Trimethylaluminum

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Contents

Trimethylaluminum (Me₃Al) is a clear colorless liquid (*b.p.* 125–126 °C, *m.p.* 15 °C), readily miscible with saturated aromatic and aliphatic hydrocarbons. The reagent is very stable under inert atmosphere, but highly pyrophoric and reacts violently with protic solvents. It is commercially available as pure compound in stainless steel containers or as less pyrophoric solution in inert solvents (hexane, heptane, toluene). Me₃Al, as other trivalent aluminum compounds, acts as a Lewis acid. On the other side it behaves as an organometallic compound, hence being able to add a methyl group to electrophilic centres and to deprotonate acidic compounds (CH, OH, NH) under methane evolution. The chemistry of organoaluminum compounds has been reviewed thoroughly [1].

1. Transfer of Methyl Groups by Me₃Al

1.1 Nucleophilic Displacements

Nucleophilic displacements of appropriate functional groups by Me₃Al have been described. So η^6-arene tricarbonylchromium complexes of benzylic alcohols and the corresponding acetates react with Me₃Al under stereoselective methylation to give the corresponding methylated products [2] (equation 1). A phenylsulfonyl group in 2-position of a piperidine derivative was readily substituted by a methyl group on reaction with Me₃Al in CHCl₂ at room temperature [3] (equation 2).

Highly selective S_N' reactions of allylic phosphates with Me₃Al were observed under CuCN catalysis (equation 3). Analogous reactions with allylic halides gave lower yields and selectivities [4]. Glycals react with Me₃Al to give C-glycosides in high yields and good to excellent *trans/cis* ratios [5] (equation 4).
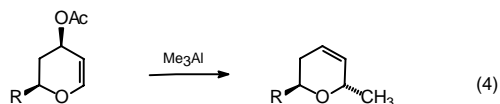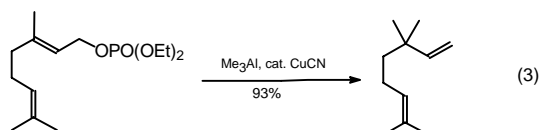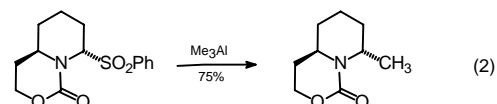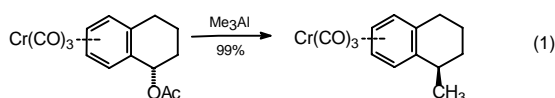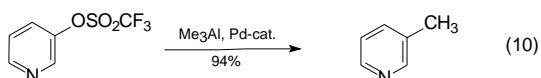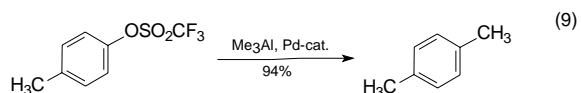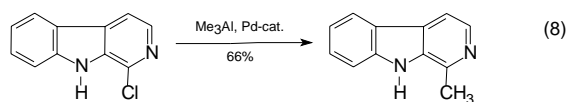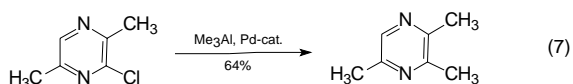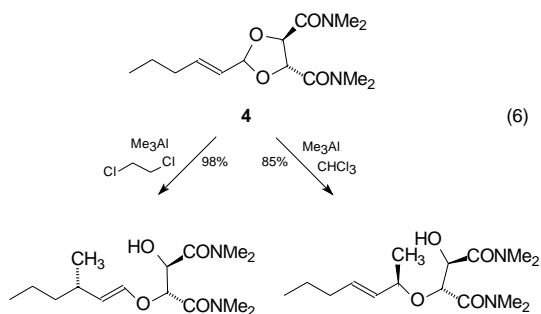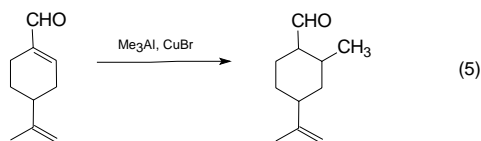

1.2 Additions to Activated Double Bonds

CuBr-assisted conjugate methylation of vinylogous aldehydes can be effected with Me₃Al (equation 5). The ratio of 1,4- *vs.* 1,2-addition can be controlled by the choice of reaction conditions and solvents [6]. The stereochemical control of Me₃Al addition to chiral α,β-unsaturated acetals was also found to be highly dependent on the solvent. Whereas reaction of acetal with Me₃Al in dichloroethane gave a 6.5:1 preference for 1,4- *vs.* 1,2-addition, reaction in CHCl₃ exclusively resulted in 1,2-addition [7] (equation 6). Corresponding ketals of α,β-unsaturated ketones reacted under clean 1,4-addition [8].

1.3 Palladium-catalyzed Cross Coupling Reactions

Me₃Al serves as a convenient source of methyl groups for the Pd-catalyzed cross coupling reaction of aryl halides and aryl triflates to give the corresponding arylmethyl compounds. Methyl groups have been introduced into pyrazine [9], benzene, pyridine [10], purine [11] and β-carboline rings [12] (equations 7–10). In an analogous manner enol phosphates were converted into methylated olefins [13] under Pd-catalysis, and ketones were prepared by reaction of acid chlorides with an Me₃Al/Cu(acac)₂/Ph₃P system [14].

Me3Al, CuBr (5)

4 (6)

Me3Al, Cl—CH2CH2—Cl 98%

Me3Al, CHCl3 85%

Me3Al, Pd-cat. 64% (7)

Me3Al, Pd-cat. 66% (8)

Me3Al, Pd-cat. 94% (9)

Me3Al, Pd-cat. 94% (10)

aldehydes by periodate oxidation [17]. Methylation of 2,3-epoxy amines with Me_3Al occurs selectively at C-2 position with retention of the configuration at C-2 to give 2-methyl-3-amino alcohols. The reaction requires two equivalents of Me_3Al and is considered to proceed via an aziridinium intermediate [18].

Me3Al, 94% (11)

Me3Al (12)

62% + 24%

Me3Al, 81% (13)

1.4 Additions to Epoxides

Stereoselective nucleophilic opening of epoxides by Me_3Al is an appropriate method to prepare chiral secondary alcohols. In the last years this reaction has been of especial interest for the synthesis of highly functionalized building blocks. So epoxy alcohols, readily available also in enantiomeric pure form by the Sharpless epoxidation, can be opened stereoselectively by Me_3Al to give either 1,2- or 1,3-diols which in turn are convenient building blocks for natural product synthesis [15, 16]. Some representative examples are given in equations 11–13. It is noteworthy that Me_3Al shows opposite regioselectivity (62:24) compared to cuprates (23:59) (equation 12). The resulting 1,2-diols can be converted to substituted alcohols by further mono-tosylation and coupling reaction with organocuprates [16] or degraded to chiral

On the other hand, Me_3Al can also serve as an auxiliary for the nucleophilic addition of other residues to epoxides. Thus, alkenyl alanates prepared from vinyllithium compounds and Me_3Al readily react with epoxides under BF_3-catalysis to give homoallylic alcohols (equation 14) [19]. In an analogous manner alkinyl trimethylaluminates can be prepared from lithiated alkynes and Me_3Al and react with epoxides to result in a nucleophilic alkynylation of the epoxide (equation 15). This method has considerable advantages compared to the addition of dialkylaluminum acetylides [20].

Me3Al, BF3 (14)

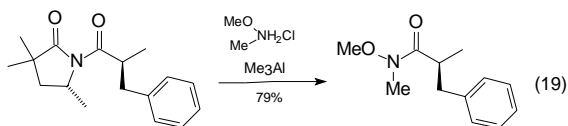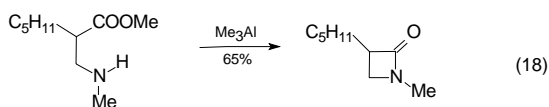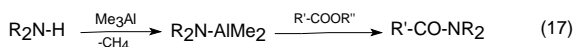BF3, 85% (15)
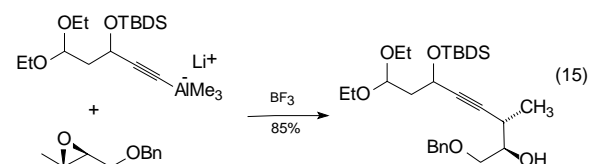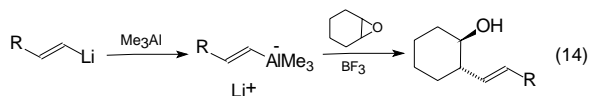
2. Cyclopropanations

The trialkylaluminum/methylene iodide system has been described to be an efficient reagent for cyclopropanation of olefins [21, 22]. This methodology has recently been applied to an efficient synthesis of the dehydrogenase inhibitor spiropentaneacetic acid (equation 16). For the selective cyclopro-

panation of an isolated olefinic group in the presence of an allylic alcohol, however, triisobutylaluminum was clearly superior to Me$_3$Al.

(16)
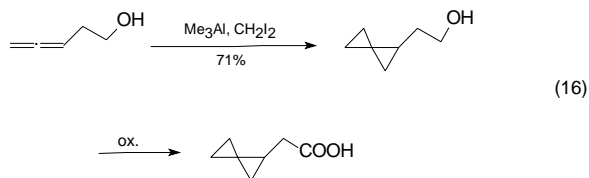
3. Me$_3$Al-mediated Synthesis of Carboxylic Amides and Lactams

In 1977, Weinreb and coworkers reported on a mild method for the preparation of amides from carboxylic esters based on the reaction of Me$_3$Al with ammonia, primary or secondary amines to give highly reactive dimethylaluminum amides. These reagents readily react with esters to afford the corresponding amides (equation 17) [23]. This methodology has also been used for the synthesis of leukotriene antagonists [24] and carboxylic acid hydrazides from esters and hydrazine derivatives [25]. Another interesting application of this reaction is the preparation of β-lactams from β-aminoesters. In 1966,

$$R_2N\text{-}H \xrightarrow[-CH_4]{Me_3Al} R_2N\text{-}AlMe_2 \xrightarrow{R'\text{-}COOR''} R'\text{-}CO\text{-}NR_2 \quad (17)$$

(18)

(19)

Woodward and coworkers described the first total synthesis of the β-lactam antibiotic cephalosporin C using a triisobutyl-aluminum-mediated lactamization of a β-aminoester [26]. Later Oppolzer and Bracher found that even monocyclic β-lactams can be efficiently prepared from β-aminoesters with Me$_3$Al (equation 18) [27]. Corresponding N-acylcamphor-sultams could also be converted into β-lactams by this method, but two equivalents of Me$_3$Al were required, and partial racemization could not be avoided. In this case triisobutyl-aluminum caused complete racemization, whereas enantio-merically pure β-lactam was obtained by using ethylmag-nesium bromide. Very recently, direct aminolysis of chiral N-acyl pyrrolidinones with dimethylaluminum amides has been

reported to offer an efficient, non-racemizing approach to carboxylic amides and Weinreb amides (equation 19) [28].

4. Rearrangements

A regiospecific Beckmann rearrangement–alkylation sequence promoted by trialkylaluminum reagents has been studied extensively by Yamamoto and coworkers (reviewed in [1a]). Cyclic and acyclic oxime sulfonates rearrange upon treatment with Me$_3$Al to give imines under introduction of a methyl group. These imines can be reduced to amines or be further alkylated by addition of Grignard reagents (equation 20). This methodology has been applied to the synthesis of alkaloids as pumiliotoxin C and selenopsin A and B. In the selenopsin synthesis (equation 21) an interesting stereoselectivity in the reduction of the intermediate imine to the corresponding

(20)

(21)

rac-selenopsin A

(22)

(23)
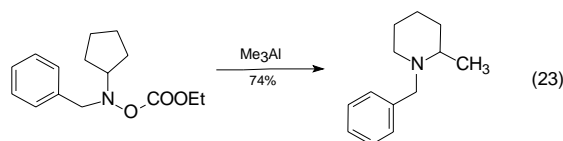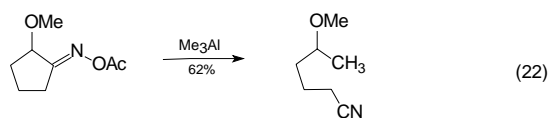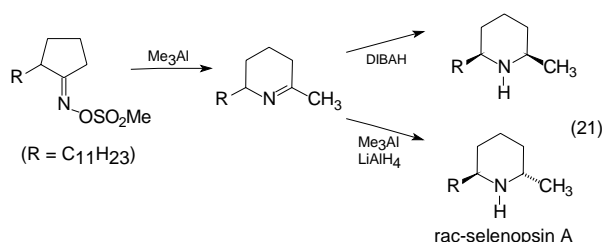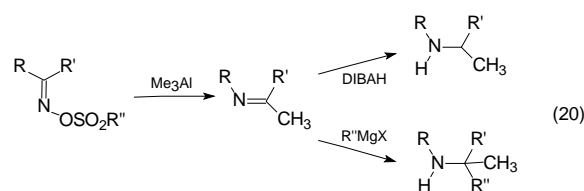
piperidines has been observed. While DIBAH reduction gave pure *cis*-isomer, complexation of the imine with Me$_3$Al and reduction with LiAlH$_4$ led to the *trans*-product selenopsin A in excellent yield and stereoselectivity.

The reaction of α-alkoxycycloalkanone oxime acetates with Me$_3$Al caused Beckmann fragmentation and subsequent carbon–carbon bond formation to give ω-cyano-α-methyl ethers (equation 22) [29]. A rearrangement–alkylation sequence of hydroxylamine carbonates with Me$_3$Al was found to open a new entry to nitrogen-containing heterocycles (equation 23) [30]. Finally, trialkylsilyl ketene acetals undergo a 1,3-rearrangement to trialkylsilyl acetic acid esters in the presence of catalytic amounts of Me$_3$Al [31].

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