Metal Trifluoromethanesulfonate Catalysis in Organic Synthesis

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Dr Jeffrey DePinto of Gelest summarises some of the uses of metal triflates as catalysts in organic synthesis

Metal trifluoromethanesulfonate catalysis, or metal triflates, offer a number of advantages in their strong Lewis acidity and their increased tolerance for protic solvents and water, which can result in by-products of the chemical reaction of interest. In addition, metal triflates are generally considered to be environmentally friendly catalysts. This mini-review will present some examples of the applications of various metal triflates in synthetic organic chemistry.

Examples include the use of scandium triflate (Sc(OTf)3) to catalyse Friedel-Crafts acylation, an important chemical reaction in the bulk chemical industry, and of zinc triflate (Zn(OTf)2) in the reductive amination of aldehydes. Although a variety of metal triflates have been employed as active catalysts for organic transformations, Sc(OTf)3 and Zn(OTf)2 are dominant in terms of the numbers of examples.

Scandium

The use of scandium triflate as a water-stable Lewis acid in organic synthesis was pioneered by Kobayashi in the early 1990s.1 Traditional Lewis acids, such as AlCl3, react rapidly with water and require strictly anhydrous conditions in synthetic organic reactions, plus they require more than stoichiometric amounts in many cases. Kobayashi’s demonstration that Sc(OTf)3 acts as an excellent Lewis acid in both water and organic solvents opened the door to many more Lewis acid-catalysed synthetic organic transformations and simplified the process chemistry associated with these reactions.

Scandium triflate has been shown to catalyse Friedel-Crafts transformations in a number of applications. For example, it catalyses the intramolecular Friedel-Crafts acylation of substituted Meldrum’s acid, resulting in highly substituted indanones (Figure 1).3 The more highly substituted systems provided higher yields of the indanones. Although the yields are low, the Sc(OTf)3-catalysed cis-cycloaddition of electron-rich aromatics provides a direct route to these difficult to obtain substrates. Thus, for example, (+)-naringenin was reacted with D-glucose to give an adduct in about 20% yield.4 In an example of the use of water-stable Sc(OTf)3, the reaction occurs via direct acylation of the Lewis acid-activated carbonyl.5 The reaction was tolerant of both water and alcohol.6 The yields were not optimal, the stability of the reagents to the aqueous medium was impressive and potentially useful (Figure 2).7 The reaction also occurred in a highly diastereoselective fashion.

An interesting and useful approach to the synthesis of tert-butyl ethers was reported in which the source of the tert-butyl group is di-tert-butylcarbonate. Thus, the reaction of an alcohol with Boc2O under catalysis with Sc(OTf)3 results in the formation of the corresponding tert-butyl ether of the alcohol employed (Figure 3). Catalysis with AlCl3 or Zn(OTf)2 is the best for any tert-butyl ethers.8 Scandium triflate readily catalyses the transamination of an imine to an amino and a primary amine. The results are a thermodynamic equilibrium of the amines and the imines. Sc(OTf)3 was shown to be much more reactive than other lanthanide triflates, with the relative rates being Sc(OTf)3 > Yb(OTf)3 > Sm(OTf)3 > La(OTf)3.9

Based on their earlier work in the preparation of steroselectively prepared functionalised pyrans, the Panek group has shown that 2-arylated pyrans can be reductively opened with triethylsilane under Sc(OTf)3 catalysis (Figure 4).10 The reaction takes advantage of the known ability of organocatalysts to reduce boric acid and ethers to the methylene, due to the enhanced stability of the carbocation produced at that position.11 The reaction is tolerant of a variety of functional groups and proceeds best with microwave irradiation. In addition, it was shown that trimethylsilylnucleophiles other than hydride could be introduced under similar conditions. Thus, alkyl, alkenyl, and alkyne were all successfully carried out. This combination of triflylsilane and Sc(OTf)3 was applied in a synthesis of geldanamycin, which has been shown to have inhibitory effects on Hsp90 and therefore, potential as a therapeutic reagent for certain cancers.12

Zinc

The rearrangement of α-pinene oxide can be directed to several different product. Among these is campholenic aldehyde, which is a component of some fragrances. Zn(OTf)2, fixed onto a bed of silica catalyses the rearrangement of α-pinene oxide to campholenic aldehyde with high selectivity. Thermal gravimetric analysis has confirmed that the Zn(OTf)2 was attached to the silica and that it was not simply triflic acid on the silica that was the active catalyst.13 Zinc triflate was shown to catalyse the reductive amination of aldehydes with PMHS, a polymerised silylamine, as the reducing agent Figure 5. The reaction was tolerant of various functional groups, including esters and ketones. Aconophenone was reductively aminated in modest conversion at higher temperatures.

Other sialic-reducing agents, with the exception of phenylsilyl, were not as effective.14

Conclusion

Metal triflates have been used in a wide variety of synthetic organic transformations and offer an efficient, environmentally friendly alternative to traditional Lewis acids. Metal triflates can typically be recovered and reused without loss of catalytic activity.

Reactions catalysed by metal triflates range from various C-C bond-forming reactions, such as Friedel-Crafts acylation and alkylation to C-N bond-forming reactions and others.

Contact

Dr Jeffrey T. DePinto
Product Manager, Metal Organics & Research Products
Gelest, Inc.
Tel: +1 215 547 1015
E-mail: jdepinto@gelest.com
Website: www.gelest.com

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Figure 4 – Reductive opening of 2-arylated pyrans with triethylsilane catalysed by scandium triflate

Figure 5 – Reductive amination of aldehydes with PMHS catalysed by zinc triflate

Figure 1 – Intramolecular Friedel-Crafts acylation of substituted Meldrum’s acid catalysed by scandium triflate

Figure 2 – Aqueous Mukaiyama reaction on an epoxy aldehyde catalysed by scandium triflate

Figure 3 – Synthesis of t-butyl ethers catalysed by scandium triflate

Figure 6 – Reductive amination of aldehydes with PMHS catalysed by zinc triflate

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Examples include the use of scandium triflate (Sc(OTf)3) to catalyse Friedel-Crafts acylation, an important chemical reaction in the bulk-chemical industry, and of zinc triflate (Zn(OTf)2) in the reductive amination of aldehydes. Although a variety of metal triflates have been employed as active catalysts for organic transformations, Sc(OTf)3, and Zn(OTf)2, are dominant in terms of the numbers of examples.

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In an excellent example of the water-stability of the triflate catalysts, Sc(OTf)3 was used in a Mukayama reaction on epoxy aldehyde 1 in water. Although the yields were not optimal, the stability of the reagents to the aqueous medium was impressive and potentially useful (Figure 2).5 The reaction also occurred in a highly diastereoselective fashion.

An interesting and useful approach to the synthesis of tert-butyl ethers was reported in which the source of the tert-butyl group is di-tert-butylcarbonate. Thus, the reaction of an alcohol with Boc2O under catalysis with Sc(OTf)3 results in the formation of the corresponding tert-butyl ether of the alcohol employed (Figure 3).6 Catalysis with AlCl3-Wo MO or MgCl2Wo is best and is more economical than Sc(OTf)3, for aliphatic tert-butyl ethers and Sc(OTf)3 is best for any tert-butyl ethers.7 Scandium triflate readily catalyses the transamination of an amine with an imine and a primary amine. The results are a thermodynamic equilibrium of the amines and the imines. Sc(OTf)3 was shown to be much more reactive than other lanthanide triflates, with the relative rates being Sc(OTf)3 > Y(OTf)3 > Sm(OTf)3 > La(OTf)3.8

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The reaction is tolerant of a variety of functional groups and proceeds best with microwave irradiation. In addition, it was shown that trimethylsiloxanes other than hexylide could be introduced under similar conditions. Thus, alkylation, amination and glycosylation were all successfully carried out. This combination of triethylsilane and Sc(OTf)3 was applied in a synthesis of geldanamycin, which has been shown to have inhibitory effects on Hsp90 and therefore, potential as a therapeutic reagent for certain cancers.11

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Zinc triflate readily catalyses the reductive amination of aldehydes with PMHS catalysed by zinc triflate

Other silane-reducing agents, with the exception of phenylsilane, were not as effective.12

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Contact

Dr Jeffrey T. DePinto
Product Manager, Metal Organics & Research Products
Gelest, Inc.
Tel: +1 215 547 1015
E-mail: jdepinto@gelest.com
Website: www.gelest.com