[(3-Dimethylamino)propyl]dimethylaluminum: A Convenient Reagent for Methylation and Ethynylation of Carbonyl Compounds

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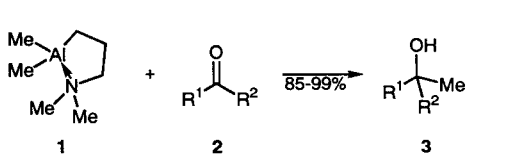
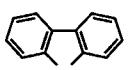
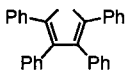
Dedicated to the memory of Dr. Abraham Felsenstein who died untimely at the peak of his career

At 60–80 °C the title compound methylates a variety of mono- and diketones. Aromatic aldehydes undergo simple methylation by the reagent only after initial treatment with an equivalent amount of $AlCl_3$. Upon reaction of $Me_2Al(CH_2)_3NMe_2$ with terminal acetylenes the aluminum complex is converted into a carbonyl-alkynylation reagent.

Although trialkylaluminum compounds are widely used as co-catalysts in Ziegler—Natta, Phillips and ring-opening metathesis polymerizations, and serve as alkylating agents in several important industrial processes,[1] their application to laboratory scale organic synthesis is limited owing to their pyrophoric nature. In recent years much effort has been directed towards stabilization of the air-sensitive organoaluminum compounds, by substitution of an alkyl group in R_3Al by a chelating moiety that can undergo intramolecular Lewis complexation.[2] These stabilized complexes are substantially less sensitive to air, and therefore, are useful substitutes for R_3Al in the various polymerization processes.[3] In this study we found that some stabilized dialkylaluminum complexes operate under common laboratory conditions and can replace Grignard and organolithium reagents in the carbonyl alkylation reactions shown in Schemes 1–7.

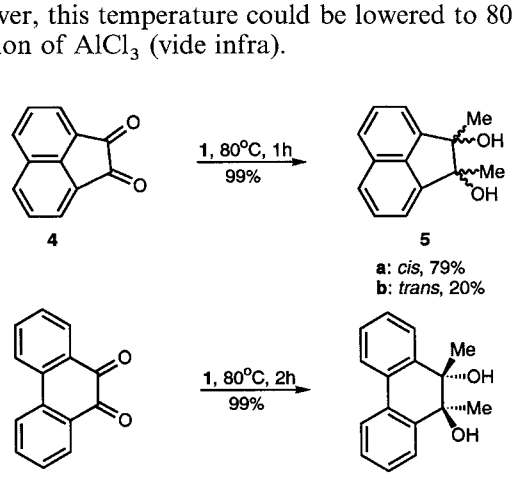


1 2 3

Compd.	R^1	R^2	Compd.	R^1	R^2
a	Ph	Ph	e		
b			f	Ph	PhC≡C
c	△	Ph	g		
d	C_6H_{11}	Ph	h	C_6H_{11}	H

Scheme 1

We chose [(3-dimethylamino)propyl]dimethylaluminum, $Me_2Al(CH_2)_3NMe_2$ **(1)** (which has recently been prepared from [(3-dimethylamino)propyl]lithium, $Me_2N(CH_2)_3Li$ and dimethylaluminum chloride, Me_2AlCl[4]) as representative stabilized monomeric[4,5] carbonyl alkylation agent. When one equivalent of benzophenone **(2a)** and 1.3 equivalents (0.65 mol) of **1** was heated under N_2 in toluene for 2 h, followed by treatment with dilute hydrochloric acid, 93% of 1,1-diphenylethanol **(3a)** was obtained (see Scheme 1). Likewise, 9-fluorenone **(2b)**, cyclopropylphenylacetone **(2c)**, cyclohexylphenylacetone **(2d)**, the bulky tricyclo[3.3.1.1^{3,7}]decan-2-one (2-adamanthanone) **(2e)**, as well as the diketones acenaphthene-1,2-dione **(4)** and phenanthrene-9,10-dione **(6)** were methylated by **1** in high yields (see Schemes 1 and 2 and Table 1). The alkylation of **2d** required a substantially higher temperature than the other ketones (155 °C), however, this temperature could be lowered to 80 °C by addition of $AlCl_3$ (vide infra).



Scheme 2

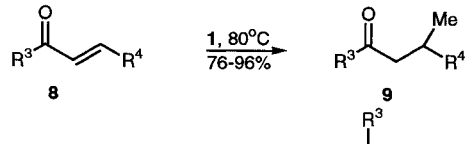
Table 1. Methylation of Several Ketones by **1** in Toluene

Starting ketone	Reaction temp. (°C)	Reaction time (h)	Yield (%)[a]	Products
2a	80	2	93	**3a**
2b	80	3	88	**3b**[24]
			4.7	**26**[23]
2c	80	1	96	**3c**
2d	155	7	93	**3d**[6]
2e	80	2	94	**3e**[7]
4	80	1	79	**5a**[8]
			20	**5a**[8]
6	80	2	99	**7**[9]

[a] Except for the methylation products of **4** that were determined by NMR, the yields refer to isolated products that have been compared with authentic samples.

Sterically unhindered α,β-unsaturated ketones gave, under the above conditions, mainly the 1,4-methylation products (Scheme 3). 1-Phenylbut-1-en-3-one **(8a)** yield-

ed within 30 minutes 5-phenylhexan-3-one **(9a)** (89%) and 2-methyl-4-phenylbuta-1,3-diene **(10a)** (only 7%) (see Table 2). 1,3-Diphenylprop-2-en-1-one **(8b)** reacted more slowly than **8a** to give solely the 1,4-addition product, **9b**. In contrast to the above enones, the analogous ynones underwent exclusively 1,2-methylation, according to Scheme 1. For example, 1,3-diphenylprop-2-yn-1-one **(2f)** yielded after 5 hours at 80 °C 2,4-diphenylbut-3-yn-2-ol **(3f)** (91%). The overcrowded 2,3,4,5-tetraphenylcyclopenta-2,4-dien-1-one **(2g)** was methylated only at the unhindered C-1 position to give 1-methyl-2,3,4,5-tetraphenylcyclopentadien-1-ol **(3g)**. The alkylation of optically active (+)-(*S*)-2-methyl-5-(1-methylethenyl)cyclohex-2-en-1-one (carvone) **(11)** by **1** yielded two pairs of diastereomers of 1,2-dimethyl-5-(1-methylethenyl)cyclohex-2-en-1-ol **(13)** (1,2-addition) and 2,3-dimethyl-5-(1-methylethenyl)cyclohexan-1-one **(12)** (1,4-addition) as the minor and major products, respectively, without any racemization at C-5 (Scheme 4).



Scheme 3

Scheme 4

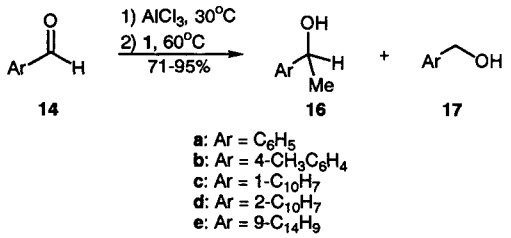
Table 2. Methylation of Some α,β-Unsaturated Ketones by **1** in Toluene

Starting ketone	Reaction temp (°C)	Reaction time (h)	Yield (%)[a]	Products	Ref
8a	80	0.5	89	**9a**	10
			7	**10a**	11
8b	80	4	76	**9b**	10
2f	80	5	91	**3f**	12
2g	80	5	85	**3g**	13
11	25	24	61	**12**	14
			23	**13**	15

[a] Yields refer to isolated products.

The mode of reaction of carbaldehydes with **1** was found to depend on the nature of the substrate. Cyclohexanecarbaldehyde **(2h)** was shown to react similarly to the saturated ketones (Scheme 1), and to form at room temperature after 24 hours, 85% of 1-cyclohexylethanol **(3h)** accompanied by 4% of the reduction product, cyclohexylmethanol. The reactions of arenecarbaldehydes prove to be strongly influenced by the conditions employed. In pentane, benzaldehyde **(14a)** and **1** underwent only the Tichenko reaction to form, after 5 hours at 80 °C (in a pressure tube), benzyl benzoate **(15)** (91%) (Scheme 5). When the reaction was conducted either in benzene or toluene (8 h at 80 °C), **8b** (41%) and 1-phenylmethanol **(17a)** (41%) as well as **15** (4%) were obtained. The formation of **8b** is rationalized by the initial transformation of **14a** to 1-phenylethanol **(16a)** followed by **1**-assisted transfer–hydrogenation that results in the formation of one equivalent of each of **17a** and acetophenone. Condensation of the latter with unreacted **14a** may then give **8b** under the basic reaction conditions. Support for this explanation about the involvement of an intermolecular hydrogen transfer process in the formation of **8b**, has been provided by an experiment in which a phenylacetylene–aluminum adduct (formed by reaction of the acetylene and **1** at 50 °C for 30 min) and 4-methylbenzaldehyde **(14b)** yielded (2 h, 80 °C) equimolar quantities of 1-(4-methylphenyl)-3-phenylprop-2-yn-1-one **(18)** and (4-methylphenyl)methanol **(17b)** (vide infra) (Table 4). By using toluene-d_8, we have shown that the solvent is not involved in the formation of **8b**. The reaction proceeded entirely differently when, prior to the addition of **1**, **14a** was treated for 30 minites at room temperature with one equivalent of $AlCl_3$ (see Scheme 6). By this procedure smooth methylation of the aldehyde was found to take place, and 88% of 1-phenylethanol was obtained (Table 3). If less than one equivalent of $AlCl_3$ was employed the phenylethanol was contaminated with **8b**, and with **17a**. Aldehydes, 1- and 2-naphthalenecarbaldehyde (**14c** and **14d**, respectively), as well as 9-anthracenecarbaldehyde **(14e)** were shown to react in a similar fashion as **14a** (see Table 3). The successful methylation of the aromatic aldehydes is conditioned by the initial interaction of the $AlCl_3$ with the carbonyl compound rather than with **1**, otherwise mainly polymers are formed.

Scheme 5



Scheme 6

Aluminum chloride also facilitates the methylation of the ketones. As an example **2d**, which could be methylated under the conditions of Table 1 only at 155 °C, formed 2-cyclohexylethenylbenzene at 80 °C in almost quantita-

Table 3. Alkylation of Some $AlCl_3$-Treated Arenecarboxaldehydes by **1**[a]

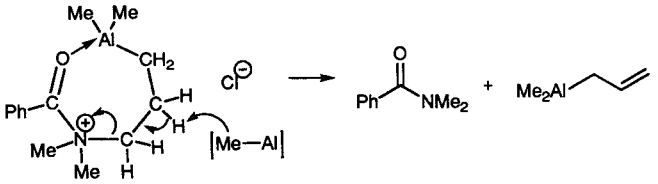
Starting Aldehyde	Solvent	Yield (%)[b]	Products
14a	PhMe	88	**16a**
14b	PhMe	95	**16b**
14c	PhH	71	**16c**
		15	**17c**
14d	PhH	81	**16d**
		12	**17d**
14e	PhH	95	**16e**[16]

[a] Reaction conditions: 2 mmol aldehyde in 2 mL solvent stirred with 2.1 mmol of anhyd $AlCl_3$ at 30 °C for 30 min; then 1.3 mmol of **12** was added and the mixture heated at 60 °C for 2 h.
[b] Yields refer to isolated products that have been compared with authentic samples.

tive yield when the ketone had been pretreated with $AlCl_3$.

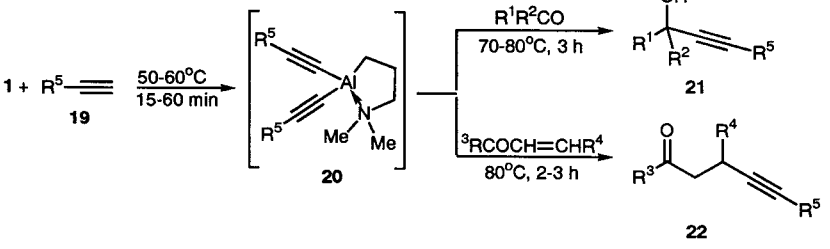
Apart from being a methylation agent, **1** has also been used for ethynylation of ketones (Scheme 7). When a toluene solution of phenylethyne **(19a)** was heated at 50 °C for 15 minutes with **1**, and the resulting [(3-dimethylamino)propyl]diphenylethynyl)aluminum **(20a)**, treated at 70 °C for 3 hours with **2a**, 1,3,3-triphenylprop-1-yn-3-ol **(21a)** was obtained in 93 % yield. This procedure could also be applied to α,β-unsaturated ketones. Some representative examples are listed in Table 4. If the time allotted for the conversion of **1** into the bis(ethynyl) complex was insufficient, both ethynylation and methylation products could be isolated. Thus, when hept-1-yne **(19b)** was reacted with **1** for only 15 minutes prior to the addition of **2a** the resulting alkynol was accompanied by **3a** (20 %). When the first step was conducted for 1 hour at 60 °C, 1,1-diphenyloct-3-yn-1-ol **(21b)** became the sole product.

In contrast to the above mentioned carbonyl compounds, acid chlorides could not be alkylated by **1**. They were shown to readily eliminate the dimethylamine moiety from the aluminum reagent, and form the corresponding dimethylcarboxamides $RCONMe_2$. Benzoyl chloride, for example, gave *N,N*-dimethylbenzamide. The process is assumed to follow the mechanism shown in Scheme 8. The eliminated proton reacts with an aluminum-bound methyl group to form CH_4 (cf. ref. 21).



Scheme 8

Finally, we have found that stabilized dimethylaluminum complexes other than **1** can substitute the latter as methylation agents. The monomeric [(3-dimethylamino)ethoxy]dimethylaluminum[4] **(23)**, [prepared from trimethylaluminum and 2-(dimethylamino)ethanol] as well as the dimeric alkoxides $[Me_2Al(\mu\text{-}OCH_2CH_2C(Me_2)OMe)]_2$[22] **(24)** [from trimethylaluminum and 3-methoxy-3-methylbutan-1-ol], and $[Me_2Al(\mu\text{-}OC_6H_4\text{-}2\text{-}OMe)]_2$[22] **(25)** [from trimethylaluminum and 2-methoxyphenol] proved to methylate dione **4** at 80 °C within 1 hour to the extent of 67, 22 and 65 %, respectively. While **23** and **24** resembled **1** in that they formed 4:1 mixtures of *cis*- and *trans*-1,2-dihydro-1,2-dimethylacenaphthylene-1,2-diol (**5a** and **5b**, respectively), the aluminum complex **25** yielded exclusively the *cis*-isomer under the same reaction conditions.



Scheme 7

a, c: R^5 = Ph
b: R^5 = $Me(CH_2)_4$

a: $R^1 = R^2 = R^5$ = Ph
b: $R^1 = R^2$ = Ph R^5 = $Me(CH_2)_4$
c: $R^3 = R^4 = R^5$ = Ph

Table 4. Ethynylation of Carbonyl Compounds by **1** in Toluene

Carbonyl Compd.	Alkyne	Conditions for Alkynylation of **1**, T(°C)/t(h)	Conditions for the Second Step T(°C)/t(h)	Yield[a] (%)	Products	Ref
2a	PhC≡CH	50/0.25	70/3	93	**21a**	17
2a	$Me(CH_2)_4C$≡CH	60/1	80/3	74	**21b**	18
8b	PhC≡CH	50/0.25	80/3	78	**22c**	19
14b	PhC≡CH	50/0.5	80/2	43	**17b**	
				43	**18**	20

[a] Yields are based on isolated products.

Alkylation of Carbonyl Compounds Without Additives; Typical Procedure:
A reaction flask was charged under N_2 with **1** (193.5 mg, 1.5 mmol), fluorenone **(2b)** (351 mg, 1.95 mmol) and Na dried toluene (1.5 mL). The stirred mixture was heated in an oil bath thermostated at 80 °C for 3 h. The cooled mixture was quenched with excess 7% HCl, extracted with Et_2O (2 × 20 mL) and the combined organic solutions dried ($MgSO_4$) and concentrated. Chromatography on silica gel, using mixtures of hexane and Et_2O as eluent afforded 9-methylene-9*H*-fluorene **(26)**;[23] yield: 16.3 mg (4.7%); mp 53 °C as the first fraction and 9-methyl-9*H*-fluoren-9-ol **(3b)**;[24] yield: 336.3 mg (88%); mp 172–174 °C as the second fraction. The two products proved identical in every respect (IR, ^1H and ^{13}C NMR, and GC-MS) with authentic samples.

Methylation of Aromatic Aldehydes; Typical Procedure:
Under N_2 atmosphere, a mixture of benzaldehyde **(14a)** (212 mg, 2 mmol) and anhyd $AlCl_3$ (280 mg, 2.1 equiv) in toluene (2 mL) was stirred at 30 °C for 30 min. To the reddish solution was added complex **1** (168 mg, 13 mmol) and stirring was continued for 2 h at 60 °C. Quenching with excess 7% aq HCl and chromatography on silica gel afforded 1-phenylethanol **(16a)**; yield: 215 mg (88%) as the only isolable product.

Alkynylation of Ketones; Typical Procedure:
A mixture of **1** (193.5 mg, 1.5 mmol) and phenylacetylene **(19a)** (306 mg, 3 mmol) in anhyd toluene (2 mL) was stired under N_2 for 15 min at 50 °C. A solution of diphenylacetone **(2a)** (400 mg, 2.2 mmol) in toluene (500 μL) was added and the mixture heated at 70 °C for 3 h. Workup as in the previous procedures yielded 1,1,3-triphenylprop-2-yn-1-ol **(21a)**;[17] yield: 581 mg, 93%; mp 80–81 °C as the only isolable product.

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