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N-Methoxy-*N*-methylamides (Weinreb Amides) in Modern Organic Synthesis

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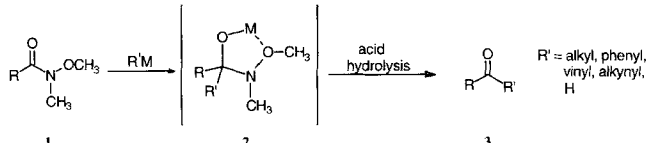
Abstract. *N*-Methoxy-*N*-methylamides (Weinreb amides) have facililated access to functionalized aldehydes and ketones in organic synthesis, including the total synthesis of complex natural products.

Since the first report by Nahm and Weinreb [1] on the use of *N*-methoxy-*N*-methylamides (**1**) in the synthesis of ketones this functional group has rapidly established itself in organic synthesis.

Weinreb *et al.* [1] discovered that *N*-methoxy-*N*- methylamides (**1**) combine cleanly with Grignard and organolithium reagents to form ketones (**3**) in a one-pot reaction (equation 1).

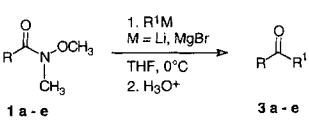


(1)

The main reasons for the utility of this functionality are ease of preparation, few side-reactions during the nucleophilic addition and mild, selective *acidic* workup (**2** → **3**). These advantages can be ascribed to the stability of the tetrahedral metal-chelated intermediate (**2**) which is formed by addition of nucleophiles to *N*-methoxy-*N*-methylamides. The propensity of reactive Grignard and organolithium reagents to overadd to the substrate, producing a tertiary alcohol is low [2].

These reactions proceed in good to excellent yields under fairly mild conditions. They are carried out at −78° or 0 °C, and solvents such as THF, ether or DME have been used. Weinreb [1] showed that a variety of *N*-methoxy-*N*-methylamides undergo nucleophilic addition to provide ketones in excellent yields (equation 2).

The typical workup procedure involves quenching of the reaction with dilute hydrochloric acid to decompose

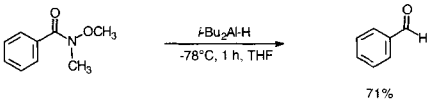


3	R	R¹	Yield (%)
a	phenyl	methyl	96
b	phenyl	*n*-butyl	91
c	phenyl	phenyl	95
d	cyclohexyl	phenyl	100
e	cyclohexyl	*n*-butyl	97

(2)

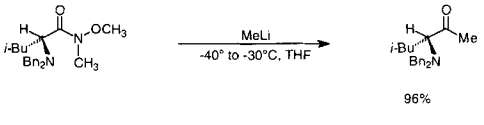
the chelated intermediate followed by extraction with an organic solvent.

Reduction of Weinreb amides leads to aldehydes (equation 3) as shown by Weinreb [1] himself. Diisobutylaluminium hydride is superior to $LiAlH_4$ in this reaction.



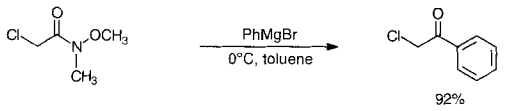
(3)

Reetz *et al.* [3] used *N*-protected amino acids to prepare α-amino ketones (equation 4). The conversion pro-



(4)

ceeded in good to high yields. Racemization of the chiral center using various organometallic reagents was not observed [3]. Tillyer [4] described the preparation of potentially sensitive α-halogen ketones (equation 5). Trifluoromethyl ketones [5] can also be prepared by the use of *N*-methoxy-*N*-methylamides (eq 6). Even cyclic ketones [6] are accessible, illustrating the chemoselectivity of metalation (equation 7). After a metal/



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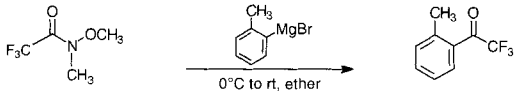

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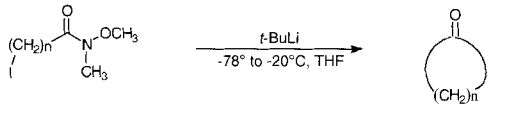


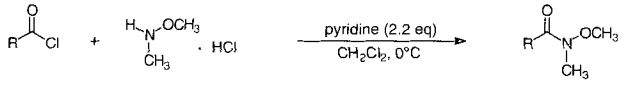
(7)

halogen exchange with *t*-BuLi, the reaction is concluded by intramolecular nucleophilic attack at the carbonyl terminus.

Synthesis of *N*-Methoxy-*N*-methylamides

Several methods are available for preparing *N*-methoxy-*N*-methylamides.

The first and most common method is the conversion of an acid chloride into an *N*-methoxy-*N*-methylamide. Treatment of an acid chloride (in CH_2Cl_2 or $CHCl_3$) and *N,O*-dimethylhydroxylamine hydrochloride at 0 °C with 2.2 equivalents of pyridine affords the corresponding amides in excellent yields (eq 8) [1]. *N*-Methoxy-*N*-methylamides have also been prepared from the corresponding carboxylic acids by a variety of coupling procedures. The usual peptide coupling reagents like BOP (benzotriazol-1-yloxytris[dimethylamino]-phosphonium hexafluorophosphate) [7] or DCC (dicyclohexylcarbodiimide) [8] work quite well.

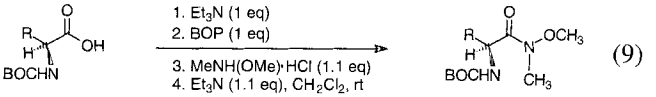


(8)

These procedures are especially useful for the prepararation of amides (**5**) from α-amino acids (**4**) without any racemization of the chiral center (equation 9).

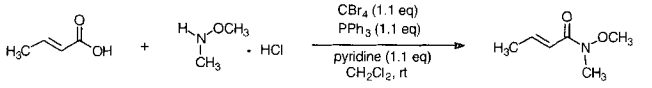
Einhorn *et al.* [9] have developed a very mild and efficient route to *N*-methoxy-*N*-methylamides from carboxylic acids using carbon tetrabromide and triphenylphosphine (eq 10).

The reaction between *N,O*-dimethylhydroxylamine and lactones is also viable. Kocienski and coworkers



5	R	yield (%)
a	methyl	85
b	*i*-propyl	80
c	*i*-butyl	94
d	benzyl	95

(9)



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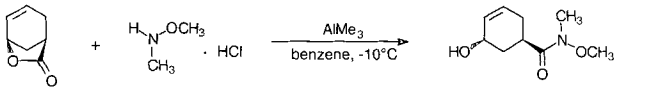
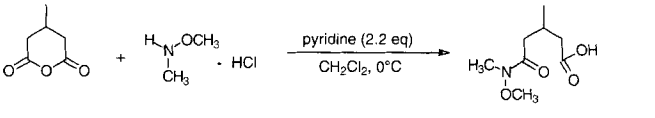


(11)

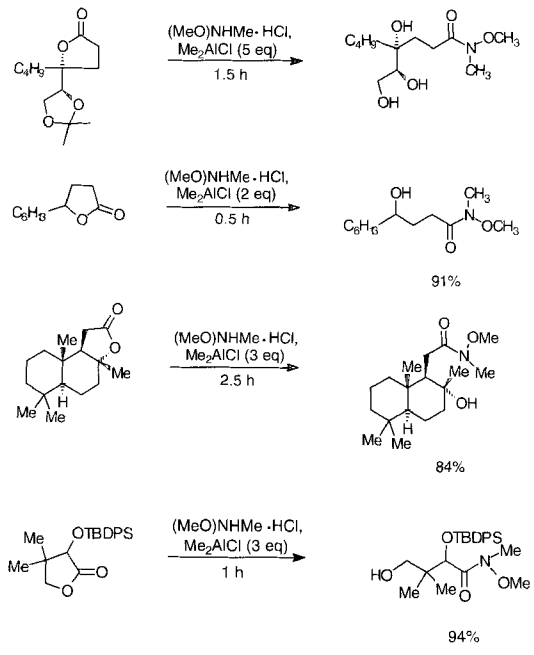
[10] have used this method for the preparation of cyclohexene carboxamide (**6**) (eq 11) en route to the C24–C34 segment of FK 506, which in turn is a potent immunosuppressant. *N*-Methoxy-*N*-methylamides can also be obtained from the corresponding anhydrides and *N,O*-dimethylhydroxylamine by nucleophilic displacement. Equation 12 illustrates the conversion of cyclic anhydride (**7**) into the half amide acid (**8**), an intermediate in the synthesis of (±)-Paniculide-A.



(12)

Recently Shimizu *et al.* [12] reported an efficient method for the preparation of *N*-methoxy-*N*-methylamides by allowing a lactone or an ester to react with dimethylaluminum chloride and *N,O*-dimethylhydroxylamine hydrochloride (equations 13 to 16). All these reactions were carried out in CH_2Cl_2 at rt. This method succeeded smoothly even with sterically hindered lactones or esters [12].

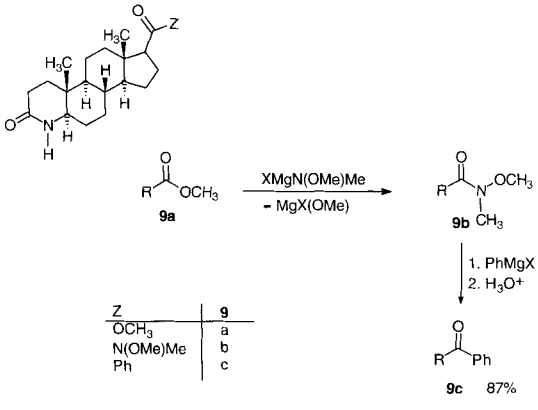
Weinreb amides have considerably stability and can be purified by chromatography, crystallization and/or destillation. *N,O*-Dimethylhydroxylamine hydrochloride is commercially available although a convenient procedure for its preparation has been reported [13].



N-Methoxy-*N*-methylamides in Modern Organic Synthesis

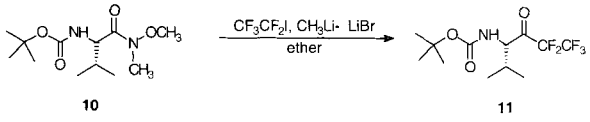
N-Methoxy-*N*-methylamides are probably the reagents of choice in the synthesis of ketones and many functionalized ketones *via* coupling with Grignard or other organometallic reagents. High yields with little or no overaddition are obtained even when using an excess of nucleophilic reagent. Due to these advantages Weinreb amides are often the preferred acylating agents in the synthesis of complex molecules. There are many applications for *N*-methoxy-*N*-methylamides [14]. Only a few examples will illustrate the remarkable utility of Weinreb amides in organic synthesis.

Williams *et al.* [15] have introduced a general method for preparing *N*-methoxy-*N*-methylamides from esters. The direct conversion of a highly hindered ester, the azasteroid 5α-reductase inhibitor MK-0434 (**9a**), is described in equation 17.



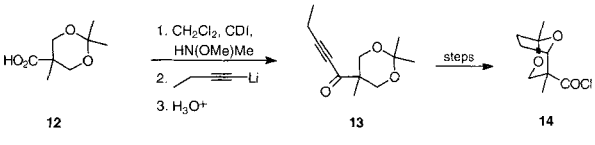
N,*O*-Dimethylhydroxylamine was deprotonated with an organomagnesium reagent and combined with (**9a**) to give amide (**9b**). Without isolation, subsequent reaction with phenylmagnesium chloride provided ketone (**9c**) in 87% overall yield. This method is also suitable for large scale production as demonstrated by the direct conversion of 16 kg of ester into phenyl ketone [15].

Angelastro and coworkers [16] used Weinreb amides in the synthesis of valylprolylvalyl pentafluoro ethyl ketones which were evaluated *in vitro* and *in vivo* as potent inhibitors of human neutrophil esterase (HNE). The key step in the preparation of different inhibitors is the reaction of the BOC-protected L-valine derivate (**10**) with pentafluoroethyl lithium generated *in situ* (eq. 18).



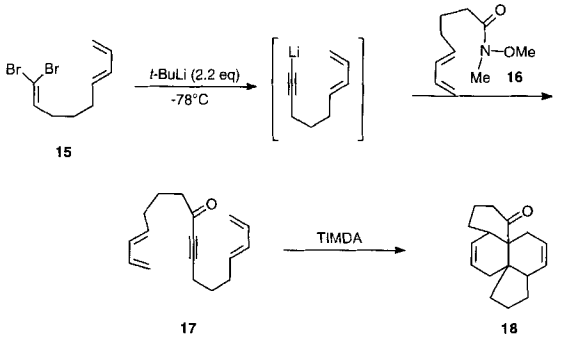
The reaction was carried out on a multigram scale and provided ketone (**11**) in 85% yield. The carbamate moiety did not interfere. Removal of the BOC protecting group with hydrogen chloride in ethyl acetate ($HCl_{(g)}$, 0 °C to rt) allowed generation of, *e.g.* various tripeptide pentafluoroethyl ketones which were studied as HNE-inhibitors [16].

The multifarious utility of Weinreb amides in synthesis of complex molecules has been shown by Heathcock in the asymmetric synthesis of (–)-secodaphniphylline [17]. The characteristic daphniphyllum alkaloid 2,8-dioxabicyclo[3.2.1]octane unit (**14**) was prepared starting with ketal acid (**12**) shown in equation 19.



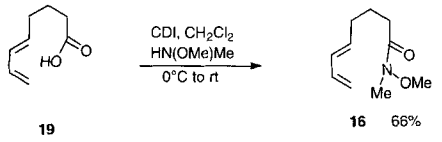
Acetylenic ketone ketal (**14**) was obtained in 86% yield. Daphniphyllum alkaloids are triterpenes possessing an intricate pentacyclic framework [18].

Giguere and coworkers have reported a further important application of *N*-methoxy-*N*-methylamides in their studies of tandem intramolecular Diels–Alder (TIMDA) reactions [19]. This transformation has significant potential for the stereoselective synthesis of tetracyclic molecules. Hitherto, there have been only a few reactions reported for the generation of *four* rings by a one-pot procedure [20]. The synthesis of the TIMDA substrate (**17**) is shown in equation 20.



(20)

Nucleophilic attack of the intermediate acetylene anion on Weinreb amide (**16**) provided the desired tetraenynone (**17**) in 55–65% yield from dibromide (**15**). *N*-Methoxy-*N*-methylamide (**16**) was prepared from diene acid (**19**) using Heathcock's protocol (eq 21), *i.e.* from an imidazolide precursor which in turn was obtained from the carboxylic acid and Staab reagent (CDI) [17].

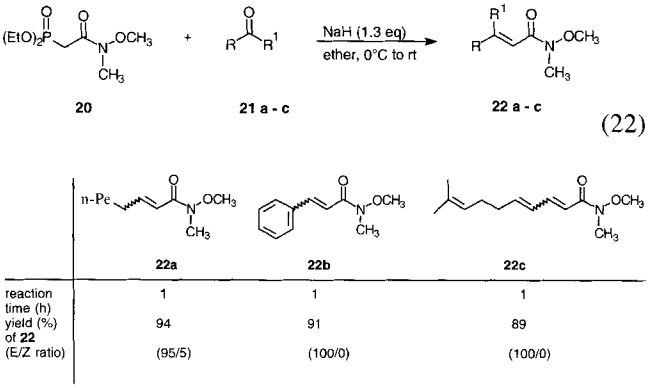


(21)

Acetylene ketones such as (**13**) and (**17**) are Michael acceptors and not compatible with reactive nucleophiles including organometallics. In the past, these compounds have often been prepared by mild oxidation of propargylic alcohols. Due to the *acidic* work up step (**2** → **3**) the synthesis of a wide variety of base-sensitive α,β-unsaturated ketones is feasible. A suitable route to α,β-unsaturated carbonyl compounds has been demonstrated by Nuzillard and coworkers [21]. They used *N*-methoxy-*N*-methyldiethylphosphonoacetamide (**20**) for the preparation of α,β-unsaturated aldehydes in two steps (equation 23).The Emmons–Horner Wittig reagent (**20**) which combines Weinreb and Wittig–Horner chemistry, can easily been synthesized as shown by Seidel *et. al.* [22]. Addition of carbonyl compounds (**21**) under Wittig–Horner conditions provided α,β-unsaturated Weinreb amides (**22**) in good yields, being almost pure *E*-products (equation 22).

N-Methoxy-*N*-methylamides of type (**22**) find various applications in organic synthesis since they can be converted into α,β-unsaturated aldehydes or ketones by the usual Weinreb reduction with metal hydride or addition of organometallic reagents (equation 23).

Weinreb amide enolates have been generated as a Reformatzky donor and as lithium salts derived from bromo *N*-methoxy-*N*-methyl acetamide (**24**) and *N*-methoxy-*N*-methyl acetamide (**25**), respectively. Combination with carbonyl compounds, followed by reaction with a Grignard reagent, which offers a route to β-hydroxy ketones in what amounts to a controlled overall cross-aldol reaction (equation 24) [23].



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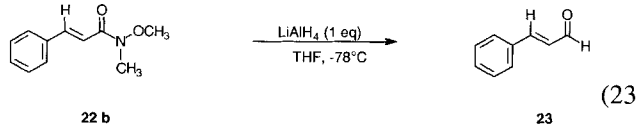

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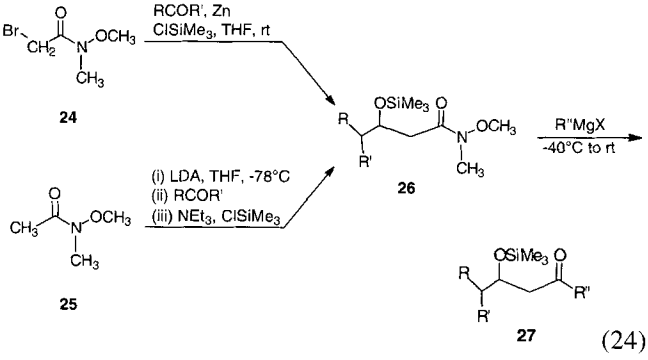
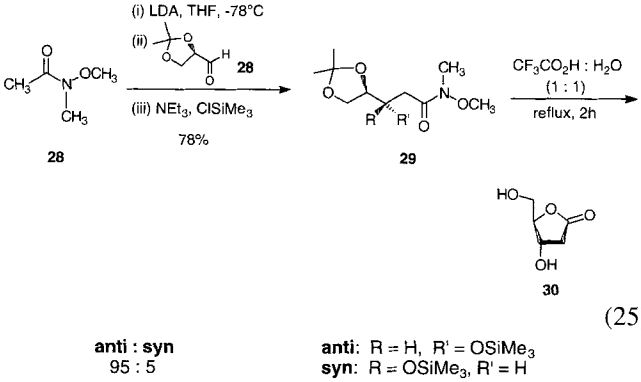


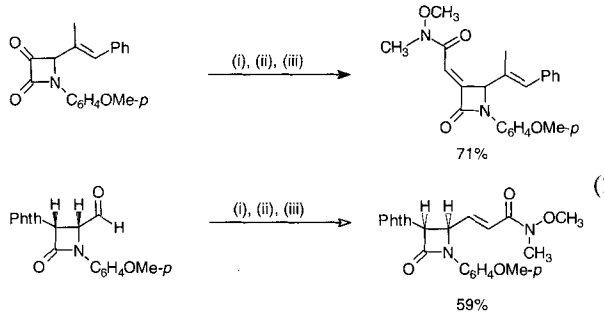
(24)

The adduct (**29**) of protected (*R*)-glycerol aldehyde (**28**) has been cyclized to a nucleoside building block (equation 25) [23].



(25)

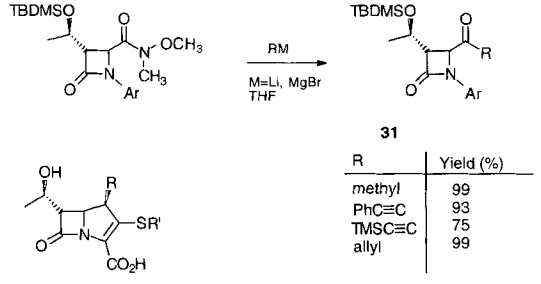
β-Lactams have been elaborated in similar fashion (equation 26).



(26)

reagents and conditions:
(i) MeCON(OMe)Me, LDA, THF, -40°C, 1h (ii) $MeSO_2Cl$, NEt_3, CH_2Cl_2
(iii) DBU, benzene, 80°C, 30min Phth = phthalimido group

Prasad and Liebeskind [24] have also applied Weinreb methodology to the preparation of a variety of functionalized 4-acylated monocyclic β-lactams (**31**) in good yields. These lactams have been used as precursors in the synthesis of 1β-methylcarbapenems. Carbapenems such as thienamycin (**32a**) have attracted much attention in recent years because of their broad spectrum of antibacterial properties [23]. Equation 27 illustrates the simple route to 1β-methylcarbapenem precursors (*e.g.* **32b**, R = Me).



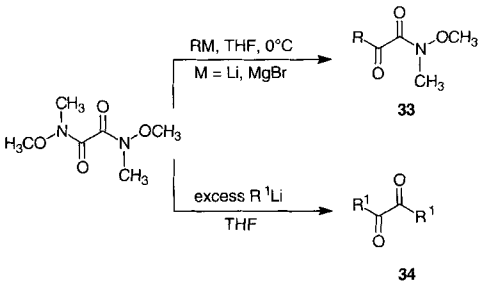
R	Yield (%)
methyl	99
PhC≡C	93
TMSC≡C	75
allyl	99

(27)

32 a : R = H, R' = $CH_2CH_2NH_2$
b : R = Me, R' = $CH_2C(NH_2)$=NH

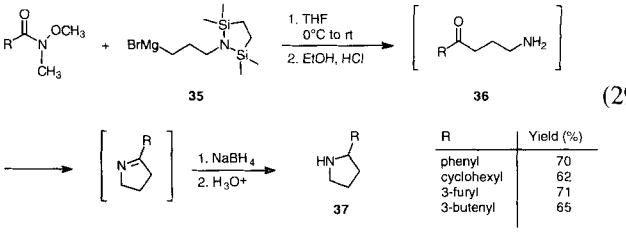
Sibi and coworkers [25] have explored the utility of a 1,2-dicarbonyl synthon derived from oxalic acid in the preparation of α-ketoamides (**33**) and of symmetrical, nonenolizable 1,2-diarylketones (**34**) (eq 28). 1,2-Diketones are useful functional groups, and peptidyl 1,2-diketones have been shown to be potent protease inhibitors [26]. Therefore development of a new methodology for preparation of these functionalities is welcome.

In a novel route to 2-substituted pyrrolidines, Basha and DeBernardis [27] have utilized the amino protected Grignard reagent (**35**) as a nucleophile and prepared sensitive γ-amino ketones (**36**) (eq. 29). Without isolation these intermediates were cyclized to the pyrrolid-



(28)

R	Yield (%)	R^1	Yield (%)
phenyl	95	phenyl	76
p-chlorophenyl	88	*p*-chlorophenyl	66
benzyl	61	*p*-tolyl	86
n-butyl	75	*p*-methoxyphenyl	52

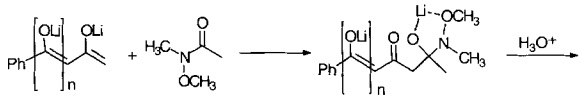


(29)

R	Yield (%)
phenyl	70
cyclohexyl	62
3-furyl	71
3-butenyl	65

ines (**37**) by reduction of the transient imines using $NaBH_4$.

Acetylations of the lithium salts of di-, tri-, and tetraanions of ketones with esters are generally problematic resulting in very low yields of the desired products. Oster and Harris [28] achieved an efficient acetylation of the multiple anions of oligo-β-carbonyl compounds by the use of *N*-methoxy-*N*-methylamides, obtaining skipped oligocarbonyl chains. Equation 30 ilustrates this method.



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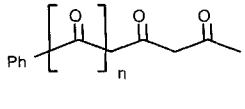
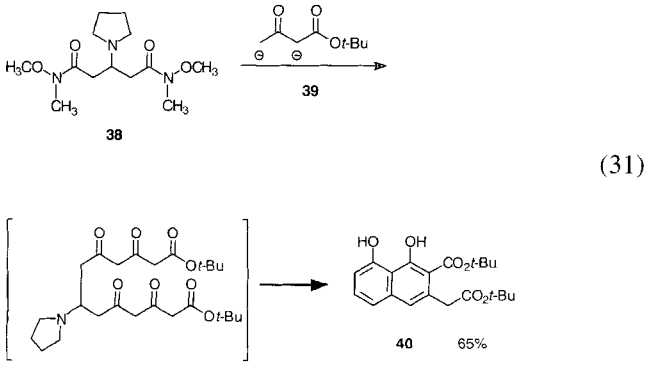


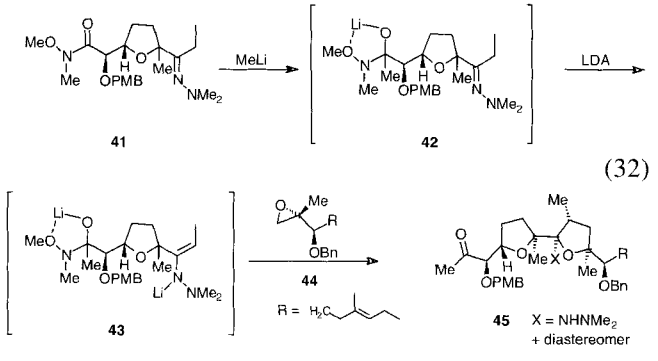
n	Yield (%)
1	86
2	80
3	88

In another example Harris and coworkers [29] have successfully used a 1,5-dicarbonyl synthon to prepare a key intermediate in their elegant, biomimetic synthesis of Pretetramide. The Weinreb diamide (**38**) undergoes condensation with the dilithium salt of *t*-butyl acetoacetate (**39**) to furnish the naphthalene diester (**40**) (eq 31).



(31)

Evans and his coworkers have impressively demonstrated the utility of *N*-methoxy-*N*-methylamides in total synthesis [30]. In their synthesis of the polyether antibiotic X-206 [30a] they made use of the stability of the tetrahedral intermediate formed by the addition of a nucleophile to *N*-methoxy-*N*-methylamide. The strategy allowed a further chemoselective functionalization at the remote site of the molecule (equation 32).

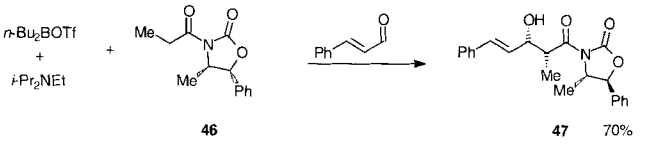


(32)

Specifically, treatment of the amide/Schiff base (**41**) with methyl lithium afforded the tetrahedral intermediate (**42**), which was metallated *in situ* using LDA to furnish intermediate dianion (**43**). Quenching with epoxide (**44**) produced methyl ketone (**45**), an advanced intermediate in the synthesis of polyether X-206.

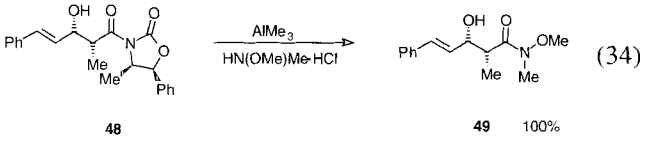
The antineoplastic macrolide antibiotic Cytovaricin, an extremely complex molecule, is another example for the use of Weinreb amides in natural product synthesis [31]. Evans and his group accomplished the convergent, asymmetric total synthesis using their auxiliaries in asymmetric aldol and enolate alkylation reactions [32]. These methodologies rank among the most reliable methods for stereoselective carbon-carbon bond formation and have had a profound impact on organic synthesis [33].

For example, acylated oxazolidinone (**46**) was converted into boron enolate and combined with a wide range of aldehydes with high *facial* selectivity, the product being essentially a single *syn*-isomer [32b] (eq. 33) [30c].



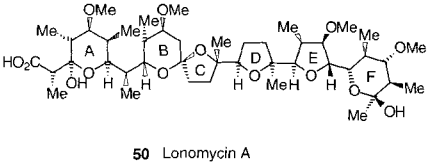
(33)

Evans applied the transamination procedure described by Weinreb [34] for the further elaboration of the carbon chain. The cyclic chiral auxiliary is a better leaving group than N(OMe)Me and can be recovered. Equation 34 illustrates this route.



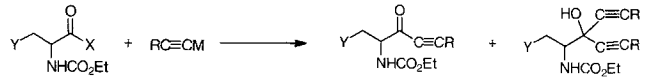
(34)

The aluminium amine solution is prepared by careful addition of trimethylaluminium in toluene to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride in methylene chloride at 0 °C. Again, the resulting Weinreb amides such as (**49**) are intermediates in the synthesis of extremely complex macrolides and highly oxygenated polyketides including X-206 [30a], Ionomycin [35], Cytovaricin [31], Ferensimycin [36], Calyculin A [30b] and Lonomycin A [37] (**50**). Lonomycin A with 23 stereogenic centers and the latent β-keto acid moiety which is masked as an internal hemiketal can be compared with Brevetoxin B [38] with respect to structural complexity.

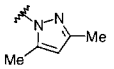


Rapoport and coworkers [39] have evaluated a variety of carboxylic acid derivatives in the synthesis of

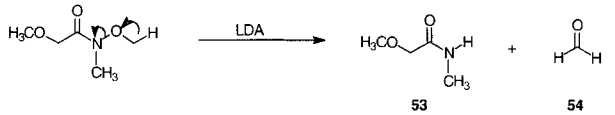
ynones (**51**) (eq. 35). Their comparative studies of acyl leaving groups showed that Weinreb amides are very inert to excess nucleophilic attack when compared to acid chlorides, lithium carboxylates, 2-pyridylthioate esters and *N*-acylpyrazoles. Tertiary alcohol (**52**) was not formed (compare equation 35 entry 6 with entries 1 to 5). The reactivity of the *N*-methoxy-*N*-methylamides was found to be comparable to isoxazolidines (entries 6 and 7).



(35)

entry	X	M [eq]	ratio **51**:**52**	Yield **51** (%)
1	OH	Li [3.5]	–	no reaction
2	Cl	Li [1.1]	1:2	<5
3	Cl	MgBr [2.3]	1:10	<1
4		Li [1]	1:10	<1
5		MgBr [2]	1:20	<1
6	$-N(CH_3)OCH_3$	Li [2.5]	>100:1	84
7		Li [2.5]	>100:1	88

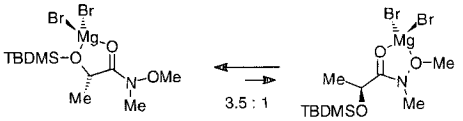
A limitation of Weinreb amide chemistry has been reported for nucleophilic additions with sterically hindered and/or highly basic reagents. For example, Graham and Scholz [40] observed the formation of *N*-methylamides such as (**53**) and formaldehyde (**54**) when treating Weinreb amides with a strong and sterically hindered base (eq 36).



(36)

As a mechanism an E2-pathway can be envisaged but other mechanistic possibilities have been postulated. However, the rapidity with which the decomposition of Weinreb amide occurred at –78 °C indicated that possible intermediates are very short-lived.

Finally, it should be borne in mind that Weinreb amides may not be necessary when dealing with α-hydroxy carboxylic acids. Protection of the alcoholic hydroxyl group by benzyl or *t*-butyldimethylsilyl furnishes a tether for a bidentate interaction with a metal cation. In complexation studies with $MgBr_2$ the α-benzyloxy group was found superior to N_α(OMe) and even *t*-butyldimethylsiloxy was a somewhat better donor (equation 37) [41].

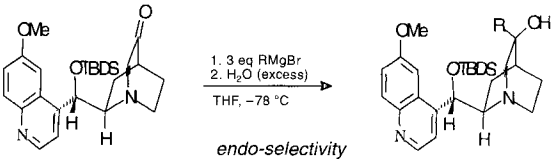


(37)

C_α-OBn > C_α-OTBDMS > N_α-OMe

The chemistry of protected lactic acid, mandelic acid, malic acid and tartaric acid bears vivid testimony to such bidentate interactions and has been laid out in a recent book [42].

A recent example of the coordination ability of a OTBDS-group has been observed (equation 38) [43]. The remote OTBDS-tether of the protected rubanone (**55**) directs the nucleophilic attack of the organomagnesium reagent to the sterically more hindered *endo* π-face of the carbonyl group. The ketone reacts in a *masochistic* manner to provide an excess of *endo* alcohol (**56**) with the desired natural configuration at carbon C-3 of the *Cinchona* alkaloid.



(38)

56	R	endo:exo	Total Yield (%) [a]
a	$-CH{=}CH_2$	4,5:1	85
b	$-C_6H_5$	6:1	86
c	$-CH(CH_3)_2$	7:1	70

[a] mixture of diastereomers

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