

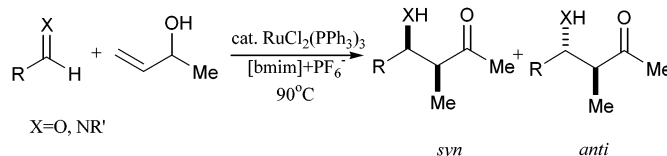
Aldol- and Mannich-Type Reactions via
in Situ Olefin Migration in Ionic LiquidXiao-Fan Yang,[†] Mingwen Wang,[†] Rajender S. Varma,[‡] and Chao-Jun Li^{*,†}

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ABSTRACT



An aldol-type and a Mannich-type reaction via the cross-coupling of aldehydes and imines with allylic alcohols catalyzed by $\text{RuCl}_2(\text{PPh}_3)_3$ was developed with ionic liquid as the solvent. The solvent/catalyst system could be reused for at least five times with no loss of reactivity.

Aldol-type reactions are recognized as one of the most important reactions for forming carbon–carbon bonds. However, under the classical aldol reaction conditions,¹ dimerization, polymerization, and self-condensation (some of the undesirable reactions) also occur. To avoid such competing processes, an important modification of the classical aldol reaction has been developed by treating enol silyl ether with carbonyl compounds in the presence of Lewis acids (the Mukaiyama aldol reaction).² Recently, attention has been focused on developing cross-aldol reactions by alternative approaches. Toward this goal, Trost reported a highly efficient formation of aldol-type products via vanadium-catalyzed coupling of propargyl alcohols with aldehyde.³ Recent developments also include hydrometalation-aldol⁴ and C–H activation-aldol reactions of carbonyl compounds.⁵ Motherwell developed the Rh- and Ni-catalyzed isomerization of allylic lithium alkoxide to lithium enolate, which

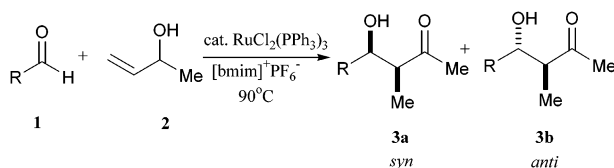
underwent further aldol reaction.⁶ Grée and co-workers recently reported the isomerization of allylic alcohol to enol catalyzed by $\text{Fe}(\text{CO})_5$ under photolytic conditions, which then reacted with aldehydes to give aldol products (in addition to other products).⁷

Recently, interest has been growing to develop organic reactions in environmentally friendly media, i.e., “green solvents”.⁸ For aqueous aldol-type condensations, Chan developed the tin- and zinc-mediated cross-couplings of halo-ketones with aldehydes.⁹ Lubineau,¹⁰ Kobayashi,¹¹ Loh,¹² and others¹³ developed the aqueous Mukaiyama-type reactions.

Another group of promising green solvents that have

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Scheme 1



gained much attention recently is “ionic liquids.” Their nonvolatile nature gives them significant advantage in minimizing solvent consumption. Their polarity renders them good solvents for transition metal catalysis and therefore good reaction media for homogeneous catalysis.¹⁴ Because of their unique solubility properties, i.e., miscibility gap between water and organic solvents, they have become interesting candidates for separation processes by simple liquid–liquid extraction with either aqueous or conventional organic solvents.¹⁵

Previously, we reported that in the presence of a catalytic amount of $\text{RuCl}_2(\text{PPh}_3)_3$ functional groups of homoallylic alcohols and allylic alcohols underwent rearrangement in air and water.¹⁶ A side reaction of the isomerization is the formation of a ketone, which was rationalized by a competing process involving the cleavage of the allylic C–H bond (instead of the C–O bond) to form a ruthenium-enol complex,¹⁷ followed by hydrolysis to give the ketone. We envisioned that in the presence of an aldehyde, such a ruthenium-enol complex may be captured,¹⁸ and indeed we found that aldol products were formed via a $\text{RuCl}_2(\text{PPh}_3)_3$ -catalyzed cross-coupling of allylic alcohols and aldehydes in water.¹⁹ We now report for the first time aldol-type (Scheme 1) and Mannich-type (Scheme 3) reaction between aldehydes and imines with allylic alcohol catalyzed by $\text{RuCl}_2(\text{PPh}_3)_3$ in ionic liquid.

In many applications ionic liquids with weakly coordinating anions, such as BF_4^- and PF_6^- , together with suitably substituted cations often result in an altered chemical

reactivity of the dissolved catalyst and therefore improve both reactivity and selectivity.¹⁴ Among the commonly used ionic liquids, 1-butyl-3-methylimidazoliumhexafluorophosphate ($[\text{bmim}]\text{PF}_6$) is a popular reaction medium for a wide variety of transition metal catalyzed organic transformations such as hydrogenation,²⁰ oxidation,²¹ hydroformylation,²² oligomerization,²³ etc.

In initial explorations, when 3-buten-2-ol was stirred with benzaldehyde and a catalytic amount of $\text{RuCl}_2(\text{PPh}_3)_3$ (5 mol %) in $[\text{bmim}]\text{PF}_6$ for 24 h at room temperature, no desired product was obtained. When the mixture was heated at 90°C in an oil bath, the reaction mixture became homogeneous and a smooth reaction occurred to give the desired aldol product (with a syn:anti ratio of 71:29, stereochemistry determined by comparison with literature data)¹³ in 81% isolated yield.²⁴ Decomposition of the desired product was observed after prolonged reaction time, e.g. overnight, possibly due to elimination of the hydroxy group to give an α,β -unsaturated ketone. A small amount of 2-butanone was detected by GC, although exact quantification was difficult to achieve because of the volatility of the ketone. Subsequently, a variety of aromatic aldehydes were examined under similar reaction conditions (Table 1). In most cases,

Table 1. Coupling of Aldehydes with Allylic Alcohol in Ionic Liquid

entry	aldehyde (R)	solvent	time (h)	yield (%) ^a	syn/anti ^b
1	Ph	I.L.	1.5	81	71/29
2	<i>m</i> -F-C ₆ H ₄	I.L.	1.5	68	68/32
3	<i>p</i> -Cl-C ₆ H ₄	I.L.	2	75	71/29
4	<i>p</i> -Br-C ₆ H ₄	I.L.	1	79	75/25
5	<i>p</i> -MeO-C ₆ H ₄	I.L.	1	80	72/28
6	<i>p</i> -Ph-C ₆ H ₄	I.L.	1	84	71/29
7	2-naphthyl	I.L.	2	94	69/31
8	<i>n</i> -C ₇ H ₁₅	I.L.	1	67	37/63
9	diphenylmethyl	I.L.	2	46	16/84
10	2-phenylethyl	I.L.	2	52	33/67
11	cyclohexyl	I.L.	2	65	42/58
12	<i>p</i> -Cl-C ₆ H ₄	H ₂ O	5	35	60/40
13	<i>p</i> -Cl-C ₆ H ₄	H ₂ O–toluene (4:1)	5	70	76/26
14	2-naphthyl	H ₂ O–toluene (4:1)	5	44	63/37

^a Isolated yields were reported. ^b the diastereoselectivity was based on ¹HNMR analysis of the crude products.

the desired aldol products were obtained in good yields even with less reactive aldehydes such as 2-naphthaldehyde or *p*-anisaldehyde. The only exception was 4-hydroxybenzaldehyde, with which a very low yield was achieved. One

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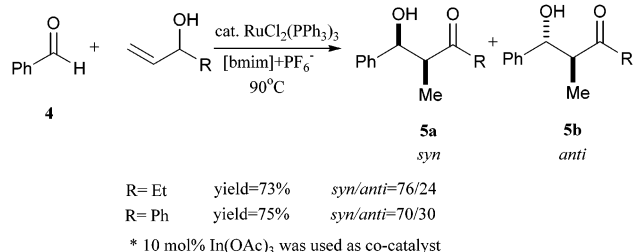
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Scheme 2



plausible explanation was the hydroxy group on the benzene ring coordinating with and deactivating the ruthenium catalyst. Comparing with other solvents such as water and water–organic solvent mixture (entries 3, 12, and 13, Table 1) the catalyst exhibits higher activity in ionic liquid, with improved yield and shortened reaction time. Moreover, the results exhibit a “reverse” trend in the reactivity of aldehydes as compared to aldol condensation in organic solvents and aqueous solutions (entries 7 and 14, Table 1), in which electron-deficient aldehydes give better yields and electron-rich substrates normally result in low yields or no reaction. Although a detailed explanation is unavailable at this moment, this trend could be a result of the unique solvation properties of the ionic liquid, where more polarized electron-deficient aldehydes tend to be more readily solvated by anions and cations of the solvent and therefore less likely to be approached by catalyst-activated enols. Nevertheless, the reaction provides good substitution for other aldol reactions when electron-rich aromatic aldehydes are desired reactants. The diastereoselectivity remains relatively consistent, favoring the *syn* product.

The reaction of 3-buten-2-ol with aliphatic aldehyde in $[\text{bmim}]\text{PF}_6$ was also examined. Unlike the aqueous condition, the reaction went smoothly in ionic liquid with all aliphatic aldehydes, although the yields were considerably lower than for aromatic substrates. It was also observed that unlike aromatic aldehydes, which gave a relatively constant *syn-anti* ratio, the diastereoselectivity in the condensation of aliphatic aldehydes was substrate-dependent, favoring the *anti* product. However, when this catalytic system was applied to ketones, neither aromatic nor aliphatic substrates gave satisfactory yields. Work is in progress to increase the conversion rate of ketone condensation and subsequently broaden the application of this methodology.

Other allylic alcohols such as 1-penten-3-ol and α -vinylbenzyl alcohol readily react with aldehydes in a similar way (Scheme 2). A control reaction of methyl ethyl ketone with benzaldehyde under the same reaction condition was carried out and only starting material was recovered after 24 h. When

(24) **Typical Experimental Procedure.** A mixture of aldehyde/imine (0.1 mmol), 3-buten-2-ol (0.25 mmol), and $\text{RuCl}_2(\text{PPh}_3)_3$ (0.005 mmol) in $[\text{bmim}]\text{PF}_6$ (0.3 mL) was stirred at 90°C in a sealed reaction vessel. After 1.5 h, the reaction mixture was cooled to room temperature and extracted with ethyl ether (3×2 mL), and the combined ether phase was washed with brine and dried over anhydrous Na_2SO_4 . The mixture was then concentrated under reduced pressure. The residue was purified by preparatory TLC on silica gel to afford the desired aldol product.

Table 2. Coupling of Imines with Allyl Alcohol in Ionic Liquid

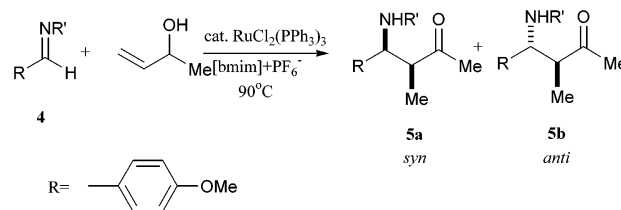
entry	imine (R)	solvent	time (h)	yield (%) ^a	syn/anti ^b
1	Ph	I.L	3	77	56/44
2	<i>m</i> -F-C ₆ H ₄	I.L	3	61	61/39
3	<i>p</i> -Cl-C ₆ H ₄	I.L	2	79	58/42
4	<i>p</i> -Br-C ₆ H ₄	I.L	2.5	72	50/50
5	<i>p</i> -MeO-C ₆ H ₄	I.L	3	84	53/47
6	<i>o</i> -Me-C ₆ H ₄	I.L	3.5	70	43/57
7	2-naphthyl	I.L	3	75	54/46
8	<i>p</i> -Cl-C ₆ H ₄	MeOH	10	68	59/41
9	<i>p</i> -Cl-C ₆ H ₄	H ₂ O–toluene (1:4)	10	38	55/45

^a Isolated yields were reported. ^b Diastereoselectivity was based on ^1H NMR analysis of crude products.

benzaldehyde was treated with 4-phenyl-2-hydroxy-3-butene, elimination of water from the alcohol took place, which indicates that the migration of the double bonds could become difficult by stabilizing it with conjugated aromatic systems.

Following this success, a related Mannich-type reaction via olefin migration was also examined under similar reaction conditions.²⁴ As a model study, *p*-anisidine was used to synthesize the imine, which was subsequently treated with allylic alcohol and Ru catalyst. The desired Mannich products were obtained efficiently (Scheme 3, Table 2). Compared with other solvents, the reaction went faster in ionic liquids, with a higher yield (entries 3, 8 and 9). Unlike the aqueous medium, where aldol products were also formed as a result of decomposition of imine, only Mannich products were detected in ionic liquids.

Scheme 3



Having established the viability of this reaction, attention was focused on recycling of the Ru catalyst in $[\text{bmim}]\text{PF}_6$. 2-Naphthaldehyde was used as substrate in view of the high conversion rate. After ether extraction of the product, the ionic phase was dried in air, and the catalytic system was reloaded with 2-naphthaldehyde and 3-buten-2-ol for the next run. As shown in Table 3, the solvent/catalyst system could be reused for at least five times with essentially no loss of activity. Whether this high recycling efficiency can be achieved with other aromatic and aliphatic aldehydes remains to be established.

In summary, we have developed an aldol-type and a Mannich-type reaction via the cross-coupling of aldehydes

Table 3. Recycling Studies of Ru–Ionic Liquid Catalytic System

cycle	yield (%)	<i>syn/anti</i>	time (h)
1	92	72/28	2
2	89	71/29	2
3	90	70/30	2.5
4	93	70/30	3
5	88	70/30	4

and imines with allylic alcohols catalyzed by $\text{RuCl}_2(\text{PPh}_3)_3$ in ionic liquid. The solvent/catalyst system is very reactive and could be reused for at least five times with no loss of

reactivity. The scope, mechanism, and synthetic applications of the reactions are currently under investigation

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Supporting Information Available: Representative experimental procedure and the full characterization of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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