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Effect of Substituents and Stability of Transient Aluminum-Aminals in the Presence of Nucleophiles

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Abstract

Disubstituted hydroxylamines were synthesized and used to form aluminum–amide complexes. These reagents masked carbonyl groups in situ from nucleophilic addition. The stability and utility of the aluminum–aminals are presented in the context of selectively controlling nucleophilic addition on substrates with multiple carbonyl groups.

Graphical Abstract

Keywords

aluminum; amides; amines; nucleophilic addition; carbonyl complexes

Carbonyl groups are prominent functional groups on many organic compounds and naturally occurring molecules. The careful manipulation of these groups and control of their reactivity as electrophiles is critical in the synthesis of complex targets.^{1–3} The primary methods to address these issues are the use of carbonyl protecting groups or the implementation of oxidation/reduction strategies. An alternative tactic is the incorporation of a Weinreb amide, an aldehyde or ketone precursor, into the synthesis.^{4,5} The process of transforming a Weinreb amide into a carbonyl group requires a nucleophilic addition that results in the formation of a transient, but stable amina (Scheme 1).^{6,7} This amina is resistant to subsequent nucleophilic attack but collapses to a carbonyl in the presence of aqueous acid.

Recently, Colby and coworkers demonstrated the effectiveness of trapping reactive carbonyl groups as aminals using an aluminum–amide complex rather than forming them from Weinreb amides (Scheme 1).⁸ This aluminum complex is prepared with diisobutylaluminum hydride (DIBALH) and *N,O*-dimethylhydroxylamine. It is an alternative to prior methods of using highly basic lithium–amides.^{9–12} The intermediate aluminum–aminal is resistant to different types of reactive nucleophiles such as Grignard reagents and organolithiums. Using this in situ masking method, selective additions to esters were accomplished in the presence of aldehydes and ketones (Table 1). In a similar fashion, selective additions to ketones in the presence of aldehydes were executed. Specifically, the more reactive carbonyl group was trapped after treatment with a mixture of DIBALH and *N,O*-dimethylhydroxylamine. An equivalent of *i*-PrMgCl was used as a base to remove the last acidic proton and stabilize the aminal. Substrates **1–3**, each containing two distinct carbonyl groups, readily participated and the products **4–6** were isolated in good yields with either an organolithium or Grignard reagent adding selectively to the less reactive carbonyl group.

This methodology enables the aluminum–amide to add to the more reactive carbonyl group and eliminate its electrophilic nature by creating a stable aminal following addition of a base, usually *i*-PrMgCl. A drawback of this approach is the use of a base to remove the last acidic proton and stabilize the aminal intermediate. By re-designing the generation of the aminal and adding the base earlier in the sequence, we speculated that the scope of compatible reactions would be enhanced. Specifically, we aimed to create a discrete aluminum reagent that would form the aminal in one step.¹³ In order to achieve this objective, adding *n*-BuLi or *i*-PrMgCl to HN(OMe)Me•HCl succeeded in consuming the acidic proton of the hydrochloride and then subsequent treatment with Me₃Al formed the requisite aluminum–amide complex. Substrates **1–3**, each with two distinct carbonyl groups, participated in this more efficient method and provided access to products **4–11** upon addition of organolithiums, Grignard reagents, reducing reagents, Wittig reagents, and enolate anions (Table 2). High levels of chemoselectivity were observed, good yields of products were isolated, and the scope of the reaction was enhanced as more nucleophiles participated in the process.

Next, the stability of the aluminum–amide complex was investigated across three weeks (Table 3).¹⁴ A 0.5 M solution of the aluminum–amide reagent in THF was prepared using HN(OMe)Me•HCl, *n*-BuLi, and Me₃Al and stored at 0 °C. This reagent was used to transform methyl 4-formylbenzoate **1** into the alcohol **4** following treatment with *n*-BuLi. The reagent performed superbly at the time points: one hour, one day, one week, two weeks, and three weeks when compared to the baseline reaction yield of 91% following immediate use. A slight enhancement in yields was observed and this result may be attributed to the additional time that the reagent has to form the aluminum–aminal.

Following the collection of these promising data, the aminal was re-designed to understand its stability when the methyl groups on the *N,O*-dimethylhydroxylamine were replaced by other large alkyl groups (Scheme 2). We have already demonstrated the aluminum species can be derived from Me₃Al or DIBALH and the respective methyl or isobutyl group is compatible with the process. The next site to investigate was the contribution of substituents on the nitrogen and oxygen of the hypothesized aluminum–aminal intermediate.

Two synthetic strategies for the *N,O*-dialkylhydroxylamines were undertaken according to the literature precedents for these new stability studies (Scheme 3).^{15,16} A combination of *N*-hydroxyphthalimide **12** and a benzylhalide followed by treatment with hydrazine generated the corresponding *O*-benzylhydroxylamine **13**. The amine **13** was protected and the intermediate carbamate was treated with NaH and an alkyl halide to give the carbamate **14**. Acidolysis of carbamate with TFA provided the corresponding *N,O*-dialkylhydroxylamines **15a–d**. Alternatively, the *N,O*-dibenzylhydroxylamine **17** was synthesized from *O*-benzylamine hydrochloride **16** with benzyl bromide in the presence of potassium carbonate.¹⁶

The utility of the new aluminum–amide precursors was investigated by treating the amines with Me₃Al and using them for the in situ masking of carbonyl groups on substrates **1** and **2** (Table 4). The selective addition of *n*-BuLi and EtMgBr to the less reactive carbonyl group was examined and compared to the isolated yields when *N,O*-dimethylhydroxylamine was the precursor. Typically, the major product was isolated in modest to good yields, and these yields were lower than observed with the *N,O*-dimethylhydroxylamine. Specifically, the use of amine **15a** that displays an ethyl and benzyl group provided a moderate yield of product **4**. Exchanging the ethyl group for an allyl group (i.e., amine **15b**) had a minimal effect on the yield compared to **15a**. Similarly, the amine **15c** with a *para*-methoxybenzyl substituent provided yields similar to the benzyl amine **15b**. The highest yield was obtained using the naphthyl substituted amine **15d**; however, the lowest yield was obtained when using the dibenzyl amine **17**. Overall, the yields of products **4** and **9** were in the range of 51–72% and these results are somewhat lower than using *N,O*-dimethylhydroxylamine that provided 85–91%. The conclusion is that exchanging the methyl substituents of *N,O*-dimethylhydroxylamine with other alkyl groups is well tolerated with only a modest effect on yields.

In conclusion, we have demonstrated that aluminum complexes derived from *N,O*-dialkylhydroxylamines can serve as reagents to trap reactive carbonyl groups as amination from reactive nucleophiles and that there is substantial flexibility in the implementation of this method. The broad scope of this process has been established by synthesizing and reacting *N,O*-dialkylhydroxylamines with different carbonyl group-containing substrates. The effect on using different substituents on the nitrogen atom was modest despite exchanging methyl groups with substantially larger substituents. These data are compelling as they lay a foundation to design new classes of reagents in which these substituents can potentially participate in synthetic transformations or direct addition reactions along with masking the carbonyl group from nucleophiles.

Compounds **4–6**⁸ and **7–11**¹³ have been previously described. Syntheses of amines **15a**,¹⁷ **15b**,¹⁸ **15c**,¹⁹ **15d**,²⁰ and **17**¹⁶ were conducted according to the literature methods. Characterization data for each of the known compound matched previous reports.

General Procedure for Formation of Aluminum–Aminal followed by Addition of Organolithium Reagent

To a 0 °C solution of amine **15a**¹⁷ (74.9 mg, 0.49 mmol) in THF (2 mL) was added Me₃Al (250 µL, 2.0 M in hexanes). The mixture was warmed 0 °C to rt across 30 minutes. Next, the resultant mixture was added to a 0 °C solution of methyl 4-formylbenzoate **1** (67 mg, 0.41 mmol) in THF (10 mL), and the mixture was stirred for 2 hours at rt. Following cooling to –78 °C, *n*-BuLi (650 µL, 2.5 M in hexanes) was added, and the mixture was stirred for 35 minutes at –78 °C. The reaction was quenched with sat. aqueous NH₄Cl (10 mL) and extracted with EtOAc (3 × 15 mL). The organics were dried over Na₂SO₄, filtered, concentrated under reduced pressure. SiO₂ flash chromatography (8:2 hexanes/EtOAc) afforded product **4**, (58.8 mg, 58% yield). Characterization data was identical with the reported data.⁸

General Procedure for Formation of Aluminum–Aminal followed by Addition of Grignard Reagent

To a 0 °C solution of amine **17**¹⁶ (103 mg, 0.48 mmol) in 4:1 Et₂O/THF (5.5 mL) was added Me₃Al (484 µL, 1.0 M in heptane). The mixture was warmed from 0 °C to rt across 30 minutes. Next, the resultant mixture was added to a 0 °C solution of 4-acetyl benzaldehyde **2** (65 mg, 0.439 mmol) in Et₂O (22 mL), and the mixture was stirred for 2 hours at rt. Following cooling to 0 °C, EtMgBr (293 µL, 3.0 M in Et₂O) was added, and the mixture was stirred for 40 minutes with warming from 0 °C to rt. The reaction was quenched with sat. aqueous NH₄Cl (20 mL) and extracted with EtOAc (3 × 25 mL). The organics were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. SiO₂ flash chromatography (3:1 hexanes/EtOAc) afforded product **9** (40 mg, 51% yield). Characterization data was identical with the reported data.¹³

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Scheme 1.
Strategies for the formation of stable amins.

Scheme 2.

Design of aluminum–amide reagents to evaluate the effects of substituents on the nitrogen and oxygen atoms.

Scheme 3.
Two synthetic routes for substituted hydroxylamines.

Table 1

Stability of Aluminum–Aminals to Nucleophilic Additions

substrate $\xrightarrow[\text{ii. } i\text{-PrMgCl, R-M, then H}_2\text{O}]{\text{i. DIBALH, HN(OMe)Me}\cdot\text{HCl}}$ product 1–3 4–6				
Entry	Substrate	R-M	Product	Yield ^a
1		<i>n</i> -BuLi ^b		87%
2	1	MeMgBr		70%
3		MeLi	5	63%
4	2	MeMgBr	5	86%
5		MeLi ^b		83%
6	3	MeMgBr	6	76%

^a Isolated yields.^b Organolithium was used instead of *i*-PrMgCl.

Table 2

Stability of Aluminum–Aminals Formed by a Reagent

substrate $\xrightarrow[\text{ii. R-M, then H}_2\text{O}]{\text{i. HN(OMe)Me}\cdot\text{HCl, } n\text{-BuLi, Me}_3\text{Al}}$ product 1–3 4–11				
Entry	Substrate	R-M	Product	Yield ^a
1	1	<i>n</i> -BuLi	4	91%
2	1	allylMgBr ^b	7	83%
3	1	DIBALH ^b	8	89%
4	2	MeLi	5	86%
5	2	EtMgBr ^b	9	85%
6	2	Ph ₃ P=CH ₂	10	86%
7	2		11	70%
8	3	MeMgBr	6	70%

^a Isolated yields.^b *i*-PrMgCl was used instead of *n*-BuLi.

Table 3

Effect of Time on Reagent Prior to Formation of Aminoal

<div> <div>1</div> <div> i. $\text{Me}_2\text{AlN}(\text{OMe})\text{Me}\cdot\text{LiCl}$ solution in THF (0.5 M) </div> <div>→</div> <div>4</div> </div> <div>ii. <i>n</i>-BuLi, then H_2O</div>		
Entry	Storage Time for Reagent at 0 °C (step i) ^a	Yield ^b
1	immediate use	91%
2	one hour	99%
3	one day	99%
4	one week	97%
5	two weeks	98%
6	three weeks	99%

^a A 0.5 M solution of the aluminum–amide reagent in THF was prepared using $\text{HN}(\text{OMe})\text{Me}\cdot\text{HCl}$, *n*-BuLi, and Me_3Al and stored at 0 °C.

^b Isolated yields.

Table 4

Effects of Substitution Pattern of Hydroxylamines on the Stability of the Aminoal.

Entry	Substrate	i. amine (15a–d, 17), Me ₃ Al ii. R-M, then H ₂ O		Product	Yield ^a
		1–2	4, 9		
1	1	HN(OMe) Me•LiCl ^b	<i>n</i> -BuLi	4	91%
2	1		<i>n</i> -BuLi	4	58%
3	1		<i>n</i> -BuLi	4	67%
4	1		<i>n</i> -BuLi	4	66%
5	2	HN(OMe) Me•LiCl ^b	EtMgBr	9	85%
6	2		EtMgBr	9	72%
7	2		EtMgBr	9	51%

^a Isolated yields^b Formed from *n*-BuLi and HN(OMe)Me•HCl.