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Control of Transient Aluminum–Aminals for Masking and Unmasking Reactive Carbonyl Groups

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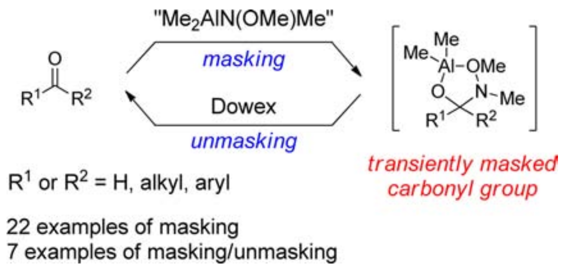
ABSTRACT



A new reagent, the dimethylaluminum *N,O*-dimethylhydroxylamine complex, is effective at masking reactive carbonyl groups in situ from nucleophilic addition. This reagent allows chemoselective addition of reducing reagents, Grignard reagents, organolithiums, Wittig reagents, and enolates into substrates with multiple carbonyl groups. Moreover, the trapped carbonyl group, a stable aminal, can be unmasked in situ for additional synthetic manipulations.

Carbonyl groups are one of the most important functional groups in organic chemistry and their reactivity toward nucleophiles is well-known. One of the frequent problems associated with compounds with multiple carbonyl groups is the selective modification of a less reactive carbonyl group in the presence of a more reactive group. Even though using protecting groups or reduction/oxidation sequences are reasonable strategies to control chemoselectivity, both of the plans accumulate additional synthetic steps.[1,2] An alternative approach to control chemoselectivity in the presence of multiple reactive carbonyl groups is to mask the more reactive carbonyl group transiently.[3−9] Although some in situ masking strategies for carbonyl groups have been reported, most are limited in scope and none have exploited the transient nature of the trapped intermediate to unmask the captured carbonyl group in situ for subsequent manipulation. Herein, we describe a discrete reagent to mask carbonyl groups as stable aminals from nucleophiles and demonstrate the in situ unveiling of the trapped carbonyl group for immediate use.

In his pioneering work, Luche reported the first method to reduce a ketone selectively in the presence of an aldehyde using $CeCl_3$ and $NaBH_4$ in aqueous ethanol.[3] Although the aldehyde is masked in situ from reduction, a disadvantage is the requirement of aqueous solvent, which limits the use of common nucleophiles. Reetz[4] and Yamamoto[5] applied titanium-dialkylamides and aluminum-dialkylamides respectively, to transform an aldehyde into an unreactive intermediate in situ. The drawback of these methods is the requirement of low temperatures to prevent reversion to the aldehyde. Yamamoto further refined his method to create bulky aluminum-based Lewis acids (e.g., MAD)

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(1) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197–201.
(2) Young, I. S.; Baran, P. S. *Nat. Chem* **2009**, *1*, 193–205.
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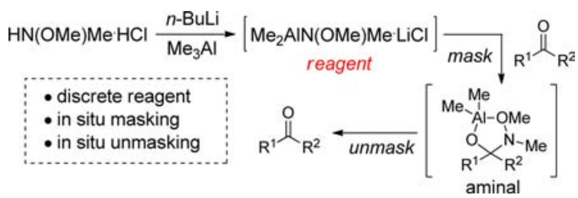
that will selectively block carbonyl groups.[6] More recently, diethylaluminum benzenethiolate has been reported to enable the chemoselective reduction of carbonyl groups with DIBALH in the presence of aldehydes.[7] A more versatile method has been described using phosphonium salts to mask reactive carbonyl groups from reducing reagents, such as DIBALH and BH_3·THF, and Grignard reagents.[8] Our laboratory has reported a strategy to mask reactive carbonyl groups as an aminal using complexes of dialkylaluminum and *N*,*O*-dimethylhydroxylamine.[9] This approach was designed from the stable intermediate formed following addition of a nucleophile to a Weinreb amide.[10] The limitation of this method was the necessity of 1 equiv of base to stabilize the aminal intermediate. We speculated that if the requirement for additional base could be eliminated, a discrete reagent for masking would be discovered and enable the development of a subsequent unmasking strategy. These two advances would be a substantial innovation over all other reported methods and enable the broadest compatibility with nucleophiles. Accordingly, we hypothesized that a combination of *N*,*O*-dimethylhydroxylamine·HCl with *n*-BuLi and Me_3Al would generate an aluminum−amide reagent to accomplish these objectives (Scheme 1).

Scheme 1. Reagent for Masking/Unmasking Carbonyl Groups



Cossy et al. have exploited the stable aminal formed after nucleophilic addition to a Weinreb amide to prevent the reduction of a carbonyl group under Birch conditions,[11] and Evans protected a ketone from a metalated hydrazone in a similar fashion.[12] Comins,[13] Hoffmann,[14] and Roschangar[15] have used lithium amides to access stabilized aminals from carbonyl groups, but the high basicity of these reagents can lead to unavoidable deprotonation at other sites if acidic protons are present.[16] Our prior application of aluminum−amide complexes avoids the high basicity of lithium amides.[9] Accordingly, we investigated several conditions for the preparation of the new aluminum−amide reagent, and the most efficient synthesis was accomplished by first reacting HN(OMe)Me·HCl with *n*-BuLi or *i*-PrMgCl to consume the acidic proton of the hydrochloride

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(12) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526.
(13) Comins, D. L. *Synlett* **1992**, 615–625.
(14) Hoffmann, R. W.; Munster, I. *Tetrahedron Lett.* **1995**, *36*, 1431–1434.
(15) Roschangar, F.; Brown, J. C.; Cooley, B. E.; Sharp, M. J.; Matsuoka, R. T. *Tetrahedron* **2002**, *58*, 1657–1666.
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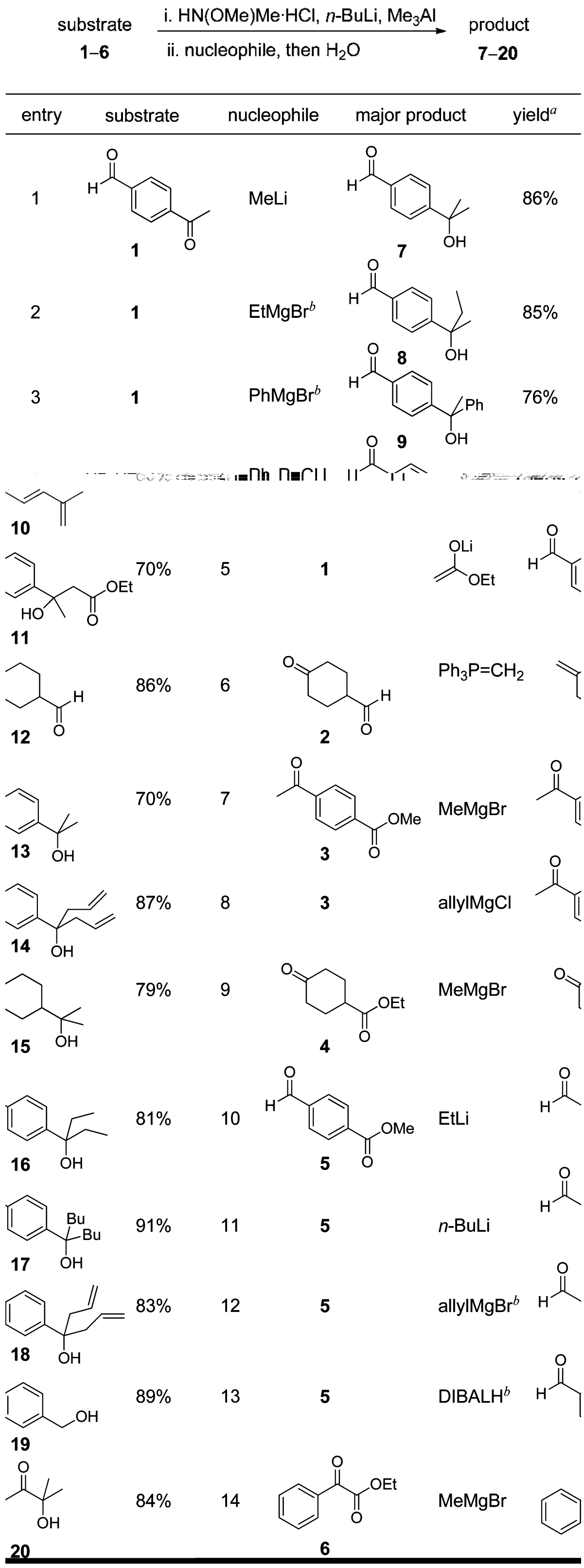
Table 1. Chemoselective Additions to Carbonyl Groups



entry	substrate	nucleophile	major product	yield[a]
1	1	MeLi	7	86%
2	1	EtMgBr[b]	8	85%
3	1	PhMgBr[b]	9	76%
4	[illegible]	[illegible]	10	[illegible]
5	1	(lithium enolate, OLi/OEt)	11	70%
6	2	$Ph_3P{=}CH_2$	12	86%
7	3	MeMgBr	13	70%
8	3	allylMgCl	14	87%
9	4	MeMgBr	15	79%
10	5	EtLi	16	81%
11	5	*n*-BuLi	17	91%
12	5	allylMgBr[b]	18	83%
13	5	DIBALH[b]	19	89%
14	6	MeMgBr	20	84%

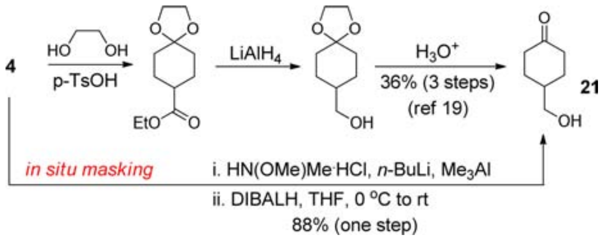
[a] Isolated yields. [b] *i*-PrMgCl was used instead of *n*-BuLi.

and then adding Me_3Al to form the complex. Either an organolithium or a Grignard reagent can serve as the requisite base. Next, we investigated the utility of this reagent for in situ masking with substrates **1**−**6**, each bearing two different carbonyl groups (Table 1). The broad scope of this approach was striking, because high levels of chemoselectivity were easily achieved during nucleophilic addition with reducing reagents, Grignard reagents, organolithium reagents, Wittig reagents, and enolate anions. Following treatment with the complex on 4-acetylbenzaldehyde (**1**), MeLi addition occurred exclusively at the ketone to give the tertiary alcohol **7** in excellent 86% yield. The Grignard reagents, EtMgBr and PhMgBr, also provided high yields of the tertiary alcohols **8** and **9**, respectively. Indeed, the role of Grignard reagents in synthesis continues to expand with recent advances in the preparation of organomagnesium reagents.[17,18] Wittig olefination using Ph_3PCH_3Br and *n*-BuLi following in situ trapping with the aluminum−amide reagent gave the alkene **10** in 80% yield. To our knowledge, prior in situ masking strategies have not demonstrated compatibility with Wittig olefinations.[3−9] Also, a Claisen condensation was performed with the lithium-derived enolate of EtOAc after in situ masking of **1**, and the product **11** was obtained in 70% yield. This approach using dimethylaluminum−dimethylhydroxylamine was then applied to the nonaromatic substrate, 4-oxocyclohexanecarbaldehyde (**2**), and selective Wittig olefination at the ketone provided the alkene **12** in 86% yield. Two additional selective Grignard additions using MeMgBr and allyl MgCl were performed with 4-acetylmethylbenzoate (**3**), and double addition to the ester gave alcohols **13** and **14**, respectively. Ethyl 4-oxocyclohexanecarboxylate (**4**) participates in a similar fashion to provide the double-addition product **15** in 79% yield. Also, methyl 4-formylbenzoate (**5**) was subjected to in situ trapping with the aluminum−amide followed by selective addition of the organolithiums, EtLi and *n*-BuLi, at the ester to give **16** and **17**, respectively. Grignard addition to the masked derivative of **5** yielded 83% of the double-addition product **18**. Complete reduction of the ester in the presence of the aldehyde was achieved using **5** and providing the primary alcohol **19**. Lastly, the reactive ethyl benzoylformate **6** was subjected to in situ masking followed by Grignard addition, and despite the proximity of the trapped α-ketoester, double addition gave the tertiary alcohol **20** in 84% yield. Overall, this strategy can efficiently use aromatic and alkyl substrates, regardless of the presence of acidic α-protons, and also it is compatible with many types of nucleophiles, including Wittig reagents and enolate anions.

A side-by-side comparison to demonstrate the in situ masking approach with dimethylaluminum−dimethylhydroxylamine against a traditional protection/deprotection sequence was executed (Scheme 2). A three-step synthesis of 4-(hydroxymethyl)cyclohexanone **21** from 4-oxocyclohexanecarboxylate (**4**) has been reported by acetal formation, reduction of the ester, and acetal hydrolysis.[19] The target **21** was isolated in 36% yield across these three steps, and this compound has been used as a tool to study chemical[19] and enzyme kinetics.[20] Using the in situ masking followed by reduction with DIBALH yielded the same target **21** in 88% yield in a single step! This comparison clearly illustrates the power of this process to eliminate protection/deprotection sequences and enhance isolated yields.

Next, we turned our attention to developing a simple protocol to unmask the trapped carbonyl groups for immediate synthetic manipulation. First, ^{19}F NMR data were acquired for 4-fluorobenzaldehyde (**22**), following treatment with the dimethylaluminum *N*,*O*-dimethylhydroxylamine complex (Figure 1A). A single signal was observed at −117 ppm, and this peak was distinct from the starting material **22** at −105 ppm (data not shown). After an extensive screen of reagents and conditions, it was discovered that the trapped intermediate could be quantitatively unmasked to the precursor carbonyl group in the ^{19}F NMR spectrum using Dowex and sonication (Figure 1B). A new peak at −105 ppm appeared, which indicates complete regeneration of 4-fluorobenzaldehyde **22**. The addition of acid to collapse the intermediate aminal was anticipated, because an acidic workup is required to hydrolyze this type of aminal, which is usually formed following nucleophilic addition to a Weinreb amide.

Scheme 2. Comparison of in Situ Masking versus Stepwise



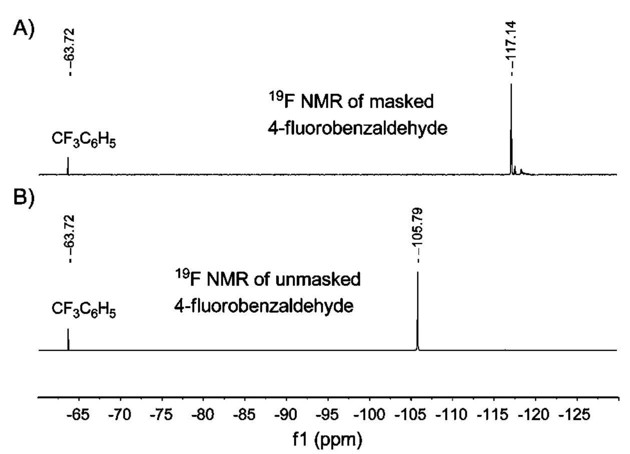


Figure 1. Comparison of ^{19}F NMR data of 4-fluorobenzaldehyde at 276 MHz. (A) 4-Fluorobenzaldehyde after treatment with the dimethylaluminum *N*,*O*-dimethylhydroxylamine complex. (B) After unmasking the mixture in 1A with Dowex and sonication. $C_6H_5CF_3$ was used as an internal standard.

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(18) Fleury, L. M.; Ashfeld, B. L. *Tetrahedron Lett.* **2010**, *51*, 2427–2430.
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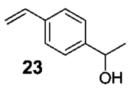
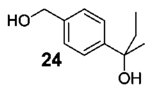
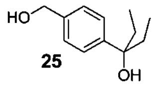
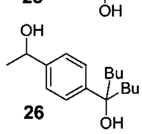
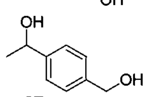
The compatibility of the unmasking strategy with nucleophilic additions to the newly unveiled carbonyl group was explored using substrates **1** and **5** (Table 2). A major initial finding of these studies was that molecular sieves must be included to remove small amounts of water that are released from the Dowex resin upon sonication. The overall process was to trap the more reactive carbonyl group, add the first nucleophile, unmask the trapped carbonyl group, and then add the second nucleophile. The products **23**–**27** were obtained in good 57–76% isolated yields, and these yields suggest that roughly 90% conversion occurs during each individual step. The compatible nucleophiles listed in Table 2 span a reducing agent, organolithiums, Grignard reagents, and a Wittig reagent. These data provide substantial support for the flexibility of the masking/unmasking protocol.

Table 2. In situ Masking and Unmasking of Carbonyl Groups

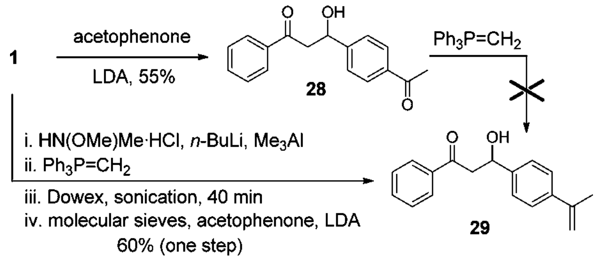
substrate **1 or 5** → product **23**–**27**: i. HN(OMe)Me·HCl, *n*-BuLi, Me_3Al; ii. R^1-M, THF; iii. Dowex, sonication, 40 min; iv. molecular sieves, R^2-M

entry	substrate	R^1-M	R^2-M	major product	yield[a]
1	**1**	DIBALH	$Ph_3P{=}CH_2$	 **23**	57%
2	**1**	EtMgBr[b]	DIBALH	 **24**	59%
3	**5**	EtLi	DIBALH	 **25**	76%
4	**5**	*n*-BuLi	MeMgBr	 **26**	71%
5	**5**	DIBALH[b]	MeMgBr	 **27**	66%

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

A cursory overview of the entries presented in Table 2 may lead to an obvious question about the synthetic utility of the unmasking process, because the alternative method would be to add the more reactive carbonyl group first and the less reactive one second. Although this strategy is logical for simple starting materials that bear two distinct types of carbonyl groups, the real power of this method becomes apparent when more complex substrates are examined. Indeed, discriminating between two types of ketones is a substantial synthetic challenge.[21,22] For example, aldol reaction between 4-acetylbenzaldehyde and acetophenone gives the dione **28**, and this product bears two ketones that are nearly identical (Scheme 3). The chemoselective manipulation of one ketone on this substrate is challenging, as Wittig olefination of **28** with $Ph_3P{=}CH_2$ (from $MePPh_3Br$ and *n*-BuLi) provided predominately products from the β-elimination of the secondary alcohol.[23] Clearly, a protecting group strategy is required for the secondary alcohol and to distinguish between the ketones. The masking/unmasking approach offers a stark contrast, because the reactivity of the two ketones can be controlled and the desired product **29** was isolated in 60% yield as single step!

Scheme 3. Comparison of Masking/Unmasking versus Stepwise



In summary, we have discovered a novel strategy to mask a reactive carbonyl group in situ using an aluminum–amide complex and regenerate the reactive carbonyl group after manipulation of a less reactive carbonyl group. We demonstrated the broad scope of substrates and nucleophiles that are compatible in the process, and we have discovered that this method is compatible with enolate anions and Wittig reagents, which have not been used in any prior reports. We have shown that this approach can provide superior yields for chemoselective manipulations compared to protection/deprotection sequences, and it can be easily incorporated into the assembly of a complex structure that would require multiple synthetic steps to build.

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Supporting Information Available. Full experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Bhar, S.; Guha, S. *Tetrahedron Lett.* **2004**, *45*, 3775–3777.
(23) Using 1 equiv of $Ph_3P{=}CH_2$ provided mixtures of olefins, all without the secondary alcohol, and using 2 equiv did not provide any improvement.

The authors declare no competing financial interest.