

# Trimethylaluminium

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Sammy Drissi-Amraoui was born in Bressuire, France in 1990. In 2011, he worked as a one-year student in the Chemistry Department of Merck Serono, Geneva, under the supervision of Dr. Cyril Montagne and Dr. Dominique Swinnen, working on photochemistry for the synthesis of drug-like compounds. In 2013, he graduated from the Ecole Nationale Supérieure de Chimie de Montpellier (ENSCM) in organic chemistry and received his M.Sc. in chemistry of biomolecules for health. He started his Ph.D. studies in 2013 under the supervision of Prof. Jean-Marc Campagne and Dr. Renata Marcia de Figueiredo and his research focuses on asymmetric conjugate additions and total synthesis.



## Introduction

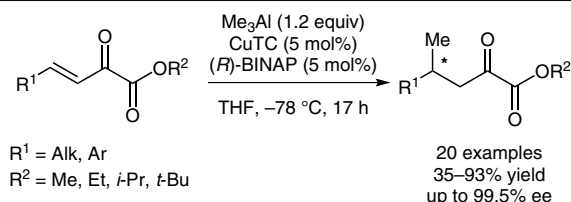
Trimethylaluminium (or trimethylaluminum, TMA) [CAS Reg. No. 75-24-1] is an organometallic reagent from the family of alanes, described first in 1939.<sup>1</sup> This highly pyrophoric compound is a liquid at room temperature (mp 15 °C) and is commercialized neat or as a solution in an organic solvent (hexane, heptane, toluene, chlorobenzene).

This reagent can be prepared, amongst other methods, from aluminium and chloroform, dimethylaluminium chloride or methylaluminium sesquichloride, treated with sodium or sodium/potassium.<sup>2</sup> The preparation has been industrialized above all by Ziegler,<sup>3</sup> who later reported the Ziegler–Natta polymerization with TMA.

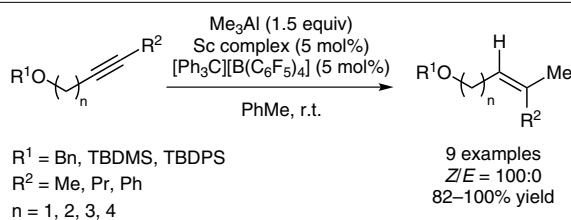
This versatile reagent has a high Lewis acid character, much more than zinc or magnesium organometallic compounds. In addition, the reagent is used as methyl nucleophilic donor, the cheapest one thanks to its industrial use.

**Table 1** Use of Trimethylaluminium

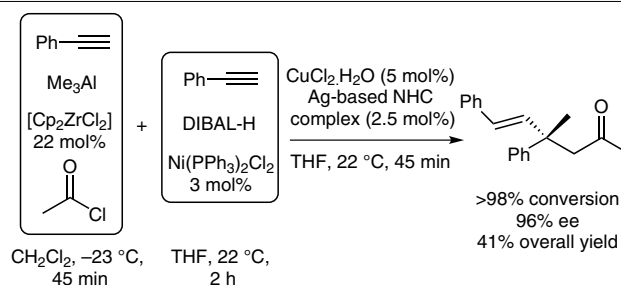
(A) Gremaud and Alexakis accomplished the copper-catalyzed enantioselective 1,4-addition of TMA on  $\beta,\gamma$ -unsaturated  $\alpha$ -keto esters.<sup>4</sup> The reaction was performed with excellent 1,4-regioselectivity, yield, and enantiomeric excess only with the simple commercially available ligand BINAP.



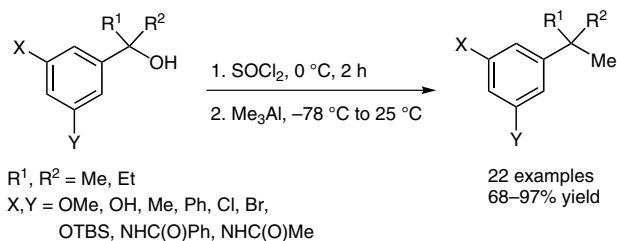
(B) Alternatively to the well-known zirconium-catalyzed carbometalation of alkynes, a new regio- and stereospecific scandium-catalyzed methodology was employed by Hou and co-workers.<sup>5</sup>



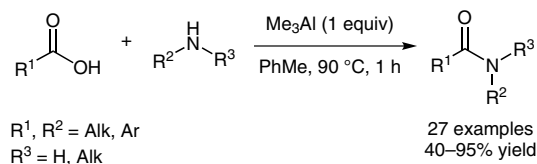
(C) The Cu-catalyzed enantioselective conjugate addition of a  $\beta$ -alkenylaluminum reagent (prepared via Ni catalysis) to an  $\alpha,\beta$ -unsaturated ketone (which is issued by Zr-catalyzed carboalumination using TMA) was reported by McGrath and Hoveyda.<sup>6</sup> This multicomponent reaction allowed the enantioselective synthesis of  $\beta,\beta$ -disubstituted ketones from alkynes.



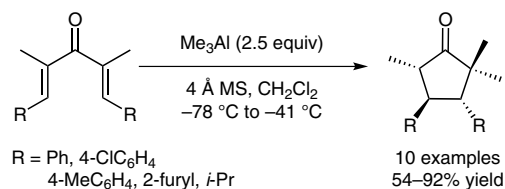
(D) Although *m-tert*-alkylbenzenes are not accessible by traditional Friedel–Crafts reaction, Carlier and co-workers synthesized this kind of compounds by methylation of activated tertiary benzylic alcohols using TMA.<sup>7</sup> Alcohol activation could be carried out using thionyl chloride or concentrated hydrochloride solution.



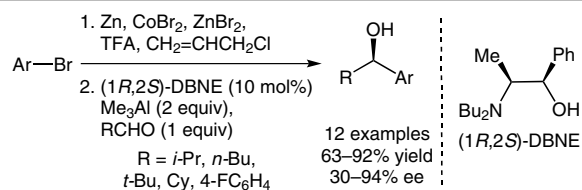
(E) Even though the direct amidation of esters using TMA is a well-known strategy, Chen and co-workers reported the direct amidation of carboxylic acids using a stoichiometric amount of TMA. The amide bond formation proceeded with high yields even though bulky or weakly nucleophilic amines were employed.<sup>8</sup>



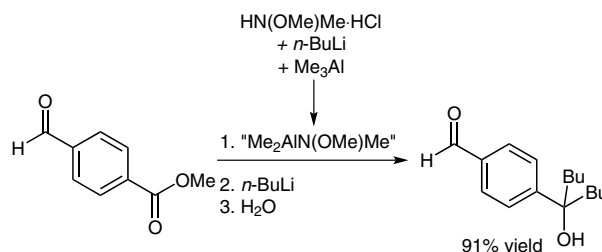
(F) West and co-workers were able to show that TMA promotes Nazarov reaction on dienones. Symmetrical dienones afforded cyclopentanone products in good yields as single diastereoisomers.<sup>9</sup>



(G) Woodward and co-workers described the 1,2-asymmetric addition of organozinc halides to aldehydes promoted by TMA. Optimization using an in situ prepared organozinc reagent afforded higher yields and enantioselectivities.<sup>10</sup>



(H) Colby and co-workers proposed a simple carbonyl group differentiation between an aldehyde and an ester (or ketone). Indeed, if the aldehyde moiety is masked as an aluminium aminal, a chemoselective addition to the ester (or ketone) moiety is allowed. In situ unmasking is then performed by hydrolysis or using a Dowex® resin.<sup>11</sup>



## Acknowledgment

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