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Synthesis and Reactivity of Mixed Alkynylalanes by Direct Triethylamine-Catalyzed Alumination of Terminal Alkynes[†]

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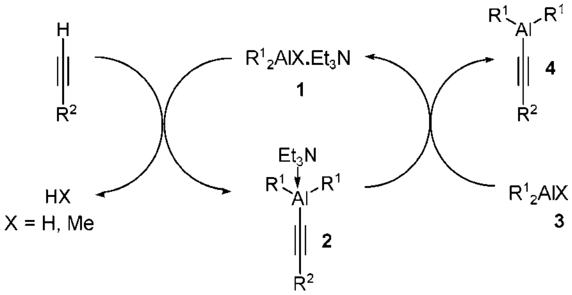
ABSTRACT



Terminal alumination of alkynes by DIBALH or trimethylaluminum can be performed in a simple manner in the presence of a small amount of triethylamine. This new Lewis-base-catalyzed process delivers mixed alkynyldialkylalanes of great interest, without the need of an initial deprotonation step with lithium or sodium derivatives followed by a transmetalation.

Metal acetylides are powerful reagents in organic synthesis, delivering compounds that are well configured for many subsequent chemical manipulations. Beside the classical palladium-catalyzed alkynylation,[1] a number of methods have been recently devised for the enantio- or diastereoselective alkynylation of carbonyls and various imino derivatives.[2] Among them, the in situ catalytic activation of an alkyne, involving a substoichiometric amount of base or a metal salt in the presence of a base, has emerged as a particularly attractive strategy.[3] One of the drawbacks of this approach is the need for suitable reaction conditions for alkyne deprotonation, generally performed under basic conditions, in the presence of the electrophile. The use of a stoichiometric amount of metal acetylide is a way to overcome this problem, and very good results have been reported in the addition of lithium,[2f] zinc,[2l,m] or boron acetylides[2d] on carbonyl groups.

We recently reported the use of mixed alkynylaluminum reagents in the stereoselective synthesis of α-substituted propargylamines.[4] Although aluminum acetylides have been reported to present interesting reactivity patterns,[5] their scope in organic synthesis is still under-investigated. One of the reasons may be the need for a simpler access to this class of reagents than their preparation by transmetalation from the corresponding lithium or sodium salt, generated under strongly basic conditions. We report here a novel access to such reagents, based on a base-catalyzed metalation of terminal alkynes.

While the reaction between a terminal alkyne and an organoaluminum reagent generally delivers a complex mixture of metalated species,[6] it has been known since the

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[†] Dedicated to Professor Henri-Philippe Husson on the occasion of his 65th anniversary.

(1) Negishi, E.-I.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

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pioneering work of Binger that a tertiary amine complex of trialkylalanes or dialkylaluminum hydrides **1** reacts with alkynes to furnish solely the corresponding acetylide−tertiary amine complexes **2** (Figure 1).[7]

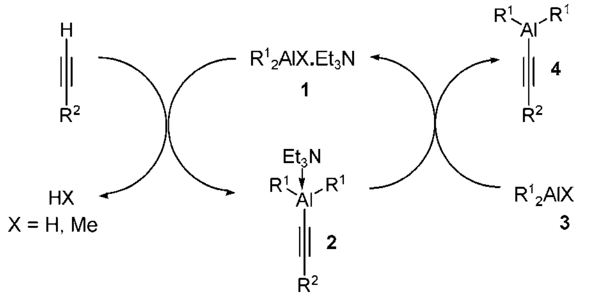
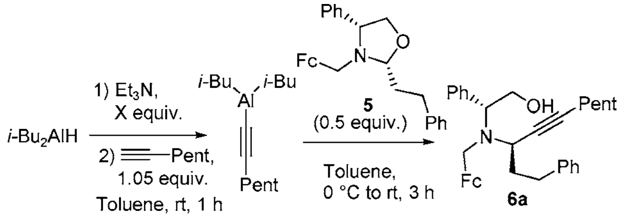


Figure 1. Catalytic cycle of terminal alumination in the presence of triethylamine.

We have shown that this unreactive species can then react with different electrophiles after decomplexation with trimethylaluminum.[4a] We reasoned that this decomplexation could in fact be performed by the metalating agent **3** itself, leading to a process catalytic in triethylamine and affording uncomplexed reactive mixed alkynylalanes **4**.

First experiments were conducted with DIBALH as a metalating agent and oxazolidine **5** as standard electrophile (Table 1).

Table 1. Effect of the Amount of Triethylamine in the Alumination of Heptyne with DIBALH



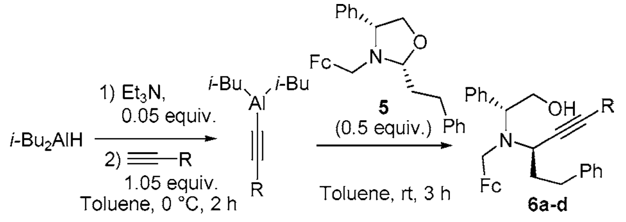
entry	Et_3N equiv (X)	yield (%)[a]	de (%)[b]
1	0.2	65	>97
2	0.05	86	>97
3	0.005	25	>97
4	0.05[c]	90	>97

[a] Yield of isolated pure compound based on **5**. [b] Determined by ^{1}H NMR on the crude reaction mixture. [c] Metalation was performed at 0 °C for 2 h.

A fast metalation could be observed using 20% triethylamine, evidenced by a rapid evolution of hydrogen gas at room temperature (entry 1).[8] This reaction occurred within less than 1 h using only 5% triethylamine (entry 2), whereas a smaller amount of catalyst led to a significantly lower conversion (entry 3). The best results were obtained when preparing the acetylide at 0 °C (entry 4).[9] In all the cases, compound **6a** was obtained as a single diastereomer.[10]

In such conditions, the reaction becomes highly efficient and general, as exemplified in Table 2. This procedure is far superior to our previously reported procedure[4a−d] since it uses a substoichiometric amount of triethylamine and an

Table 2. Diastereoselective Alkynylation of Oxazolidines with Mixed Alkynylorganoaluminum Reagents



entry	R	compound	yield (%)[a]	de (%)[b]
1	pent	**6a**	90	>97
2	Ph	**6b**	95	>97
3	$(CH_2)_3Cl$	**6c**	80	>97
4	$(CH_2)_6C\equiv CH$	**6d**	85	>97

[a] Yield of isolated pure compound based on **5**. [b] Determined by ^{1}H NMR on the crude reaction mixture.

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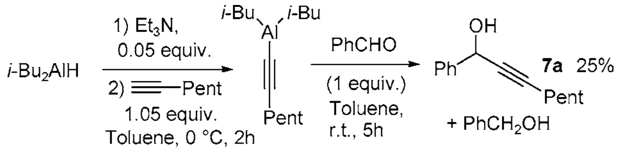
(8) Kinetics of deprotonation can be followed by ^{1}H NMR. The use of a concentrated (1.5 M) toluene DIBALH solution enables the direct observation of the reaction, *without the need for a deuterated solvent*.

(9) About 5% competitive hydroalumination product was detected when the metalation was conducted at room temperature.

additional equivalent of trimethylaluminum is not required for the delivery of a reactive nucleophilic species. Interestingly, the use of 1,9-decadiyne as a nucleophile led only to the monoalkynylation product **6d** (entry 4), a selectivity that would be difficult to achieve with a catalytic in situ metalation process.

The reaction of mixed alkynyldiisobutylalanes proved to be more troublesome with benzaldehyde, leading to a 1/3:2/3 ratio of propargyl alcohol **7a** and benzyl alcohol (Scheme 1).

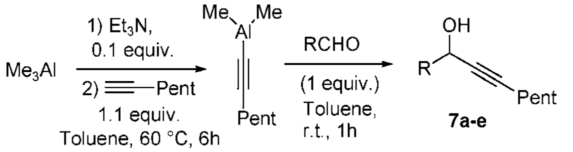
Scheme 1. Competitive Reduction in the Alkynylation of Aldehydes with Alkynyldiisobutylalanes



Since this side reaction probably comes from a competitive hydride transfer from the two isobutyl groups, we then investigated the base-catalyzed metalation using trimethylaluminum as a metal source. The best results were obtained when performing alumination in the presence of 10% triethylamine for 6 h at 60 °C.

Using this procedure afforded propargyl alcohols **7a**−**e** in 58−98% yield, without any competitive reduction or methyl transfer onto the carbonyl group (Table 3).

Table 3. Triethylamine-Catalyzed Alumination of Terminal Alkynes with Trimethylaluminum and Addition to Aldehydes

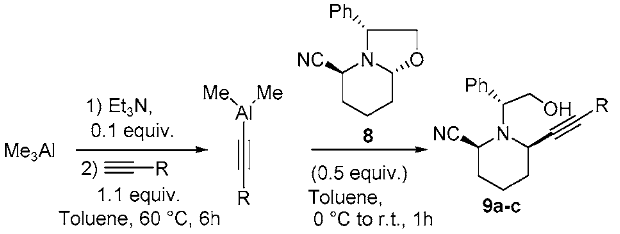


entry	R	compound	yield (%)[a]
1	Ph	**7a**	98
2	Ph(CH$_2$)$_2$	**7b**	67
3	PhCH═CH	**7c**	89
4	pent	**7d**	58[b]
5	Et	**7e**	59[b]

[a] Yield of isolated pure compound based on the aldehyde. [b] Lower chemical yield is the result of a competitive aldol condensation.

The unique reactivity pattern of these mixed alkynylaluminum reagents is illustrated in the following examples: while organolithium or cuprate derivatives[11] are known to react with the cyano group of compound **8** and Grignard reagents lead to its substitution via a Bruylant reaction,[12] mixed alkynyldialkylalanes only reacted with the oxazolidine moiety of **8**, in a completely regio- and stereoselective manner (Table 4).

Table 4. Regio- and Stereoselective Alkynylation of Cyano-oxazolopiperidine **8**



entry	R	compound	yield (%)[a]	de (%)[b]
1	pent	**9a**	71	>97
2	(CH$_2$)$_3$Cl	**9b**	76	>97
3	(CH$_2$)$_6$C≡CH	**9c**	49	>97

[a] Yield of isolated pure compound based on **8**. [b] Determined by ^{1}H NMR on the crude reaction mixture.

In summary, we have reported a new general synthesis of aluminum acetylides.[13] This pathway involves a new Lewis-base (triethylamine)-catalyzed metalation reaction of terminal alkynes, delivering reactive mixed alkynylorganoaluminum species, without the need for the prior preparation of their lithium or sodium salt. This salt-free, straightforward procedure should contribute to the development of the chemistry of aluminum acetylides, which is still under-investigated, despite some very promising reactivity and selectivity

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(10) This reaction, conducted in the absence of triethylamine at 60 °C, leads to hydroalumination and to the corresponding allylic amine in a stereoselective manner, see: Blanchet, J.; Bonin, M.; Micouin, L.; Husson, H.-P. *Tetrahedron Lett.* **2000**, *41*, 8279.

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(13) **Typical Procedure.** The preparation of **6d** is typical. The commercial DIBALH solution and triethylamine were used without any purification. Oxazolidine **5** was prepared according to the procedure described in ref 4a. A DIBALH solution in hexanes (1M) can also be used. A dry and argon-flushed flask equipped with a magnetic stirrer and a septum was charged with diisobutylaluminum in toluene (1.5 M, 1.45 mL, 2.18 mmol). Triethylamine (15 μL, 0.109 mmol, 0.05 equiv) was then added, and the reaction mixture was cooled to 0 °C. 1,9-Decadiyne (374 μL, 2.29 mmol, 1.05 equiv) was then added dropwise, and the reaction mixture was stirred for 2 h. The solution was then added via a syringe to a solution of oxazolidine **5** (500 mg, 1.09 mmol, 0.5 equiv) in anhydrous toluene (2 mL), and the reaction mixture was stirred for 3 h at room temperature and poured into a cooled 2 M aqueous solution of Rochelle's salts (CAUTION: gas evolution). After 30 min of vigorous stirring, the organic phase was separated and the aqueous phase was extracted with ether (3 × 5 mL). The organic layer was dried over anhydrous MgSO$_4$; the solvent was evaporated, and the crude residue was purified by column chromatography (silica gel, 9/1 cyclohexane/ethyl acetate) to give **6d** (542 mg, 85%, de > 97%). $[\alpha]_D = +4$ ($c = 1.0$, CHCl$_3$). ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.30$ (m, 10H), 4.23 (s, 1H), 4.14 (m, 1H), 4.12 (s, 5H), 4.04 (m, 4H), 3.78 (d, $J = 14.0$ Hz, 1H), 3.68 (d, $J = 14.0$ Hz, 1H), 3.59 (m, 1H), 2.56 (br. s, 1H), 2.48 (m, 2H), 2.23 (m, 4H), 1.96 (t, $J = 2.5$ Hz, 1H), 1.72 (m, 2H), 1.54 (m, 4H), 1.54 (m, 4H). ^{13}C NMR (100 MHz): $\delta = 141.9$, 139.8, 128.8−127.4, 124.8, 86.5, 85.8, 84.5, 70.1−68.0, 64.7, 61.8, 51.5, 46.1, 36.7, 32.9, 28.9, 28.5, 28.3, 18.8, 18.5. MS (CI): 586 (MH$^+$). IR (cm^{-1}): 3507, 3307, 3020, 2937, 2860, 1495. Anal. Calcd for $C_{38}H_{43}FeNO\cdot H_2O$: C, 75.61; H, 7.51; N, 2.32. Found: C, 76.03; H, 7.69; N, 2.27.

patterns. The scope of this new reaction for the preparation of functional acetylides is under study in our laboratory.

Acknowledgment. We thank the CNRS for financial support and Prof. H.-P. Husson for fruitful discussions and encouragement.

Supporting Information Available: Analytical data for all new compounds (**6c**, **9a**−**c**) and NMR spectra of compounds **6a**, **6b**, **7a**−**d**, and **9a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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