Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 374

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Intramolecular hydroalkoxylation in Brønsted acidic ionic liquids and its application to the synthesis of (±)-centrolobine†

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Received 10th September 2010, Accepted 25th October 2010
DOI: 10.1039/c0ob00701c

The SO_3H-tethered imidazolium and triazolium salts, non-volatile and recyclable Brønsted acidic ionic liquids, efficiently mediate intramolecular hydroalkoxylations of alkenyl alcohols. They have been successfully employed in the synthesis of (±)-centrolobine.

Substituted tetrahydrofurans and tetrahydropyrans are frequently found in many cyclic ether antibiotics and other biologically active natural products.[1] One of the most straightforward synthetic approaches to these oxygen heterocycles is intramolecular hydroalkoxylation/cycloisomerization of unsaturated alcohols.[2] In particular, the intramolecular insertions of the O–H bonds across the unactivated C═C bond have drawn wide attention due to their high atom economy and synthetic efficiency. Recently, it was reported that intramolecular hydroalkoxylation of unactivated olefins could be promoted by Brønsted acid,[3,4] lanthanide,[5] platinum,[6] palladium,[7] aluminium,[8] gold,[9] silver,[10] copper,[11] iron,[12] ruthenium,[13] and rhodium[14] catalysts with varying degrees of success.

Although the acid-catalyzed intramolecular hydroalkoxylation of alkenyl alcohols has been reported for catalytic TfOH,[3] it occurs mainly with over-stoichiometric amounts of acid.[4] Because of environmental concerns associated with highly acidic reagents or reaction media, the development of environmentally benign and recyclable reagents has become a crucial and demanding area. In recent years, ionic liquids[15] (ILs) have attracted increasing interest as recyclable solvents or catalysts. Particularly, Brønsted acidic ILs are recognized as potential alternatives to conventional acid catalysts due to their non-volatile and recyclable properties. Therefore, their applications have been extended to esterification,[16] nitration,[17] Diels–Alder reaction,[18] and hydroamination.[19] Relevant to the development of green reagents for the synthesis of oxygen heterocycles, we describe herein intramolecular hydroalkoxylation of alkenyl alcohols in recyclable Brønsted acidic ILs. This protocol also has been successfully applied to the synthesis of (±)-centrolobine.

In this study, both Brønsted acidic imidazolium ILs and triazolium ILs have been used as non-volatile acidic media. The Brønsted acidic imidazolium ILs **1–4** (Fig. 1) were synthesized by literature procedures,[20] and the SO_3H-tethered triazolium IL **5** was prepared as shown in Scheme 1. First, n-butyl triazole (**6**) was alkylated with 1,4-butane sultone, and subsequently generated triazole sulfonate **7** was acidified with a stoichiometric amount of TfOH. The novel SO_3H-tethered triazolium salt **5** was free-flowing liquid at room temperature.

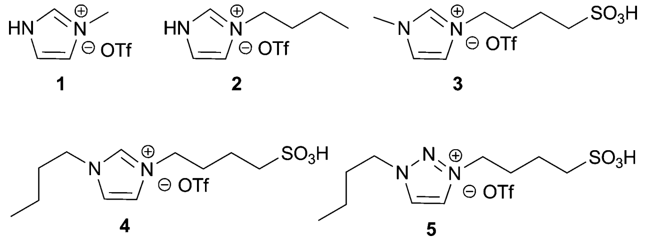
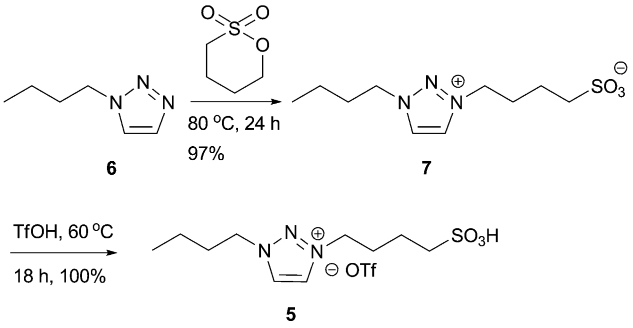


Fig. 1 Brønsted acidic ILs.



Scheme 1 Synthesis of SO_3H-tethered triazolium IL.

Having prepared both Brønsted acidic imidazolium and triazolim ILs, we tested the intramolecular hydroalkoxylation of (±)-6-methyl-5-hepten-2-ol (**8a**) in the presence of various Brønsted acidic ILs (Table 1). The reaction was conducted in an NMR tube in the presence of 1–10 mol% of Brønsted acidic IL at various temperatures. The ensuing progress was monitored by ^1H-NMR based on a mesitylene internal standard. Most of the acidic ILs were quite effective, except for imidazolium-TfOH salt **1** (Table 1, entry 1). The SO_3H-tethered imidazolium salts and triazolium

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† Electronic supplementary information (ESI) available: General experimental procedures, spectral data, and copies of ^1H and ^{13}C NMR spectra for the new compounds. See DOI: 10.1039/c0ob00701c

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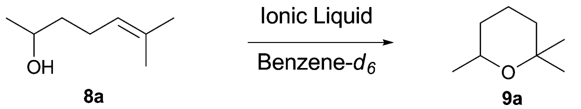
Table 1 Intramolecular hydroalkoxylation of (±)-6-methyl-5-hepten-2-ol (**8a**) in various Brønsted acidic ionic liquids[a]



8a → **9a**

Entry	Ionic liquid	Mol (%)	T/°C	Time/h	Conversion[b] (%)
1	**1**	10	80	25	0
2	**2**	10	80	1	>95
3	**3**	10	80	1	>95
4	**4**	10	40	129	>95
5	**4**	10	60	15	>95
6	**4**	10	80	1	>95
7	**4**	5	80	2	>95
8	**4**	2	80	4	>95
9	**4**	1	80	20	>95
10	**5**	10	40	142	93
11	**5**	10	60	18	>95
12	**5**	10	80	1	>95
13	**5**	5	80	2	>95
14	**5**	2	80	4	>95
15	**5**	1	80	20	>95

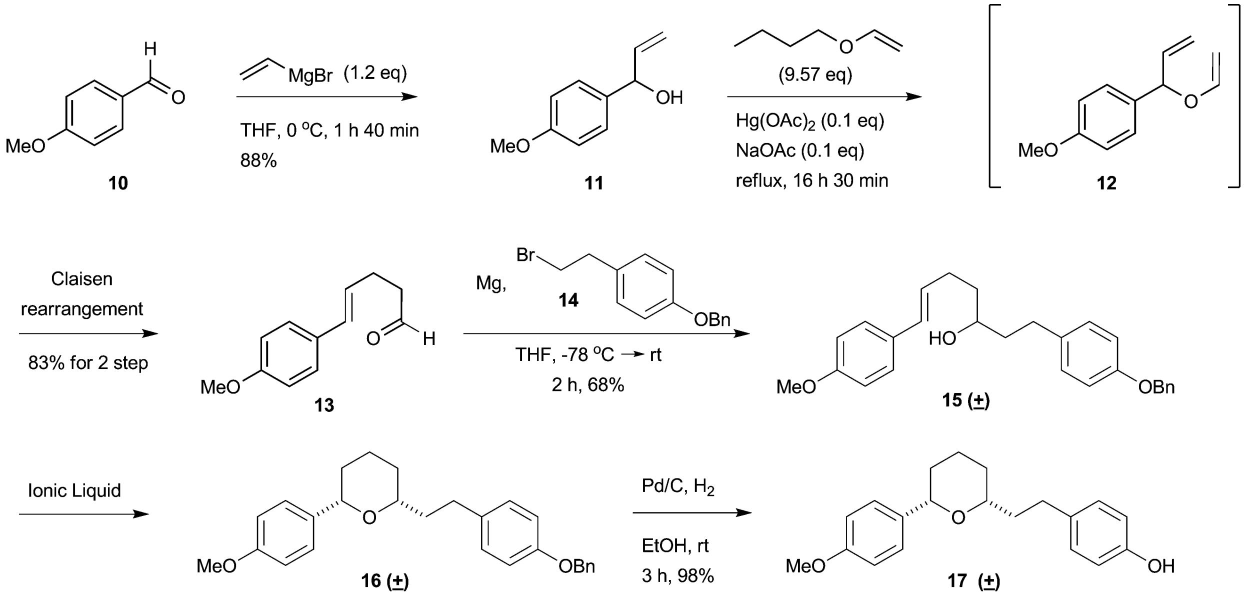
[a] Reaction conditions: (±)-6-methyl-5-hepten-2-ol (**8a**) (7.3 mg, 55.9 μmol) mesitylene (6.9 mg, 55.9 μmol), ionic liquid (1–10 mol%), benzene-d_6 0.75 mL. [b] Conversion was determined by ^{1}H NMR using an internal standard (mesitylene).

salt were equally active and produced the tetrahydropyran **9a** in excellent yield.

Next, we further explored the substrate scope of intramolecular hydroalkoxylation of a variety of alkenyl alcohols in SO_3H-tethered IL **4** and **5** (Table 2). Although all of **2**, **3**, **4** and **5** were similarly effective in the initial NMR screening studies, IL **4** and **5** were more effective than IL **2** and **3** in large-scale reactions. Thus, we selected **4** and **5** for further studies. All cyclizations were monitored by NMR-scale reactions and followed by preparative-scale reactions. Primary, secondary, aliphatic, and aromatic alkenyl alcohols smoothly afforded five- or six-membered oxygen heterocycles under standard conditions. The reactions were regioselective and preferentially generated Markovnikov products.

Presumably, the cyclization occurred at the more substituted carbocation intermediate. For 1,2-disubstituted alkenyl alcohol **8n**, five-membered ring formation was favored more than six-membered ring formation (Table 2, entries 25 and 26), and less than 10% of the corresponding tetrahydropyran isomer **9n′** was isolated. However, 6-*exo* cyclic ether **9e** was the sole product for 1,2-disubstituted alkenyl alcohol **8e**, and no 7-*endo* cyclic ether was observed (Table 2, entries 7 and 8). For low-MW alkenyl alcohols, the conversions were clean, and no side products were observed by thin-layer chromatography or NMR spectroscopy. However, the isolation of these volatile products by chromatography resulted in decreased isolated yields (Table 2, entries 1–12). Conversely, non-volatile *gem*-diphenyl substituted alkenyl alcohols reliably afforded higher isolated yields (Table 2, entries 19–26).

In general, ILs are amenable to multiple recycling cycles, which considerably decreases the production of environmentally harmful waste and the cost of a process. Therefore, the reusability of Brønsted acidic ILs also was investigated. For each cycling reaction, alkenyl alcohol **8k** and triazolium IL **5** were dissolved in benzene and heated at 80 °C for 44 h. After the reaction, the



Conditions	Isolated Yield
4 (100 mol%) benzene, rt, 110 h	77%
5 (100 mol%) benzene, rt, 38 h	82%

Scheme 2 Synthesis of (±)-centrolobine.

Table 2 Intramolecular hydroalkoxylation of alkenyl alcohols in Brønsted acidic ionic liquids[a]

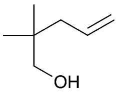
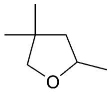
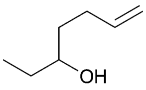
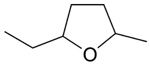
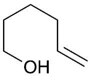
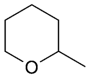
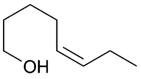
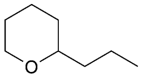
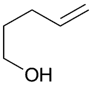
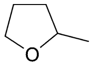
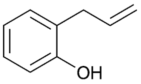
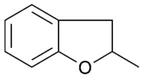
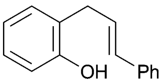
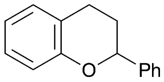
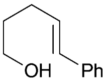
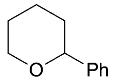
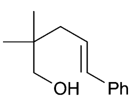
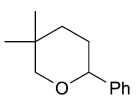
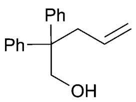
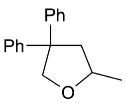
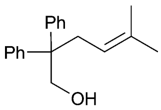
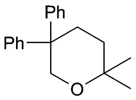
Entry	Substrate	Product	Ionic liquid	Time/h	Yield[b] (%)
1	 **8b**	 **9b**	**4** (50 mol%)	51	76 (56)
2			**5** (50 mol%)	60	86 (53)
3	 **8c**	 **9c**	**4** (10 mol%)	40	84 (48)[c]
4			**5** (10 mol%)	40	92 (79)[d]
5	 **8d**	 **9d**	**4** (50 mol%)	71	59 (62)
6			**5** (50 mol%)	71	63 (34)
7	 **8e**	 **9e**	**4** (50 mol%)	93	63 (39)
8			**5** (50 mol%)	93	71 (32)
9	 **8f**	 **9f**	**4** (50 mol%)	40	>95 (25)
10			**5** (50 mol%)	40	>95 (19)
11	 **8g**	 **9g**	**4** (100 mol%)	46	83 (52)
12			**5** (100 mol%)	44	82 (52)
13	 **8h**	 **9h**	**4** (100 mol%)	66	88 (77)
14			**5** (100 mol%)	44	>95 (91)
15	 **8i**	 **9i**	**4** (100 mol%)	55	89 (61)
16			**5** (100 mol%)	55	91 (76)
17	 **8j**	 **9j**	**4** (100 mol%)	76	>95 (62)
18			**5** (100 mol%)	76	>95 (78)
19	 **8k**	 **9k**	**4** (100 mol%)	71	>95 (96)
20			**5** (100 mol%)	24	>95 (93)
21	 **8l**	 **9l**	**4** (100 mol%)	2	>95 (86)
22			**5** (100 mol%)	3	>95 (83)

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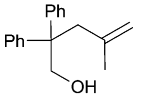
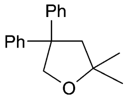
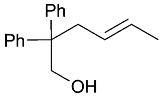
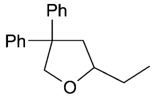
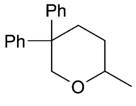
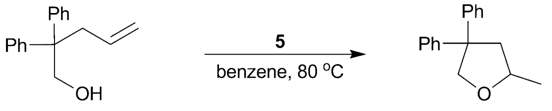
Table 2 *(Contd.)*

Entry	Substrate	Product	Ionic liquid	Time/h	Yield[b] (%)
23 24	 **8m**	 **9m**	**4** (100 mol%) **5** (100 mol%)	1 1	>95 (93) >95 (96)
25 26	 **8n**	 **9n**  **9n'**	**4** (100 mol%) **5** (100 mol%)	41 117	>95 (87)[e] >95 (81)[f]

[a] Yield was determined by ^{1}H NMR using an internal standard (mesitylene). [b] Yields in parentheses refer to isolated yields of the preparative scale reaction: alkenyl alcohol (1 mmol), ionic liquid (10–100 mol%), benzene (5 mL), 80 °C. [c] Inseparable *trans/cis* isomers (1.7 : 1) were observed. [d] Inseparable *trans/cis* isomers (1.8 : 1) were observed. [e] **9n:9n′** (78 : 9). [f] **9n:9n′**; (74 : 7).

Table 3 Reuse of the ionic liquid **5**[a]



8k → **9k**

Cycle	Yield[b]
1	95
2	87
3	88

[a] Reaction conditions: 2,2-diphenyl-4-penten-1-ol (**8k**) (238 mg, 1.00 mmol), ionic liquid **5** (412 mg, 1.00 mmol), benzene (5 mL), 80 °C, 44 h. [b] Isolated yield.

product **9k** could be extracted with Et_2O and decanted out from IL **5**. After drying IL **5** under reduced pressure, a second batch of **8k** was added. IL **5** could be recycled up to three times without significant loss in yield (Table 3).

To ensure the feasibility of intramolecular hydroalkoxylation in Brønsted acidic ILs, we used this protocol for concise synthesis of (±)-centrolobine (**17**) (Scheme 2). (−)-Centrolobine is an antiprotozoal natural product isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinium potabile* in the Amazon forest.[21] Although several total syntheses have been reported previously,[22] there is no instance reported that used intramolecular hydroalkoxylation as a key step in the construction of the tetrahydropyran skeleton. In our strategy, it was envisioned that the tetrahydropyran skeleton could be atom-economically constructed from the alkenyl alcohol **15** *via* Brønsted acidic IL-mediated intramolecular hydroalkoxylation. Therefore, the synthesis iniatiated with allylic alcohol **11**, obtained from anisaldehyde (**10**) by vinyl magnesium bromide addition. Next, **11** was subjected to one-pot vinylation-Claisen rearrangement conditions.[23] This one-pot transformation involving vinylation and Claisen rearrangement was quite effectively performed in refluxing *n*-butyl vinyl ether. Allyl vinyl ether **12** generated *in situ* was rapidly rearranged to γ,δ-unsaturated aldehyde **13** in 83% yield for two steps. Subsequent addition of phenethyl magnesium bromide, which was generated from **14** and magnesium in THF, provided alkenyl alcohol **15**, the precursor of hydroalkoxylation. Then, we investigated Brønsted acidic IL-mediated hydroalkoxylation. Gratifyingly, we found that both imidazolium IL **4** and triazolium IL **5** were effective for producing cyclized tetrohydropyran **16** in 77% and 82% yields, respectively, at room temperature. Notably, only *cis*-disubstituted tetrahydropyran was isolated. The relative stereochemistry was unambiguously determined by 1D NOE experiments (see ESI†). Removal of the benzyl group was finally achieved by catalytic hydrogenation in 98% yield. The physical and spectroscopic data obtained for **17** were in full agreement with the literature.[22]

In conclusion, we developed an intramolecular hydroalkoxylation approach to tetrahydropyrans and tetrahydrfuran in recyclable Brønsted acidic ILs. Both SO_3H-tethered imidazolium and triazolium ILs were effective for mediating cycloisomerization of alkenyl alcohols and could be recycled without significant loss of yields. In addition, the utility of this methodology was demonstrated by the concise synthesis of (±)-centrolobine.

Acknowledgements

This research was supported by a Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (No. 2009-0066777). Y. Choi was supported by the Brain Korea 21 project.

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