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Metal Trifluoromethanesulfonate Catalysis in Organic Synthesis

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Metal trifluoromethanesulfonate catalysis in organic synthesis

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

Metal trifluoromethanesulfonate catalysts, or metal triflates, show 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 ($\text{Sc}(\text{OTf})_3$) to catalyse Friedel-Crafts acylation, an important chemical reaction in the bulk chemical industry, and of zinc triflate ($\text{Zn}(\text{OTf})_2$) in the reductive amination of aldehydes. Although a variety of metal triflates have been employed as active catalysts for organic transformations, $\text{Sc}(\text{OTf})_3$ and $\text{Zn}(\text{OTf})_2$ 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.^{1,2} Traditional Lewis acids, such as AlCl_3 , 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 $\text{Sc}(\text{OTf})_3$ 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

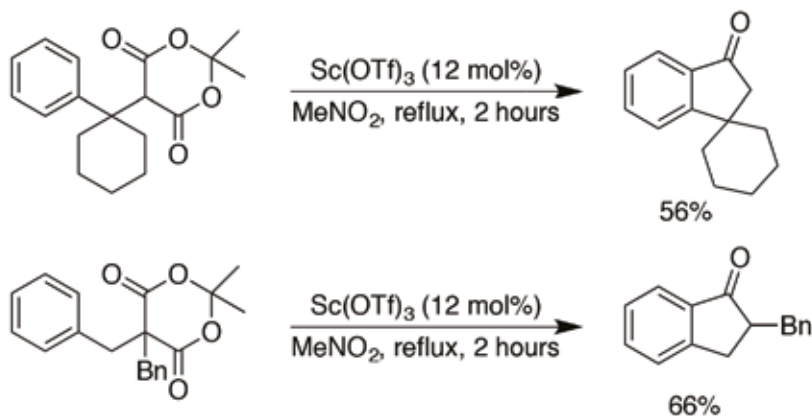


Figure 1 – Intramolecular Friedel-Crafts acylation of substituted Meldrum's acid catalysed by scandium triflate

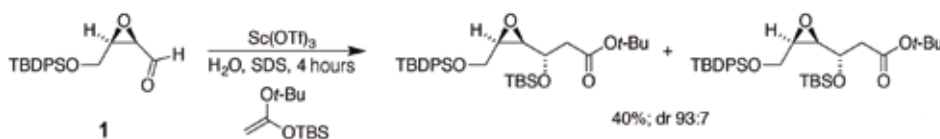


Figure 2 – Aqueous Mukaiyama reaction on an epoxy aldehyde catalysed by scandium triflate

of applications. For example, it catalyses the intramolecular Friedel-Crafts acylation of substituted Meldrum's acid, resulting in highly substituted indanones. Mechanistic investigations led to the postulate that the reaction occurs via direct acylation of the Lewis acid-activated carbonyl (Figure 1).³ The more highly substituted systems provided higher yields of the indanones.

Although the yields are low, the $\text{Sc}(\text{OTf})_3$ -catalysed C-glycosylation of electron-rich aromatics provides a direct route

to these difficult-to-obtain substrates. Thus, for example, (\pm)-naringenin was reacted with D-glucose to give an adduct in about 20% yield.⁴

In an excellent example of the water-stability of the triflate catalysts, $\text{Sc}(\text{OTf})_3$ was used in a Mukaiyama 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*-butyl carbonate. Thus, the reaction of an alcohol with Boc_2O under catalysis with $\text{Sc}(\text{OTf})_3$ results in the formation of the corresponding *tert*-butyl ether of the alcohol employed (Figure 3). Catalysis with $\text{Al}(\text{ClO}_4)_3 \cdot 9\text{H}_2\text{O}$ or $\text{Mg}(\text{ClO}_4)_2$ works best and is more economical than $\text{Sc}(\text{OTf})_3$ for aliphatic *tert*-butyl ethers and $\text{Sc}(\text{OTf})_3$ is best for aryl *tert*-butyl ethers.⁶

Scandium triflate readily catalyses the transamination reaction between an imine and a primary amine. The results are a thermodynamic equilibrium of the amines

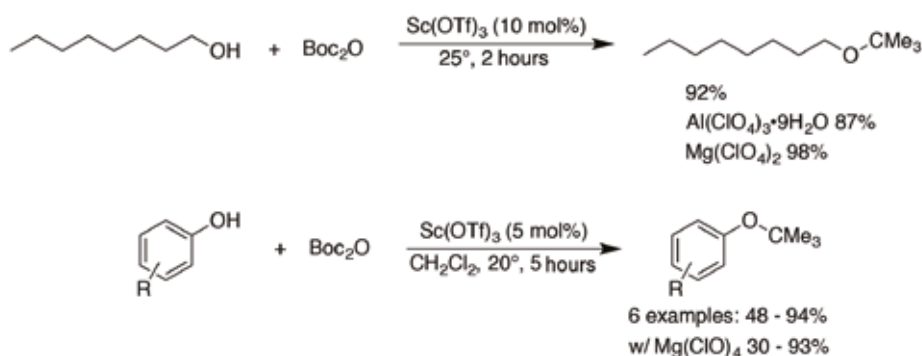


Figure 3 – Synthesis of *t*-butyl ethers catalysed by scandium triflate

and the imines. $\text{Sc}(\text{OTf})_3$ was shown to be much more reactive than other lanthanide triflates, with the relative rates being $\text{Sc}(\text{OTf})_3 > \text{Yb}(\text{OTf})_3 > \text{Sm}(\text{OTf})_3 > \text{La}(\text{OTf})_3$.⁷

Based on their earlier work in the preparation of stereoselectively prepared functionalised pyrans, the Panek group has shown that 2-arylated pyrans can be reductively opened with triethylsilane under $\text{Sc}(\text{OTf})_3$ catalysis (Figure 4).^{8,9} The reaction takes advantage of the known ability of organosilanes to reduce benzylic alcohols and ethers to the methylene, due to the enhanced stability of the carbocation produced at that position.¹⁰

The reaction is tolerant of a variety of functional groups and proceeds best with microwave irradiation. In addition, it was shown that trimethylsilyl nucleophiles other than hydride could be introduced under similar conditions. Thus, allylation, azidation and cyanation were all successfully carried out. This combination of triethylsilane and $\text{Sc}(\text{OTf})_3$ 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

Zinc

The rearrangement of α -pinene oxide can be directed to several different product. Among these is campholenic aldehyde, which is a component of various fragrances. $\text{Zn}(\text{OTf})_2$ fixed onto a bed of silica catalyses the rearrangement of α -pinene oxide to campholenic aldehyde with good selectivity. Thermal gravimetric analysis has confirmed that the $\text{Zn}(\text{OTf})_2$ was attached to the silica and that it was not simply triflic acid on the silica that was the active catalyst.¹²

Zinc triflate was shown to catalyse the reductive amination of aldehydes with PMHS, polymethylhydrogen siloxane, as the reducing agent (Figure 5). The reaction was tolerant of various functional groups, including esters and ketones. Acetophenone was reductively aminated in modest conversion at higher temperatures.

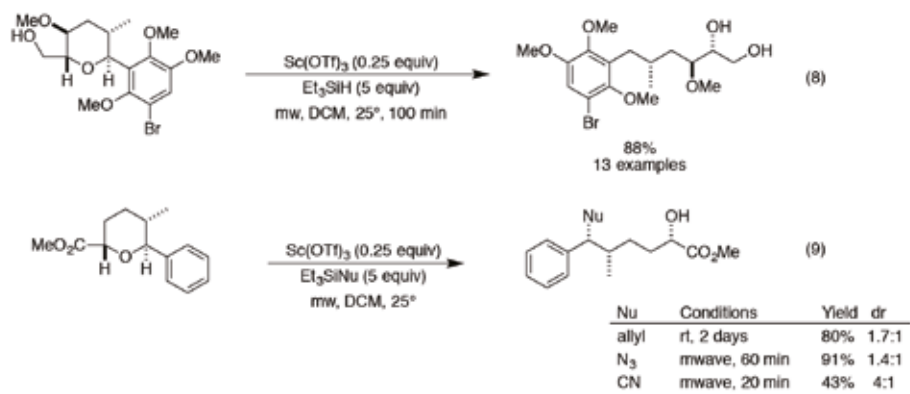


Figure 4 – Reductive opening of 2-arylated pyrans with triethylsilane catalysed by scandium triflate

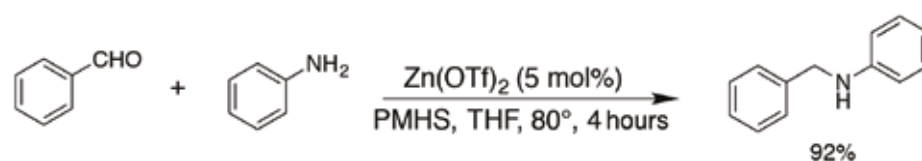


Figure 5 – Reductive amination of aldehydes with PHMS catalysed by zinc triflate

Other silane-reducing agents, with the exception of phenylsilane, were not as effective.¹³

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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GELEST, INC.
11 East Steel Road
Morrisville, PA 19067
Tel: 888-734-8344
215-547-1015
Email: info@gelest.com

GELEST, INC.
Stroofstrasse 27 Geb. 2901
65933 Frankfurt am Main
Germany
Tel: +49(0)69-3800-2150
Email: info@gelestde.com
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For more information, contact Gelest, Inc., 11 East Steel Rd., Morrisville, PA 19067

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