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Room Temperature Lewis Base-Catalyzed Alumination of Terminal Alkynes

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Abstract: An efficient and mild access to mixed dimethylalkynylaluminum reagents has been developed *via* a direct Lewis base-catalyzed alumination of terminal alkynes by trimethylaluminum. The use of bis(trimethylsilyl)methylamine enables the metalation at room temperature with only 1% of catalyst loading.

Keywords: acetylides; alanes; alkynes; Lewis base catalysis; organoaluminum reagents

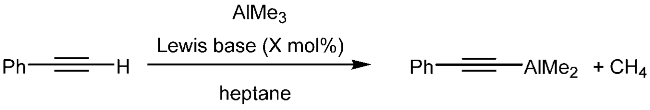
The use of metalated terminal alkynes as nucleophiles for transition metal-catalyzed or direct C–C bond formation is a well established strategy.[1] Although alkali or alkaline earth metal acetylides are popular reagents known to add to numerous electrophiles, other reactive alkynides such as aluminum acetylides have been reported to present interesting reactivity patterns.[2] Their scope in organic synthesis is however still under-investigated. One of the reasons may be the need for a simpler access to this class of reagents than their preparation from the corresponding lithium or sodium acetylide, generated under strongly basic conditions.

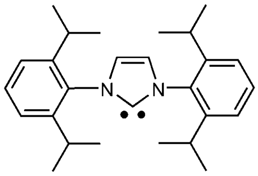
While the reaction between a terminal alkyne and an organoaluminum reagent usually delivers a complex mixture of metalated species,[3] the same reaction conducted in triethylamine had been reported by Binger to furnish solely the aluminum acetylide-triethylamine complex.[4] We have recently shown that a similar metalation can occur using only one equivalent[5] or even a sub-stoichiometric amount of triethylamine,[6] delivering a stable solution of mixed dialkylalkynylaluminum reagents in non-polar solvents with a unique reactivity pattern.[7] This salt-free procedure avoids the experimental difficulties encountered with the classical deprotonation-metal exchange procedure (use of strong bases, presence of salts or Lewis acid traces…).[8]

With DIBAL, this reaction can be conducted at 0 °C with 5% of triethylamine, but the presence of transferable hydrides on the resulting mixed diisobutylalkynides can complicate their reactivity. On the other hand, mixed dimethylalkynides can be obtained with trimethylaluminum, but the metalation requires 10% of triethylamine and harsher reaction conditions (6 h at 60 °C). While a Lewis acid-catalyzed deprotonation by a Brønsted base is generally used for the generation of nucleophilic alkynides,[9] this terminal alumination is mechanistically different, and involves a Lewis base-catalyzed process.[10] In this work, we report that an appropriate choice of the Lewis base can lead to a room temperature metalation with reduced amount of catalyst loading. Some insight into the mechanism of this reaction is also provided.

The reaction of phenylacetylene with trimethylaluminum in the presence of various Lewis bases was first investigated. The conversion was estimated by ^{1}H NMR experiments. As previously reported, almost full conversion was obtained with 10% of triethylamine after 6 h at 60 °C (Table 1, entry 1). The same reaction at room temperature proved to be much more sluggish (entry 2), an 83% conversion being obtained only after 72 h (entry 3). Similar results were obtained with tributylamine (entries 4–8). The use of $MeN(SiMe_3)_2$ led to a dramatic rate enhancement. Thus, full conversion was obtained within 6 h at room temperature with 10% of this silylated base (entry 9), and 91% conversion was achieved with only 1% of catalyst after 7 h (entry 10). A longer reaction time enables a full conversion (entry 11). This catalyst is active enough to conduct the metalation at 0 °C, with a slightly reduced conversion (entries 12–14). Mono-

Table 1. Lewis base screening for the catalyzed alumination of phenylacetylene.[a]



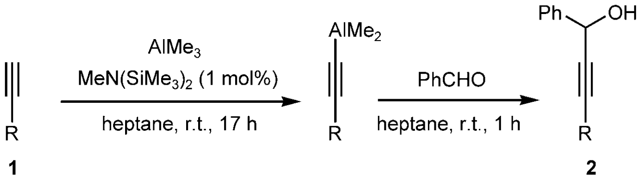
Entry	Catalyst	Load [mol%]	T [°C]	t [h]	Conv. [%][b]
1	NEt_3	10	60	6	97
2	NEt_3	10	r.t.	7	41
3	NEt_3	10	r.t.	72	83
4	N(*n*-Bu)$_3$	10	r.t.	7	39
5	N(*n*-Bu)$_3$	10	r.t.	24	58
6	N(*n*-Bu)$_3$	10	r.t.	48	74
7	N(*n*-Bu)$_3$	10	r.t.	72	83
8	N(*n*-Bu)$_3$	10	r.t.	144	97
9	$MeN(SiMe_3)_2$	10	r.t.	6	99
10	**$MeN(SiMe_3)_2$**	**1**	**r.t.**	**7**	**91**
11	**$MeN(SiMe_3)_2$**	**1**	**r.t.**	**17**	**100**
12	$MeN(SiMe_3)_2$	1	0	17	86
13	$MeN(SiMe_3)_2$	1	0	24	92
14	$MeN(SiMe_3)_2$	1	0	41	94
15	Me_2NSiMe_3	10	r.t.	7	18
16	$N(SiMe_3)_3$	10	r.t.	7	11
17	pyridine	10	r.t.	7	11
18	NPh_3	10	r.t.	7	3
19	PhSPh	10	r.t.	7	15
20	MeSMe	10	r.t.	7	6
21	PPh_3	10	r.t.	7	15
22	Me_2PPh	10	r.t.	7	5
23	*t*-BuNC	10	r.t.	7	–
24		10	r.t.	7	24
25	Et_3NO	10	r.t.	7	14
26	THF	10	r.t.	7	18

[a] *General reaction conditions:* phenylacetylene (1 equiv.), $AlMe_3$ (2 M in heptane, 1 equiv,), Lewis base (X mol%).

[b] Determined by integration of the acetylenic proton ^1H NMR signal in the presence of mesitylene as internal standard.

silylated (entry 15) or trisilylated (entry 16) amines proved to be much less active, showing that both steric and electronic properties of the Lewis base have to be carefully adjusted in this catalytic process. Other amines such as pyridine (entry 17) or triphenylamine (entry 18) were almost inactive, as were also aromatic (entry 19) or aliphatic (entry 20) thioethers or phosphines (entries 21 and 22). *tert*-Butyl isonitrile completely inhibited the reaction (entry 23), whereas a small catalytic activity could be obtained with an N-heterocyclic carbene (entry 24). An *N*-oxide (entry 25) or THF (entry 26) were poorly active.

Table 2. $MeN(SiMe_3)_2$-catalyzed alumination of terminal alkynes and reaction with benzaldehyde.



Entry	R	Compound	Yield [%][a]
1	Ph	**2a**	96
2	Pent	**2b**	88
3	*n*-Pr	**2c**	93
4	*t*-Bu	**2d**	95

[a] Isolated yield of compounds **2a–d**.

The exceptional efficiency of $MeN(SiMe_3)_2$ in this reaction was confirmed by the room temperature metalation of various alkynes and their reaction in a standard test alkynylation (Table 2). The use of this base does not only improve the metalation rate, but also enables the metalation of 3,3-dimethylbut-1-yne, a reaction that proved to be difficult with the triethylamine-catalyzed process. The metalation can be conducted with Et_3Al instead of Me_3Al, but 24 h are needed to reach 98% metalation of phenylacetylene at room temperature.

The exact reason for the high catalytic activity of $MeN(SiMe_3)_2$ is difficult to establish, as the mechanism of this base-catalyzed alumination is unknown. A possible transition state involving a tetracoordinated complex has been proposed by Surtees to explain the metalation observed by Binger in an excess of triethylamine, based on the knowledge that terminal alkynes react more readily with alkali alanates than the corresponding trialkylalanes (Figure 1, mechanism I).[11] A pentacoordinated intermediate could also be involved, in a competitive pathway between a base-catalyzed deprotonation and a thermodynamically favoured decoordination of a preformed triethyl-

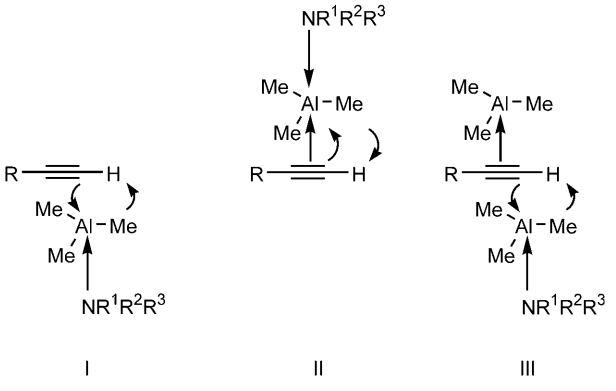
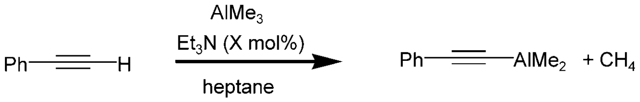


Figure 1. Plausible metalation pathways.

Table 3. Et_3N-catalyzed alumination of phenylacetylene: base stoichiometry.[a]


$$\mathrm{Ph{-}{\equiv}{-}H} \xrightarrow[\text{heptane}]{\mathrm{AlMe_3},\ \mathrm{Et_3N}\ (\text{X mol\%})} \mathrm{Ph{-}{\equiv}{-}AlMe_2} + \mathrm{CH_4}$$

Entry	Loading [%]	Time [h]	Conv. [%][b]
1	10	7	41
2	30	7	54
3	50	7	65
4	70	7	53
5	90	7	41
6	100	24	16

[a] *Reaction conditions:* phenylacetylene (1 equiv.), $AlMe_3$ (2 M in heptane, 1 equiv.).

[b] Determined by integration of the acetylenic proton ^1H NMR signal in the presence of mesitylene as internal standard.

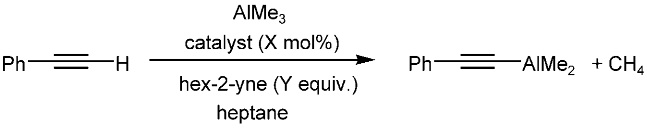
aluminum-alkyne complex (Figure 1, mechanism II), as proposed by Allen and Lough.[12] Finally, a synergy between alkyne complexation and aluminum activation could also explain the efficiency of the metalation step (Figure 1, mechanism III).

Some experimental results are noteworthy. First, we found that this base-catalyzed reaction *is faster with 10% of Et_3N than with a stoichiometric amount of catalyst.* The conversion after 7 h of reaction at room temperature increases up to 65% with the amount of triethylamine, but decreases once the $Et_3N/AlMe_3$ ratio exceeds 0.5 (Table 3, entries 1–6). Moreover, a similar amount of metalated alkyne (41%) is obtained using 0.1 or 0.9 equivalents of triethylamine, whereas a stoichiometric amount of the Lewis base dramatically slows down the metalation process, showing that a small amount of uncomplexed trimethylaluminum is needed for a good catalytic activity.

This hypothesis was further investigated using a competition experiment with an internal alkyne having a coordinating ability between a terminal alkyne and triethylamine. A similar inhibitory effect was indeed observed (Table 4). The conversion decreased with the number of equivalents of hex-2-yne, both in Et_3N- or $MeN(SiMe_3)_2$-catalyzed metalation, indicating that coordination of trimethylaluminum to the terminal alkynes is required in the deprotonation step.

Finally, the reaction rate was also impacted by the amount of $AlMe_3$, as outlined in Table 5, with a significant metalation rate improvement at low conversion correlated with the amount of alane.

Table 4. Base-catalyzed alumination of phenylacetylene: competition experiment with hex-2-yne.[a]

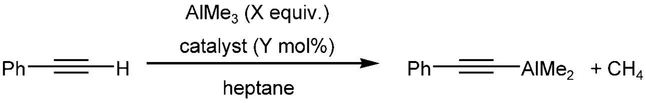

$$\mathrm{Ph{-}{\equiv}{-}H} \xrightarrow[\text{hex-2-yne (Y equiv.)},\ \text{heptane}]{\mathrm{AlMe_3},\ \text{catalyst (X mol\%)}} \mathrm{Ph{-}{\equiv}{-}AlMe_2} + \mathrm{CH_4}$$

Entry	Catalyst [%, *T*]	Hex-2-yne [equiv.]	*t* [h]	Conv. [%][b]
1	NEt_3 [10, 60]	0	6	97
2	NEt_3 [10, 60]	1	6	87
3	NEt_3 [10, 60]	2	6	86
4	NEt_3 [10, 60]	5	6	78
5	$MeN(SiMe_3)_2$ [1, r.t.]	0	7	91
6	$MeN(SiMe_3)_2$ [1, r.t.]	1	7	60
7	$MeN(SiMe_3)_2$ [1, r.t.]	2	7	49
8	$MeN(SiMe_3)_2$ [1, r.t.]	5	7	42

[a] *Reaction conditions:* phenylacetylene (1 equiv.), $AlMe_3$ (2 M in heptane, 1 equiv).

[b] Determined by integration of the acetylenic proton ^1H NMR signal in the presence of mesitylene as internal standard.

Table 5. Base-catalyzed alumination of phenylacetylene: ratio of $AlMe_3$ to phenylacetylene.[a]


$$\mathrm{Ph{-}{\equiv}{-}H} \xrightarrow[\text{heptane}]{\mathrm{AlMe_3}\ (\text{X equiv.}),\ \text{catalyst (Y mol\%)}} \mathrm{Ph{-}{\equiv}{-}AlMe_2} + \mathrm{CH_4}$$

Entry	Catalyst [%]	$AlMe_3$/ alkyne	*t* [min]	Conv. [%][b]
1	NEt_3 [10]	1/1	30	9
2	NEt_3 [10]	2/1	30	14
3	NEt_3 [10]	3/1	30	19
4	NEt_3 [10]	4/1	30	28
5	$MeN(SiMe_3)_2$ [1]	1/1	10	5
6	$MeN(SiMe_3)_2$ [1]	2/1	10	12
7	$MeN(SiMe_3)_2$ [1]	3/1	10	17
8	$MeN(SiMe_3)_2$ [1]	4/1	10	21

[a] *Reaction conditions:* phenylacetylene (0.4 M, 1 equiv.), room temperature.

[b] Determined by integration of the acetylenic proton ^1H NMR signal in the presence of mesitylene as internal standard.

These sets of experiments support a mechanism of type III, involving two molecules of trimethylaluminum with ambiphilic reactivities. The high efficiency of $MeN(SiMe_3)_2$ in this deprotonation step might be the result of a fine balance between electronic effects (electron-donating groups) favouring complexation and polarization of the Al–Me bond, and steric effects (frontal repulsion)[13] favouring dissociation and/or Al–Me bond cleavage. It is also interesting to note that no stable complex between $MeN(SiMe_3)_2$ and trimethylaluminum or mixed aluminum phenylacetylide could be observed by NMR in heptane, whereas Et_3N quantitatively forms stable complexes with both organometallic species.[14] This different behaviour could in part explain the high turnover frequency obtained with $MeN(SiMe_3)_2$.

In conclusion, we have disclosed the first room temperature catalyzed alumination of terminal alkynes. This mild procedure enables the preparation of mixed dialkylaluminum reagents with a low catalyst loading, using inexpensive and largely available trimethylaluminum as a metalating agent. This salt-free procedure advantageously avoids the use of strong bases (generally associated with low temperature), and only generates methane as a side product. Further mechanistic investigations of this reaction and its use for the preparation of functional organoaluminum reagents are now in progress.

Experimental Section

Typical Procedure for the Alumination

The alumination of phenylacetylide is representative. A dry and argon-flushed flask equipped with a magnetic stirrer was charged with a commercial trimethylaluminum solution (2 mL, 2 M in heptane, 4 mmol) (***Caution:*** trimethylaluminum is inflammable), $MeN(SiMe_3)_2$ (9 µL, 0.04 mmol) and phenylacetylene (0.4 mL, 4 mmol) were added dropwise. The reaction mixture was stirred at room temperature for 17 h until the gas evolution ceased. The prepared alane solution can be stored under argon in the darkness for several days.

Acknowledgements

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[14] See Supporting Information.