. Of particular note is the rhodium catalyst, which catalyses the reduction with ee's of up to 99% and TOFs close to 4000  $\text{mol mol}^{-1} \text{h}^{-1}$  in distilled tap water in the open air with no need for any inert gas protection throughout [10], thus making the protocol extremely easy to be adopted by laboratories or for commercial production. The chiral camphor-substituted ligand, CsDPEN, is both sterically and electronically different from TsDPEN and TsCYDN, and the carbonyl group introduces an additional functionality into the ligand, which could have some bearing on the reduction [13]. The M-CsDPEN catalysts were found to behave somewhat differently from the M-



Scheme 5. Asymmetric transfer hydrogenation of ketones in water and the resulting chiral alcohols.

TsDPEN and M-TsCYDN, with Ir-CsDPEN being the more active rather than Ru- and Rh-CsDPEN at a S/C ratio of 1000, affording the best enantioselectivity in most cases.

Alongside these diamines,  $\beta$ -amino alcohol ligands have emerged as another type of efficient ligands [58–64,71–74]. Following the first report by Noyori and coworkers in 1996 [112], a significant progress has been made by other research groups from then on [58–64,71–74]. However, the  $\beta$ -amino alcohol ligands are believed to be incompatible with formic acid as a reductant in the past [58,67]. Recent work from us [12] and others [91] shows that  $\beta$ -amino alcohol ligands do catalyse the asymmetric transfer hydrogenation of ketones by formic acid or its salts in water; however, the reduction rates and enantioselectivities were much lower than those obtained with the diamines, which have been afore-discussed. Among the ligands screened, (–)-ephedrine yields better results than others in terms of reaction rates and/or ee's, and in general the iridium catalysts exhibit a higher activity [12].

### 3.2. Transfer hydrogenation of aldehydes in water

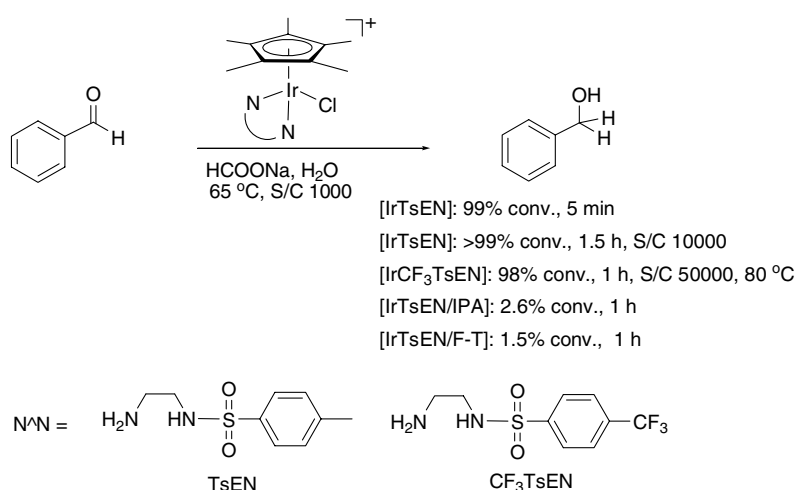
Although considerable efforts on transfer hydrogenation of ketones catalysed with transition metals have been undertaken, aldehydes remained difficult to be reduced by transfer hydrogenation catalysts in the past [58,113–119]. The most efficient catalyst for the reduction of aldehydes by transfer hydrogenation appears to be an iridium complex of an *N*-heterocyclic carbene prior to 2006, affording up to 3000 mol mol<sup>-1</sup> h<sup>-1</sup> TOF in refluxing 2-propanol [115]. With most other metal catalysts, the TOFs obtained ranges from a few to several hundreds per hour [113,114]. In fact, few catalytic systems have been reported, which enable fast, selective and productive transfer hydrogenation of aldehydes with inexpensive, eco-friendly reductants and tolerate the presence of synthetically useful functional groups [58,113–120]. In continuing our research into aque-

ous-phase reduction, we demonstrated that aldehydes can be reduced in neat water and in air with metal-monotosylated ethylenediamine catalysts at fast rates and in a highly chemoselective manner [14]. In particular, the catalyst Ir-CF<sub>3</sub>TsEN formed *in situ* from [Cp\*IrCl<sub>2</sub>]<sub>2</sub> and CF<sub>3</sub>TsEN afforded TOFs of up to 1.3 × 10<sup>5</sup> mol mol<sup>-1</sup> h<sup>-1</sup> in the transfer hydrogenation of benzaldehydes. In contrast, when carried out in isopropanol (IPA) or the azeotropic F-T mixture, a much slower reduction resulted, affording <3% conversion in 1 h (Scheme 6).

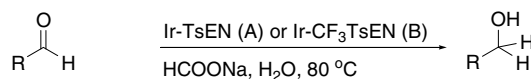
The catalyst works for aromatic,  $\alpha,\beta$ -unsaturated and aliphatic aldehydes and for those bearing functional groups such as halo, acetyl, alkenyl, nitrile and nitro groups and is highly chemoselective towards the formyl group (Scheme 7). For instance, 4-acetylbenzaldehyde was reduced only to 4-acetylphenylethanol, and the reduction of 4-acetyl-cinnamaldehyde took place without affecting the ketone and olefin double bonds. Furthermore, the reduction can be performed in the air, necessitating no inert gas protection throughout. An interesting observation arising from the aldehyde reduction was that no reaction was detected with water-soluble substrates under the conditions employed, indicating that the catalysis takes place 'on water' rather than in water in these biphasic reactions. However, the observation does not exclude the possibility of an in-water reaction that is inhibited by the high concentration of substrate [115,121]. This on-water catalysis represents a most effective, chemoselective and simple means for aldehyde reduction.

### 3.3. Effect of pH on asymmetric transfer hydrogenation in water

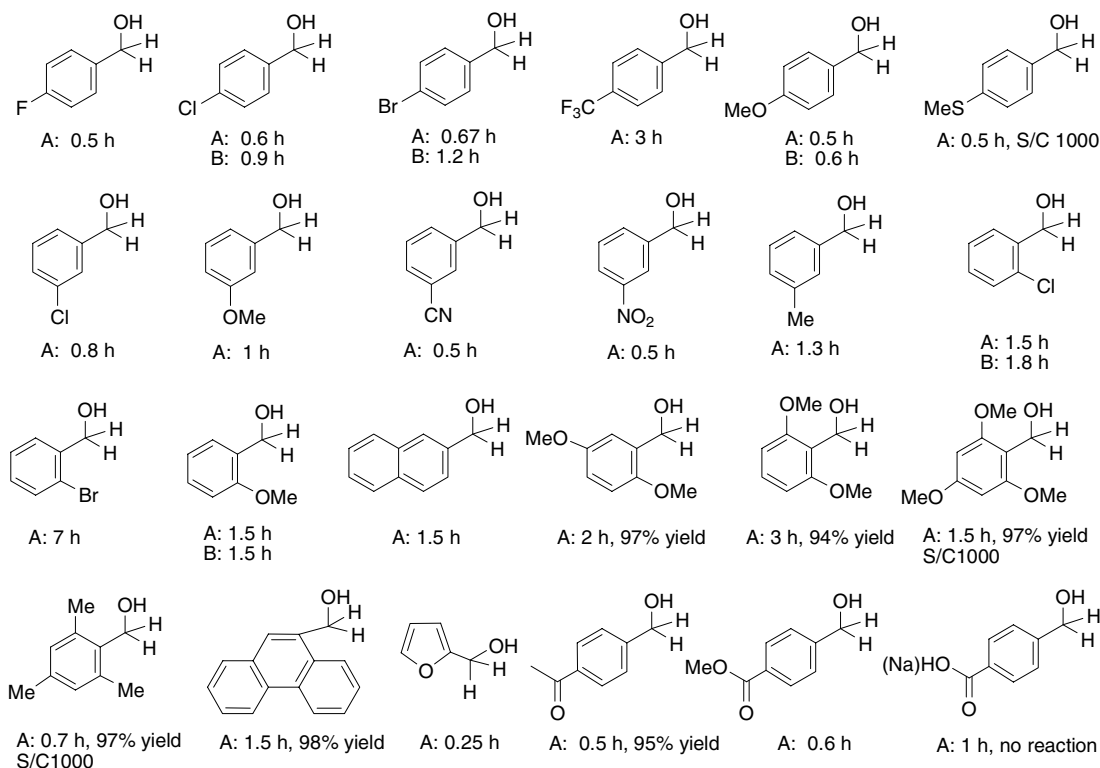
Following on from the finding that aromatic ketones can be reduced more rapidly by HCOONa in water than in F-T with the Ru-TsDPEN catalyst, we investigated the reduction with the F-T azeotrope, using water as solvent, and found the reaction to be much slower than that in



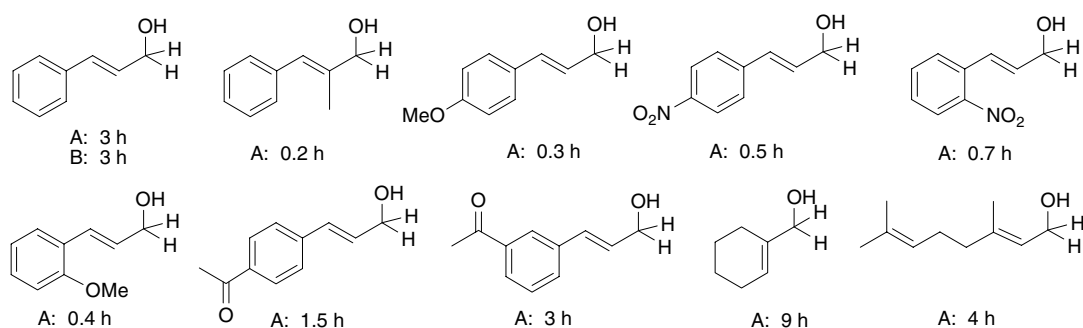
Scheme 6. Comparison of transfer hydrogenation of benzaldehyde (S/C = substrate to catalyst ratio).



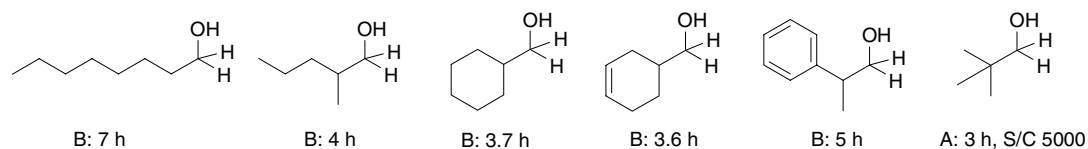
**Aromatic aldehydes [S/C 5000 (A) or 10000 (B), 96 - >99% GC conv.]**



**$\alpha,\beta$ -unsaturated aldehydes [S/C 1000 (A) or 5000 (B), 96-98% isolated yield]**



**Aliphatic aldehydes [S/C 2000 (B), 90-98% GC conv.]**



Scheme 7. Transfer hydrogenation of aldehydes with HCOONa in water.

aqueous HCOONa. The most discernable difference between the two systems was the initial solution pH. The azeotrope-water system displayed an initial pH of 3; but the aqueous HCOONa solution was far more basic, having

a pH of 7. This prompted us to investigate whether the reaction was affected by the pH value of the solution.

Taking the reduction of acetophenone with Ru-TsD-PEN as a model reaction, we showed that the reaction rates



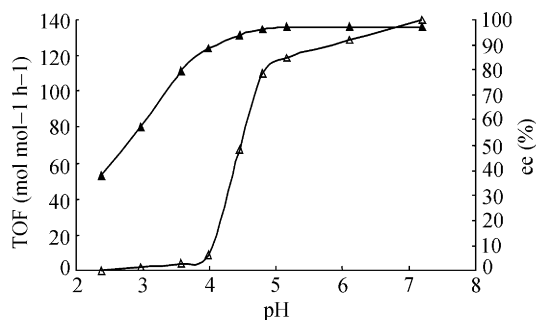


Fig. 1. Plot of initial TOF ( $-\Delta-$ ) and ee ( $-\blacktriangle-$ ) vs initial pH values in the asymmetric transfer hydrogenation of acetophenone with Ru-TsDPEN in water.

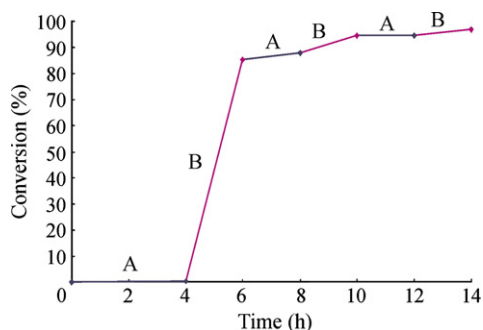


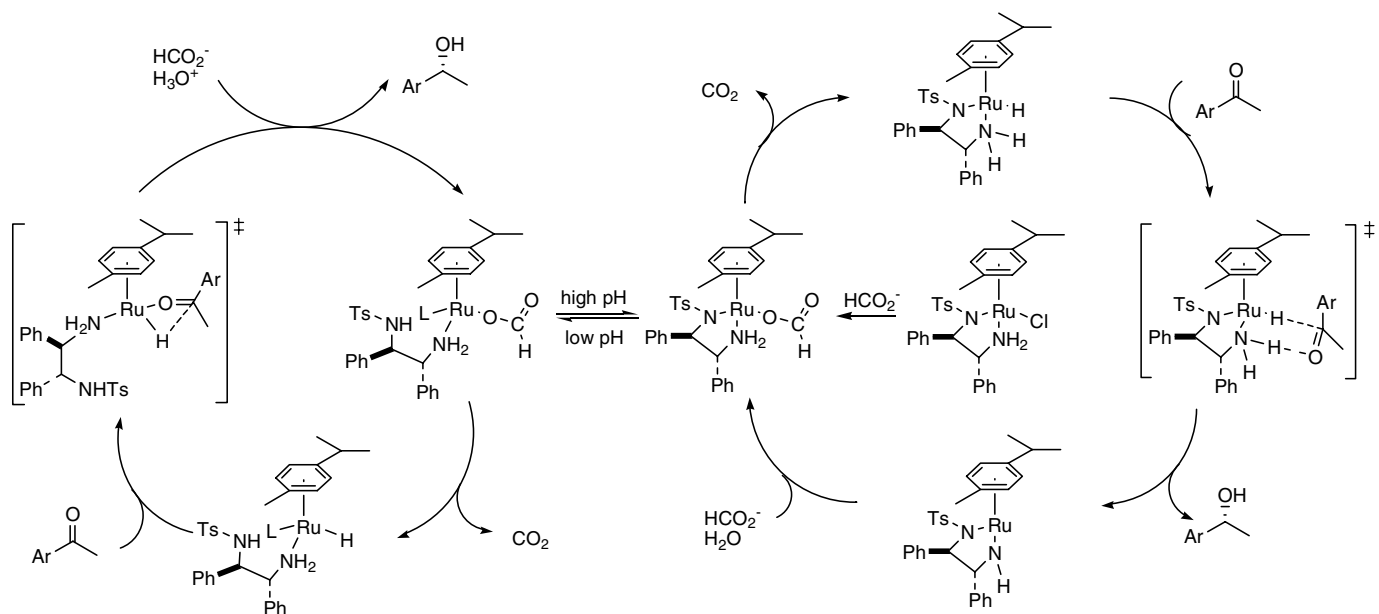
Fig. 2. Graph of conversion vs time for the reduction of acetophenone (1 M) by HCOOH-NEt<sub>3</sub> in water (1:1 initial volume ratio, 0.5 ml water) with Ru-(*R,R*)-TsDPEN at 40 °C. In region (A) the initial HCOOH/NEt<sub>3</sub> molar ratio was maintained at 4.6:1.0 (pH 2.8), whereas in region (B) HCOOH/NEt<sub>3</sub> = 2.3:1.0 (pH 3.7).

varied indeed with solution pH, as revealed in Fig. 1. The reaction barely took place at low pH values, it accelerated at pH 3.9, with the acceleration slowing down at approximately pH 4.8. The rate appeared to level off at pH >7. Remarkably, an increase of 1 pH unit at ca. pH 3.9 resulted

in an increase at the rate of ca. 20 times. Further studies of the reduction starting at pH 2.3 revealed that the reaction was accompanied with a long induction period of ca. 9 h. Little reduction occurred during this time; but decomposition of HCOOH into CO<sub>2</sub> and H<sub>2</sub> by the catalyst was observed and as a consequence, the pH increased with time. Still further, it was found that the enantioselectivity varied with pH, rising quickly from <60% ee at ca. pH 2.3 to >90% ee at ca. pH 4 (Fig. 1).

The observed change in reaction rates with solution pH values suggests that the rates can be modulated by the pH, and we have found that this is indeed the case. Thus, as illustrated in Fig. 2, the reduction of acetophenone could be rapidly initiated by raising the pH value by simply adding NEt<sub>3</sub>, and suppressed by adding HCOOH.

Taking the above observations into consideration, we propose that the aqueous-phase asymmetric transfer hydrogenation proceeds via two competing pathways, one primarily operating under basic conditions, which affords fast rates and high enantioselectivities, whilst the other becoming dominant under acidic conditions, generating lower rates as well as lower ee's (Scheme 8). The one under basic conditions follows Noyori's concerted mechanism [68,71], whilst the one at low pH starts with protonation of the coordinated TsDPEN. The low rates and low ee's in the case of the latter can thus be interpreted as resulting from the conventional, stepwise reduction of ketones and/or from a similar concerted mechanism with a less well-organised transition state. Additional support for the proposed protonation of the ligand arose from the observation that introduction of 1 equiv. (*S,S*)-TsDPEN into the catalytic solution containing Ru-(*R,R*)-TsDPEN at low pH resulted in almost a racemic alcohol product in the reduction of acp at high pH, due to ligand dissociation and the consequent formation of a mixture



Scheme 8. Proposed mechanism for the asymmetric transfer hydrogenation of ketones under acidic and basic conditions (L may be a water molecule).

of equimolar Ru-(*R,R*)-TsDPEN and Ru-(*S,S*)-TsDPEN catalysts [9].

More recently, the dependence of asymmetric transfer hydrogenation on pH in water has also been revealed from work of other groups [87,89,90,93,102,121,122]. The effect of solution pH on achiral transfer hydrogenation is known from the earlier literature [123–125].

### 3.4. Catalyst separation and reuse

For pharmaceutical applications, ease in separation of the metal catalysts from the products is necessary. With water as the solvent, this can be made easy, particularly when the catalyst is water-soluble, as the product can then be removed by simple phase separation. Examples of water-soluble TsDPEN derivatives were reported by Williams, Blacker and coworkers in 2001 and more recently by the group of Deng [82–86]. The M-diamine catalysts aforementioned are partially soluble in water but insoluble in nonpolar solvents. The product of the reduction can thus be extracted with a solvent such as diethyl ether, and this has been demonstrated in our laboratories.

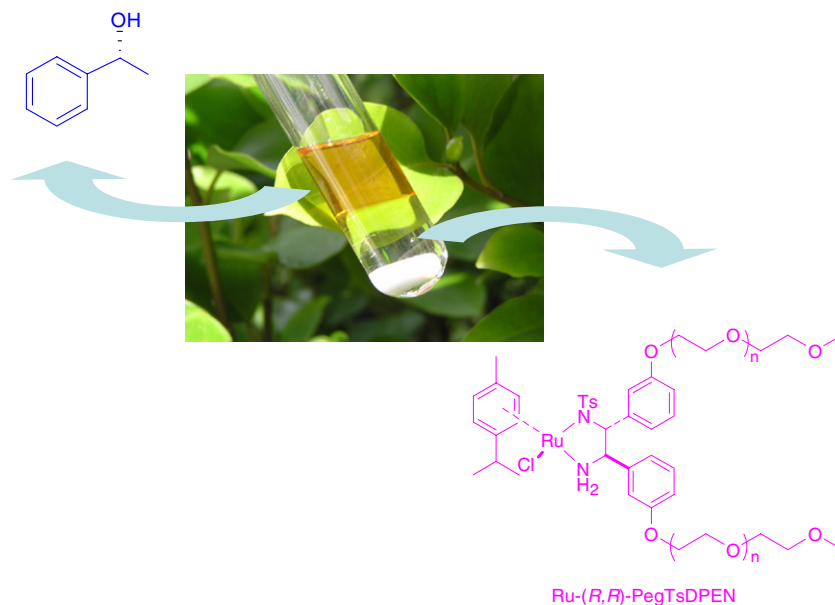
For aqueous ketone reduction by the M-diamine catalysts, an easier and effective method for catalyst separation is to use our Peg-supported ligands, which have an enhanced water solubility, and are retained in water due to the hydrophilic polyethylene glycol chain [8,81]. To demonstrate this, we carried out the reduction of acetophenone by HCOONa with Ru(II)-PegTsDPEN in water (Peg was polyethylene glycol 2000 monomethyl ether), with the product extracted with diethyl ether [8]. As with the non-supported Ru-TsDPEN, Ru(II)-PegTsDPEN is highly effective in water towards a wide range of aromatic ketones. In the case of acetophenone reduction, we measured the leached ruthenium; ICP analysis showed that

only 0.4 mol% of ruthenium leached into the organic phase. Remarkably, the Peg-immobilized catalyst could be reused 14 times with no loss in enantioselectivity, demonstrating its excellent recyclability and lifetime under aqueous conditions (Scheme 9). This represented probably the best example of catalyst recycling in asymmetric aqueous-phase catalysis. When HCOOH-NEt<sub>3</sub> was used without water, the recycle experiments could not be carried out for more than two runs without the rates and ee's being eroded [81].

## 4. Conclusions

In the past few years we have developed methods for the regioselective Heck reaction of electron-rich olefins and for the asymmetric transfer hydrogenation of ketones. A common feature of these methods is that they allow for easy, practical and eco-friendly production of a variety of synthetically valuable fine chemical and pharmaceutical intermediates. In the case of the Heck chemistry, our results demonstrate that imidazolium ionic liquids in combination with the readily available Pd(OAc)<sub>2</sub> and DPPP form an excellent catalytic system, in which highly regioselective and yielding arylation of electron-rich olefins can be accomplished with a wide range of aryl halides with no need for any halide scavengers. In most cases, the arylation furnished essentially only the branched olefins. The unique regiocontrol appears to stem from the ionic environment provided by the ionic liquid solvent, which alters the reaction mechanism in such a way that the key ionic pathway responsive for the olefin under question is made favourable.

Our work on asymmetric transfer hydrogenation has established that ketones can be readily reduced by formate in neat water with the M-diamine catalysts (M = Ru, Rh,



Scheme 9. Catalyst recycling with Ru-PegTsDPEN in water and product in ether.

Ir). The aqueous-phase reduction affords various chiral secondary alcohols in excellent rates and enantioselectivities, and is easy to perform, requiring no tailoring of catalyst, no substrate solubility in water, and often no protection by inert gas. Equally important is the reduction of aldehydes with Ir-TsEN and Ir-CF<sub>3</sub>TsEN, which are highly active and tolerate various synthetically important functional groups including nitro, halo, ketone, ester and olefins.

Water plays an important role in the reduction; it provides a soluble form of formate and enables easy catalyst/product separation and more significantly, it stabilises the active catalysts. Our most recent work suggests that water participates in the transition state of the aqueous-phase reduction, thereby lowering the activation barrier. The work described here provides a stepping stone towards a greener fine chemical and pharmaceutical synthesis.

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