Bi(OTf)$_3$-[Bmim]PF$_6$: A novel and Recyclable Catalytic System for the Diasteroselective Synthesis of Cis-fused Pyrano and Furanobenzopyrans

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The Stereoselective one-pot synthesis of cis-fused pyrano and furanobenzopyrans has been developed from *o*-hydroxybenzaldehydes, aromatic amines, and cyclic enol ethers in the presence of Bi(OTf)$_3$ in air- and moisture-stable ionic liquid, [bmim]PF$_6$ under mild conditions. The recovered ionic liquid containing Bi(OTf)$_3$ can be reused three to five subsequent runs with only a gradual decrease in activity. The recovery of catalyst is facilitated by its hydrophobic nature of [bmim]PF$_6$.

2*H*-1-Benzopyrans (chromenes) and 3,4-dihydro-2*H*-1-benzopyrans (chromanes) are important class of oxygenated heterocycles that have attracted much synthetic interest because of the biological activity[1,2] of naturally occurring representatives. 4-Aminobenzopyrans and their derivatives have drawn considerable attention since the last decade as modulators of potassium channels influencing the activity of the heart and blood pressure,[3] and found to exhibit a wide range of biological activities,[4,5] including antihypertensive and anti-ischemic behavior. In particular, fused tetrahydropyrano derivatives are frequently found in naturally occurring bioactive molecules. Recently, we have reported the formation of the cis isomer of cis-fused pyrano and furanobenzopyrans using lithium tetrafluoroborate.[6] These reactions cannot be carried out in one-pot operation with *o*-hydroxy benzaldehyde, aromatic amine, and enol ether, because the amine and water that exist during imine formation can decompose or deactivate the Lewis acid, and also purification of imines was difficult by distillation and column chromatography. In order to circumvent some of these problems a one-pot procedure has been developed for this conversion using hydrophobic ionic liquid as the reaction medium. However there are no reports of the use of ionic liquid as green solvents for this methodology.

Lanthanide triflates are unique Lewis acids that are currently of great research interest.[7] Bismuth(III) triflate[8] has attracted the interest of synthetic organic chemists because it is inexpensive, highly stable and it can be easily prepared even in multi-gram scale, in the laboratory from commercially available bismuth(III) oxide and triflic acid.[9]

Ionic liquids as green high tech reaction media of the future are considered as environmentally benign alternatives for volatile organic solvent.[10] They possess many interesting properties such as tunable polarity, wide liquid range, negligible vapor pressure, high thermal stability, good solvating ability for a wide range of substrates and catalysts, and also ease of recyclability. They are particularly promising as solvents for the immobilization of transition metal catalysts, Lewis acids and enzymes.[11] The hallmark of such ionic liquids is the ability to alter their properties as desired by manipulating their structure with respect to the choice of organic cation, anion, or side-chain attached to organic cation (Figure 1). Their nonvolatile nature can reduce the emission of toxic organic compounds and facilitate the separation of products and/or catalysts from the reaction solvents. Owing to the high polarity and ability to solubilize both organic and inorganic compounds, ionic liquids can enhance reaction rates and selectivities compared to conventional solvents, thus finding increasing applications in organic synthesis.[12] In view of emerging importance of ionic liquids as green solvents, we wish to report the use of bismuth(III) triflate in ionic liquids as a novel and recyclable catalytic system for the synthesis of cis-fused furano and pyranobenzopyrans through one-pot coupling of *o*-hydroxybenzaldehydes, aromatic amines, and enol ethers under mild reaction conditions.

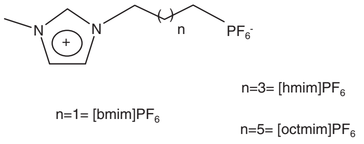
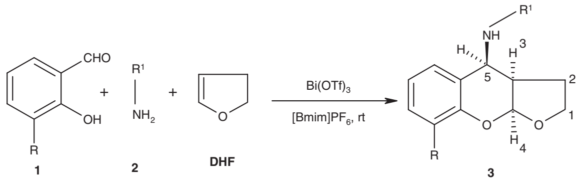


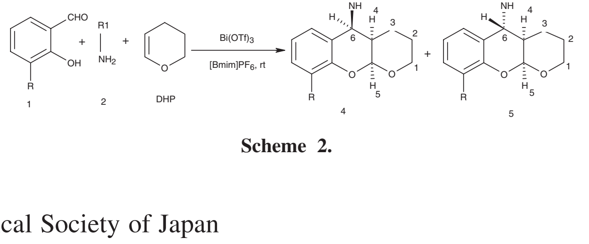
Figure 1.

For instance, treatment of *o*-hydroxybenzaldehyde (**1**) and aniline (**2**) with 2,3-dihydrofuran in the presence of 10 mol % Bi(OTf)$_3$ in 3 mL of ionic liquid, [bmim]PF$_6$ at ambient temperature affords the cis-fused furanochroman **3** in 92% yield (Scheme 1). In a similar fashion, substituted *o*-hydroxybenzaldehydes, and ortho-, para-substituted aromatic amines reacted smoothly with 2,3-dihydrofuran to give corresponding cis-fused acetals in good yields. In all cases, the reactions proceeded efficiently at room temperature with high diastereoselectivity. Only a single diastereomer was obtained in each reaction. The cis-stereochemistry of the product **3a** was established by ^{1}H NMR spectra based on chemical shifts and coupling constants and NOE studies. The assigned structure was further confirmed by direct comparison with known compound.[6,13]

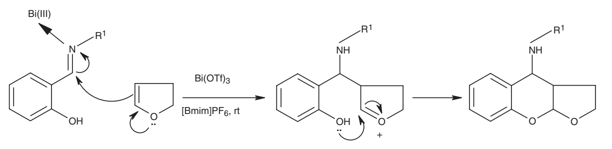


Scheme 1.

In further reactions, treatment of *o*-hydroxybenzaldehydes and aromatic amines with 3,4-dihydropyran in the presence of 10 mol % Bi(OTf)$_3$ in ionic liquid, [bmim]PF$_6$ affords the cis-fused pyranochromans as an inseparable mixture of diasteromers **4** and **5** consisting predominantly **4** with a minor amount of **5** (Scheme 2). The reactions are clean and highly diastereoselective, affording the corresponding cis-fused acetal **4** with minor amount of the other isomer **5** (Entries c, f, i, k). However, in the case of substituted *N*-arylamines the ratio of product **5** increased. The structures of the products were settled from their ^{1}H NMR spectra, further confirmed by direct comparison with known compounds.[6,13] The reaction conditions are mild so that no side products or decomposition of the products is observed. In the absence of Bi(OTf)$_3$, the reaction did not occur in ionic liquid. The reactions proceeded not only in ionic liquids but also in common organic solvents, but ionic liquids were found to give better cis-selec-



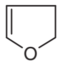
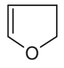
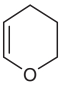
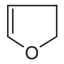
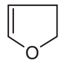
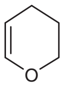
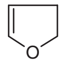
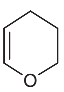
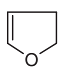
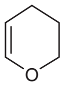
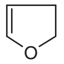
Scheme 2.



Scheme 3.

tivity than organic solvents. Moreover, the recovery and reuse of Bi(OTf)$_3$ is especially simple in ionic liquids compared to organic solvents. The reactions are completed within 1.5–3.0 h and the products were fairly soluble in ionic phase [bmim]PF$_6$, they could easily separated by simple extraction with ether. The ionic liquid phase contains Bi(OTf)$_3$, which was reused directly for next runs with gradual decrease in activity. For instance, *o*-hydroxybenzaldehyde, aniline with 2,3-dihydrofuran gave 92, 87, 83, 79% yields over four cycles. The recovery and reuse of the catalyst is especially very simple in ionic liquids compared to organic solvents. Among various ionic liquids tested such as [hmim]PF$_6$, [octmim]PF$_6$, the reaction in [bmim]PF$_6$ was found to be most effective and superior in terms of conversion. Ionic liquids used in this study were procured from Fluka and also prepared from the readily available and inexpensive *N*-methylimidazole, 1-chlorobutane, and sodium hexaflurophosphate and their purity was determined by comparing of their ^{1}H NMR spectra with commercial samples. The purity of [bmim]PF$_6$ ionic liquid is ≥97.0% (NMR).

Table 1. Bi(OTf)$_3$ -catalyzed synthesis of pyrano and furano Benzopyrans[a] in [bmim]PF$_6$

Entry	R 1	R^1 2	Enol Ether	Time /h	Yield[b] /%	Ratio[c]
a	H	C_6H_5		2.0	92	100:0
b	H	4-MeC_6H_4		1.5	86	100:0
c	H	C_6H_5		2.0	90	86:14
d	OMe	C_6H_5		2.5	80	100:0
e	H	4-OMeC_6H_4		3.0	78	100:0
f	H	4-MeC_6H_4		1.5	85	75:25
g	H	4-BrC_6H_4		2.5	88	100:0
h	OEt	4-Cl-C_6H_4		3.0	79	100:0
i	H	4-$NO_2C_6H_4$		3.0	72	70:30
j	OMe	4-MeC_6H_4		2.0	90	100:0
k	H	4-BrC_6H_4		2.5	78	80:20
l	H	2-MeC_6H_4		3.0	76	100:0

[a] All products were charactarized by ^{1}H NMR, IR, and MS.
[b] Isolated and Unoptimized yields after column chromatography.
[c] Product ratio was determined by the ^{1}H NMR spectrum of the crude product.

The reactions probably proceed through activation of imine by catalyst followed by addition and subsequent cyclization of the enol ether resulting in the formation of the fused acetal (Scheme 3). Ionic liquids are stable with amines and water and also effectively activate the imines (formed in situ from *o*-hydroxybenzaldehydes and amines) to undergo cyclization.

The scope and generality of this process is illustrated with respect to various substituted *o*-hydroxybenzaldehydes and aromatic amines and the results are summarized in Table 1.

In summary, we developed a simple and efficient one-pot method for the diasteroselective synthesis of cis-fused pyrano and furanobenzopyrans catalyzed by Bi(OTf)$_3$ in air- and moisture-stable [bmim]PF$_6$. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media is expected to contribute to the development of green strategy for the synthesis of pyrano and furanobenzopyrans.

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14 **General Procedure:** A mixture of *o*-hydroxybenzaldehyde (5 mmol), aromatic amine (5 mmol), dihydrofuran, or dihydropyran (6 mmol), Bi(OTf)$_3$ (10 mol %) in [bmim]PF$_6$ (3 mL) stirred at 27 °C for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh ethyl acetate–hexane (1:9) to afford pure cis fused pyrano and furanochromanes). The remaining ionic liquid was further washed ether and recycled in subsequent runs. Spectral data for selected compound: **3b**: colorless solid, mp 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.60–1.65 (m, 1H, H2), 1.92–1.95 (m, 1H, H$'$2), 2.29 (s, 3H, CH_3), 3.11–3.16 (m, 1H, H3), 3.73 (brs, NH), 3.85–3.91 (m, 1H, H1), 3.93–3.97 (m, 1H, H1$'$), 4.97 (d, 1H, H5, $J = 4.8$ Hz), 5.90 (d, 1H, H4, $J = 5.4$ Hz), 6.70 (d, 2H, $J = 8.3$ Hz), 6.69–6.75 (m, 2H), 7.07 (d, 2H, $J = 8.3$ Hz), 7.22–7.28 (m, 1H), 7.40 (d, 1H, $J = 7.4$ Hz). IR (KBr): ν 3384, 2974, 2860, 1600, 1584, 1519, 1481, 1216, 1035, 979, 756 cm^{-1}. EIMS: m/z: 281 (M$^+$).

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