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Facile separation catalyst system: direct diastereoselective synthesis of (*E*)-*α*,*β*-unsaturated ketones catalyzed by an air-stable Lewis acidic/basic bifunctional organobismuth complex in ionic liquids†

Renhua Qiu,[a] Yimiao Qiu,[a] Shuangfeng Yin,*[a] Xingxing Song,[a] Zhengong Meng,[a] Xinhua Xu,[a] Xiaowen Zhang,[a] Shenglian Luo,[a] Chak-Tong Au*[a,b] and Wai-Yeung Wong*[b,c]

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The catalyst system that comprises an air-stable bifunctional Lewis acidic/basic organobismuth complex and [Bmim]BF_4 is highly efficient in the cross-condensation of aldehydes with ketones. Through switching the reaction from homogeneous to heterogeneous, the system shows facile separation ability and facile reusability.

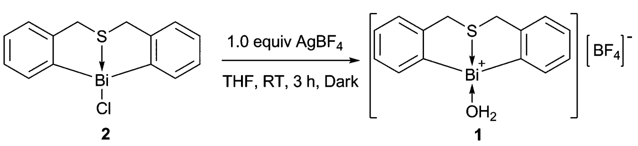
Introduction

Homogeneous catalysts offer a number of advantages, *e.g.*, all catalytic sites are accessible and fully utilized.[1] Furthermore, using homogeneous catalysts, one can tune the chemoselectivity, regioselectivity, and/or enantioselectivity of a reaction.[2] Nonetheless, systems of this kind are hard to commercialize due to the difficulty in separation of catalyst from product and/or reaction solvent.

For catalyst retrieval, two types of methods have been proposed.[1–3] In the first type, catalysts are anchored onto some kind of soluble or insoluble support, and separation is by means of filtration.[3] However, there is usually a decline of activity due to "catalyst leaching" in the processes of catalyst recycling.[4] The other type involves the design of a catalyst that is soluble in a particular solvent but under certain conditions is immiscible with the reaction product. The reactions involve two phases and are often referred to as biphasic analogous to those involving the use of ionic liquids (ILs).[5–8] ILs are recognized as environmentally-friendly reaction media and/or catalysts, and have attracted much attention due to advantages such as negligible volatility, excellent thermal stability, and remarkable solubility. Through the use of ILs, it is possible to tune the chemo- or stereo-selectivity, and to facilitate catalyst separation. Zhi *et al.* used a recyclable and temperature-dependent phase-separation system consisting of dicationic acidic ILs and toluene to synthesize benzopyrans.[6] Tan *et al.* adopted a thermoregulated IL biphasic system (composed of IL_{PEG750}, *n*-heptane and toluene) for the hydroformylation of 1-dodecene.[7] Leng *et al.* reported the temperature-controlled heteropolyanion-based acidic ILs that acted as facile separation catalysts for the esterification of citric acid with *n*-butanol.[8a] However, these catalytic systems suffered from drawbacks such as low recovery ratio, high cost, difficulty of synthesis, poor selectivity, *etc*. In recent years, we are interested in the study of organobismuth complexes because bismuth is a stable (green) heavy element.[9] Herein we report a catalytic process that is based on the facile separation approach. The catalyst system is composed of an air-stable Lewis acidic/basic bifunctional complex $[S(CH_2C_6H_4)_2Bi(OH_2)]^+[BF_4]^-$ (**1**) and [Bmim]BF_4 (1-butyl-3-methylimidazolium tetrafluoroborate); it shows high catalytic efficiency for the green synthesis of (*E*)-α,β-unsaturated ketones through cross-condensation of aldehydes and ketones.

Results and discussion

The organobismuth complex **1** can be easily synthesized by treating organobismuth chloride **2** with $AgBF_4$ (Scheme 1).



Scheme 1 Synthetic route to organobismuth complex **1**.

We observed that complex **1** is air-stable and remained as dry colorless crystals or white powders in an ambient environment within a test period of a year. According to TG-DSC analyses, complex **1** is thermally stable up to about 200 °C (Fig. S1, see ESI†). The results of the Hammett indicator analysis suggest that the complex exhibits relatively weak acidity ($3.3 < H_o \leq 4.8$) and weak basicity ($7.2 \leq H_- < 8.9$). It is envisaged that with the accessible bismuth centers as Lewis acid sites and the uncoordinated lone-pair electrons of sulfur as Lewis base sites, complex **1** can act as a bifunctional Lewis acid/base catalyst.[10]

Very recently, we reported that organobismuth complex $[S(CH_2C_6H_4)_2Bi(OH_2)]^+[OSO_2C_8F_{17}]^-$) (**3**) is a catalyst highly active for the direct diastereoselective synthesis of (*E*)-α,β-unsaturated ketone in a cross-condensation reaction.[9g] However,

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[a] *College of Chemistry and Chemical Engineering, Hunan University, Changsha, 410082, China. E-mail: sfyin73@yahoo.com.cn; Fax: +86-731-8882 1310*
[b] *Department of Chemistry, Hong Kong Baptist University, Waterloo Road, Kowloon Tong, Hong Kong, China. E-mail: pctau@hkbu.edu.hk, rwywong@hkbu.edu.hk*
[c] *Centre for Advanced Luminescence Materials, Hong Kong Baptist University, Waterloo Road, Kowloon Tong, Hong Kong, China*

† Electronic supplementary information (ESI) available: Experimental details and characterization spectras. CCDC reference number 755139. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c004940a

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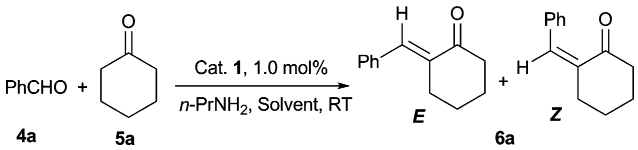
Table 1 Direct synthesis of (*E*)-α,β-unsaturated ketone catalyzed by complex **1** in various solvents.[a]



Entry	Solvent	Yield (%)[b]	*E*/*Z*[c]
1	H_2O	94	90/10
2	MeOH	93	89/11
3	EtOH	90	90/10
4	Et_2O	75	91/9
5	CH_3CN	80	88/12
6	CH_2Cl_2	93	89/11
7	Toluene	80	87/13
8[d]	$[Bmim]BF_4$	98	100/0

[a] **4a**, 20 mmol; **5a**, 60 mmol; *n*-$PrNH_2$, 20 mmol; **1**, 0.2 mmol; RT, solvent, 1.0 mL, 6 h. [b] Isolated yield. [c] Determined by ^1H NMR. [d] $[Bmim]BF_4$.

the separation of catalyst from product was difficult when water was used as reaction medium. Moreover, compared to complex **3**, complex **1** is less toxic and is much safer and cheaper to handle. In this study, we followed the biphasic approach using $[Bmim]BF_4$ as reaction solvent[11] and complex **1** as catalyst for the synthesis of (*E*)-α,β-unsaturated ketone. In model cross-condensation reactions, excellent diastereoselectivity was obtained (Table 1, entry 8, yield 98%, $E/Z = 100/0$).

During the course of reaction, the nature of catalysis switches from homogeneous to heterogeneous (Fig. 1). At the beginning, benzaldehyde **4a**, cyclohexanone **5a**, propylamine, complex **1** and $[Bmim]BF_4$ merge together and the reaction system is homogeneous (Fig. 1a). By the end of the reaction, the system becomes turbid, and after 5 min of settling, the mixture separates into two phases. The upper consists of the product and unconsumed reactants while the lower consists of $[Bmim]BF_4$, complex **1**, and water (the only side product) (Fig. 1b). The findings are congruent to the work of Leng *et al.*,[8a] in which a catalytic procedure that was monophasic at the beginning and biphasic at the end was observed. Leng *et al.* denoted the system as "reaction-induced self-separation catalyst system".[8a] In fact, our system and that of Leng *et al.* should be considered as a "facile separation catalyst system".[8] The systems show two advantages: (i) The overall reaction occurs at room temperature and (ii) there is no need to change any reaction condition. Moreover, the prominent feature of our system is its excellent solubility in water or polar solvents but immiscibility in apolar α,β-unsaturated ketones. In other words, as a catalyst complex **1** dissolves completely in $[Bmim]BF_4$ as well as in the reactants, but is insoluble in the product (α,β-unsaturated ketones). Thus at the early stage, the mixture for the cross-condensation reaction is homogeneous. With the consumption of reactants, the system becomes heterogeneous, and there is the spontaneous separation of the catalyst system (complex **1** and $[Bmim]BF_4$) and product. Eventually, the catalyst system can be easily recovered by simple decantation (Fig. 1c). It is apparent that the advantages of both homogeneous and heterogeneous catalysis are captured in this method.

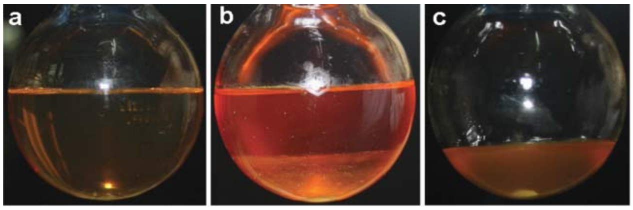


Fig. 1 Photographs of the cross-condensation reaction of benzaldehyde **4a** with cyclohexanone **5a** over organobismuth complex **1** in the presence of propylamine in $[Bmim]BF_4$. (*a*) Homogeneous mixture during reaction; (*b*) the reaction system becomes heterogeneous at completion of reaction: the upper layer is composed of the product (α,β-unsaturated ketones) and unconsumed reactants while the lower layer $[Bmim]BF_4$, complex **1**, and water generated in the reaction; (*c*) at the end of reaction, the layer of $[Bmim]BF_4$, catalyst **1**, and water was removed by decantation.

The α,β-unsaturated ketones are widely used in organic synthesis. As shown in Scheme S1 (see ESI†), (*E*)-α,β-unsaturated ketone **6a** of high stereoselectivity is applied in the synthesis (highly enantioselective) of spirobicyclic compounds, allylic alcohols, epoxy alcohols, chiral ketones, polyaza-receptors, and other building blocks of chemical synthesis.[13] It is hence highly desirable to produce α,β-unsaturated ketones in large scale. In a scale-up (×5) experiment (Fig. S2, see ESI†), we found that catalyst loading can be lowered to 0.1 mol% with the facile separation of catalyst system almost unaffected. Furthermore, the resulting ILs containing catalyst and water can be conveniently reused along with the unconsumed reactants and newly added substrates. Subject to desiccation treatment and owing to the air-stable, water-tolerant features and special interaction effect of the organobismuth complex and ILs $[Bmim]BF_4$, the catalyst system can be recycled for at least ten times without significant decline in product yield (96–100%) and stereoselectivity ($E/Z = 100/0$) (Table S1, see ESI†). Furthermore, we examined the structure integrity of the recycled catalyst (with $[Bmim]BF_4$) by NMR and found that the structure of the recycled catalyst is consistent with that of the freshly prepared one. In other words, the catalyst is stable and suitable for reuse. It should be noted that the total substrate molar ratio (**4a** : *n*-$PrNH_2$: **5a**) for ten cycles is 1.0 : 0.19 : 1.2, and the TON is up to 9893. however, it should be noted that too much water in the reaction system will lower the catalytic activity and selectivity of the catalyst.

To show the uniqueness of **1** in this facile separation catalyst system, we compared the catalytic activity of **1** with those of cationic organobismuth complex $[S(CH_2C_6H_4)_2Bi(OH_2)]^+[OSO_2C_8F_{17}]^-$ (**3**)[9g] and its precursor $[S(CH_2C_6H_4)_2BiCl$ (**2**),[14] and other catalysts such as $Bi(OSO_2CF_3)_3$ (**7**), $Bu_2Sn(OMe)_2$ (**8**),[12a] DIMCARB (*N*,*N*-dimethylammonium *N*″,*N*″-dimethylcarbamate) (**9**),[12b] NaOH (**10**), NaOMe (**11**), and HBF_4 (**12**) (Table 2). We found that catalyst **1** is superior to the other nine catalysts (**2–3**, **7–12**) (Table 2, entries 2–10) in terms of product yield and stereoselectivity.

Usually, a catalyst system is only conveniently suitable for certain substrates.[8] However, the one depicted by us here can be applied to enolizable aliphatic aldehydes as well as to aromatic aldehydes with electron-donating and electron-withdrawing groups (Table 3). In all cases, the phenomenon of facile separation was observed with high product yields. Although the reaction of furfural occurs at 0 °C (Table 3, entry 5), the *E*-selectivity for furfural is consistent with those of the other aldehydes. It

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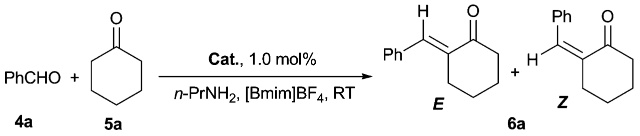
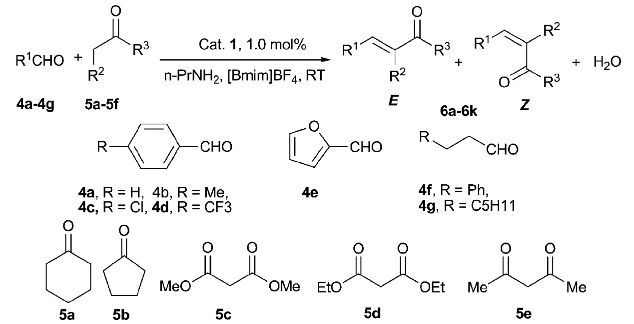
Table 2 Synthesis of α,β-unsaturated ketones over different catalysts.[a]



Entry	Catalyst	Yield (%)[b]	E/Z[c]
1	$[S(CH_2C_6H_4)_2Bi(OH_2)]^+[BF_4]^-$ (**1**)	98	100/0
2	$S(CH_2C_6H_4)_2BiCl$ (**2**)	67	43/57
3	$[S(CH_2C_6H_4)_2Bi(OH_2)]^+[OSO_2C_8F_{17}]^-$ (**3**)	95	99/1
4	$Bi(OSO_2CF_3)_3$ (**7**)	92	88/12
5	$Bu_2Sn(OMe)_2$ (**8**)	54	79/21
6	DIMCARB (**9**)	45	81/19
7[d]	NaOH (**10**)	30	83/17
8[d]	NaOMe (**11**)	34	82/18
9	HBF_4 (**12**)	42	83/17

[a] **4a**, 20 mmol; **5a**, 60 mmol; *n*-PrNH$_2$, 20 mmol; Cat., 0.2 mmol; [Bmim]BF$_4$, 1.0 mL; RT, 6 h. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Side product is 2-(hydroxy(phenyl)methyl)cyclohexanone.

Table 3 Synthesis of different α,β-unsaturated ketones catalyzed by cationic organobismuth complex **1** in [Bmim]BF$_4$.[a]



Entry	R^{1}CHO	Ketone	Product	Yield (%)[b]	E/Z[c]
1	**4a**	**5a**	**6a**	98	100/0
2	**4b**	**5a**	**6b**	93	100/0
3	**4c**	**5a**	**6c**	99	100/0
4	**4d**	**5a**	**6d**	100	100/0
5[d]	**4e**	**5a**	**6e**	98	100/0
6	**4f**	**5a**	**6f**	100	100/0
7	**4g**	**5a**	**6g**	98	100/0
8	**4a**	**5b**	**6h**	97	—
9	**4a**	**5c**	**6i**	99	—
10	**4a**	**5d**	**6j**	98	—
11	**4a**	**5e**	**6k**	95	—

[a] **4**, 20 mmol; *n*-PrNH$_2$, 20 mmol; **5**, 60 mmol; **1**, 0.2 mmol; [Bmim]BF$_4$, 1.0 mL; RT. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] 0 °C.

is worth pointing out that the reaction of enolizable aliphatic aldehydes selectively produces (E)-α,β-unsaturated ketones in almost quantitative yields without aldehyde facile condensation product or any-other side-product formation (Table 3, entries 6–7). On the other hand, the active methylene compounds appear to be efficient substrates in the present scheme (Table 3, entries 9–11). In all cases, no dibenzylidene byproduct is detected in NMR analysis. We ascribe such phenomenon to the special steric effect of monobenzylidene. In the catalyst system, it is hard for large group such as monobenzylidene to approach the active sites, and cross-condensation of monobenzylidene with cyclohexanone to form dibenzylidene byproduct is unlikely.

Due to the fact that complex **1** plays a major role in this facile separation catalyst system, we studied the crystal structure of **1** by X-ray analysis. An ORTEP representation of **1**, and the selected bond lengths and angles are shown in Fig. 2. It is clear that the organobismuth component in **1** is cationic. The oxygen atom of the coordinating water occupies a vacant site of the cationic bismuth centre, making the coordination geometry distorted and equatorially vacant. One can see a trigonal bipyramidal structure with the sulfur and the oxygen atoms in the apical positions and the two carbon atoms in the equatorial positions. The Bi–S(1) distance (2.699(19) Å) is shorter than that (2.845 Å) of precursor **2**,[14] clearly suggesting stronger sulfur-to-bismuth coordination in **1**. The Bi–O(1) distance (2.499(6) Å for **1**) is longer than that of covalent Bi–O bonds (*e.g.*, Bi–O bond distances of monomeric diorganobismuth alkoxides within 2.15–2.20 Å),[9a–d] indicating that the weakly coordinated water molecule can be replaced by a substrate.[9f–g] The dihedral angle of the two phenyl planes (*ca.* 107°) is equal to the C(1)–Bi–C(14) angle (97.2°) and the C(7)–S(1)–C(8) angle (101°). This butterfly-shaped cationic organobismuth ion is similar to that of 1,1′-binaphthol template used as asymmetric catalyst in organic synthesis.[10b]

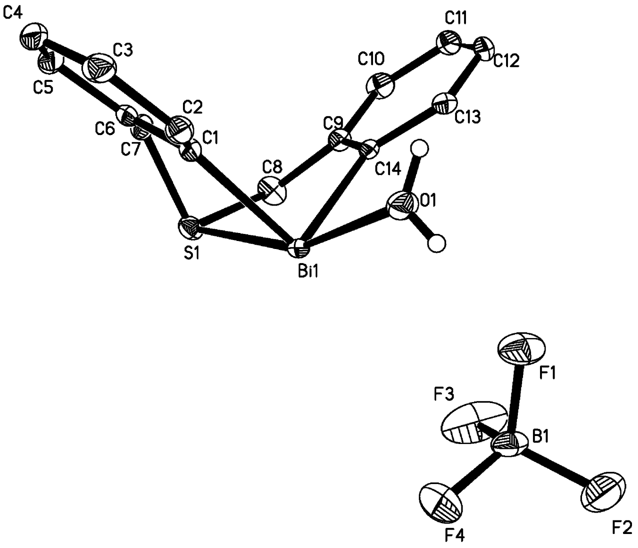


Fig. 2 An ORTEP view (30% probability level) of **1**. Selected bond lengths (Å) and angles (°): Bi(1)–C(1), 2.256(7); Bi(1)–C(14), 2.262(7); Bi(1)–O(1), 2.499(6); Bi(1)–S(1), 2.6992(19); S(1)–C(7), 1.815(8); S(1)–C(8), 1.816(9); O(1)–H(1A), 0.8180; O(1)–H(1B), 0.7499; C(1)–Bi(1)–C(14), 97.2(2); C(1)–Bi(1)–O(1), 86.3(2); C(14)–Bi(1)–O(1), 90.7(2); C(1)–Bi(1)–S(1), 78.01(19); C(14)–Bi(1)–S(1), 78.01(19); O(1)–Bi(1)–S(1), 159.20(14); C(7)–S(1)–C(8), 101.0(4); C(7)–S(1)–Bi(1), 95.7(3); C(8)–S(1)–Bi(1), 94.7(3); Bi(1)–O(1)–H(1A), 109.5; Bi(1)–O(1)–H(1B), 119.8.

According to the crystal structure of complex **1** and the result of Hammett indicator analysis, we postulate that the catalytic pathway undergoes a six-member cycle transition state comprised of the tetrahydrodibenz[*c*,*f*][*1*,*5*]thiabismocine framework and substrate (Scheme 2).[9g]

In the reaction, the complex with the above framework displays Lewis acidic/basic bifunctional properties with the

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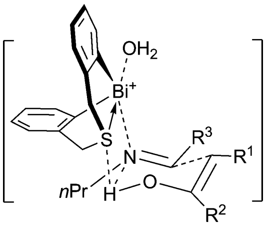
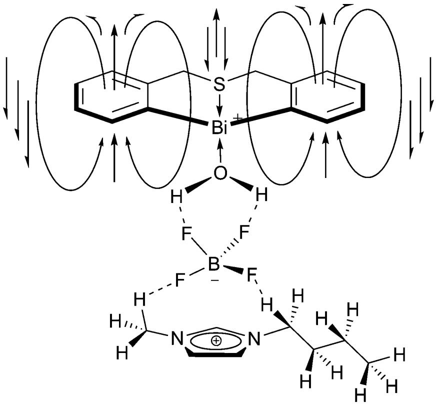


Scheme 2 Transition state for cross-condensation reaction in the synthesis of α,β-unsaturated ketones catalyzed by complex **1**.

accessible bismuth centers acting as a Lewis acid sites and the uncoordinated lone-pair electrons of sulfur as Lewis base sites.[10] When organobismuth complex **1** is used as the catalyst in the presence of propylamine in ILs, high catalytic activity was observed in cross-condensation of benzaldehyde and cyclohexanone, displaying high synthetic yield and diastereoselectivity (Table 1, entry 8, yield 98%, $E/Z = 100/0$). A very different result is obtained when water is used as solvent (Table 1, entry 1, yield 94%, $E/Z = 90/10$), suggesting that the ILs play an important role in the control of diastereoselectivity. We used NMR to investigate the interaction of complex **1** with [Bmim]BF_4. Because of interactions such as hydrogen bonding and the special phenyl planar geometry (Scheme 3), we postulate that the ^1H NMR singlet of water molecules or ILs coordinated with the Bi catalyst should shift to high field. The change of ^1H NMR chemical shift that is related to methyl and methylene group linked to the nitrogen atom of [Bmim]BF_4 is consistent with our hypothesis, implying that hydrogen bonding is apparent. With hydrogen bond formation, there should be an enhanced electron-withdrawing ability, consequently enhancing the diastereoselectivity of the reaction (Fig. 3). Furthermore, the adduct formed from the Bi complex and ILs leads to miscibility of the catalyst in the ILs. The water generated is absorbed by the hydrophilic ILs, inducing stronger polarity of ILs that is beneficial for the facile separation process. With the consumption of reactants and the generation of apolar α,β-unsaturated ketones, facile separation of products from the polar solution occurs. In other words, the product can be transferred to the apolar organic phase directly and efficiently, breaking the equilibrium of cross-condensation reaction in a controlled manner.



Scheme 3 Proposed interaction of complex **1** and imidazolium cationic ion $[Bmim]^+$ in ionic liquids.

Fig. 3 Interaction of catalyst **1** with [Bmim]BF_4 in the catalyst system. (a) The upper layer contains reactants benzaldehyde, cyclohexanone, and propylamine while the lower layer ILs and catalyst **1**. (b) Homogeneous mixture during reaction. (c) Heterogeneous mixture at completion of reaction; the upper layer is α,β-unsaturated ketones and unconsumed reactants while the lower layer ILs, catalyst **1**, and water generated during reaction.

Conclusion

We have developed a facile separation catalyst system (composed of [Bmim]BF_4 and air-stable organobismuth tetrafluoroborate **1**) that is highly efficient (showing high catalytic activity, stereoselectivity, stability, and reusability) for the synthesis of (E)-α,β-unsaturated ketones from aldehydes and ketones through direct crossed-condensation.

Experimental

Preparation of $[S(CH_2C_6H_4)_2Bi(OH_2)]^+[BF_4]^-$ (1)

To a solution of $S(CH_2C_6H_4)_2BiCl$ (**2**) (0.456 g, 1.0 mmol) in THF (20 mL), a solution of $AgBF_4$ (0.195 g, 1.0 mmol) in THF (10 mL) was added. After the mixture was stirred in darkness at RT for 3 h, it was subject to filtration. The filtrate was then mixed with hexane (1.0 mL), and after 24 h there was the formation of colorless crystals (525 mg, 99%). Crystals suitable for X-ray diffraction analysis were obtained by recrystallization of **1** from THF–hexane solution. Mp 155–158 °C. (Found: C, 31.97; H, 2.69; S, 6.08%; Calc. for $C_{14}H_{14}BiClO_5S$: C, 31.96; H, 2.68; S, 6.09%); δ_H (400 MHz; acetone-d_6; Me_4Si) 3.64 (2H, br, H_2O), 4.82 (2H, d, J = 16.0 Hz, $PhCH_2$), 5.14 (2H, d, J = 16.0 Hz, $PhCH_2$), 7.45 (2H, t, J = 7.2, 7.6 Hz, PhH), 7.56 (2H, t, J = 6.8 Hz, Ph), 7.88 (2H, d, J = 7.8 Hz, Ph), 8.23 (2H, d, J = 6.8 Hz, Ph); δ_C (100 MHz, acetone-d_6; Me_4Si) 45.79, 128.61, 130.86, 132.61 (2C), 137.69, 153.79, 189.80, 206.00. δ_F (376 MHz, acetone-d_6) −144.61 (s, BF_4). Crystal data for **1**: $C_{14}H_{14}BBiF4OS$; M = 526.11; Monoclinic; space group $P2_1/c$; a = 13.8004(8) Å, b = 11.5529(6) Å, c = 9.8253(6) Å; β = 93.0050(10)°; V = 1564.34(15) Å^3; T = 296(2) K; Z = 4; Reflections collected/unique, 9576/3783, $R_{int} = 0.023$; Final R indices [$I > 2\sigma(I)$], $R_1 = 0.0390$, w$R_2 = 0.1081$; R indices (all data), $R_1 = 0.0399$, w$R_2 = 0.1089$. GOF = 1.047. CCDC 755139.

Typical procedure of synthesis of (E)-α,β-unsaturated ketones in ionic liquids catalyzed by catalyst 1

To a 50 mL round bottomed flask were added catalyst **1** (0.106 mg, 0.2 mmol), PhCHO (**4a**, 2.120 g, 20.0 mmol), n-$PrNH_2$ (1.080 g, 20.0 mmol), cyclohexanone (**5a**, 5.880 g, 60.0 mmol) and [Bmim]BF_4 (1.0 mL). Then the mixture was stirred for 6 h under TLC analysis until PhCHO as well as the intermediate imine obtained from PhCHO and $n$$PrNH_2$ were

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consumed completely. Then the mixture was allowed to settle for 5 min, and the resulting mixture was found facile separated into two phases. The upper layer comprises reactants and products, and the lower layer ILs, catalyst, and water (generated during reaction). After simple separation by decantation, the upper phase was subject to column chromatography on silica gel (200–300 meshes) (petroleum ether/ethyl acetate = 5/1, v/v). The yield of **6a** was 3.650 g (98% based on PhCHO). All the products were characterized by comparison of ^{1}H and ^{13}C NMR spectral data.[15]

Acknowledgements

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