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Cycloaddition Reactions

Direct Synthesis of 1,4-Disubstituted-5-alumino-1,2,3-triazoles: Copper-Catalyzed Cycloaddition of Organic Azides and Mixed Aluminum Acetylides[**]

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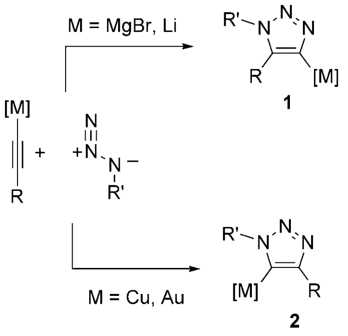
Dedicated to Professor Alexandre Alexakis on the occasion of his 60th birthday

The development of functionnalized organometallic compounds is a dramatically growing field, and considerably broadens the scope of these nucleophilic reagents.[1] An important breakthrough in the preparation of these reactive species, which contain sensitive functional groups, has been the discovery of alternative synthetic pathways 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 are powerful tools, especially in the field of aromatic or heterocyclic chemistry.[4] Using these methods, which are based on the selective formation of a carbon–metal bond in the presence of sensitive functional groups, the metallic bond is established after the functional groups are introduced. However, one can 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 using organoboron or organotin reagents, which shows that several synthetic transformations can be conducted on remotely embedded functional groups of these compounds.[5]

If one considers the difference in electronegativity between a metal and a carbon atom as an empirical criterion for the development of functionalized organometallic compounds, as proposed by Knochel and co-workers in their 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, which are two very important classes of functional organometallic reagents. However, despite some very recent important works on the preparation and reactivity of organoaluminum compounds,[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 aluminum acetylides using a copper-catalyzed [3 + 2] cycloaddition reaction.

The reaction of alkynes with organoazides has emerged as a very popular transformation since the groups of Meldal and Sharpless reported that this reaction can be dramatically accelerated by copper(I) catalysts.[8] Starting from terminal alkynes, this reaction regioselectively delivers a 1,4-disubstitued-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-disubstitued-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 add directly onto organoazides leading to compound **1**, whereas copper acetylides undergo a [3+2] cycloaddition process with the possible involvement of a bimetallic intermediate leading to **2** (Scheme 1).[12]

The reaction of dimethylphenylalkynylaluminum **3** (prepared by a base-catalyzed metalation reaction in toluene)[13] with benzylazide was first investigated in THF (Table 1). No



Scheme 1. Syntheses of metalated triazoles from metal acetylides.

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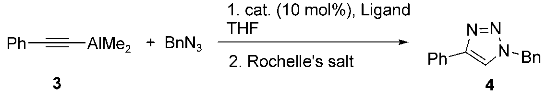
Table 1: Optimization of the reaction conditions: catalyst and ligands.[a]



Entry	Cat.	Ligand (mol%)	T [°C]	t [h]	Conversion [%][b]
1	–	–	RT	24	n.r.
2	–	–	150[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	24	86
13	CuI	PMDTA (10)	55	48	99

[a] Reaction conditions: $PhC{\equiv}CAlMe_2$ (0.6 mmol), BnN_3 (0.6 mmol), THF (2 mL). [b] Determined by GC methods after hydrolysis, with mesitylene as internal standard; n.r. = no reaction. [c] Mixture of regioisomers. [d] Heated under microwave conditions. Bn = benzyl.

reaction was observed at room temperature (Table 1, entry 1) and heating under microwave activation led to a mixture of regioisomers after hydrolysis (Table 1, entry 2). The addition of copper salts led to a dramatic improvement in the rate of reaction at room temperature (Table 1, entries 3–6). However, longer reaction times did not improve the conversion (Table 1, entries 3 and 4). The inclusion of various ligands was then investigated. Of the different ligands examined (phosphines, carbenes, amines, phenanthrolines), the addition of phosphines led to an improvement in conversion (Table 1, entries 8–10). Finally, 99% conversion could be obtained using copper iodide and $[Me_2N(CH_2)_2]_2NMe$ (PMDTA) in THF at 55 °C.

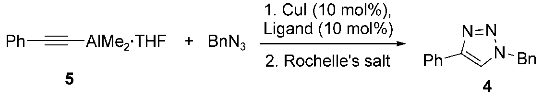
The influence of the solvent on the reaction was then investigated. Although the reaction in toluene led to a complex mixture, the addition of one equivalent of THF, presumably leading to the in situ formation of a THF–complex, resulted in a large improvement of the reaction conversion (Table 2, entries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

The exclusive regioselective formation of a 1,4-disubstitued-5-aluminotriazole was assessed by a deuterolysis experiment (Scheme 2). The high percentage of deuterium incorporation ensured that the metallic bond was still intact after the triazole formation.

Optimized experimental conditions were then applied to a variety of dimethylaluminum alkynides and azides (Table 3). In all the cases, the 1,4-disubstitued triazoles were obtained as unique regioisomers. This selectivity is noteworthy, as the copper-catalyzed cycloadditions 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 were well-tolerated in this transformation.

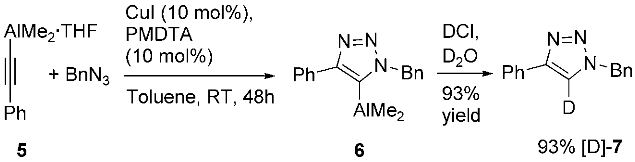
The reactivity of these new aluminated heterocycles was then explored (Scheme 3). As an example, compound **6** led to

Table 2: Solvent compatibility study.[a]



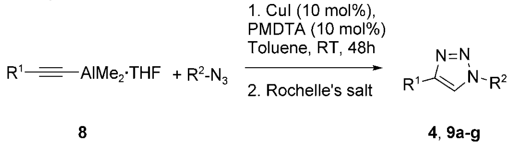
Entry	Ligand	Solvent	t [h]	Conversion [%][b]
1	–	toluene	24	89
2	–	toluene	48	92
3	PMDTA	toluene	24	93
4	PMDTA	toluene	48	97 (92)[c]
5	PMDTA	CH_2Cl_2	24	90
6	PMDTA	*n*-hexane	24	75
7	PMDTA	MTBE	24	95
8	PMDTA	MTBE	48	97 (89)[c]

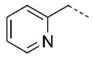
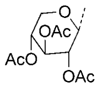
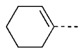
[a] Reaction conditions: $PhC{\equiv}CAlMe{\cdot}THF$ (0.6 mmol), BnN_3 (0.6 mmol), solvent (2 mL). [b] Determined by GC after hydrolytic workup with mesitylene as an internal standard. [c] Yield of isolated product given in parentheses. MTBE = methyl *tert*-butyl ether.



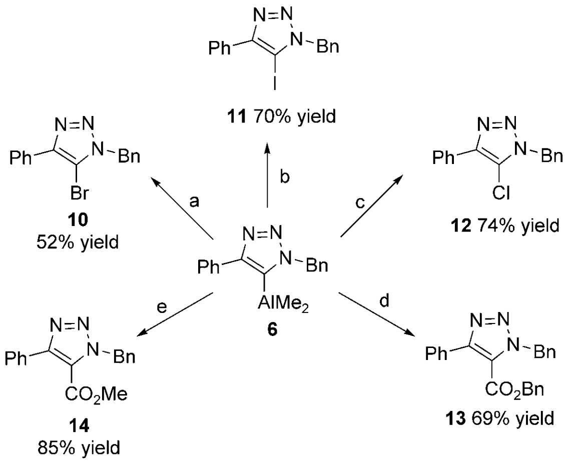
Scheme 2. Deuteration study. 93% deuterated product. PMDTA = $[Me_2N(CH_2)_2]_2NMe$.

Table 3: Scope of the reaction.[a]



Entry	R1	R2[b]	Product	Yield[c] [%]
1	Ph	Bn	**4**	92
2	*n*Pr	Bn	**9a**	96
3	*t*Bu	Bn	**9b**	91
4	Ph	Ph	**9c**	87
5	Ph	 N	**9d**	97
6	Ph	 O OAc AcO OAc	**9e**	57[d]
7		Bn	**9f**	96
8	$Cl(CH_2)_3$	Bn	**9g**	98

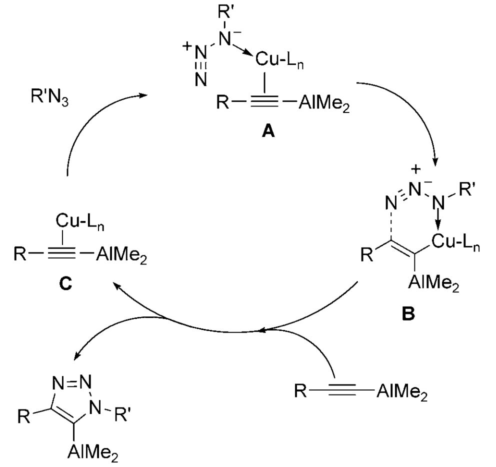
[a] Reaction conditions: $R^1C{\equiv}CAlMe_2{\cdot}THF$ (0.6 mmol), R^2N_3 (0.6 mmol), toluene (2 mL). [b] Dotted line indicates point of attachment. [c] Yield of isolated product. [d] 96 h reaction time, 22% yield of recovered azide.



Scheme 3. Reaction conditions: a) NBS (3 equiv), RT, 4 h. b) NIS (3 equiv), RT, 4 h; then 55 °C, 2 h. c) NCS (3 equiv), RT, 4 h. d) $ClCO_2Bn$ (2 equiv), RT, 7 h. e) $ClCO_2Me$ (2 equiv), RT, 7 h. NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide, NIS = *N*-iodosuccinimide.

triazoles **10**–**12** by reaction with several *N*-halo-succinimides. Reactions with chloroformates led to the corresponding 1,4-disubstituted-triazoloesters **13** and **14**. These transformations clearly show that, despite its stability during triazole formation, the carbon–aluminum bond is still reactive enough to be engaged in further synthetic transformations.

Although a detailed examination of the mechanism of this new reaction has not yet been completed, a closely related mechanism to the one recently proposed for the copper-catalyzed cycloaddition reaction with iodoalkynes could be responsible for the highly regioselective formation of the 1,4-disubstitued-5-metallotriazoles (Scheme 4).[14] Such a pathway would involve a transient sp^2 geminal organobimetallic intermediate, which is already suspected to be a key intermediate in the CuAAC (copper(I)-catalyzed azo–alkyne cycloaddition) reaction.[15] The regioselective formation of a six-membered transition state from the reaction of the terminal azide nitrogen with the positively charged secondary carbon atom of the polarized metallic acetylide could explain the excellent regioselectivity of the process.[16] Furthermore, the known stability of 1-alumino-1-metalloalkenes[17] would explain the excellent stability of the carbon–aluminum bond during the catalytic cycle.



Scheme 4. Proposed mechanistic pathway.

In summary, we have reported a copper-catalyzed cycloaddition of organic azides with dialkyl aluminum acetylides. 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 the functional group tolerance of organoaluminum reagents, is currently underway in our laboratory.

Experimental Section

Representative procedure (compound **12**): $[Me_2N(CH_2)_2]_2NMe$ (12.5 μL, 0.06 mmol) was added dropwise to a dry, argon-flushed flask that was charged with CuI (11.4 mg, 0.06 mmol), toluene (2 mL) and a magnetic stirrer. After 10 minutes, dimethylphenylalkynylaluminum (as a solution in toluene, 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 hours, 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 hours 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 was 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 on silica gel (cHex/EtOAc 93:7) to give **12** as a colorless liquid (120 mg, 74 % yield).

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