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# Efficient aromatic and heteroatom acylations using catalytic indium complexes with lithium perchlorate

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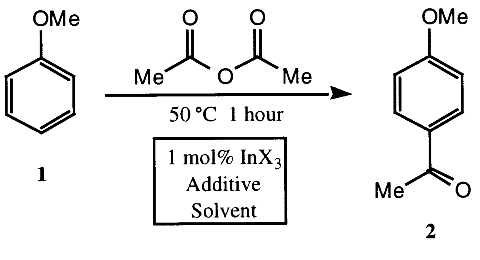
**Abstract**—The combination of an indium complex with lithium perchlorate affords a potent system for the catalytic acylation of electron-rich aromatics and alcohols. The use of isopropenyl acetate as acyl donor results in cleaner methodology with acetone as the only by-product. The study has also revealed an indium-catalysed ketalisation reaction. © 2001 Elsevier Science Ltd. All rights reserved.

The catalytic Friedel–Crafts acylation reaction provides a practical alternative for the synthesis of aromatic ketones avoiding the use of stoichiometric promoters such as aluminium trichloride.[1] The most effective systems to emerge have employed lanthanide(III) perfluoroalkylsulfonates,[2] (perfluoroalkylsulfonyl)amides[3] and (perfluoroalkylsulfonyl)methides[4] as Lewis acid catalysts. The use of robust indium(III) complexes as efficient Lewis acids is becoming increasingly widespread in catalytic organic synthesis, for example Diels–Alder reactions,[5] Michael additions,[6] Mukaiyama-aldol reactions[7] and glycosylations.[8] In this report, an efficacious catalyst system is presented for the Friedel–Crafts acylation of aromatics and heteroatom acylations which employs low loadings of the active indium(III) complex.

In previous work we have demonstrated that indium(III) triflate functions as an efficient Lewis acid catalyst at very low catalyst loadings (0.5–1 mol%).[9] It is desirable to maintain this level of activity to reduce problems associated with catalyst removal and product purification, we therefore focussed on developing conditions that required the use of only 1 mol% of the indium catalyst. The acylation reaction of anisole **1** with acetic anhydride to afford product **2** was investigated to identify the optimum catalyst and solvent combination (Scheme 1).



**Scheme 1.**

As evidenced in Table 1, the reaction was sensitive to variations in the catalyst, additive and solvent combinations. Other solvents were tried including water, dichloromethane, nitrobenzene, ethyl acetate and acetic anhydride but all proved less effective than nitromethane. The type of anionic ligand employed is confirmed to be critical to obtaining a high yield in the

**Table 1.** The acylation of anisole

| Entry | Catalyst | Additive | Solvent | Yield (%) |
|---|---|---|---|---|
| **1** | $InCl_3$ | – | MeCN | 25 |
| **2** | $In(OTf)_3$ | – | MeCN | 28 |
| **3** | $In(ClO_4)_3 \cdot 8H_2O$ | – | MeCN | 57 |
| **4** | $InCl_3$ | 3 mol% $AgSbF_6$ | MeCN | 7 |
| **5** | $InCl_3$ | 3 mol% $AgBF_6$ | MeCN | 55 |
| **6** | $InCl_3$ | 3 mol% $AgClO_4$ | MeCN | 82 |
| **7** | $In(OTf)_3$ | 4 mol% $LiClO_4$ | MeCN | 40 |
| **8** | $In(OTf)_3$ | 4 mol% $LiClO_4$ | $MeNO_2$ | 79 |
| **9** | $In(OTf)_3$ | 25 mol% $LiClO_4$ | $MeNO_2$ | 88 |
| **10** | $In(OTf)_3$ | 100 mol% $LiClO_4$ | $MeNO_2$ | 96 |
| **11** | – | 100 mol% $LiClO_4$ | $MeNO_2$ | <5 |
| **12** | $In(OTf)_3$ | 100 mol% $LiClO_4$ | $MeNO_2$ | 99[a] |

[a] Reaction was conducted at room temperature for 40 hours.

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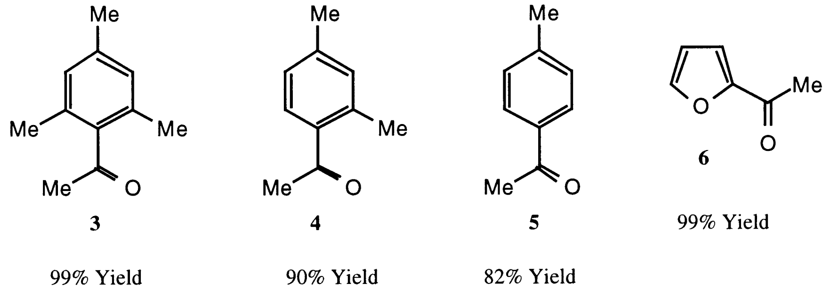
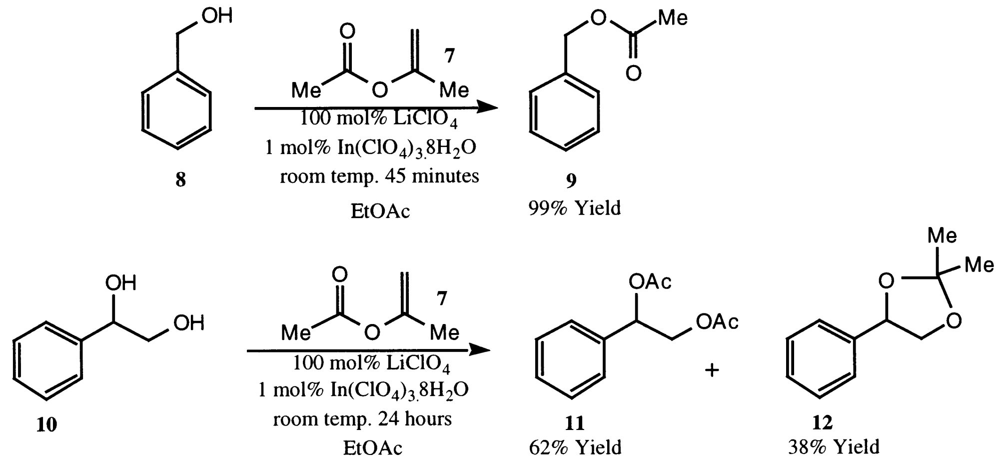


Scheme 2.



Scheme 3.

catalytic Friedel–Crafts process.[10] The use of perchlorate as counterion (entry 6) or the use of lithium perchlorate as an additive provided the most active system. In the absence of indium catalyst the lithium perchlorate did not promote the illustrated reaction (entry 11). The acceleration of the Friedel–Crafts acylation reaction in the presence of lithium perchlorate has been noted with other catalysts and is reported to be due to the formation of a reactive cationic species when combined with the acyl donor.[11] The efficiency of this unique catalyst system is demonstrated by the room temperature synthesis of ketone **2** using only 1 mol% of indium(III) triflate (entry 12).

The present catalyst system is highly effective for the acylation of anisole and other electron-rich aromatics such as mesitylene, *m*-xylene and furan to afford products **3**, **4** and **6** (Scheme 2). It was less effective with toluene which required 10 mol% of indium catalyst to achieve an 82% yield of product **5**. The reaction did not proceed cleanly with unactivated aromatics. As well as acetic anhydride, acetyl chloride and isopropenyl acetate **7** performed as satisfactory acyl donors affording the product **2** in 87 and 76% (using 2.5 mol% of In(OTf)$_3$) yield, respectively. The use of alternative acyl sources such as **7** is advantageous as after acylation, the resultant enolate rapidly tautomerises to furnish acetone as the predominant side-product.[12]

This methodology has also been extended to the catalytic acylation of alcohols under the optimised conditions outlined in Scheme 3. A typical example is the extremely efficient acylation of benzyl alcohol **8** to furnish benzyl acetate **9** in quantitative yield. Whilst attempting the diacylation of 1-phenyl-1,2-ethanediol **10** we noted the formation of **12** in significant yield along with the expected product **11**. It appeared that the acetone generated in situ from the acylation process was being consumed in a competitive ketalisation reaction of **10**. Given that Lewis acids are known to promote such transformations the diol **10** was independently reacted with acetone (1.1 equiv.) to reveal an efficient indium-catalysed ketalisation process (Scheme 4).[13]

In summary, this paper highlights the important results obtained in the development of an efficient yet mild indium-catalysed acylation reaction. The scope of the reactions outlined above are currently being explored along with a more detailed investigation into the structure and operation of indium catalysts.

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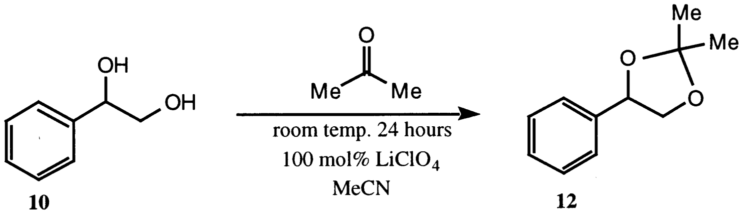

**10** **12**

| | |
|---|---|
| No Indium catalyst | <5% Yield |
| 0.5 mol% $In(ClO_4)_3.8H_2O$ | 50% Yield |
| 0.5 mol% $In(OTf)_3$ | 87% Yield |

**Scheme 4.**

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