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HAL Id: hal-02185392

<https://hal.science/hal-02185392>

Submitted on 16 Jul 2019

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Direct Synthesis of 1,4-Disubstituted-5-alumino-1,2,3-triazoles By a Copper-Catalyzed Cycloaddition of Organic Azides and Mixed-Aluminum acetylides**

Yuhan Zhou,^[a, b] Thomas Lecourt,^[a] and Laurent Micouin^{*[a]}

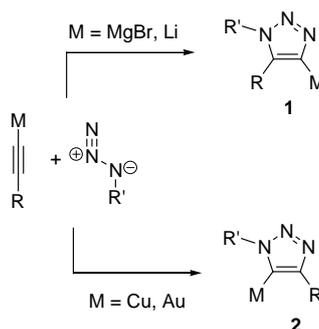
Dedicated to Prof. Alexandre Alexakis on the occasion of his 60th birthday

The development of functionalized organometallics is a dramatically growing field, and considerably broadens the scope of these nucleophilic reagents.^[1] An important breakthrough for the preparation of such reactive species bearing sensitive functional groups has been the discovery of synthetic pathways alternative to the Grignard or Barbier oxidative addition of activated metals to organic halides, such as halogen-metal exchange^[2] or new selective metalation processes.^[3] Both approaches enable the preparation of numerous functional organometallic reagents, and provide powerful tools, especially in the field of aromatic or heterocyclic chemistry.^[4] Using these methods, based on a selective formation of a carbon-metal bond in the presence of sensitive functional groups, the metallic bond is established *after* the function. One can however conceive an alternative strategy, with the formation of the metallic bond *prior* to functional group introduction. Such an approach is only possible if the carbon-metal bond is kinetically and/or thermodynamically stable enough to withstand functional group manipulations. As a matter of fact, numerous examples of such a strategy have recently been reported with organoboron or organotin reagents, showing that several synthetic transformations can be conducted on remotely embedded functional groups of these compounds.^[5]

If one considers the electronegativity difference between a metal and carbon as an empiric criterion for the development of functionalized organometallics, as proposed by Knochel in his seminal review on this field,^[6] it is striking to see that the carbon-aluminum bond can be located between the carbon-zinc and the carbon-magnesium bond, two very important classes of functional organometallics. However, despite some very recent important works on organoaluminum preparation and reactivity,^[7] the development of functional organoaluminum reagents is still

underinvestigated. In this paper, we report that functional organoaluminum reagents are accessible by a post-modification of aluminium acetylides using a copper-catalyzed [3+2] cycloaddition reaction.

The reaction of alkynes with organoazides has emerged as a very popular transformation since the report by the groups of Meldal and Sharpless that this reaction can dramatically be accelerated by copper (I).^[8] Starting from terminal alkynes, this reaction regioselectively delivers a 1,4-disubstituted-5-cuprotriazole intermediate, which has been isolated and fully characterized.^[9] Similar metalated triazoles have also been described starting from gold(I) acetylides.^[10] Although a new carbon-metal bond is formed during this process, the reactivity of these intermediates has only been sparingly exploited. On the other hand, the uncatalyzed exothermic reaction of azides with lithium or magnesium acetylides has been reported to regioselectively deliver 1,5-disubstituted-4-metallotriazole intermediates, which can be trapped by different electrophiles.^[11] This different behavior between metallic species can be explained by a distinct mechanistic pathway: nucleophilic acetylides directly add to organoazides, leading to compound **1**, whereas copper acetylides undergo a 3+2 cycloaddition process with a possible involvement of a bimetallic intermediate leading to **2** (Scheme 1).^[12]



Scheme 1. Syntheses of metalated triazoles from metal acetylides.

The reaction of dimethylphenylalkynylaluminum **3** (prepared by a base-catalyzed metalation in toluene)^[13] with benzylazide was first investigated in THF (Table 1). No reaction was observed at room temperature (entry 1) and heating under microwave activation led to a mixture of regioisomers after hydrolytic treatment (entry 2). Addition of copper salts led to a dramatic improvement of the reaction rate at room temperature (entries 3-6). However, longer reaction time did not improve the conversion (entries 3-4). The inclusion of various ligands was then investigated. Among different

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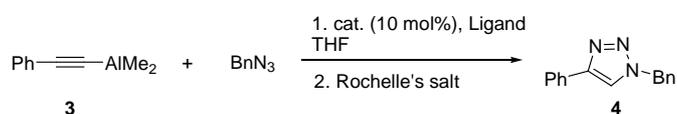
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[**] Financial support from ANR (ANR blanc AluMeth) is acknowledged.



ligands (phosphines, carbenes, amines, phenanthrolines), adjunction of phosphines led to a conversion improvement (entries 8-10). Finally, 99% conversion could be obtained using copper iodide and $[\text{Me}_2\text{N}(\text{CH}_2)_2]_2\text{NMe}$ (PMDTA) in THF at 55 °C.

Table 1. Optimization of the reaction conditions: catalyst and ligands.^[a]

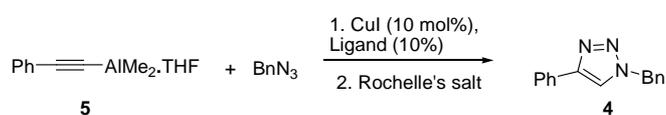


Entry	Cat	Ligand (%)	Temp	Time (h)	Conv (%) ^[b]
1	-	-	rt	24	nr
2	-	-	150 °C ^[d]	1.5	75 ^[c]
3	CuBr	-	rt	24	80
4	CuBr	-	rt	48	80
5	CuCN	-	rt	24	55
6	CuCl ₂	-	rt	24	50
7	CuI	-	rt	24	60
8	CuI	PPh ₃ (20)	rt	24	75
9	CuI	PPhMe ₂ (20)	rt	24	79
10	CuI	PPhMe ₂ (20)	rt	48	92
11	CuI	PMDTA (10)	rt	24	81
12	CuI	PMDTA (10)	55 °C	24	86
13	CuI	PMDTA (10)	55 °C	48	99

[a] Reaction condition: $\text{PhC}\equiv\text{CAI}\text{Me}_2$ 0.6 mmol, BnN_3 0.6 mmol, THF 2 mL. [b] Determined by GC after hydrolytic workup with mesitylene as internal standard [c] Regioisomers mixture. [d] Microwave heating.

Solvent influence was then investigated. Although the reaction in toluene led to a complex mixture, addition of one equivalent of THF, probably leading to the *in-situ* formation of a THF-complex, resulted in a large improvement of the reaction (Table 2, entries 1-2). Thus, without any ligand, 89% conversion could be achieved at room temperature after 24 hours. Best results were obtained using 10% copper iodide and 10% of ligand (entry 4). A lower reactivity was observed in dichloromethane and hexane (entries 5-6), whereas a good conversion was obtained using Methyl *ter*-Butyl ether but with the formation of a small proportion of side products (entry 8).

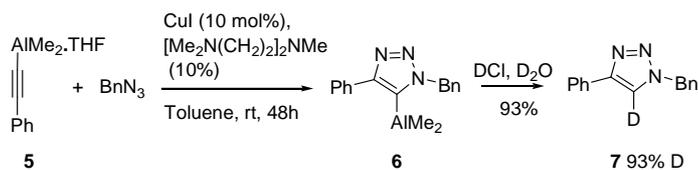
Table 2. Solvent compatibility study^[a]



Entry	Ligand	Solvent	Time (h)	Conv (%) ^[b]
1	-	Toluene	24	89
2	-	Toluene	48	92
3	PMDTA	Toluene	24	93
4	PMDTA	Toluene	48	97 (92) ^c
5	PMDTA	CH_2Cl_2	24	90
6	PMDTA	<i>n</i> -Hexane	24	75
7	PMDTA	MTBE	24	95
8	PMDTA	MTBE	48	97 (89) ^c

[a] Reaction condition: $\text{PhC}\equiv\text{CAI}\text{Me}_2$.THF 0.6 mmol, BnN_3 0.6 mmol, solvent 2 mL. [b] Determined by GC after hydrolytic workup with mesitylene as internal standard. [c] Isolated yield.

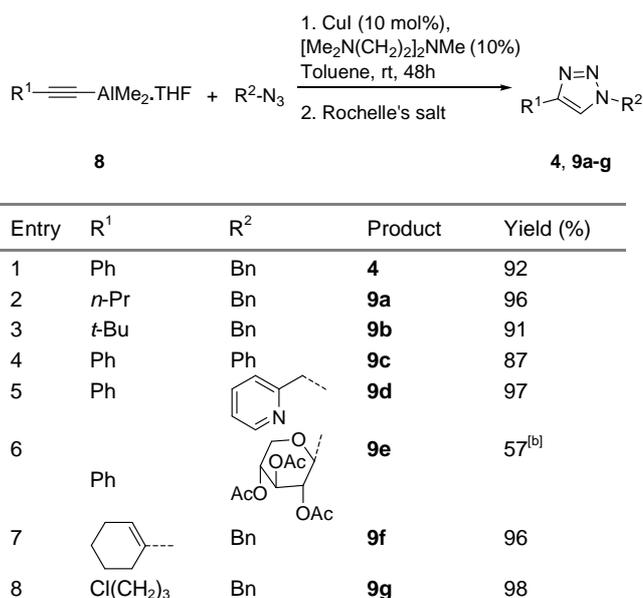
The exclusive regioselective formation of the 1,4-disubstituted-5-aluminotriazole was assessed by a deuterolysis experiment (Scheme 1). The high percentage of deuterium incorporation ensures that the metallic bond is still intact after the triazole formation.



Scheme 1. Deuteration study.

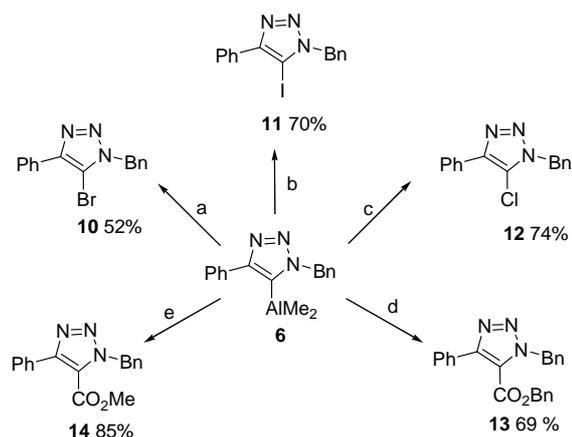
Optimized experimental conditions were then applied to a variety of dimethylaluminum alkynides and azides (Table 3). In all the cases, the 1,4-disubstituted triazoles were obtained as unique regioisomers. This selectivity is noteworthy, since copper-catalyzed cycloaddition of internal alkynes and azides are known to be poorly regioselective, with the notable exception of 1-Iodoalkynes, as recently reported by Hein, Fokin and co-workers.^[14] Interestingly, some functional groups bearing basic (Table 3, entry 5) or electrophilic (entry 6) character are well tolerated in this transformation.

Table 3. Scope of the reaction^[a]



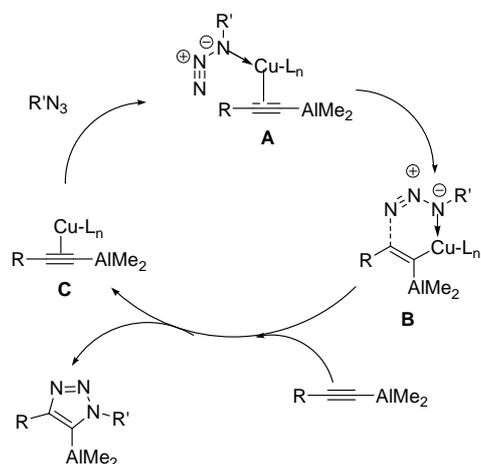
[a] Reaction condition: $\text{R}^1\text{C}\equiv\text{CAI}\text{Me}_2$.THF 0.6 mmol, R^2N_3 0.6 mmol, Toluene 2 mL. [b] reaction time: 96 h, 22% azide recovered.

The reactivity of these new aluminated heterocycles was explored (Scheme 2). As an example, compound **6** led to triazoles **10-12** by reaction with several *N*-halo-succinimides. Reaction with chloroformates led to the corresponding 1,4-disubstituted-triazoloesters **13**, **14**. These transformations clearly show that, despite its stability during the triazole formation, the carbon-aluminum bond is still reactive enough to be engaged in further synthetic transformations.



Scheme 2. Reaction conditions: a) NBS (3 equiv), rt, 4h. b) NIS (3 equiv), rt, 4h, then 55 °C, 2h. c) NCS (3 equiv), rt, 4h. d) ClCO₂Bn (2 equiv), rt, 7h. e) ClCO₂Me (2 equiv), rt, 7h.

Although a detailed examination of the mechanism of this new reaction has not been completed, a mechanism closely related to the one recently proposed for the copper-catalyzed cycloaddition with iodoalkynes could be responsible for the highly regioselective formation of the 1,4-disubstituted-5-metallotriazoles (Scheme 3).^[14] Such a pathway would involve a transient sp² geminated organobimetallic intermediate, already suspected to be a key intermediate in the CuAAC reaction.^[15] The regioselective formation of a six-membered transition state with the reaction of the terminal azide nitrogen and the positively charged secondary carbon of the polarized metallic acetylide could explain the excellent regioselectivity of the process.^[16] Furthermore, the known stability of 1,1-alumino-metaloalkenes^[17] would explain the excellent stability of the carbon-aluminum bond during the catalytic cycle.



Scheme 3. Proposed mechanistic pathway.

In summary, we have reported a new copper-catalyzed cycloaddition of organic azides with dialkylaluminumacetylides. The regioselectivity of this reaction, combined with the reactivity of the final aluminotriazoles, enables a rapid and simple access to 1,4,5-trisubstituted triazoles. In a more general context, we have shown that complex heterocyclic organoaluminum compounds can be prepared from simple mixed alkynylaluminum reagents by chemical transformation, without affecting the metallic bond.

Extension of this concept, as well as the exploration of functional group tolerance of organoaluminum reagents, are currently underway in our laboratory.

Experimental Section

Typical procedure: The preparation of compound **12** is representative. To a dry and argon-flushed flask equipped with a magnetic stirrer charged with CuI (11.4 mg, 0.06 mmol) and toluene (2 mL), [Me₂N(CH₂)₂N]Me (12.5 μL, 0.06 mmol) was added dropwise. 10 min later, dimethylphenylalkynylaluminum (toluene solution prepared according to ref 13) complexed by THF (0.41 mL, 0.6 mmol) and benzyl azide (80 μL, 94%, 0.6 mmol) were added sequentially. After stirring at room temperature for 48 h, NCS (240 mg, 1.8 mmol) and dried THF (2 mL) were added at 0 °C. The mixture was stirred at room temperature for 4 h and poured into a cooled 2 M aqueous solution of Rochelle's salts (CAUTION: gas evolution). The organic phase was separated and the aqueous layer extracted with ethyl acetate (2 × 20 mL). The organic layer was dried over anhydrous magnesium sulfate; the solvent was evaporated, and the crude residue was purified by column chromatography (silica gel, 93/7 cHex/AcOEt) to give **12** as a colorless liquid (120 mg, 74% yield).

Received:

Published online on

Keywords: alanes · click chemistry · aluminum · regioselectivity · functionalized organometallics.

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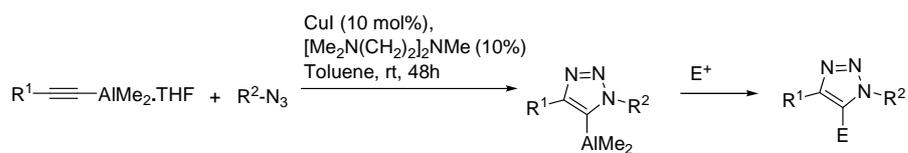
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Direct Synthesis of 1,4-Disubstituted-5-
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Catalyzed Cycloaddition of Organic
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Al together: alumino-triazoles are obtained in a fully chemo and regio-selective manner by a copper-catalyzed cycloaddition of organic azides with mixed-aluminum acetylides. The carbon-aluminum bond, unaffected by the first transformation, is still able to react further with different electrophiles.