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Short Review

Synthesis and Reactivity of Mixed Dimethylalkynylaluminum Reagents

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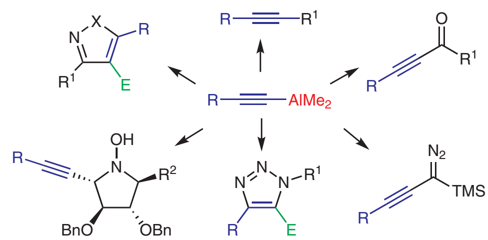

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Abstract Organoaluminum derivatives are mostly appreciated for their Lewis acidity properties, but generally not considered as reagents of choice in synthetic transformations involving the creation of C–C bonds. Among these species, dimethylalkynylaluminum 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.

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Key words organometallics, alkynes, organoaluminum reagents, alkynylation, metalation

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.[1] 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.[2] 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.[3]

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.[4] Furthermore, competitive hydride transfer can occur with substituents bearing an sp^3-C–H bond β to the sp^3-C–Al bond.[5] 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 magnesium reagents, they dramatically reduce the reactivity of alkylaluminum reagents through the formation of Lewis acid-base adducts.*[6] 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.

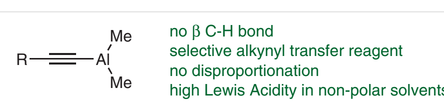

Figure 1 General properties of mixed dimethylalkynylaluminum reagents

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Serge Turcaud (left) obtained his CNAM Engineer degree in 1995. After working for 19 years in the laboratory of Prof. B. Roques at the University of Paris Descartes, he joined the group of Dr. J. Royer in 2003 and obtained his Ph.D. in 2009. He then joined the group of Dr. L. Micouin where he works on aluminum chemistry.

Laurent Micouin (2nd from left) obtained his Ph.D. in 1995 under the supervision of Prof. H.-P. Husson and Dr. J.-C. Quirion. After a post-doctoral stay at the Philipps Universität Marburg in the group of Prof. P. Knochel, he was recruited as a CNRS researcher at Paris Descartes University. His main research interests are methodological developments including organoaluminum chemistry, asymmetric synthesis, diversity-oriented synthesis, and developments at the interface between chemistry and biology, such as the design of new RNA binders.

Erica Benedetti (2nd from right) obtained her Ph.D. in 2011 under the supervision Prof. L. Fensterbank (UPMC-Sorbonne Universités) and Prof. A. Penoni (Università degli Studi dell'Insubria). In 2012, she joined the group of Prof. K. M. Brummond at the University of Pittsburgh as a postdoctoral fellow. After a second post-doctoral experience at the ESPCI ParisTech in the group of Prof. J. Cossy, she was recruited in 2014 as a CNRS researcher at Paris Descartes University in the team of Dr. L. Micouin. Her current research mainly involves the development of synthetic methodologies providing access to new chemical space.

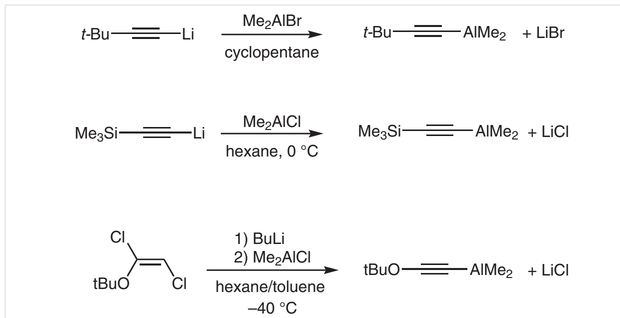
Riccardo Piccardi (right) obtained his Ph.D in 2005 under the supervision of Prof. P. Renaud at the University of Bern. The same year, he moved to Germany for a post-doctoral stay at the Technical University of Munich in the group of Prof. T. Bach. He then joined the team of Prof. O. Baudoin at University Claude Bernard Lyon I for a second postdoctoral experience. In 2008, he joined the group of Prof. M.-C. Scherrmann at University of Paris Sud. The next year he was recruited as a CNRS researcher in the same group. He finally joined the team of Dr. L. Micouin in 2014, where he is developing new methods combining flow chemistry and organoaluminum reactivity.

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^3-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.[7]

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 trialkylsilyl groups,[9] or showing weak acidity such as alkoxyacetylenes.[10]

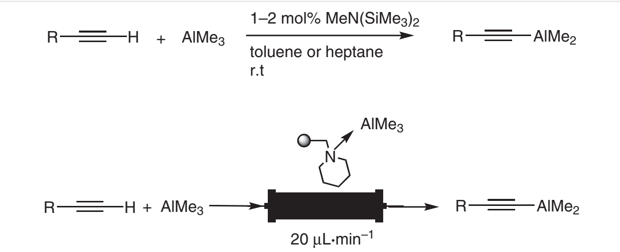


Scheme 1 Preparation of dimethylalkynylaluminum reagents by transmetalation

This approach requires a first metalation 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_2O.

Trimethylaluminum is not sufficiently basic to metalate 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 metalation occurs at room temperature in triethylamine, as reported by Binger in 1963.[12] This observation led to the development of a base-catalyzed alumination 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)methylamine (Scheme 2).[14] Using this base, clean terminal alumination 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



Scheme 2 Preparation of dimethylalkynylaluminum reagents by base-catalyzed terminal alumination

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]

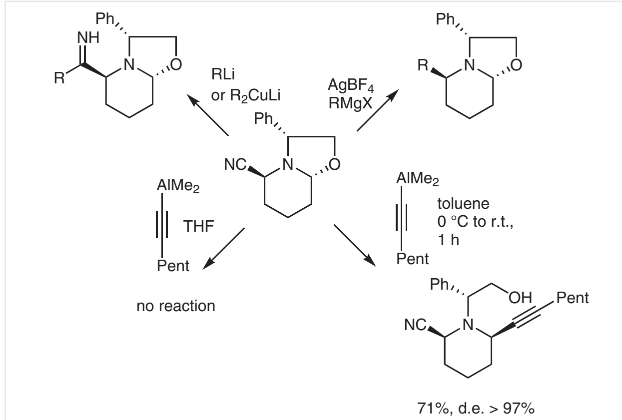
3 Reactivity of Dimethylalkynylaluminum Reagents

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 reagents[18] 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 Csp^3 Electrophiles

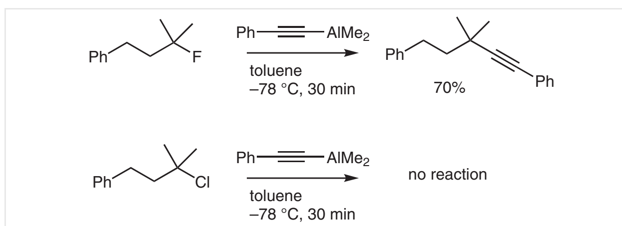
3.1.1 Alkyl Halides

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



Scheme 3 Example of a selective Lewis acidity triggered reaction of dimethylalkynylaluminum reagents

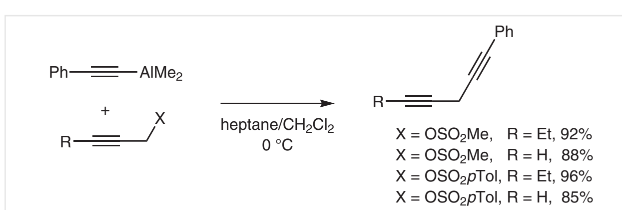
for fluorine (663 kJ mol^{-1}) has been exploited for the selective alkynylation of tertiary alkyl fluorides (Scheme 4).[19] Interestingly, no reaction was observed using the corresponding chloro analogues.



Scheme 4 Nucleophilic substitutions of alkyl fluorides

3.1.2 Propargylic Sulfonates

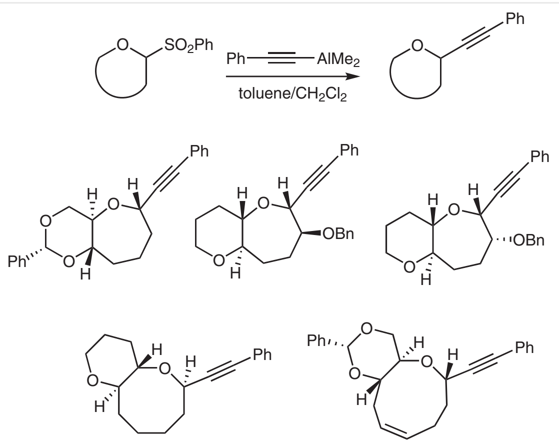
The Lewis base activation of dimethylalkynylaluminum reagents associated with their low basicity has been exploited in a very elegant synthesis of skipped diynes from propargylic electrophiles (Scheme 5).[20] The coordination of the metallic nucleophile to the electrophile drives a clean S_N2 reaction and avoids an undesired S_N2' 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.



Scheme 5 Selective synthesis of skipped diynes

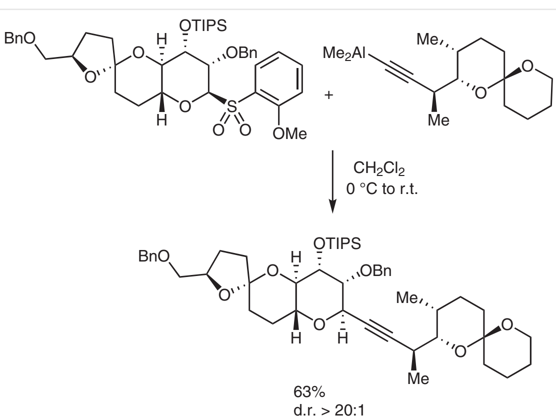
3.1.3 Thioacetals

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).[21]



Scheme 6 Alkynylation of lactone-derived sulfones

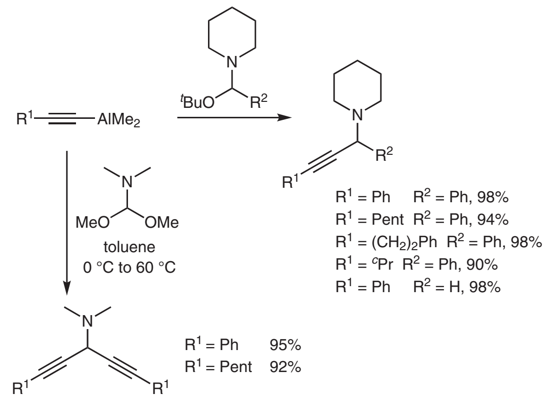
Such selective alkynylation was exploited in the synthesis of the C15–C38 fragment of okadaic acid (Scheme 7).[22] This example is particularly illustrative of the great functional group tolerance of organoaluminum species as well as their excellent chemoselectivity.



Scheme 7 Selective alkynylation as a key step in the synthesis of the C15–C38 fragment of okadaic acid

3.1.4 Hemiaminals

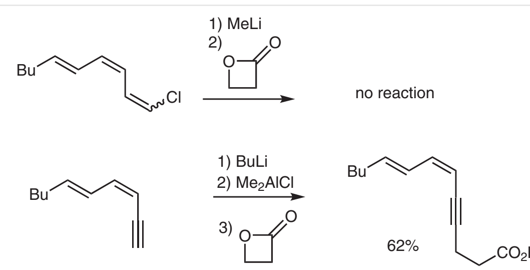
Like oxoniums, iminium precursors such as hemiaminals can react with dimethylalkynylaluminum reagents in a similar manner. This reactivity enables a simple access to various substituted propargylamines (Scheme 8).[23]



Scheme 8 Synthesis of mono- and bis-propargylamines

3.1.5 β-Lactones

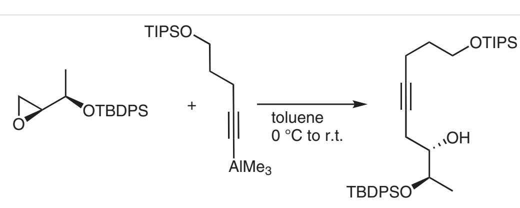
Alkynylaluminum compounds are excellent partners in alkyne-propanoic acid homologation reactions based on the regioselective ring opening of β-propiolactone.[24] This reaction was used as a key step in the synthesis of unsaturated fatty acids (Scheme 9); the same reaction with the corresponding organolithium was unsuccessful.[25]



Scheme 9 Homologation of alkynes with β-propiolactone

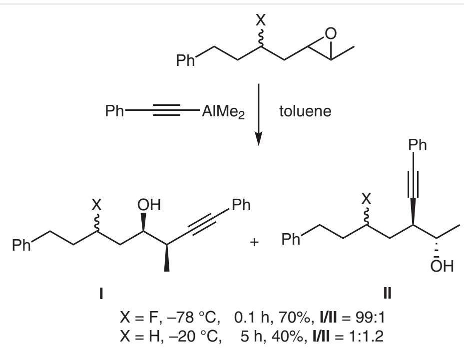
3.1.6 Epoxides

Epoxides react readily with dimethylalkynylaluminum reagents (Scheme 10).[26] As expected, the ring opening is generally fully regioselective with terminal epoxides, the least substituted carbon being the most reactive one.



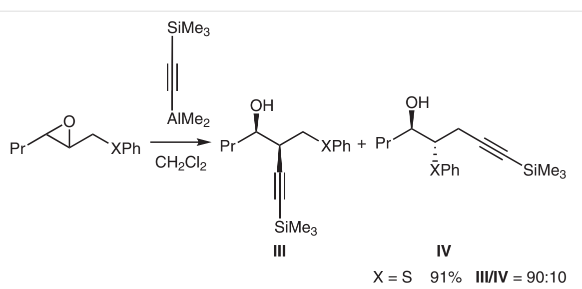
Scheme 10 Regioselective epoxide opening by dimethylalkynylaluminum reagents

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 fluorine-substituted substrates (Scheme 11). Thus, a β-fluorinated epoxide (X = F) reacted in less than 10 minutes at –78 °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 fluorine assistance can be explained by the high affinity of aluminum to fluorine, leading to the formation of a transient pentacoordinate complex that delivers its alkynyl group in a regioselective manner.[27]



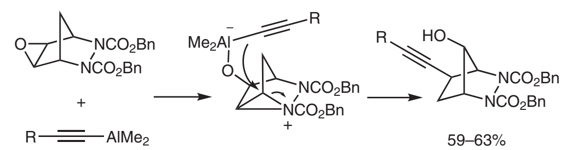
Scheme 11 Fluorine-assisted epoxide opening

The formation of an acid-base complex prior to the alkynyl group delivery can lead to interesting rearrangements. The regioselective alkynylation 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 alkynylation product **III** was preferentially obtained with a global retention of configuration, whereas alkynylation occurred at C-1 to give **IV** starting from the corresponding selenium precursor.



Scheme 12 Alkynylations of 2,3-epoxy sulfides or selenides

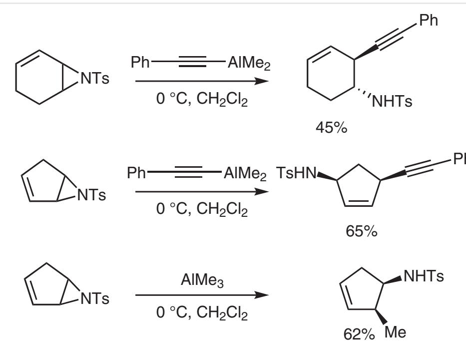
Another chemo- and regioselective alkynylation of an epoxide involving a neighboring group participation can be observed on bicyclic hydrazines (Scheme 13).[30] This behavior is a remarkable example of the synthetic potential of strong Lewis acidic, poor nucleophilic reagents such as organoaluminum compounds.



Scheme 13 Neighboring group participation in bicyclic hydrazine epoxide alkynylation

3.1.7 Aziridines

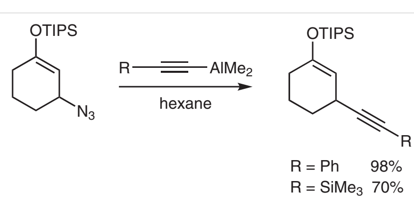
Dimethylalkynylaluminum compounds react with *N*-sulfonylaziridines. The reaction has to be conducted in CH_2Cl_2 and proceeds via coordination of the organometallic compound to the aziridine-protecting group with subsequent intramolecular alkynylation.[31] Interestingly, a *trans*-1,2-disubstituted 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).



Scheme 14 Ring opening of cyclic vinyl aziridines

3.1.8 β-Azido Enol Ethers

β-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 β-alkynyl enol ethers in 70–98% yield (Scheme 15).[32]

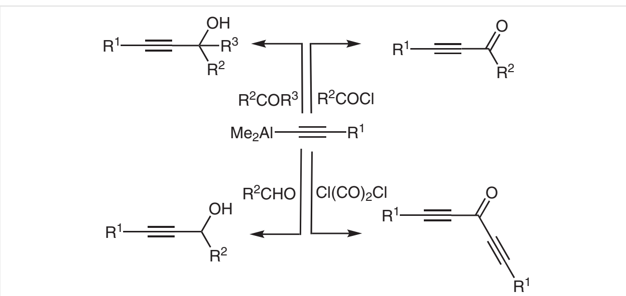


Scheme 15 Alkylation of β-azido silyl enol ethers

3.2 Reactions with Csp^2 Electrophiles

3.2.1 Carbonyl Compounds

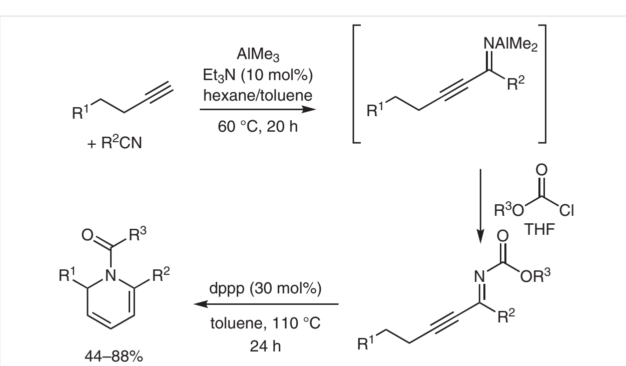
Dimethylalkynylaluminum reagents react readily with carbonyl compounds by selectively transferring their alkynyl moiety (Scheme 16).[33] The general order of reactivity is acyl chlorides > aldehydes > ketones >> esters. Of particular interest is the reaction with acyl chlorides, which provides a very simple and convenient access to ynones.[34] 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.[34]



Scheme 16 Reaction of dimethylalkynylaluminum reagents with carbonyl compounds

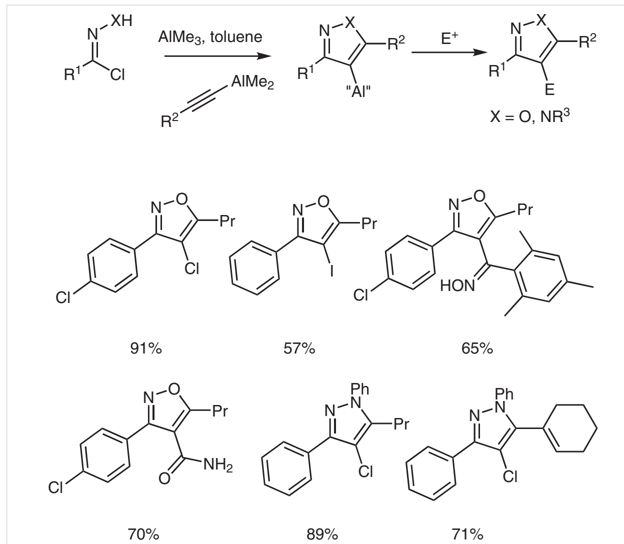
3.2.2 Amino Derivatives

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.[35] Interestingly, in a one-pot procedure, treatment of the *N*-(dimethylalumino)-α,β-alkynylketimine addition product with a chloroformate led to an ynimine carbamate; this straightforward reaction enabled a very efficient access to 1,2-dihydropyridines via an alkyne isomerization/electrocyclization sequence (Scheme 17).[36]



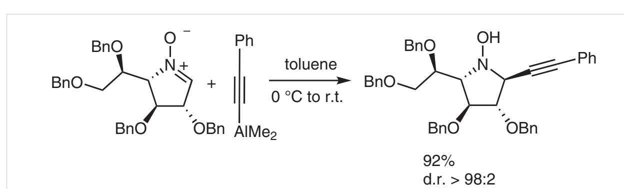
Scheme 17 Two-step synthesis of disubstituted dihydropyridines from nitriles

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.[37]



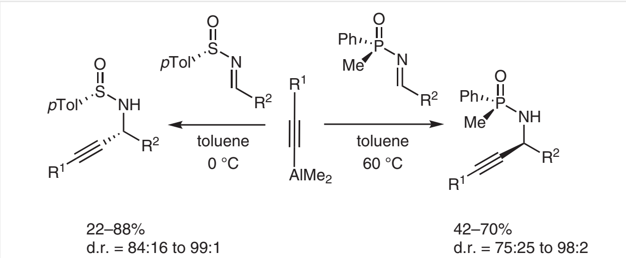
Scheme 18 One-pot, two-step synthesis of trisubstituted oxazoles and pyrazoles

The reaction of dimethylalkynylaluminum compounds with carbohydrate-derived nitrones was highly stereoselective (Scheme 19);[38] cyclization onto the triple bond was not observed. In absence of any other competitive Lewis basic center, nitrones themselves catalyzed the terminal alumination of alkynes, leading to a one-pot α-addition from terminal alkynes in the presence of trimethylaluminum.[39]



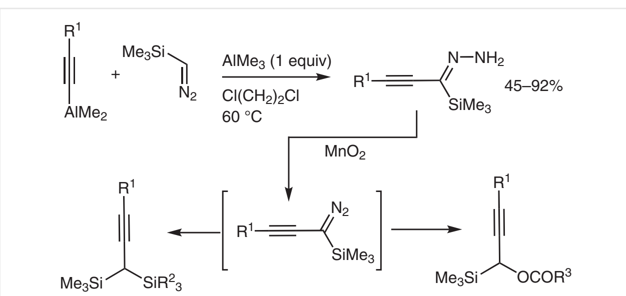
Scheme 19 Reaction of alkynylaluminum reagents with cyclic nitrones

Activated imines, such as *N*-phosphinoyl[40] or *N*-sulfinylimines,[41] 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.



Scheme 20 Diastereoselective synthesis of propargylamines

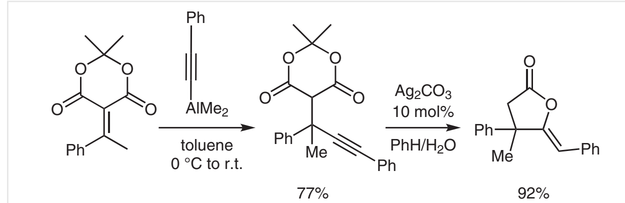
The reaction of dimethylalkynylaluminum reagents with diazo(trimethylsilyl)methane is particularly noteworthy. Instead of attacking the metal center, as classically described with diazomethane and alkyl-, alkenyl-, or arylaluminum compounds, diazo(trimethylsilyl)methane behaves as an electrophile with dimethylalkynylaluminum compounds. This unique reactivity enabled a simple access to α-silylated alkynyl hydrazones.[42] These species were readily oxidized into the corresponding diazo derivatives, which served as useful precursors for geminal bis-propargylsilanes[43] or α-silylated propargyl esters (Scheme 21).[44]



Scheme 21 Reaction of dimethylalkynylaluminum reagents with diazo(trimethylsilyl)methane and subsequent transformations

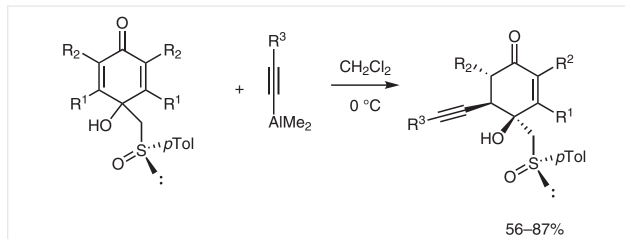
3.2.3 Enones

Dimethylalkynylaluminum reagents add to conjugated enones provided they can adopt a chelated transition state, leading to an intramolecular delivery of the alkynyl moiety.[45] As a consequence, enones devoid of a proximal coordinating group can undergo a 1,4-addition only if they are able to adopt a cisoid conformation. This strategy was used for the two-step synthesis of γ-butyrolactones from a Meldrum's acid derivative (Scheme 22).[46] The low basicity of organoaluminum reagents enabled a clean 1,4-addition whereas any attempts to add lithium alkynides resulted in nearly quantitative recovery of starting material, probably because of undesirable γ-deprotonation at the methyl position.



Scheme 22 1,4-Addition to a Meldrum's acid derivative

The need for a coordinating group in 1,4-addition onto cyclic enones has been exploited in the diastereoselective desymmetrization of *p*-quinols by dimethylalkynylaluminum reagents (Scheme 23).[47]

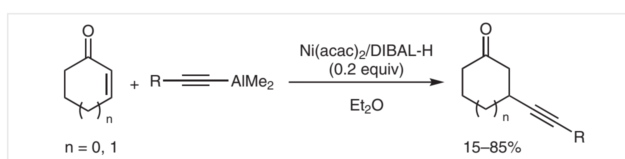


Scheme 23 1,4-Addition to *p*-quinols

4 Transition-Metal-Catalyzed Reactions

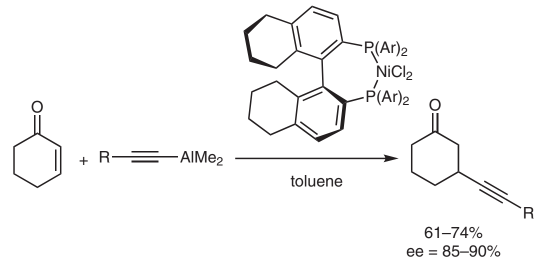
4.1 Addition to α,β-Unsaturated Enones

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 α,β-unsaturated compounds can be observed in the presence of nickel catalysts (Scheme 24).[48] 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.



Scheme 24 Nickel-catalyzed 1,4-alkynylations

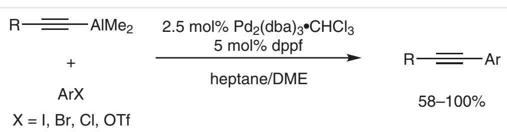
Interestingly, enantioselective 1,4-additions can be achieved either in the presence of a Ni(II)–bisoxazolidine catalyst, or using nickel(II) complexes with chiral biphosphine ligands (Scheme 25). In this last case, the alkynylating species proposed to be a bis(phosphine)nickel diacetylide, while the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



Scheme 25 Asymmetric nickel-catalyzed 1,4-alkynylations

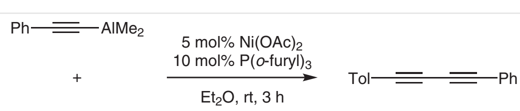
4.2 Coupling Reactions

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.



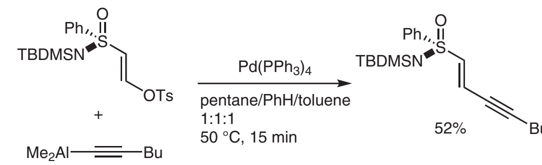
Scheme 26 Palladium-catalyzed cross-coupling reactions

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]



Scheme 27 Synthesis of unsymmetrical diynes

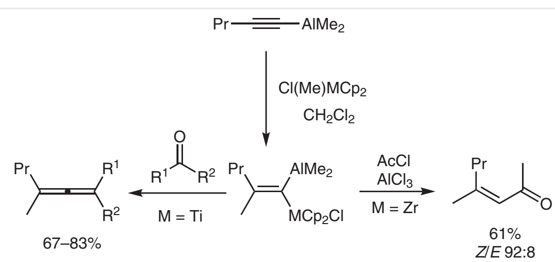
An interesting palladium-catalyzed coupling between β-tosylvinylsulfoximines and alkynylaluminum reagents has been reported for the stereospecific synthesis of enynylsulfoximines (Scheme 28).[52]



Scheme 28 Stereospecific synthesis of enynylsulfoximines

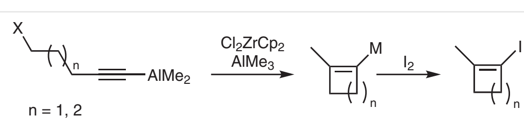
5 Triple Bond Reactivity

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 dimetallic 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 bismetallic compound a slow *E*/*Z* isomerization can occur at room temperature, the zirconium derivative has proven to be stereochemically stable.[53]



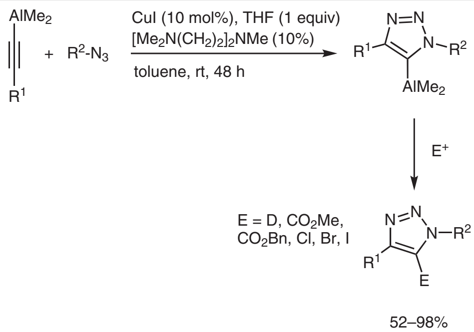
Scheme 29 Methylmetalation of alkynylaluminum reagents

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



Scheme 30 Intramolecular reaction of bis-metalated reagents

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]



Scheme 31 Copper-catalyzed 3+2 cycloaddition of azides with dimethylalkynylaluminum reagents and subsequent transformations

6 Conclusion

As shown in this short review, the reactivity of dimethylalkynylaluminum reagents is, in many aspects, unique and complementary to classical reactivities observed with polar organometallic reagents. The combination of a metal atom acting as strong Lewis and a rather stable carbon–metal bond with significant covalent character leads to interesting regio- and chemoselectivities, which can generally be observed at room temperature or under refluxing solvent conditions. In all the cases the alkynyl group is selectively transferred, while the methyl groups remain spectator substituents. This reactivity, associated with the low price and wide availability of trimethylaluminum, make these compounds valuable reagents for many synthetic applications.

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