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Lanthanide triflate-catalyzed three component synthesis of α-amino phosphonates in ionic liquids. A catalyst reactivity and reusability study

Sang-gi Lee,*[a] Jung Hwan Park,[a] Jahyo Kang[b] and Jae Kyun Lee[a]

[a] *Life Sciences Division, Korea Institute of Science and Technology, PO Box 131, Cheongryang, Seoul 130-650, Korea. E-mail: sanggi@kist.re.kr*
[b] *Department of Chemistry, Sogang University, Seoul 121-742, Korea*

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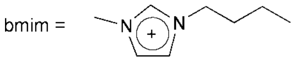
The catalyst reactivity and reusability for the lanthanide triflate-catalyzed three component synthesis of α-amino phosphonates have been examined in room temperature ionic liquids, [bmim][X], in which the catalytic activities were very dependent on the counter anion, X, as well as on the phosphorus nucleophile, and moreover, the catalyst immobilized in an ionic liquid was reused several times without any loss of activity.

The use of environmentally benign reaction media is very important in view of today's environmentally conscious attitude. In connection with this, room temperature ionic liquids that are air and moisture stable have received a good deal of attention in recent years as novel solvent systems for organic synthesis. A number of reactions such as Friedel–Crafts reactions, Diels–Alder cycloadditions, hydrogenation, and Heck reactions have employed ionic liquids as solvents.[1] More recently they have been introduced in halogenations of alkenes and alkynes[2] and in asymmetric epoxidation[3] and asymmetric hydrogenations.[4] Here we report lanthanide triflate-catalyzed three component reactions in room temperature ionic liquids, [bmim][X], to give α-amino phosphonates.

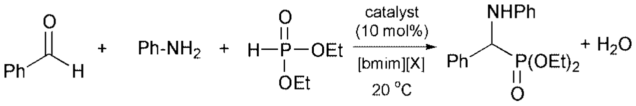


X = PF_6^-, SbF_6^-, BF_4^-, OTf^-

α-Amino phosphonates are an important class of compounds in modern pharmaceutical chemistry. Consequently, their synthesis has received an increasing amount of attention.[5] It has been recently reported that ytterbium triflates[6] and indium trichloride[7] are effective catalysts for three component reactions of aldehydes, amines, and diethyl phosphonate in organic solvents to give α-amino phosphonates. Kobayashi discovered that similar three component reactions using triethyl phosphite were also efficiently promoted by a catalytic amount of scandium-surfactant-combined catalysts in water to give α-amino phosphonates.[8] To examine the catalytic activities of lanthanide triflates as well as indium trichloride in ionic liquids, we carried out the three component reactions of benzaldehyde, aniline and diethyl phosphonate, $HP(O)(OEt)_2$, in the presence of 10 mol% of catalyst at 20 °C for 27 h. The results are summarized in Table 1.†

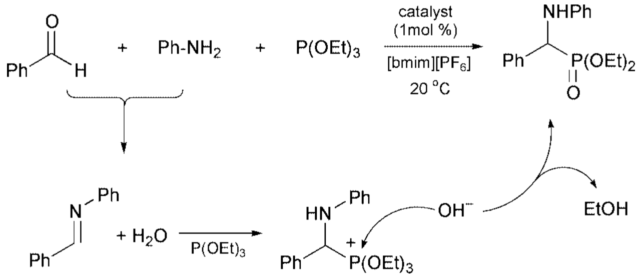
It has been found that, using anhydrous lanthanide triflates as catalysts, the reactions in $[bmim][PF_6]$ proceeded highly efficiently (entries 1–4 in Table 1). Among the anhydrous lanthanide triflates catalysts, $Sm(OTf)_3$ is superior to other catalysts in an ionic liquid (entry 4 in Table 1) whereas $Yb(OTf)_3$ is more effective in an organic solvent.[6] More interestingly, although it has been known that the lanthanide triflates are generally stable and function well in water,[9] the yields decreased greatly with hydrated catalysts, $Yb(OTf)_3{\cdot}H_2O$ (entry 5 in Table 1) and $La(OTf)_3{\cdot}H_2O$ (entry 6 in Table 1). The catalytic activity of $Sm(OTf)_3$ was retained even at 1 mol% (95%, entry 7 in Table 1). However, the activity of the recovered catalyst immobilized in ionic liquid decreased (74%, entry 8 in Table 1) which may be due to water generated during

Table 1 The three component reactions of benzaldehyde, aniline and diethyl phosphonate in ionic liquids in the presence of lanthanide triflates and indium trichloride



Entry	Ionic liquid	Catalyst	Yield (%)[c]
1	$[bmim][PF_6]$	$Yb(OTf)_3$	95
2	$[bmim][PF_6]$	$Sc(OTf)_3$	80
3	$[bmim][PF_6]$	$Dy(OTf)_3$	94
4	$bmim][PF_6]$	$Sm(OTf)_3$	99
5	$[bmim][PF_6]$	$Yb(OTf)_3{\cdot}H_2O$	63
6	$[bmim][PF_6]$	$La(OTf)_3{\cdot}H_2O$	39
7[a]	$[bmim][PF_6]$	$Sm(OTf)_3$	95
8[b]	$[bmim][PF_6]$	$Sm(OTf)_3$	74
9	$[bmim][SbF_6]$	$Sm(OTf)_3$	71
10	$[bmim][BF_4]$	$Sm(OTf)_3$	18
11	[bmim][OTf]	$Sm(OTf)_3$	89
12	$[bmim][PF_6]$	$InCl_3$	90
13	CH_2Cl_2	$Sm(OTf)_3$	70

[a] Used 1 mol% catalyst. [b] Used recovered catalyst of entry 7. [c] Isolated yield.



Scheme 1 Plausible mechanism of the three component reaction using $P(OEt)_3$.

Table 2 The three component reactions of benzaldehyde, aniline and triethyl phosphite in $[bmim][PF_6]$ in the presence of 1 mol% of lanthanide triflates and recycled catalysts

Entry	Catalyst	1st[a]	2nd	3rd	4th	5th	Average
1	$Sc(OTf)_3$	97	94	97	93	> 99	96.2
2	$Yb(OTf)_3$	57	54	—	—	—	55.5
3	$Sm(OTf)_3$	87	87	—	—	—	87.0
4	$Gd(OTf)_3$	84	77	—	—	—	80.5
5	$InCl_3$	86	50	—	—	—	68.0

[a] Isolated yield.

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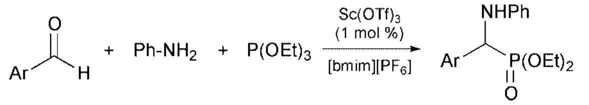
Table 3 The three component reactions of aldehydes, aniline and triethyl phosphite in [bmim][PF_6] in the presence of $Sc(OTf)_3$ as catalyst



Entry	Aldehyde	Yield (%)[a]
1	Benzaldehyde	97
2	*p*-Methoxybenzaldehyde	> 99
3	*o*-Tolualdehyde	90
4	*m*-Tolualdehyde	> 99
5	*p*-Tolualdehyde	> 99
6	*p*-Fluorobenzaldehyde	93
7	α,α,α-Trifluoro-*p*-tolualdehyde	97
8	1-Naphthaldehyde	> 99
9	3-Thiophenecarboxaldehyde	93
10	3-Furaldehyde	90

[a] Isolated yield

the reaction. The counter anion of the ionic liquids affected the catalytic activity considerably (entries 9–11), thus, only 18% of product was obtained upon using BF_4 anion (entry 10 in Table 1). By employing indium trichloride as a catalyst in [bmim][PF_6], the reaction also proceeded efficiently (entry 12 in Table 1). However, the reaction in dichloromethane solvent using $Sm(OTf)_3$ afforded product only in 70% yield (entry 13 in Table 1).

We expected that employing triethyl phosphite, $P(OEt)_3$, as a phosphorus nucleophile could overcome the drawback of catalyst recycling in the three component reactions. Mechanistically, the water generated during formation of imine could be used for the hydrolysis of phosphonium intermediate[10] to give α-amino phosphonates and EtOH as shown in Scheme 1.

The use of $P(OEt)_3$ instead of $HP(O)(OEt)_2$ changed the catalytic activities of the lanthanide triflates. In this reaction system, $Sc(OTf)_3$ exhibited the highest catalytic activity (97%, entry 1 in Table 2), and the reaction was completed within 2 h. The $Sc(OTf)_3$ can be used five times without any loss of catalytic activity (entry 1 in Table 2). In second cycle reactions, as we expected, the catalytic activities of the recovered catalysts except $InCl_3$ (entry 5 in Table 2) were almost retained.

The three component reactions of various aldehydes and aniline with $P(OEt)_3$ in the presence of 1 mol% $Sc(OTf)_3$ in ionic liquid, [bmim][PF_6], gave the corresponding α-amino phosphonates in excellent yields as shown in Table 3.

In summary, the catalytic activities of various lanthanide triflates as well as indium trichloride were examined for the three component reactions of aldehydes, amines and phosphorus nuleophiles, $HP(O)(OEt)_2$ and $P(OEt)_3$, in room temperature ionic liquids. The catalytic activities were very dependent on the counter anion, X, as well as on the phosphorus nucleophile. The catalysts immobilized on ionic liquid can be reused several times without any loss of activity.

Notes and references

† *General procedure for the three component reactions and catalyst recycling*: aniline (0.25 mmol), an aldehyde (0.25 mmol) and a phosphorus nucleophile, $HP(O)(OEt)_2$ (1 mmol) or $P(OEt)_3$ (1 mmol), were successively added to a solution of catalyst (0.25×10^{-2} mmol) in an ionic liquid (1 mL) at 20 °C. The mixture was stirred at the same temperature for 27 h for $HP(O)(OEt)_2$ or 2 h for $P(OEt)_3$. The mixture was extracted with benzene (4 mL × 5) and concentrated. Purification by silica gel chromatography afforded the desired product. More reactants (aldehyde, aniline and $P(OEt)_3$) were added to the ionic liquid solution remaining in the vessel. This was the start of the second cycle.

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10 In ref. 8, Kobayashi stated that the phosphonium intermediate was hydrolyzed rapidly in water as solvent.

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