Synthesis and Reactivity of Mixed Dimethylalkynylaluminum Reagents

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Abstract
Organoaluminum derivatives are mostly appreciated for their Lewis acidity properties, but generally not considered as reagents of choice in synthetic transformations involving the creation of C–C bonds. Among these species, dimethylalkynylaluminum reagents represent a special class of compounds, with, in many cases, unique reactivity. This review summarizes the preparation and reactivity of these organometallic reagents with a focus on their synthetic potential.

1 Introduction

Organoaluminum reagents have been known for more than 150 years since the first synthesis of ethylaluminum sesquiiodide by Hallwachs and Schafarik in 1859. However, the chemistry of these organometallic species is still mostly restricted to the fields of olefin polymerization and thin-film fabrication by chemical vapor deposition techniques. The range of applications of organoaluminum reagents is surprisingly limited, especially if one considers that aluminum, the most abundant metal in the earth’s crust, is produced at low price (a mole of aluminum is now cheaper than a mole of lithium). Trimethylaluminum is also a major, widely available inexpensive organometallic compound that can act not only as a cheap methyl donor, but also as metalating or transmetalating agent for the synthesis of more elaborated organoaluminum reagents.

There are probably a few reasons why organoaluminum reagents are still less frequently used in organic synthesis than other main group organometallic reagents, such as organolithium or organomagnesium reagents. One of the limitations is that generally only one of the 3 C–Al bonds will react in synthetic transformations. Furthermore, competitive hydride transfer can occur with substituents bearing an sp3-C–H bond to the sp3-C–Al bond. Finally, the main reason for the rather low popularity of organoaluminum as synthetic reagents has been highlighted by Eisch in his seminal review on the history of aluminum chemistry: if ether solvents are essential in the reactivity of organolithium or organomagnesium reagents, they dramatically reduce the reactivity of alkylaluminum reagents through the formation of Lewis acid-base adducts. However, these solvents are still generally used for the preparation of organoaluminum reagents by transmetalation, C-H activation, or direct insertion, leading to organometallic species with limited reactivity.

Among the large variety of organoaluminum compounds, dimethylalkynylaluminum reagents (Figure 1) look quite attractive.

Figure 1 General properties of mixed dimethylalkynylaluminum reagents
These species are indeed devoid of the major limitations described above. The three substituents on aluminum do not bear a C–H bond in the β-position. The greater reactivity of the sp–C–Al bond compared to that of sp$^1$–C–Al bond will enable selective transfer of the alkynyl moiety, the methyl group behaving as a nontransferable moiety. Finally, we were able to propose a new route to these reagents in non-polar solvents, providing compounds with enhanced reactivity.

In this short review, our goal is to focus on the preparation and reactivity of mixed dimethylalkynylaluminum reagents with a special focus on their peculiar reactivity and synthetic utility in selective organic transformations.

2 Preparation of Dimethylalkynylaluminum Reagents

A classical way to prepare dialkylalkynylaluminum compounds is by salt metathesis from the corresponding alkali acetylides (Scheme 1). This is the method of choice starting from terminal acetylenes bearing tert-butyl$^8$ or trialkylsilyle groups,$^9$ or showing weak acidity such as alkoxycetylenes.$^{10}$

![Scheme 1](image)

This approach requires a first metatation step, generally conducted at low temperature, and careful control of the transmetalation experimental conditions to avoid the presence of residual traces of dialkylaluminum halides. The equivalent of lithium or sodium chloride produced in the second step can be removed by filtration if a non-polar solvent is used, but can affect the reactivity of the resulting organoaluminum reagents if the transmetalation step is conducted in Et$_2$O.

Trimethylaluminum is not sufficiently basic to metate a terminal alkyne at room temperature in non-polar solvents. The use of higher temperatures generally leads to a mixture of compounds resulting from competitive carboalumination side reactions.$^{11}$ Interestingly, clean metatation occurs at room temperature in triethylamine, as reported by Binger in 1963.$^{12}$ This observation led to the development of a base-catalyzed aluminiation of terminal alkynes with trimethylaluminum.$^{13}$ A mechanistic investigation showed that several Lewis bases can catalyze this transformation, the most efficient being N,N-bis(trimethylsilyl)methylenamine (Scheme 2).$^{14}$ Using this base, clean terminal aluminiation can be obtained at room temperature with only 1 or 2 mol% of the catalyst. In 2018, the use of zwitterionic neodymium(III) heterobimetallic compounds was reported to catalyze a similar reaction.$^{15}$

Dimethylalkynylaluminum reagents are typically prepared by simply adding MeN(SiMe$_3$)$_2$ and the alkyne to a 2 M commercial solution of AlMe$_3$, leading to a stable 1.6 M solution of the organometallic reagent. The prepared air- and moisture sensitive organoaluminum solutions can be stored under argon in the dark for several days at room temperature. Although commercially available heptane or...
toluene solutions can both be used indiscriminately, dimethyl(phenylethynyl)aluminum tends to crystalize in alkanes and is better prepared in toluene.

An alternative to this batch procedure based on flow chemistry has also been proposed. In this case, a resin-supported tertiary amine is used to promote the metalation step. This procedure delivers dimethylalkynylaluminum reagents without any residual traces of the catalyst with an increased reaction rate (Scheme 2).16

3 Reactivity of Dimethylalkynylaluminum Reagents

Alkynylaluminum reagents exhibit a rather low nucleophilic character. This reactivity can be explained by the low ionic character of the C–Al bond, and their bridged dimeric nature in non-coordinating solvents. As a result, most of the reactions involving the carbon–metal bond will be triggered by the complexation of the acidic aluminum center to the substrate, leading to activation of the nucleophile. As a consequence, the nature of the solvent will play a major role in the reactivity of dimethylalkynylaluminum reagents. This typical behavior is perfectly illustrated in the reaction with chiral oxazolopiperidines (Scheme 3). These polyfunctional compounds are known to react with organolithium, -cuprates,17 or -magnesium reagents18 at their aminonitrile moiety. Dimethylalkynylaluminum reagents react, in a complementary manner, selectively with the oxazolidine motif by coordinating the most Lewis basic part of the substrate; diastereoselective alkynylation, without methyl transfer, is obtained.14 The reaction proceeds at 0 °C in toluene. No reaction occurs if THF is used as a cosolvent, highlighting the role of coordination in this transformation.

3.1 Reactions with Csp³ Electrophiles

3.1.1 Alkyl Halides

The reaction of dimethylalkynylaluminum reagents with alkyl halides takes place through a dissociative pathway and involves the coordination of the metal center to the leaving group. The exceeding high affinity of aluminum for fluorine (663 kJ mol⁻¹) has been exploited for the selective alkynylation of tertiary alkyl fluorides (Scheme 4).19 Interestingly, no reaction was observed using the corresponding chloro analogues.

3.1.2 Propargylic Sulfonates

The Lewis base activation of dimethylalkynylaluminum reagents associated with their low basicity has been exploited in a very elegant synthesis of skipped diynes from propargylic electrophiles (Scheme 5).20 The coordination of the metallic nucleophile to the electrophile drives a clean SN₂ reaction and avoids an undesired SN₂' substitution at the triple bond. Particularly noteworthy is the reaction of terminal propargylic sulfonates, known to generally react predominately on the least substituted carbon and lead to allene intermediates. The corresponding chloro or iodo derivatives do not react under similar reaction conditions. A six-membered aluminum-coordinated transition state has been proposed to explain this difference in reactivity.
3.1.3 Thioacetals

Sulfones are excellent leaving groups for the synthesis of medium-sized α-substituted cyclic ethers; the nucleophilic substitution involves a reactive oxonium intermediate. Interestingly, thioacetals are selectively activated in the presence of acetals (Scheme 6).

Such selective alkynylation was exploited in the synthesis of the C15–C38 fragment of okadaic acid (Scheme 7). This example is particularly illustrative of the great functional group tolerance of organoaluminum species as well as their excellent chemoselectivity.

3.1.4 Hemiaminals

Like oxoniums, iminium precursors such as hemiaminals can react with dimethylalkynylaluminum reagents in a similar manner. This reactivity enables a simple access to various substituted propargylamines (Scheme 8).

3.1.5 β-Lactones

Alkynylaluminum compounds are excellent partners in alkynyl-propanoic acid homologation reactions based on the regioselective ring opening of β-propiolactone. This reaction was used as a key step in the synthesis of unsaturated fatty acids (Scheme 9); the same reaction with the corresponding organolithium was unsuccessful.

3.1.6 Epoxides

Epoxides react readily with dimethylalkynylaluminum reagents (Scheme 10). As expected, the ring opening is generally fully regioselective with terminal epoxides, the least substituted carbon being the most reactive one.
The regioselectivity of the reaction is less pronounced with internal epoxides. It can however be controlled by neighboring coordination groups. This effect has been beautifully illustrated with fluoride-substituted substrates (Scheme 11). Thus, a \( \beta \)-fluorinated epoxide \((X = F)\) reacted in less than 10 minutes at \(-78^\circ C\) to give a homopropargyl alcohol I in a fully regioselective manner and 70% chemical yield. In marked contrast, the corresponding non-fluorinated substrate \((X = H)\) was less reactive, delivering an almost equimolar mixture of isomers I/II in only 40% yield. This fluoride assistance can be explained by the high affinity of aluminum to fluoride, leading to the formation of a transient pentacoordinate complex that delivers its alkynyl group in a regioselective manner.\(^{27}\)

The formation of an acid–base complex prior to the alkynyl group delivery can lead to interesting rearrangements. The regioselective alkylation of 2,3-epoxy sulfides\(^{28}\) or selenides\(^{29}\) (Scheme 12) involves an episulfonium or episelenium intermediate. In the case of sulfur derivatives, the C-2 alkylation product III was preferentially obtained with a global retention of configuration, whereas alkylation occurred at C-1 to give IV starting from the corresponding selenium precursor.

Another chemo- and regioselective alkylation of an epoxide involving a neighboring group participation can be observed on bicyclic hydrazines (Scheme 13).\(^{30}\) This behavior is a remarkable example of the synthetic potential of strong Lewis acidic, poor nucleophilic reagents such as organoaluminum compounds.

3.1.7 Aziridines

Dimethylalkynylaluminum compounds react with \(N\)-sulfonylaziridines. The reaction has to be conducted in CH\(_2\)Cl\(_2\) and proceeds via coordination of the organometallic compound to the aziridine-protecting group with subsequent intramolecular alkylation.\(^{31}\) Interestingly, a trans-1,2-disubstituted cyclohexene was obtained from an aziridine-fused cyclohexene whereas cis-1,4-disubstituted cyclopentene was formed from an aziridine-fused cyclopentene. The same aziridine reacted with trimethylaluminum to give a cis-1,2-disubstituted cyclopentene (Scheme 14).

3.1.8 \(\beta\)-Azido Enol Ethers

\(\beta\)-Azido silyl enol ethers can be ionized by Lewis acids like AlMe\(_3\) and generate a reactive enonium that can undergo a conjugate 1,4-addition. This original reactivity was used to prepare \(\beta\)-alkynyl enol ethers in 70–98% yield (Scheme 15).\(^{32}\)
3.2 Reactions with Csp² Electrophiles

3.2.1 Carbonyl Compounds

Dimethylalkynylaluminum reagents react readily with carbonyl compounds by selectively transferring their alkyne moiety (Scheme 16). The general order of reactivity is acyl chlorides > aldehydes > ketones >> esters. Of particular interest is the reaction with acyl chlorides, which provides a very simple and convenient access to ynones. The use of 1,2-dichloroethane as a solvent is crucial in this transformation since no reaction occurs in THF. The preparation of symmetrical diynones from oxalyl chloride is also noteworthy.

Hydroximoyl chlorides and hydrazinoyl chlorides reacted readily with dimethylalkynylaluminum reagents; the transient aluminate underwent an intramolecular cyclization, leading to aluminated isoxazoles and pyrazoles. The stability of the C–Al bonds enables this transformation to be performed at 50 °C without degradation by β-elimination (Scheme 18). These aluminated heterocycles were then reacted with strong electrophilic reagents such as isocyanates or N-halosuccinimides.

3.2.2 Amino Derivatives

The reaction of dimethylalkynylaluminum with nitriles requires a higher temperature than that used with acyl chlorides, but this is an alternative way to prepare ynones after hydrolysis of the α,β-alkynylketimine. Interestingly, in a one-pot procedure, treatment of the N-(dimethylaluminum)-α,β-alkynylketimine addition product with a chloroforimate led to an ynimine carbamate; this straightforward reaction enabled a very efficient access to 1,2-dihydropyridines via an alkyne isomerization/electrocyclization sequence (Scheme 18).

The reaction of dimethylalkynylaluminum compounds with carbohydrate-derived nitrones was highly stereoselective (Scheme 19); cyclization onto the triple bond was not observed. In absence of any other competitive Lewis basic center, nitrones themselves catalyzed the terminal aluminination of alkynes, leading to a one-pot α-addition from terminal alkynes in the presence of trimethylaluminum.

Activated imines, such as N-phosphinoyl or N-sulfinylimines, react with dimethylalkynylaluminum reagents. Good to excellent diastereoselectivities were generally obtained when performing the reaction in toluene (Scheme 20). No reaction was observed in THF or diethyl ether, highlighting the importance of coordination for this transformation.
The reaction of dimethylalkynylaluminum reagents with diazo(trimethylsilyl)methane is particularly noteworthy. Instead of attacking the metal center, as classically described with diazomethane and alkyl-, alkenyl-, or arylaluminum compounds, diazo(trimethylsilyl)methane behaves as an electrophile with dimethylalkynylaluminum compounds. This unique reactivity enabled a simple access to $\alpha$-silylated alkynyl hydrazones. These species were readily oxidized into the corresponding diazo derivatives, which served as useful precursors for geminal bis-propargyilsilanes or $\alpha$-silylated propargyl esters (Scheme 21).

The need for a coordinating group in 1,4-addition onto cyclic enones has been exploited in the diastereoselective desymmetrization of $\beta$-quinols by dimethylalkynylaluminum reagents (Scheme 23).

### 4 Transition-Metal-Catalyzed Reactions

#### 4.1 Addition to $\alpha,\beta$-Unsaturated Enones

Conjugated addition of dimethylalkynylaluminum reagent to cyclic enones can be quite challenging due to the lack of a polar directing group allowing the delivery of the alkynyl group to the enone moiety. This problem can however be circumvented by using transition-metal-catalyzed reactions. Indeed, the selective 1,4-addition of alkynyl groups to $\alpha,\beta$-unsaturated compounds can be observed in the presence of nickel catalysts (Scheme 24). In this case, an excess of the dimethylaluminum reagent was necessary to prevent undesired side reaction of the final aluminum enolate with the unreacted enone.

Interestingly, enantioselective 1,4-additions can be achieved either in the presence of a Ni(II)-bisoxazolidine catalyst, or using nickel(II) complexes with chiral biphosphine ligands (Scheme 25). In this last case, the alkynylation species proposed to be a bis(phosphine)nickel diacetylide,
while the dimethylaluminum chloride formed during the metathesis activates the enone by coordinating to the carbonyl group.49

4.2 Coupling Reactions

Compared to terminal alkynes or other metallated alkynes, dimethylalkynylaluminum reagents are rarely used in transition-metal-catalyzed coupling reactions. These compounds can nonetheless be employed as valuable reagents in palladium-catalyzed cross-couplings for the selective alkynylation of aromatic halides or triflates (Scheme 26).50 This approach prevents the formation of undesired homodimeric byproducts frequently observed in Glaser-type reactions.

Dimethylalkynylaluminum reagents can also react with alkynyl bromides in the presence of nickel(0) catalysts to generate unsymmetrical diynes in good yields (Scheme 27).51

5 Triple Bond Reactivity

Although dimethylalkynylaluminum reagents behave mostly as σ-nucleophilic alkynides, their triple bond can also be engaged in several reactions. This reactivity, combined with the stability of the C–Al bond, can be exploited in the synthesis of various organoaluminum compounds. Thus, dimethylalkynylaluminum reagents undergo carbometalation reactions in the presence of titanium- or zirconium-based catalysts to form geminal dimetallocycloalkenes via the formation of cyclic organometallic intermediate species (Scheme 29). Such compounds can also react easily with different electrophiles, such as aldehydes, ketones, halogens, or acyl chlorides. Remarkably, while for the Al/Ti bis-metallic compound a slow E/Z isomerization can occur at room temperature, the zirconium derivative has proven to be stereochemically stable.53

Zirconium-catalyzed reactions can also be used to convert ω-halogenated alkynylaluminum derivatives into iodo- and bromoalkenes via the formation of cyclic organometallic intermediate species (Scheme 30).54

Another remarkable transformation is the copper-catalyzed 3+2 cycloaddition of azides. This reaction delivered various aluminated triazoles in a regioselective manner. The new organometallic species were then reacted with various electrophiles (Scheme 31). This synthetic route enables a straightforward access to trisubstituted triazoles.55
6 Conclusion

As shown in this short review, the reactivity of dimethylalkynylaluminum reagents and subsequent transformations makes these compounds valuable reagents for many synthetic applications.

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