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Indium triflate: An Efficient Catalyst For The Friedel-Crafts Acylation of Aromatics

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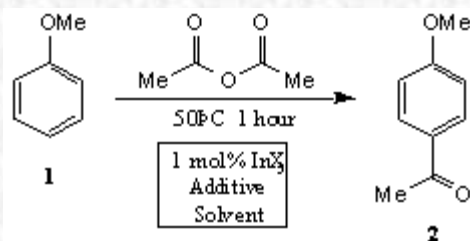
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Abstract: The combination of an indium complex with lithium perchlorate affords a potent system for the catalytic acylation of electron-rich aromatics.

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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 used lanthanide (III)perfluoroalkyl-sulfonates,² -amides³ and -methides⁴ 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 reactions⁷ 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.



Scheme 1.

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).

As evidenced in Table 1, the reaction was sensitive to variations in the catalyst, additive, solvent combinations. Other solvents were tried including water, dichloromethane, nitrobenzene, ethyl acetate and acetic anhydride but all proved

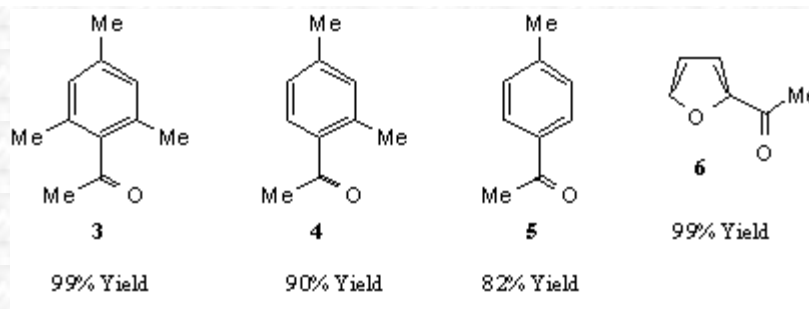
less effective than nitromethane. The type of anionic ligand employed is confirmed to be critical to obtaining a high yield in the catalytic Friedel-Crafts process.¹⁰ The use of perchlorate as counterion (entry 6) or the use of lithium perchlorate as an additive provided the most active system. In the 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).

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 ·8H ₂ O | — | 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 [^] |

[^] Reaction was conducted at room temperature for 40 hours

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.



Scheme 2.

Acknowledgement

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