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Addition of activated olefins to cyclic *N*-acyliminium ions in ionic liquids

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Abstract—Organoindate(III) ionic liquid (BMI·$InCl_4$) was successfully employed in the nucleophilic addition of allyltrimethylsilane, silyl enol ethers and ketene silyl acetals to in situ generated cyclic *N*-acyliminium ions at room temperature without the need of an external Lewis acid. The corresponding α-substituted heterocycles were obtained in good yields and the recovered ionic liquid phase could be reused at least three times.

The use of *N*-acyliminium ions as valuable intermediates in organic synthesis is well documented.[1] For preparative purposes, these electrophilic species are usually generated from the corresponding α-haloalkyl, α-hydroxyalkyl, α-alkoxyalkyl, α-acyloxyalkyl, or α-sulfonyl precursors under the influence of a wide range of Lewis acids such as $BF_3{\cdot}OEt_2$, $TiCl_4$, $SnCl_4$, $InCl_3$, $NbCl_5$, $Zn(OTf)_2$ or silylating agents (TMSOTf) and in situ trapped by a competent nucleophile. However, the search for additional protocols to perform Lewis acid-mediated nucleophilic additions to iminium and *N*-acyliminium ions is still actively pursued in organic synthesis,[2–4] particularly those employing environmentally benign conditions.

Ionic liquids (ILs)[5] have attracted extensive interest as excellent alternatives to organic solvents, due to their favorable properties such as non-flammability, low toxicity, reusability and low cost. The products are usually removed from the reaction mixture by decantation and when a catalyst is employed the ionic liquid phase containing the catalyst can be separated and reused after product isolation. In these cases, the biphasic system has the potential to combine the advantages of both homogeneous (greater catalyst efficiency and mild reaction conditions) and heterogeneous (ease of catalyst recycling and separation of the products) catalysis. Moreover, due to their inherent ionic patterns,[6] reactions paths that involve charge-separated intermediates or transition states are accelerated—by lowering the activation barrier—in the presence of ILs[7] when compared with those performed in classical organic solvents or in water. These properties have been recently exploited in some reactions such as in the asymmetric Mannich-type reactions catalyzed by $InCl_3$ or $In(OTf)_3$,[8,9] in the Mukaiyama aldol reaction between ketene silyl acetals and aldehydes in ILs bearing chloride as the counter ion at ambient temperature without Lewis acid catalysis[10] and in the tetrahydropyranylation of alcohols at room temperature in organoindate BMI·$InCl_4$. In this latter case, BMI·$InCl_4$ was shown to possess Lewis acidity but the use of sub-stoichiometric amounts of $InCl_3$ (5 mol %) was required to achieve best yields of O-protected alcohols.[11]

However, to the best of our knowledge there has been no report so far describing the use of ionic liquids to promote the formation of *N*-acyliminium ions and their in situ trapping by nucleophiles.[1] This reaction is quite interesting to be performed in such a medium since it involves ionic intermediates/transition states. Indeed, we report herein our results on the BMI·$InCl_4$-mediated nucleophilic additions of allyltrimethylsilane, silyl enol ethers and ketene silyl acetals to cyclic *N*-acyliminium

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ions at room temperature without external Lewis acid catalysis.

Initially, we examined the addition of allyltrimethylsilane (**3**) to the *N*-acyliminium ion derived from carbamate *N*-Boc-2-methoxypyrrolidine (**1a**) in different imidazolium ionic liquids (**2a**–**c**) (Fig. 1, Table 1). While no reaction was observed with commercially available ionic liquid **2a** after 24 h at room temperature and trace amounts of 2-allyl carbamate **4** could only be observed when the reaction was carried out at 50 °C in **2b**, we observed that upon addition of 5 mol % of $InCl_3$ to imidazolium ionic liquid **2a** the desired product could be isolated in 25% yield, together with recovered carbamate **1a** (52% yield). We then reasoned that the use of imidazolium ionic liquid BMI·$InCl_4$ (**2c**) could be beneficial to the reaction as a potential source of $InCl_3$ (Table 1, entry 4).[12] In fact, when a mixture of α-methoxy carbamate **1a**, allyltrimethylsilane (**3**) and BMI·$InCl_4$ (**2c**) was stirred at room temperature, a two-phase system was formed. After stirring for 24 h at room temperature, Et_2O was added and the organic phase was separated. The desired product was isolated in 80% yield after column chromatography.[13]

These preliminary results indicated that the tetrachloroindate(III) anion might be in equilibrium with $InCl_3$, which is known to promote the formation of *N*-acyliminium ions (Fig. 2, Table 2).[2] At this point, we investigated the recycling of the ionic liquid in the allylation reaction of α-methoxy carbamate **1a**. A slight decrease in the yield of carbamate **4** was observed after its first reutilization, which became more significant after the second and third reutilization of the ionic liquid phase (Table 2, entries 1–4). The efficiency of the system to promote the allylation reaction of **1a** was restored by the addition of 5 mol % of $InCl_3$ to the ionic liquid recovered from the third reutilization (Table 2, entry 5).

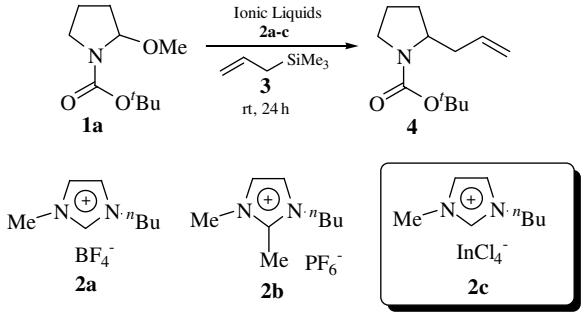

Figure 1.

Table 1. Nucleophilic addition of allyltrimethylsilane (**3**) to *N*-acyliminium ion derived from **1a** in ionic liquids[a]

Entry	Ionic liquid	**4** (%)[b]
1	**2a**	—
2	**2b**	Trace[c]
3	**2a**[d]	25
4	**2c**	80

[a] Reactions were carried out employing 0.25 mmol of **1a**, 0.50 mmol of allyltrimethylsilane in 0.1 mL of ionic liquid at rt, except where noted otherwise.
[b] Chemical yields after column chromatography.
[c] Reaction carried out at 50 °C.
[d] 5 mol % of $InCl_3$ was employed and 52% of **1a** was recovered.

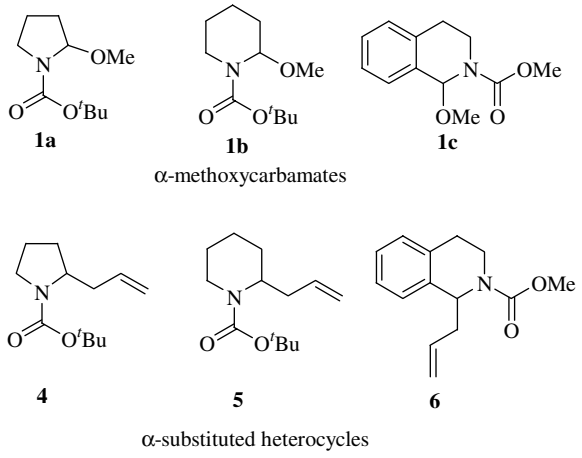

Figure 2.

Table 2. Nucleophilic addition of allyltrimethylsilane (**3**) to *N*-acyliminium ions derived from **1a**–**c** in BMI·$InCl_4$ (**2c**)

Entry[a]	Substrate	Product (%)[b]
1	**1a**	**4** (80)
2	**1a**	**4** (78)[c]
3	**1a**	**4** (65)[d]
4	**1a**	**4** (45)[e]
5	**1a**	**4** (74)[f]
6	**1b**	**5** (68)
7	**1b**	**5** (69)[g]
8	**1c**	**6** (89)

[a] Reactions were carried out employing 0.25 mmol of substrate, 0.50 mmol of allyltrimethylsilane (**3**) in 0.1 mL of BMI·$InCl_4$ (**2c**) at rt.
[b] Chemical yields after column chromatography.
[c] Recharge from entry 1.
[d] Recharge from entry 2.
[e] Recharge from entry 3.
[f] Recharge from entry 4, $InCl_3$ (5 mol %) added.
[g] $InCl_3$ (5 mol %) employed.

BMI·$InCl_4$ (**2c**) also proved to be a good reaction medium for the allylation of *N*-acyliminium ion precursors **1b**,**c** and the corresponding α-allyl substituted products **5** and **6** were isolated in good yields (Table 2, entries 6 and 8). As in the reactions carried out in organic solvents, the yield of the piperidine derivative **1b** was inferior to those observed for the pyrrolidine analogue **1a**, which may be due to a difference in the intrinsic electrophilic character of the five- and six-membered *N*-acyliminium ions,[14] in their relative rates of formation and/or to the competitive formation of the corresponding enecarbamate from **1b** (Table 2, entries 1 and 6). Attempt to improve the yield of carbamate **5** by the addition of 5 mol % of $InCl_3$ to the reaction mixture was not successful (Table 2, entry 7). The resonance

stabilized *N*-acyliminium ion derived from α-methoxy tetrahydroisoquinoline **1c** provided the corresponding allyl derivative **6** in excellent yield (Table 2, entry 8).

Silyl enol ethers **7** and **8** and ketene silyl acetal **9** have also shown to be competent nucleophiles and reacted with *N*-acyliminium ion precursors **1a–c** affording **10–17** in good yields when BMI·$InCl_4$ (**2c**) was employed (Fig. 3, Table 3). As before, better yields of the corresponding coupling products were observed when five-membered *N*-acyliminium ions (Table 3, entries 1, 4 and 6) and resonance stabilized *N*-acyliminium ion derived from **1c** were involved (Table 3, entry 8). In the reactions of prochiral (*Z*)-1-trimethylsilyloxy-1-phenylpropene (**8**) with α-methoxy carbamates **1a** and **1b**, *erythro*-**13** and *erythro*-**14** were formed preferentially (Table 3, entries 4 and 5, respectively)[15] with higher diastereoisomeric ratio being observed in the reaction of six-membered α-methoxy carbamate **1b**.[4]

In summary, the use of organoindate BMI·$InCl_4$ (**2c**) in the nucleophilic additions to cyclic *N*-acyliminium ions at room temperature and without any external Lewis acid was successfully demonstrated. The corresponding α-substituted heterocycles were obtained in good yields and the recovered ionic liquid phase could be reused at least three times. Studies are underway in order to probe the structure of the ionic species involved in these reactions and to extend the utilization of BMI·$InCl_4$ (**2c**) as the reaction medium in organic synthesis.

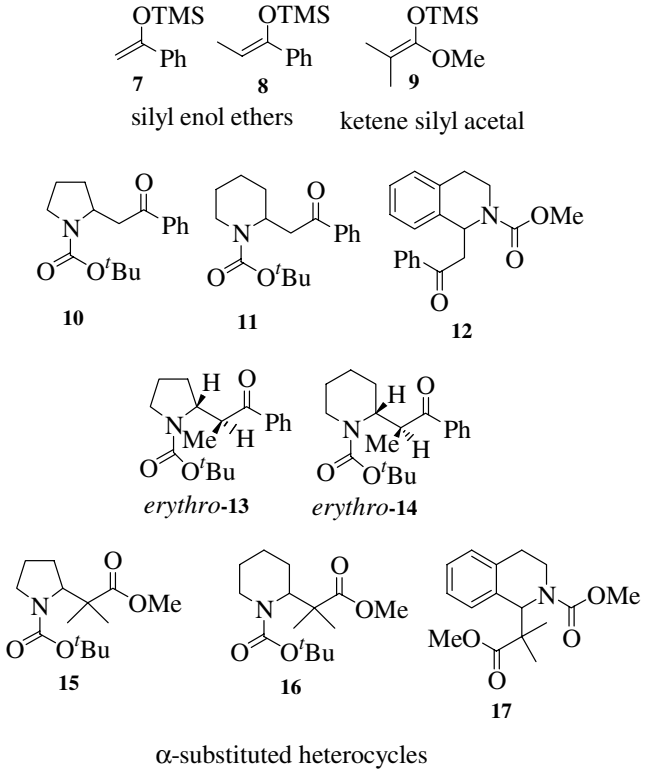

Figure 3.

Table 3. Nucleophilic addition of **7–9** to *N*-acyliminium ions derived from **1a–c** in BMI·$InCl_4$ (**2c**)

Entry[a]	Substrate	NuH	Product (%)[b]
1	**1a**	**7**	**10** (77)
2	**1b**	**7**	**11** (65)
3	**1c**	**7**	**12** (78)
4	**1a**	**8**	*erythro*-**13** (76, dr = 5:1)[c]
5	**1b**	**8**	*erythro*-**14** (66, dr = 12:1)[c]
6	**1a**	**9**	**15** (77)
7	**1b**	**9**	**16** (67)
8	**1c**	**9**	**17** (79)

[a] Reactions were carried out employing 0.25 mmol of substrate, 0.38 mmol of nucleophile in 0.1 mL of BMI·$InCl_4$ (**2c**) at rt.
[b] Chemical yields after column chromatography.
[c] Diastereoisomeric ratio was determined by GC analysis.

Acknowledgements

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References and notes

1. For recent reviews on the chemistry of *N*-acyliminiun ions, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817, and references cited therein; (b) Pilli, R. A.; Rosso, G. B. In *Science of Synthesis. Houben-Weyl Methods of Molecular Transformations*; Padwa, A., Ed.; Thieme: Stuttgart, 2004; Vol. 27, p 375.
2. (a) Russowsky, D.; Petersen, R. Z.; Godoi, M. N.; Pilli, R. A. *Tetrahedron Lett.* **2000**, *41*, 9939; (b) Camilo, N. S.; Pilli, R. A. *Tetrahedron Lett.* **2004**, *45*, 2821.
3. Andrade, C. K. Z.; Matos, R. A. F. *Synlett* **2003**, 1189.
4. Pilli, R. A.; Robello, L. G. *Synlett* **2005**, 2297.
5. For recent reviews, see: (a) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667; (b) Sheldon, R. *Chem. Commun.* **2001**, 2399; (c) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267.
6. Consorti, C. S.; Suarez, P. A. Z.; de Souza, R. F.; Burrow, R. A.; Farrar, D. H.; Lough, A. J.; Loh, W.; da Silva, L. H. M.; Dupont, J. *J. Phys. Chem. B* **2005**, *109*, 4341.
7. Dupont, J. *J. Braz. Chem. Soc.* **2004**, *15*, 341.
8. Chen, S. L.; Ji, S. J.; Loh, T. P. *Tetrahedron Lett.* **2003**, *44*, 2405.
9. For more reactions promoted by indium compounds immobilized in ionic liquids, see: (a) Yadav, J. S.; Reddy, B. V. S.; Gnaneshwar, D. *New J. Chem.* **2003**, *27*, 202; (b) Gordon, C. M.; Ritchie, C. *Green Chem.* **2002**, *4*, 124; (c) Yadav, J. S.; Reddy, B. V. S.; Bhaishya, G. *Green Chem.* **2003**, *5*, 264.
10. Chen, S. L.; Ji, S. J.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 375.
11. da Silveira Neto, B. A.; Ebeling, G.; Gonçalves, R. S.; Gozzo, F. C.; Eberlin, M. N.; Dupont, J. *Synthesis* **2004**, 1155.
12. BMI·$InCl_4$ (**2c**) was prepared according to the procedure previously reported in the literature (Ref. 11).
13. A representative procedure follows: A mixture of α-methoxy carbamate **1a** (0.25 mmol), BMI·$InCl_4$ (**2c**)

(0.1 mL) and allyltrimethylsilane (**3**) (0.50 mmol) was stirred at room temperature for 24 h. After that, 5 mL of diethyl ether was added and the organic phase was separated, washed with brine (2 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (10% ethyl acetate/hexanes) to afford **4** in 80% yield.

14. (a) Pilli, R. A.; Böckelmann, M. A.; Alves, C. F. *J. Braz. Chem. Soc.* **2001**, *12*, 634; (b) D'Oca, M. G. M.; Moraes, L. A. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2001**, *66*, 3854.
15. For clarity, only the structures of the major diastereoisomers *erythro*-**13** and *erythro*-**14** are depicted in Table 3. Data for *erythro*-**13**, see Ref. 2b. Data for *erythro*-**14**, see Ref. 4.