The Growing Synthetic Utility of the Weinreb Amide

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Abstract: N-Methoxy-N-methylamide, popularly addressed as the Weinreb amide, has surfaced as an amide with a difference. This amide has served as an excellent acylating agent for organolithium or organomagnesium reagents and as a robust equivalent for an aldehyde group. These two aspects have been exploited exhaustively in various synthetic endeavors. This review presents the growing synthetic utility of the Weinreb amide not only in academic circles, but also its popular use on kilogram scale by various pharmaceutical industries across the globe.

1 Introduction

N-Methoxy-N-methylamides (1; Scheme 1), now popularly called Weinreb amides (WAs) after their discoverer,1 have reached a center stage for clean and effective acylations of organolithium and organomagnesium reagents. The emerging interest and confidence in the use of this functionality in the synthetic organic chemistry domain is clearly substantiated by the surge in the number of publications over recent years. A quick search on Scifinder® under the phrase ‘Weinreb amide’ reflects this fact (Figure 1). Our continued interest since the late 1990s towards developing small building blocks based on the WA functionality for use in organic synthesis and its growing use on kilogram scale by industry is the trigger for this review. Given the recent rise in the number of publications that invoke the use of WA functionality, the earlier reviews by Sibi,2a Hoffmann2b and by us,2c that foresaw the potential and promise then, despite the field’s infancy, were appropriate, succinct and justified. Another review by Khlestkin3 discussed, in general, the advances of the application of N,O-dialkylhydroxylamines in organic chemistry, and thereby did survey some part of Weinreb amide chemistry, because N,O-dimethylhydroxylamine (DMHA; also named N-methoxy-N-methylamine) is used for installing the WA functionality. The present review predominantly covers the literature published during the period of 2000 to 2008. Occasional reference to the work preceding this period is included only for the sake of relevance and completeness of discussion.

Figure 1 The growing use of WAs based on a Scifinder® literature search

The successful acylation by a variety of organolithium and organomagnesium reagents or reductions by lithium aluminum hydride or diisobutylaluminum hydride is due to the putative and stable tetrahedral intermediate2 or 3 formed upon addition of the first equivalent of the organometallic species or reducing agent (Scheme 1). This stability precludes the collapse to a ketone or aldehyde under the reaction conditions and thus prevents the formation and subsequent possibility of addition to the ketone or aldehyde.

The aqueous workup not only facilitates the collapse of tetrahedral intermediate 2 or 3 to furnish the respective ketone or aldehyde, but also ensures simultaneous

Scheme 1

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The aqueous workup not only facilitates the collapse of tetrahedral intermediate 2 or 3 to furnish the respective ketone or aldehyde, but also ensures simultaneous
quenching of all the excess equivalents of organometallic species or reducing agent, thereby explaining why no over-addition product is formed despite the use of a large excess of reagents. Recent investigations into the mechanism of acylating the phenylacetylide with WA, which clearly indicate no detectable IR stretching frequency for carbonyl until the reaction is quenched, substantiate this rationale.

The growing synthetic utility of the WA stems from four attractive features associated with this functionality. They are summarized as the four S’s: (i) Simplicity associated with its preparation by in situ activation of the carboxyl group or through its stable ester derivative, even in a highly functionalized molecule; (ii) the Success it has met as an effective acylating agent for organometallics, facilitating convenient access to highly functionalized ketones, particularly in the total synthesis of complex natural products; (iii) Scale-up through which these amides have been prepared and routinely used; and finally, (iv) the Stability and hence easy storability. Their facile reduction to aldehydes with hydride reducing agents, coupled with all the above attractive features makes them serve as an excellent base alone. Carbon-centered nucleophiles, such as organolithiums which normally undergo clean acylation with WA, fail to add to the carbonyl carbon at an appreciable rate, for steric reasons, and instead act as a base and effect demethoxylation. The addition of octyllithium to WA serves to illustrate this point. Despite several changes in the reaction conditions (solvent, temperature and number of equivalents of octyllithium), the desired ketone 9 was always obtained in 5–24% yield, whereas the demethoxylated compound 9 remained the major product (36–63%). It was reasoned that the gem-dimethylallyl moiety at the α-position in WA being sterically more demanding, impeded the attack of octyllithium and hence diverted its course to that of an in-

1.1 Limitations

Given the fact that it is the N-methoxyl-N-methyl part of the WA which makes it different from other amides, any perturbation in it would result in the loss of its significance. With certain inherent structural features embedded in the compound containing the WA, two observations have been mentioned as being the only apparent limitations associated with WA functionality (Scheme 3). Gratifyingly, one of these has been recently addressed with a simple and convenient solution. The first observation was made by Graham and Scholz. The WA 4, when treated with lithium diisopropylamide at –78 °C, resulted in demethoxylation and formation of 5 as the major product (73%). This decomposition, with concomitant release of formaldehyde, was shown to take place through an E2 elimination mechanism as depicted. A similar observation was made when 6 was added to 7a with a view to effect Michael addition; it resulted only in the formation of 7b.

Such observation of demethoxylation with the release of formaldehyde is not restricted to the nitrogen-centered base alone. Carbon-centered nucleophiles, such as organolithiums which normally undergo clean acylation with WA, fail to add to the carbonyl carbon at an appreciable rate, for steric reasons, and instead act as a base and effect demethoxylation. The addition of octyllithium to WA during the synthesis of isoavenaciolide serves to illustrate the point. Despite several changes in the reaction conditions (solvent, temperature and number of equivalents of octyllithium), the desired ketone 9a was always obtained in 5–24% yield, whereas the demethoxylated compound 9 remained the major product (36–63%). It was reasoned that the gem-dimethylallyl moiety at the α-position in WA, being sterically more demanding, impeded the attack of octyllithium and hence diverted its course to that of an in-

Biographical Sketches

Sivaraman Balasubramaniam (1981) was born in Chennai, India and received his B.Sc. and M.Sc. degrees from Loyola College Chennai (2003). In 2005, he joined Professor Indrapal Singh Aidhen’s group at IIT Madras. His Ph.D. research focuses on the development of new synthetic equivalents based on the Weinreb amide functionality, and their uses in synthetic organic chemistry.

Indrapal Singh Aidhen (1960) was born in Pune, India and received his Ph.D. degree (1990) from the Department of Chemistry, University of Pune under the guidance of Professor N. S. Narasimhan. He undertook his first postdoctoral studies at the University of California, Santa Cruz, with Professor Rebecca Braslau. He was awarded an Alexander Von Humboldt fellowship (1993) to work with Professor R. R. Schmidt at Universität Konstanz, Germany on the synthesis of the challenging targets, C-glycosides of neuraminic acid. In 1995, he was appointed as an Assistant Professor of Organic Chemistry at the Department of Chemistry, IIT-Madras, India and is currently a Full Professor there. In 2003, he was awarded a JSPS Invitation Fellowship to work in the laboratories of Professor Shoichi Kusumoto at the University of Osaka, Japan on the synthesis of immuno adjuvants. Besides the synthesis of important molecules, his research interests include both the development of new synthetic equivalents based on the Weinreb amide functionality and synthesis of biologically important C-glycosides in particular.
evitable base for demethoxylation. The successful addition of octyllithium in high yield (85%), when the α-position had an allyl moiety, supported the author’s argument. Intentional reductive cleavage of the N–O bond in the WA at room temperature, leading to demethoxylation, has been achieved using lithium powder in presence of 4,4′-di(tert-butyl)biphenyl as a catalyst in 10 mol%. An elegant solution to this problem of demethoxylation has been provided by Genet and Phansavath with the advent of N-(tert-butoxy)-N-methylamides. For the convenient synthesis of these amides, the authors developed a practical multi-gram scale procedure for access to the requisite amine, N-methyl-O-(tert-butoxy)hydroxylamine, as its hydrochloride salt (Scheme 4). The amide 11, obtained using this amine 10, behaved identically to WA in its reactivity towards organolithiums and organomagnesiums, as well as disobutylaluminum hydride. A clean reaction ensued with octyllithium and furnished the desired ketone 9a in 73% isolated yield. With the replacement of N-methoxy group in 8 with N-(tert-butoxy) as in 11, the elimination possibility was completely excluded and hence only nucleophilic addition occurred, however slow this addition may have been because of steric reasons.

Keck independently reported the formation of demethoxylated product 12 and rearranged product 12a, when WA 13 was exposed to tert-butylidemethylsilyl triflate in the presence of triethylamine or collidine as a base (Figure 2). The formation of these products has been ra-
tionalized through a retro-ene reaction on the initially formed enol derivative 14 resulting in the formation of 15 and monomeric formaldehyde. Quenching of the intermediate 15 during aqueous workup would explain the formation of 12. However, the formation of product 12a necessitates the reaction of 15 at nitrogen with the TBS-activated formaldehyde, before aqueous workup. The ratio of these products was found to be a function of stoichiometry of tert-butyldimethylsilyl triflate and the base used. Excess triethylamine consumed the liberated formaldelye by reacting with it or with TBS-activated formaldehyde; hence the exclusive formation of 12 observed with triethylamine as base. Collidine fails to do so and hence allows the reaction between 15 and TBS-activated formaldehyde; this explains the formation of the rearranged product 12a when collidine is used as a base.

2 Methods for Preparation

These amides have been prepared from either the acid or its derivatives (Scheme 5). The amine DMHA is commercially available in the form of its hydrochloride salt. The hydrochloride salt 16 can also be conveniently prepared on large scale starting from the inexpensive hydroxylamine hydrochloride (17; Scheme 6). In most of the synthetic operations, largely because of convenience, the amine is generated in situ, with the help of one equivalent of a base. Occasional reports of preparing free amine DMHA as a distillable liquid (bp 47–50 °C) from the hydrochloride salt 16 do exist. Among the various methods, the direct conversion of the acid into the WA is the most prominent and attractive, as it obviates the need to first convert the acid into one of its derivatives. This direct conversion relies on in situ activation of the carboxyl carbon for attack by DMHA.

To this end, several acid activating agents have been successful. These include DCC, DEPC, HOBT/DCC, HOBT/EDC, BOP-PF₆, CDI, alkyl chloroformates, CB₃/TPP, 2-halo-1-alkylpyridinium salts, py-BOP, EDCl, PPA. During recent times, development of new methods that are less expensive, operational-

![Figure 2](https://example.com/figure2.png)  
**Figure 2** Role of the base in explaining the unusual reactivity of WA

![Scheme 5](https://example.com/scheme5.png)  
**Scheme 5** Various substrates from which the WA is prepared

![Scheme 6](https://example.com/scheme6.png)  
**Scheme 6** Various acid activating agents

iodomethane furnishes 19 as a crystalline solid. Because of the N-methylation in the imidazole ring, these salts have enhanced reactivity over the corresponding carbamoylimidazoles. The salt, 19, is more readily handled than 18, and its preparation also precludes the direct use of phosgene or triphosgene.

With both these reagents 18 and 19, the conversion of the acid into the WA in the presence of triethylamine proceeds through the mixed anhydride 20 (Scheme 7). In the case of the former, the added DMAP results in the formation of acylpyridinium species 21 through attack on the activated carbon, whereas in the latter, the expelled N-methylimidazole during the first step furnishes acyl imidazolium species 22. Both of these attacks concomitantly release carbon dioxide and free DMHA, attack of the released DMHA on the activated intermediates 21 and 22 results in the formation of the WA.

Scheme 7

Besides the popular use of alkyl chloroformates for in situ generation of mixed anhydride of carboxylic acid wherein the carbonyl groups differ electronically, use of other mixed anhydrides wherein the carbonyl groups differ either sterically or electronically have also been made.32 To this end, use of simple pivaloyl chloride,32a,b methanesulfonyl chloride32c or 1-((methanesulfonyl)benzotriazole (BtMs))32d have been equally successful (Scheme 8). The mixed anhydride 23 resulting from the use of pivaloyl chloride is attacked by DMHA at –5 to 0 °C furnishing the WA 24 in good yield. The attack of DMHA on the pivaloyl carbonyl carbon in the mixed anhydride 23 is precluded due to steric factors. Similarly, the mixed anhydride 25, formed during the reaction of carboxylic acid with 1.1 equivalents of methanesulfonyl chloride in the presence of 3 equivalents of triethylamine, has also enabled the formation of WA. This method has been very useful with hindered carboxylic acids, where several other procedures for the construction of WA 26 gave disappointing results. The possible byproduct, N-methoxy-N-methylmethanesulfonamide, formed by the attack of DMHA on the sulfur in the mixed anhydride 25, is claimed to be easily removed by gentle warming under vacuum overnight. The use of 1-((methanesulfonyl)benzotriazole was developed by Katritzky.32d The mixed anhydride 27 formed by the reaction of carboxylic acid and 1-((methanesulfonyl)benzotriazole in presence of 1.0 equivalent of triethylamine is attacked by the liberated benzotriazole (Bt) to give the activated acid as acylbenzotriazoles 28. This, on refluxing with DMHA hydrochloride in tetrahydrofuran with 2.2 equivalents of triethylamine, afforded the WA 29. The benzotriazole by-product formed in the reaction can be easily removed and recovered by washing with saturated sodium carbonate solution.

Conversions into acid halides (Scheme 9) in situ or otherwise have been used to arrive at functionalized WAs.33 The use of bis(2-methoxyethyl)aminosulfur trifluoride 30 (Deoxo-Fluor reagent) as a reagent for the conversion of carboxylic acids into the corresponding acid fluorides 31 and subsequent reaction with DMHA have been made for the synthesis of N-Boc a-amino WA 32.33a The acid fluorides react more like active esters than any other acid halides, their stability is much higher than that of acid chlorides towards water and methanol, and they react smoothly with amines and anionic species.33b It is also of note that no significant loss of optical purity is observed during the conversion of acid fluorides into amides. The
combination of effective fluorination properties, enhanced safety features will make this reagent a cost-effective alternative for many uses. In fact, the successful activation with Deoxo-Fluor and formation of WA have been applied to the one-pot synthesis of aldehydes and ketones, specifically for long-chain fatty ketones.\textsuperscript{33c} As an alternative to the use of the expensive Deoxo-Fluor reagent, Sureshbabu et al. recently claimed the successful conversion of various N-Fmoc-protected amino acids into the corresponding acid chlorides using conventional thionyl chloride as the reagent.\textsuperscript{33d} The N-Fmoc-protected amino acid chlorides 33 react with DMHA, itself derived from the hydrochloride salt, in the presence of N-methylmorpholine to yield the corresponding WA 34 in excellent yields.

Esters and lactones (Scheme 10) have been converted into their WAs by the combined use of two to five equivalents of trimethylaluminum, or dimethylaluminum chloride, or disobutylaluminum hydride, with DMHA hydrochloride.\textsuperscript{34–37} As the aluminum reagents are air sensitive, they must be used under strictly inert conditions. The use of Me\textsubscript{3}Al in conjunction with DMHA hydrochloride for converting esters into WAs was originally developed by Weinreb\textsuperscript{34a} himself, and the method continues to enjoy the confidence of synthetic chemists in various endeavors. It works exceedingly well even in highly functionalized key intermediates encountered during long synthetic schemes aimed at the total synthesis of challenging targets.\textsuperscript{34b–d} As an illustrative example, this combination has been used for converting \( \alpha \)-hydroxy esters 35a or \( \alpha \)-hydroxy-protected esters 35b into the corresponding WAs 36a and 36b.\textsuperscript{35a} Although no rationale has been proposed, aryl esters furnished better yields of the corresponding WAs than do the alkyl esters.\textsuperscript{35b} Shimizu et al. observed some unsatisfactory results while attempting the conversion of sterically crowded lactones with the trimethylaluminum and DMHA hydrochloride combination. This led to the development of an alternative combination of dimethylaluminum chloride and DMHA hydrochloride for the same purpose.\textsuperscript{36a} Substantial improvement in the yields and reaction time were observed with this combination. This combination has been also used for converting esters into WAs in various total syntheses of natural products.\textsuperscript{36b–e} The real species formed in situ by the combination of this reagent is Cl\textsubscript{2}Al-NMe(O\textsubscript{Me}), with concomitant evolution of two equivalents of methane. As the handling of disobutylaluminum hydride is comparatively easier than that of trimethylaluminum, the only report of using disobutylaluminum hydride as a source of aluminum reagent along with DMHA or DMHA hydrochloride for converting ester 37 or lactone 38 into their corresponding WA, in excellent yield,\textsuperscript{37} should hold significant promise for further use in other synthetic endeavors.
Incorporation of WA functionality through the disconnection shown in Scheme 12 was accomplished under palladium catalysis in cases where the residue R was alkenyl, alkylnyl or aryl. N-Methoxy-N-methylcarbamoyl chloride 18 has been used under Stille-type cross-coupling conditions with vinyl, alkylnyl and aryl stannanes 45 for the synthesis of WA 46 through the proposed disconnection. The coupling was effected with catalytic amounts of bis(triphenylphosphine)palladium(II) dichloride in tetrahedofuran at 60 °C and in yields ranging from 60 to 90%. Another useful method based on the aforementioned disconnection was developed by Buchwald. It comprises the aminocarboxylation of aryl bromides with DMHA hydrochloride and carbon monoxide at atmospheric pressure under Heck coupling conditions [2 mol% Pd(OAc)\(_2\) with 2 mol% Xantphos as ligand in toluene at 100 °C]. This method has been used for the coupling of ketone-, lactone- and thiolactone-derived triflates 47a–d for the synthesis of alicyclic 48a and heterocyclic WAs 48b–d.48

Scheme 12

The cyanohydrins available from aldehydes, in principle after oxidation and subsequent treatment with DMHA, should afford the corresponding WAs through the intermediacy of the acyl cyanides. The successful formation of WA 49 based on this concept was observed during the synthesis of phomactin D (Scheme 13). Very recently, Nemoto et al. developed an attractive procedure, based on the intermediacy of an acyl cyanide, for converting aromatic and aliphatic aldehydes into the corresponding \(\alpha\)-siloxy WAs 50. The conversion proceeds through the addition of carbanion 51a, generated from 51 under the reaction conditions, to the aldehyde, followed by silyl migration, collapse to acyl cyanide 52 and attack of DMHA. For high yields and efficiency, for aromatic aldehydes, DMAP and acetonitrile were the best choices of base and solvent, whereas for nonaromatic aldehydes, it was imidazole and diethyl ether.

Scheme 13

3 Applications

The major application of WA functionality in organic synthesis centers on its facile conversion into ketones and aldehydes. For the formation of ketones, invariably the nucleophilic species have been in the form of either organolithium or organomagnesium reagents, and for the formation of aldehydes the hydride source has been either lithium aluminum hydride or disobutylaluminum hydride. Very rarely have nucleophiles other than organolithium or organomagnesium species been used. With the first disclosure from Murphy’s research group that alkylidenetriphenylphosphoranes 53 also react with WA as nucleophiles, yet another synthetic potential of WA was uncovered. It is presumably a case of successful Wittig reaction on the amide carbonyl, wherein the oxaphosphetane intermediate 54, upon cycloreversion and extrusion of triphenylphosphine oxide, afforded the putative enamine 55, which on hydrolysis furnished the ketone as the final product of the reaction. Importantly, the phosphonates react in a completely different way. The phosphonate anion 56 does not lead to olefination of the amide carbonyl, but instead leads to \(\beta\)-ketophosphonates 57 with the expulsion of an amine residue. The extension of Murphy’s successful addition of alkylidenetriphenylphosphoranes onto WA 58, derived from formic acid, resulted in formylation of phosphoranes (Scheme 14).
For the reader to gauge the confidence that the WA functionality enjoys in various organic synthetic endeavors, the broad-ranging applications have been classified under the following four categories: (a) use in heterocyclic chemistry; (b) use in total synthesis of natural products; (c) use on kilogram scale in industry; and (d) synthetic equivalents and building blocks based on the WA functionality, and its uses in synthesis.

### 3.1 Use in Heterocyclic Chemistry

The alkynones 59 (Scheme 15), anticipated as products through the nucleophilic addition of alkynyl lithium or magnesium derivatives, appear to be reactive enough for a facile Michael reaction. The extruded DMHA, during or after the workup, simply adds in a Michael fashion, thereby furnishing N-methoxy-N-methyl-β-enamino ketones 60. These have become versatile building blocks and the versatility arises from the fact that the DMHA unit does not remain as an imposing structural feature in the β-enamino ketones, but can be readily exchanged with any amine to afford novel amine segments on the vinylic system of β-enamino ketones for further synthetic endeavors. With the choice of appropriate amine, diverse and highly functionalized heterocycles have been synthesized. The WAs 61a and 61b obtained from N-protected L-phenylalanine and L-threonine, respectively, when treated with ethynylmagnesium bromide, afforded through corresponding yrones the N-methoxy-N-methyl-β-enamino ketones 60a and 60b. To demonstrate the significance of these enaminoketones, compound 60b, when reacted with phenylhydrazine or 62 as an amine, not only displaces the DMHA residue, but also undergoes further cyclocondensation to furnish functionalized heterocycles 63 and 64 respectively.

Acetylenic keto esters 65, apparently attractive scaffolds for condensation with hydrazine for 3-carboxy-functionalized pyrazoles (Scheme 16), are rare synthetic intermediates as they are available only through the corresponding aldehydes. Despite the well-documented successful addition of alkynyl residues to activated acids, the addition of alkyl propynoates has been restricted to potentially explosive silver acetylide alone. Interestingly, the addition of lithium or sodium acetylide of ethyl propynoate, on N-methoxy-N-methylacetamide 66 as a representative WA, again did not furnish the expected ethyl-4-oxopent-2-ynoate framework 65a, but led instead to the formation of enamines 67 and 68.
an elegant route toward 3-carboxy-functionalized pyrazoles.\textsuperscript{51}

The Michael addition of DMHA to alkynes only during or after the workup is not a rule, since successful formation of alkynes for further synthetic endeavors has also been achieved (Scheme 17).\textsuperscript{52} Couty and co-workers have successfully prepared and used N-Boc-oxazolidine-based alkynes \textit{69a}\textsuperscript{52a} as valuable building blocks, obtained from the corresponding WA \textit{69b}, for various synthetic targets.\textsuperscript{52b} Similarly, Cox and co-workers, in their efforts towards 3,5-diaryl-5-alkyl-4,5-dihydropyrazole through cyclocondensation of hydrazine with β-alkyl chalcones \textit{70}, have synthesized the requisite chalcones through 1,4-addition of the alkyl residue as organocuprate on the readily obtained alkynes \textit{71}.\textsuperscript{52d} These alkynes were simply prepared by addition of the lithium salt of the tertiary amine with DMHA liberated from its salt, in the presence of dicyclohexylcarbodiimide or N’-(3-dimethylaminopropyl)-N-ethylenediamine.

Recently, the reliability of WA–alkynylide coupling for the synthesis of the alkyne functionality has been exploited by Williams for the synthesis of macrolide pectenotoxin-4 which is discussed in the application of WAs in natural product synthesis (vide infra).

The building block \textit{72} has paved the way for an efficient and novel synthetic route to 3,4-disubstituted pyrrole-2-carboxaldehyde \textit{73} and 3-pyrrolidin-2-one \textit{74} (Scheme 18). The key reaction is the cyclocondensation between the α-nitroalkene or β-nitroacetate and the activated isocyanide functionality in \textit{75}.\textsuperscript{53}

3-Acylindazoles and 3-formylindazoles are valuable building blocks in medicinal chemistry\textsuperscript{54} for wide range of applications, particularly in the development of serotonin receptor ligands (SHT).\textsuperscript{55} In the context of low-yielding routes reported in the literature for this class of compounds, the recently disclosed strategy invoking the use of WA-based building block \textit{76} constitutes the most efficient and flexible route for 3-acylindazole libraries (Figure 4).\textsuperscript{56}

Multigram quantities of \textit{76} and \textit{77} were conveniently prepared in good yields by condensation of the corresponding indazole acid with DMHA liberated from its salt, in the presence of dicyclohexylcarbodiimide or N’-(3-dimethylaminopropyl)-N-ethylenediamine.

The Parham cyclization process, which hinges upon lithiation followed by attack of the generated aryl- or heteroaryl lithium on the tethered internal electrophile, has occupied a place of choice in the arsenal of synthetic tactics for the assembly of carbo- and heterocyclic systems (Figure 5).\textsuperscript{57} With the use of the WA functionality as the internal electrophile, the strength of the Parham cyclization process has increased manifold. Initial exploration included successful reaction of organolithiums derived from alkyliodides with tethered WA for access to cyclic ketones.\textsuperscript{58} This is interesting in light of the fact that metal–halogen exchange must be extremely fast and the initiating agent should not directly add to the carbonyl carbon of WA as a nucleophile. Application of the same concept using heteroaryl- or aryllithium has led to the synthesis of thieno[2,3-b]thiophenes,\textsuperscript{59} benzocyclobutenones,\textsuperscript{60} and methyldieneindanones.\textsuperscript{61} Applications of this concept in the syntheses of (–)-brunsvigine,\textsuperscript{62} the hexahydrobenzofuran subunit of avermectin,\textsuperscript{63} and fused indolizino systems\textsuperscript{64} have been the most important and interesting contributions.

Liebscher treated the WA of oxiranecarboxylic acid \textit{78} and the corresponding aziridinecarboxylic acids \textit{79a} and \textit{79b} with ortho-lithiated O-MOM-protected phenol \textit{80} as a nucleophilic reagent to furnish a novel route to the 3-hydroxychromanone \textit{81}\textsuperscript{65} and 3-amino-2,3-dihydropyran-4-one \textit{82b}\textsuperscript{66} heterocyclic systems (Scheme 19). The aziridine carboxamides \textit{79a} and \textit{79b} are easily prepared from the corresponding aziridine-2-carboxylate esters and are convenient equivalents for aziridine aldehydes and 2-keto aziridines.\textsuperscript{67} Aziridine aldehydes \textit{83}
and 2-keto aziridines \( \text{R}^4 \) are fine examples of compounds displaying amphoterism, wherein amine and carbonyl functionalities are kinetically stabilized against inter- or intramolecular reactions and thereby orthogonal (no amine protection is required).

Franck et al., for their neoglycopeptide program, envisioned isooxazoles \( \text{R}^9 \) and \( \text{R}^8 \) as valuable synths for peptidomimetics (Scheme 20).69 The simplicity of preparing the five-membered heterocycle via a 1,3-dipolar cycloaddition and effective use of WA functionality formed the basis of their vision. The nitrile oxide \( \text{R}^7 \) and nitrones \( \text{R}^8 \) were prepared using aldehyde \( \text{R}^9 \), the ozonolysis product of cinnamic acid derived \( \text{R}^9 \) using lithium.

A variety of substituted pyrroles \( \text{R}^{10} \) and pyrroles fused with diverse carbo- or heterocycles \( \text{R}^{11} \) have been prepared by the Knorr approach that takes advantage of the WA functionality (Scheme 21).71 The developed strategy removes the severe limitation of auto-condensation of \( \alpha \)-amino ketones usually encountered in the Knorr approach.

For pyridone annulation through [4+2] coupling of dienolates with nitriles, the reaction between the dienolate \( \text{R}^{12} \) and acetonitrile and benzonitrile simply failed.73 Even the zinc enolate in the vinylogous Blaise reaction failed to afford pyridone \( \text{R}^{13} \). However, reaction of the same dienolate \( \text{R}^{12} \) with WA \( \text{R}^{14} \) as acylating agent afforded the \( \delta \)-keto acrylates \( \text{R}^{15} \), which were easily transformed into the desired pyridone heterocycle (Scheme 22).

Conceptually, 2-acyl oxazoles \( \text{R}^{16} \) should be directly available through the reaction of 2-metallated oxazole \( \text{R}^{17} \) and a suitable acylating agent (Scheme 23). The reported instability of 2-lithio oxazoles \( \text{R}^{18} \) in tetrahydrofuran above –40 °C,74 coupled with their known propensity to ring-open and exist predominantly as the thermodynamically more stable enolate isonitrile species \( \text{R}^{19} \), has marred their apparent attractiveness for the direct use in the synthesis of 2-acyl oxazoles \( \text{R}^{20} \). However, researchers

<ref>Figure 5 Pictorial representation of Parham cyclizations</ref>

<ref>Scheme 19</ref>

<ref>Scheme 20</ref>

<ref>Scheme 21</ref>

<ref>Scheme 22</ref>

<ref>Scheme 23</ref>
at Eli Lily\textsuperscript{75a,b} have observed that at $-70$ °C, the initially formed 2-lithio oxazoles can be transmetallated to the zincate 100\textsuperscript{b} using two equivalents of zinc chloride and these zinicates are resistant to the ring-opening phenomenon. They conveniently react with aroyl, alkenoyl and alkanoyl chlorides as acylating agents to furnish 2-acyl oxazoles 99 in good yields. Despite the predominant existence of 2-magnesio oxazoles 100\textsuperscript{c} in the ring-opened form at 0 °C in tetrahydrofuran solution, Pippel et al.\textsuperscript{75c} were successful in obtaining 2-acyl oxazoles by using the attenuated reactivity of WAs as acylating agents. The slow rate of reaction between 100\textsuperscript{c} and the acylating agent, against the faster equilibration between 100\textsuperscript{c} and 101\textsuperscript{c}, was used to rationalize the success observed with the WA-based acylating agents.

Among the $\alpha$-keto heterocycles that represent a broad class of fatty acid amide hydrolase (FAAH) inhibitors, Boger’s (Z)-1-oxo-1-(3-pyridazinyl)octadec-9-ene 102 stands out as one of the most potent.\textsuperscript{76a} The addition of pyridazinylithium 103 to the WA of oleic acid furnished product 102, albeit in a low yield of 11%. It was recently\textsuperscript{76b} observed that the four-fold excess of lithium 2,2,6,6-tetramethylpiperidine for lithiating the pyridazine was deleterious and also the reason for poor yield. However, four-fold excess of pyridazinylithium with respect to the WA significantly improved the yields of 102 and also provided generality for various other acylpyridazines (Scheme 24).

During an attempt to synthesize the therapeutically important phosphorothioates 104, ketone 105, with both indole and imidazole moieties, was postulated as an elegant auxiliary (Scheme 25).\textsuperscript{77} These moieties would not only react with dichloro(methoxy)phosphine through their respective nitrogen centers, but would also serve as leaving groups on subsequent treatment with nucleosides R’OH as nucleophiles. The indole WA 106, readily available from the corresponding acid, was responsible for the convenient access to 105, through reaction with two equivalents of N-tritylimidazole anion and followed by de- tritylation. The same target could not be obtained through the coupling of N-tritylimidazole anion and 1-(phenylsulfonyl)-2-indolecarboxaldehyde.

### 3.2 Use in Total Synthesis

Cyclic peptides that provide rigid scaffolds for locking short peptides into specific configurations are potential drug candidates in medicinal chemistry. The C-terminus functionalized cyclic peptides such as 107 (Scheme 26) have been one of the important synthetic targets at Bristol-Myers Squibb.\textsuperscript{78}

A number of cyclic peptides, wherein (i) and (i + 1) residue side chains are joined by an alkyl linker, have been synthesized. Although the synthetic scheme starts with amino acid building block 108 that already contains the WA moiety, its utility for enabling functionalization at the C-terminus is employed only towards the end of the synthesis (Scheme 26). This is important because formation of an activated carbonyl at an early stage could be problematic, owing to potential epimerization at the corresponding $\alpha$-position.

Among the marine natural product macrolides, spongistatins, altohyrtins and cinachyrolides, isolated respectively by Pettit,\textsuperscript{79a} Kitagawa\textsuperscript{79b} and Fusetani,\textsuperscript{79c} constitute the most potent antitumor agents (Scheme 27). The novel architectures stimulated widespread interest in the synthetic community. Nakata’s research group, in their program towards the total synthesis of altohyrtins, achieved a
stereocontrolled synthesis of the C29–C44 portion of the target through the coupling of highly functionalized vinyl-lithium reagent 109 with the WA moiety in 110 as the key reaction.\(^7\) The successful coupling and obtainment of compound 111 in good yield (77%) as a key building block midway through the synthetic scheme demonstrates the significance of this approach for carbon–carbon bond formation. Given that 111 had to undergo several functional group manipulations spread over ten subsequent steps to furnish the target 112, its obtainment on a multi-gram scale reflects the confidence invoked by this coupling procedure during earlier stages of the synthesis.

The tricyclic pyrrolo[2,1-c][1,4]benzodiazepine (PBD; 113), a nitrogen-containing heterocyclic system, represents one of the most promising classes of compounds capable of binding to DNA in a highly sequence-selective manner. Among the many synthetic analogues, the C8-linked dimers of PBD, represented here by DSB-120 (Scheme 28), have surfaced as one of the most efficient interstrand DNA cross-linkers.\(^8\) DSB-120 is approximately 300- and 50-fold more efficient than the clinically used cross-linking agents melphalan and cisplatin, respectively.

### Scheme 26

Stereocontrolled synthesis of the C29–C44 portion of the target through the coupling of highly functionalized vinyl-lithium reagent 109 with the WA moiety in 110 as the key reaction. The successful coupling and obtainment of compound 111 in good yield (77%) as a key building block midway through the synthetic scheme demonstrates the significance of this approach for carbon–carbon bond formation. Given that 111 had to undergo several functional group manipulations spread over ten subsequent steps to furnish the target 112, its obtainment on a multi-gram scale reflects the confidence invoked by this coupling procedure during earlier stages of the synthesis.

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### Scheme 27


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**Scheme 26**

**Scheme 27**

**Scheme 28**
tively. Continued efforts in Kamal’s research group in synthesizing PBD heterocycles have led to a versatile and inexpensive strategy that involves reduction of the aromatic azides and the WAs of 114 in one step; this provides an efficient and convenient intramolecular reductive cyclization route to DSB-120.

In Danishefsky’s group, the success in arriving at the resorcinylic scaffold present in various natural products relied on a Diels–Alder reaction between dimedone-derived 1,3-dioxygenated diene 115 and ynolide 116 and a subsequent retro-Diels–Alder reaction of the adduct 117 with the loss of isobutylene. The concept has been applied to the total synthesis of xestodecalactone A (Scheme 29).

The straightforward synthesis of commercially important, γ-bicyclohomofarnesal 121 and 121a, as strong ambergris odorants from Torre’s research group, substantiates once again the importance of the WA functionality (Scheme 30). Compound 121 and its endo isomer, 121a, equally important as key synthetic intermediates, were easily prepared in 47 and 26% overall yields from commercial starting material (R)-(+) sclareolide (122). Acid-catalyzed alcoholysis of (R)-(+) sclareolide for lactone-ring opening led to an inseparable mixture of all three possible unsaturated isomers, deceivingly homogeneous under all TLC conditions explored. However, in sharp contrast, the lactone ring in 122 was easily opened with DMHA in presence of trimethylaluminum at room temperature. WA 123 was thus obtained in 88% yield and contained the sensitive tertiary hydroxy group intact. Dehydration in the presence of thionyl chloride and pyridine afforded an easily separated mixture of 124 and 124a in 60 and 32% yield. Independent reduction of the WAs using lithium aluminum hydride in anhydrous tetrahydrofuran gave the desired targets 121 and 121a in high isolated yields of 89 and 91%, respectively.

Dias et al., while working towards the total synthesis of dolabriferol, the first natural product from the mollusk family Dolabrideridae, relied on the WA-containing starting material 125 as a valuable building block that would serve as a common precursor for both the C1–C9 and the C10–C21 fragments. It was easily obtained through two convenient and high-yielding steps from the known acyl-oxazolidinone 126. A highly stereoselective asymmetric

Scheme 29

Scheme 30
aldol reaction constituted the first step, and the subsequent reaction with DMHA in presence of trimethylaluminium was the second step in furnishing the requisite WA building block (Scheme 31).

Scheme 31

Compounds 127 and 127a, isolated first as a mixture of two stereoisomers from iron-deficient cultures of *Pseudomonas aeruginosa* ATCC 15692 by Liu and Shokrani,84a and named then as pyochelin, presented a synthetic challenge. Pyochelin 127 is a hydroxyphenylthiazolinyl thiazoline-type of siderophore produced by a large number of *Pseudomonas aeruginosa* strains and by many strains of *Burkholderia* (ex *Pseudomonas*) cepacia, the species known to be involved in severe lung infections occurring in cystic fibrosis patients. The condensation of (*R*)-N-methylcysteine (128a) with aldehyde 129 constitutes the most attractive and direct approach to arrive at 127 (Scheme 32).84b Although in principle the thiazoline aldehyde 129 should be easily accessible from the reduction of the carboxylic acid or ester group in thiazoline 130a or 130b respectively, this was, however, not the case. Reduction of acid 130a with thexylborane gave a poor yield of aldehyde 129 (15%), owing to the formation of a stable boron–thiazoline complex. Reduction of ester 130b at −78 °C with diisobutylaluminum hydride (2 equiv) furnished the aldehyde 129 in 61% yield, but in an 8:2 ratio along with starting material. Attempts to improve the yield by using more than two equivalents of diisobutylaluminum hydride and raising the temperature above −50 °C resulted in considerable over-reduction of the ester to the alcohol. Finally, the method developed by Fehrentz and Castro16a for the preparation of aldehydes derived from protected amino acids based on the reduction of the corresponding WA using excess lithium aluminum hydride (5 equiv) at 0 °C paved the way for the successful obtainment of the aldehyde 129. The thiazoline acid 130a was coupled with DMHA using diethyl cyano-phosphonate (DECP) as a coupling agent. Reduction of thiazoline WA 130c with three equivalents of lithium aluminum hydride at −20 °C was complete within 20 minutes, yielding aldehyde 129 in 94% yield with no trace of starting material, epimerization, or over-reduced product.84b The availability of aldehyde 129 has enabled the synthesis of pyochelin and analogues.84c

WA alkylation has proven itself as a reliable and convergent way to establish new carbon connectivity in the assembly of yrones later in a synthetic scheme. In Ghosh’s convergent approach85 to the synthesis of the antitumor macrolide laulimalide, the sterecontrolled synthesis of the C17–C28 was centered on two key steps. These were a ring-closing olefin metathesis for the construction of the dihydroproyan unit in 131, and a carbon–carbon connectivity through addition of alkyln alion 132 to WA 133 (Scheme 33). The WA 133 not only facilitated the carbon–carbon connection but also enabled the setting up of the stereochemistry of the C20 hydroxy group and construction of the E-geometry of the C21–C22 double bond.

Scheme 32

Scheme 33

Recently this WA–alkylidyne coupling, reliable for the synthesis of yrones, was used in tackling the synthetic challenge posed by the macrolide pectenotoxin-4 (Figure 6). The synthesis of the C21–C28 segment containing WA 134 and its facile coupling with 135 is a significant contribution made by Williams.86
Koert’s stereoselective alkyllithium coupling of compound 136, the C18–C28 segment of apoptolidin, an important natural product used for cancer treatment, is a fine example that substantiates the ease of incorporating the WA moiety into a multifunctional molecule and its use as a valuable handle for synthetic operations on a key and major building block6a (Scheme 34). Transamidation using a combination of trimethylaluminum and DMHA hydrochloride afforded WA 137 in 81% yields at –10 °C. As a truncated model for the apoptolidin skeleton, the three-carbon organolithium generated from (E)-1-bromoprop-1-ene was made to react with WA 137 to obtain propenyl ketone 138 in 87% yield. This then allowed for the facile introduction of a vicinal diol moiety at C19 and C20 through Sharpless dihydroxylation using AD-mix α, and was followed by acid-catalyzed ring closure to yield the pyranoid ketal of target 136.

The central 6,6-spiroacetal segment of spirofungin A, an antifungal antibiotic isolated from Streptomyces viola-ceusniger, was envisaged to arise through an intramolecular acetalization of ketone 139 (Scheme 35). Shimizu’s efficient synthesis of the spiroacetal fragment through this approach became a reality only because of successful synthesis of ketone 140 via coupling of WA 141 with alkynyllithium 142.87 This coupling proceeded without any difficulty at –78 °C and furnished the desired ketone in an isolated yield of 81%. Reaction of the same alkynyllithium, but with lactone 143 instead, furnished the requisite ketone 140 (without TES protection) only in 23% yield.

An economical synthesis of a number of racemic diketide thioesters,88a through genetic manipulations of the organisms that synthesize these natural products, was used at Kosan Biosciences in the search for possible intermediates that would lead to (+)-discodermolide, a polyketide natural product.88b Burlingame, using 144, targeted the synthesis of WA 145 (Scheme 36), which itself had served as the key building block for three major substructures in Smith’s total synthesis of discodermolide.88c All the structural features required in 145 were present in the vinyl lactone 146, but the vinyl group had to be removed through ozonolysis and decarbonylation. Attempted ozonolysis of the double bond in the unprotected vinyl lactone 146a led to spontaneous formation of the bicyclic acetal 147, which refused decarbonylation. However, the silyl ether 146b underwent ozonolysis and subsequent decarbonylation with Wilkinson’s catalyst to furnish the desired lactone 148. Ring opening with DMHA and trimethylaluminum and protection of the primary hydroxy as the the p-methoxybenzyl ether afforded the required WA 145 for the synthesis of discodermolide.

The synthesis of macrosphelide 149, a novel 16-membered macrolide containing three ester linkages, which had shown interesting and diverse biological activities, banked on the lactic acid derived WA 150 as the starting material (Scheme 37).89 This building block enabled convenient synthesis of 151, an important common intermediate for fragments 152 and 153. The direct addition of trans-vinylogous 2,6,7-trioxabicyclo[2,2,2]octane (OBO)
ester anion 154 to the PMB-protected WA 150 furnished ketone 155. Highly stereoselective reduction with lithium triethylborohydride, followed by MEM protection and hydrolysis afforded the acid 151. It is the simplicity of each step, the higher overall yield, and the high enantiomeric purity of the intermediates that lead to 149, that attest to the efficiency and conciseness of this methodology using WA functionality.

Scheme 36

3.3 Use in Industry on Kilogram Scale

Prominent attention has been paid to the advantages associated with the WA by industry. Several synthetic schemes aiming at large-scale operation have made good use of the WA in one form or another.90–93 Merck’s continuous interest in compound 156, and the synthetic efforts towards this product in the last few years, finely illustrate the confidence that industry has in the use of the WA functionality on a multi-kilogram scale (Scheme 38).90 Compound 156, which surfaced as a developmental candidate for HIV protease inhibition, was targeted for synthesis through two disconnections, A and B, in the oxazole segment of the molecule. For disconnection A, the Boc-protected α-aminoketone 157 was required as one of the basic building blocks along with 158.

Realizing that, because of the presence of an exchangeable amino proton in the starting WA, the use of Boc- or Cbz-protected amino WA 159, en route to the synthesis of the α-protected aminoketone 157 (as a representative example) would necessitate the use of at least two equivalents of Grignard or organolithium reagent, the Merck group systematically developed a very practical solution that completely prevented the waste of expensive and difficult-to-obtain nucleophiles.90a Various α-Boc-amino WAs were treated with a little less than one equivalent of isopropylmagnesium chloride for removal of the acidic N-H proton prior to the reaction with one equivalent of the desired Grignard reagent. This pre-deprotonation strategy allowed for a convenient and practical synthesis of the amino ketone 157 that was required for the synthesis of target compound 156. This was achieved on a nine-kilogram scale and hence accelerated their synthetic program.90b The strategy is general and not restricted to synthesis of 157 alone, as various other α-Boc-amino ketones have also been synthesized on a multi-kilogram scale.90c

The stereoselective synthesis of taraanabant (160; Scheme 39), a drug targeted at Merck for the treatment of obesity, serves as a second example to illustrate the use of the WA functionality on a multi-kilogram scale.91 For the synthesis of tanaanabant, envisaged to take place through the coupling of an amine and a carboxylic acid fragment, the convenient availability of the amine 161 became imperative. Methyl ketone 162 was prepared in nearly quantitative yield on an 11.5 kilogram scale from acid 163a via WA 163b. The enantioselective reduction of ketone 162 via dynamic kinetic resolution under basic conditions at
room temperature using Noyori’s catalyst [(xyl-BI-NAP)(DAIPEN)RuCl₂] afforded the desired diastereoisomer of the alcohol 164 in 94% ee and 8:1 dr.

The commendable task of synthesizing sixty grams of discodermolide, an anticancer compound produced by the rare Caribbean sponge Discodermia dissolute, through 39 steps by the Novartis team over a period of two years presents yet another fine example wherein the WA functionality has been used in a multi-kilogram product synthesis. The synthetic scheme adopted by Mickel’s team at Novartis incorporated the best features of the syntheses reported for discodermolide by Smith and Patterson. The cornerstone of the hybrid approach was the WA building block 165 (Scheme 40). It allowed for the synthesis of three major fragments: C1–C6, C9–C14 and C15–C21. Smith’s approach to 165 from Roche ester 166 was optimized by Mickel et al. into a more efficient route capable of delivering 28 kilograms of 165.

To avoid workup problems, lithium borohydride was used instead of lithium aluminum hydride for reducing the conveniently available PMB-protected derivative 166 of Roche ester 166, to arrive at alcohol 168. A two-phase 2,2,6,6-tetramethylpiperidine N-oxyl and bleach oxidation of 168 in dichloromethane furnished the requisite aldehyde 169 in quantitative yield for a subsequent Evans syn-aldol reaction. It was directly used without purification, to avoid possible racemization at the stereogenic center. Enolization of 170 with dibutylboron triflate in the presence of triethylamine at 0 °C followed by treatment of the resulting enolate with aldehyde 169 at −78 °C furnished alcohol 171 in 46–55% yield on a 20–25 kilogram scale. As trimethyl aluminum is pyrophoric, its use in large plant-scale operations was avoided despite its great success in transamidation on such scales.

Although use of trisobutylaluminum in conjunction with DMHA hydrochloride was safe for effecting the conversion of 171 into the desired WA 165 on a multi-gram scale, the high exothermicity of the reaction, coupled with the fear of any accidental cooling failure, remained a major safety concern. Finally, cleavage of the oxazolidinone with hydrogen peroxide and lithium hydroxide afforded the corresponding acid 172, isolated as its crystalline (R)-2-phenylethylamine salt. Starting with 34 kilograms of this salt, 28 kilograms of WA 165 were obtained through activation of the acid with isobutylchloroformate and reaction with DMHA.

The large-scale synthesis of the lactone 173, an immediate precursor for the hydroxyethylene dipeptide isoter 174, by Urban et al. at Pfizer tops the list of examples demonstrating the scalability of reactions that involve the use of DMHA.

The targeted synthesis of the desired lactone 173 was envisaged to take place through the use of ketone 175 as a key building block, because of the availability of a successful and convenient procedure for the analogues ketone 175 in the literature, based on the use of WA functionality. Diederich and Ryckmann had accomplished the synthesis of 175 by the coupling of...
WA 176b derived from N,N-dibenzylyphenylalanine with 2-(1,3-dioxanyl)ethylmagnesium bromide 177b. Although the initial attempts to combine WA 176a with the preformed Grignard reagent 177b in tetrahydrofuran gave at best traces of the desired ketone 175a, their switching to a Barbier-type procedure and prior deprotonation of the amide N-H, using either methylmagnesium bromide or benzylmagnesium chloride as a sacrificial base, enabled preparation of this ketone 175a on a scale of more than 200 kilograms. The Barbier-type procedure involved addition of 2-(2-bromoethyl)-1,3-dioxane (177a) to a stirred mixture of WA 176a and magnesium turnings in tetrahydrofuran at \(-10\,^\circ C\). Addition of one equivalent of methylmagnesium bromide prior to the addition of 177a effected the necessary deprotonation.

![Figure 7](image_url)

**Figure 7** Pfizer’s use of WA on a scale of more than 200 kg

### 3.4 Synthetic Equivalents and Building Blocks

\(\alpha,\beta\)-Unsaturated WA structural units, which allow not only the synthetic manipulations associated with \(\alpha,\beta\)-unsaturated systems but also those innate to the WA, have been easily assembled using Wittig\(^{178}\) Horner–Wadsworth–Emmons\(^{178b,c}\) or Julia-based\(^{179a}\) synthetic equivalents 178, 179 and 180 respectively (Scheme 41). In an alternative approach, alkyl halides have been converted into the \(\alpha,\beta\)-unsaturated WAs using N-methoxy-N-methyl-2-(phenylsulfinyl)acetamide (181)\(^{179c}\) as the reagent. The obtained \(\alpha,\beta\)-unsaturated WA is predominantly or exclusively \(E\)-configured. For the dominant formation of \(Z\)-configured \(\alpha,\beta\)-unsaturated WA units, Ando’s N-methoxy-N-methyl(diphenylphosphono)acetamide (179b)\(^{179d}\) and Deslongchamps’ N-methoxy-N-methyl[bis(2,2,2-trifluoroethyl)phosphono]acetamide (179c)\(^{179d}\) have been very useful. Both 179b and the sterically more demanding analogue 179d\(^{179d}\) are very useful with alkyl aldehydes, whereas with aromatic aldehydes, reagent 179c is superior.

The incorporation of \(\alpha,\beta\)-unsaturated WA structural units using the synthetic equivalents mentioned in Scheme 41 has been exploited in many synthetic endeavors.\(^{95}\) Recent efforts by Chida’s group towards A-315675, an anti-influenza agent from the Abbott Laboratories, serve as a representative example (Scheme 42).\(^{96}\) This target compound contains a highly functionalized pyrrolidine core with a cis-propenyl group as well as four contiguous stereogenic centers including a vicinal diamino moiety and a tertiary ether function. These unique structural features are not only crucial for A-315675’s biological activity as an anti-influenza agent, but also offer a great synthetic challenge. The vicinal diamino moiety was stereoselectively constructed by a cascade Overman rearrangement in 182. The \(Z\)-selective Horner–Wadsworth–Emmons olefination envisaged for incorporating the \(\alpha,\beta\)-unsaturated WA structural unit in the key building block 183 relied upon the use of Ando’s reagent, 179b.

![Scheme 41](image_url)

**Scheme 41** Various reagents for \(\alpha,\beta\)-unsaturated WAs

![Scheme 42](image_url)

**Scheme 42** Recently, olefin cross-metathesis using ruthenium carbene complex 184 developed by Grubbs was also found to enable access to the \(\alpha,\beta\)-unsaturated WA structural unit (Scheme 43).\(^{97a}\) Terminal alkynes with N-methoxy-N-methylacrylamide (185) under the influence of Grubbs’
catalyst 184 and a boron-based Lewis acid as additive furnished the α,β-unsaturated WA in low to moderate yields (24–53%). This approach has been used for the preparation of starting substrate 187b from 187a for the synthesis of substituted benzoxacycles 186 via a domino ortho-alkylation–Heck-coupling sequence.97b

A similar advantage was observed during cyclopropanation of α,β-unsaturated WA (Scheme 45) for indirect access to α,β-cyclopropyl ketones, particularly when well-documented direct cyclopropanation of α,β-unsaturated ketones failed.99 It is believed that the oxygen atom of the methoxy group in the WA, through its inductive effect, is the key to the facile Michael addition of dimethylsulfoxonium ylide 193 onto 194a that took place in one hour at 50°C to yield 90% of 195, because similar attempts of cyclopropanation on the dimethyl analogue substrate 194b under the same conditions resulted in only 76% conversion, even after 48 hours. In addition, no cyclopropanation occurred with the N-hydroxy analogue 194c when it was treated with two equivalents of 193. Presumably, this was because the first equivalent of 193 abstracts the proton from the hydroxy, thereby increasing the electron density on nitrogen and decreasing the electron-deficient nature of the double bond.

The α,β-unsaturated WA structural unit has shown unique reactivity in two ways. In light of the fact that α,β-unsaturated aldehydes and ketones are poor substrates for asymmetric dihydroxylation (AD) processes, the facile reactivity in two ways. In light of the fact that (DHQ)2PHAL was required to achieve good turnover rates. The modified AD-mix-α containing (DHQ)2PHAL was required to achieve good turnover rates.

The concept has been used for the gram-scale synthesis of enantiomerically pure 2-methylglycerol acetonide building blocks (S)-188 and (R)-189 using 2-methylprop-2-enoic acid WA 190 as the starting substrate.98b These building blocks further enabled convenient access to the O-benzyl-2-methylglycidol derivatives (S)-191 and (R)-192.

The α,β-unsaturated WA structural unit allows for Michael addition with nitrogen-centered nucleophiles. From the successful diastereoselective hetero-Michael addition of lithium (S)- or (R)-N-allyl-N-α-methylbenzylamide to α,β-unsaturated WA disclosed by the Davies research group,100 the product β-aminoamide 196 has opened up many possibilities for chiral β-amino ketones and aldehydes (Figure 8).

In the first report,100a lithium (S)-N-allyl-N-α-methylbenzylamide was added to 197 to obtain (3S,αS)-hexanamide building blocks further enabled convenient access to the O-benzyl-2-methylglycidol derivatives (S)-191 and (R)-192.

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196 in 65% yield and greater than 95% de. Reduction of WA 196 with diisobutylaluminum hydride to the aldehyde and subsequent Wittig reaction furnished diene 198 in 62% yield over two steps, in greater than 95% de. Finally, ring-closing metathesis produced the N-protected cyclic amine 199 in 91% yield, which, after hydrogenation and treatment with hydrochloric acid furnished (S)-conine hydrochloride (200) in 95% yield.

Troin, while exploring the addition of 201 on cinnamic acid derived WA 202a, observed some major difficulties. It failed to furnish any product arising from Michael reaction. Instead, being a strong base, 201 effected demethoxylation of WA 202a, presumably by an E2 pathway, to afford 202b in an isolated yield of 71%. An extra step in Figure 9 not only allowed circumvention of this difficulty, but also ensured immediate and convenient access to the WA group. The diastereoselective conjugate addition of 201 onto 202c in tetrahydrofuran at –78 °C afforded ester 203a in an excellent yield of 94% (de >94%). The ester functionality was converted into WA group. The diastereoselective conjugate addition of 201 onto 202c in tetrahydrofuran at –78 °C afforded ester 203a in an excellent yield of 94% (de >94%). The ester functionality was converted into WA 203b, using a combination of DMHA hydrochloride and trimethylaluminum, in high yield (90%). The Cbz-protected WA 204 served as a building block for the asymmetric synthesis of 1,3-aminoketals 205, and 2-monosubstituted and 2,6-disubstituted piperidines 206.

![Figure 9](image)

An alternative approach to β-amino ketones using the WA functionality stemmed from an observation made during the addition of vinylmagnesium bromide to a WA (Scheme 46). In the anticipated α,β-unsaturated ketone, the reactive acryloyl unit could not possibly facilitate the Michael addition of the liberated DMHA, and hence furnished β-N-methoxy-N-methylamino ketones 207. This observation, made by Gomtsyan and others, has thus enabled the development of a direct route to β-amino ketones. In the developed route, after the initial addition of vinylmagnesium halide, a secondary amine is deliberately added; this amine successfully competes with DMHA, or the corresponding magnesium amide 208, during Michael addition to furnish β-amino ketones 209.

However, successful incorporation of the acryloyl unit through the addition of vinylmagnesium bromide onto WA 210, without any Michael addition problem from the liberated DMHA, is also possible; this was accomplished during the synthesis of compound 211 en route to the total synthesis of lasonolide.

![Scheme 46](image)

The successful addition of the N-methoxy-N-methylacetamide potassium enolate (212) onto N-sulfinyl imines 213 by the Davis research group is another approach taken to incorporate WA functionality and thereby assemble the important scaffold, N-protected β-amino WA 214, which itself is capable of delivering N-protected β-amino ketones or aldehydes (Scheme 47). N-Sulfinyl β-amino WA 214, despite the presence of the acidic sulfonamide proton, reacts with various organometallic reagents to afford the corresponding N-protected β-amino carbonyl compounds in good yields. The utility of these new β-amino carbonyl compounds has been illustrated by the con-

![Scheme 47](image)
Recent studies by Davis and co-workers have shown that of the four possible diastereoisomers, the syn-α-substituted β-aminoWA 216a is the major product.\textsuperscript{102c} Although the \(E\)-geometry of the enolate and chair-like transition state accounts for the preponderance of the syn-product, the geometry of the enolate during the reaction conditions could not be independently confirmed.

Building block 217, easily available by a simple synthetic scheme starting with fumaroyl chloride (218a), attempts to combine the strengths of \(N\)-acyliminium chemistry and WA functionality (Scheme 48). It contains the requisite precursor moiety for generating an \(N\)-acyliminium ion and thereby allowing addition of a variety of π-nucleophiles as illustrated here by the use of allytrimethylsilane. Subsequent diastereoselective double addition of a variety of Grignard reagents furnishes a new strategy for the synthesis of the β-amino alcohol structural scaffold 219.\textsuperscript{103}

The WA-based building block 220a was obtained from the corresponding acid, \(\alpha\)-(tert-butyl) \((S)-N\)-(tert-butyl)carboxylyasarpartate, using the Wernic procedure\textsuperscript{\textsuperscript{10b}} involving activation with (benzotriazol-1-yl-oxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP·PF\textsubscript{6}) and subsequent reaction with DMHA in presence of triethylamine. WA 220a has been the most practical and immediate source for (\(S\))-aspartate semi-aldehyde 220c via the protected precursor 220b (Scheme 49). This aldehyde 220c, which exists in the hydrated form, has a prominent role in a variety of biochemical studies.\textsuperscript{104a,b} Aldehyde 220b and its higher homologue 221b, obtained from the glutamyl WA 221a in a similar manner, have been subjected to the Wittig reaction for stereoselective synthesis of allyl and homoallyl glycines 222 \((n = 1\) and \(n = 2\) respectively).\textsuperscript{104c} The side-chain modification in the aspartyl and glutamyl residues through the aldehyde has been also achieved on solid support.\textsuperscript{104d} Similarly, the \(N\)-and side-chain-protected aspartyl and glutamyl WAs have served as convenient building blocks for the corresponding aldehydes. Reduction of the amides with bulky hydrides such as lithium tri-\(\text{tert}-\)butoxyaluminum hydride or lithium tris[(3-ethylpent-3-yloxy)aluminum hydride (LTEPA) proceeded better than reduction with the conventional lithium aluminum hydride.\textsuperscript{104e} Various Boc-protected natural and unnatural \(\alpha\)-amino acids have been converted into the corresponding aldehydes using this approach.\textsuperscript{104f}

Another WA-based building block from the domain of \(\alpha\)-amino acids is that derived from serine \(\alpha\)-amino acid 223a (Scheme 50). Three \(N\)-protected serine derivatives 223b–d have been converted into the corresponding WAs 224b–d by standard protocols.\textsuperscript{105} The lowered acidity of the \(\alpha\)-proton enabled convenient displacement of the \(\beta\)-hydroxy group by the azide nucleophile through the mesylate intermediate, whereas a similar attempt on the ester led to the exclusive formation of eliminated product 225. The availability of \(\beta\)-azido-substituted WA derivatives 226b–d on a multi-gram scale opened up avenues for successful nucleophilic addition that had not been possible until then. Utilization of this short reaction sequence now allows for the synthesis of \(\alpha,\beta\)-diamino acids.
The use of 224b as a template has paved the way for an elegant and straightforward synthesis of sphinganines, represented here by compound 227; further protection of 224b presented two other serine-derived WAs, 228 and 229, as valuable building blocks (Scheme 51). Use of all three of these was explored in the synthesis of 227. It is obvious that 224b, with its two exchangeable protons, would necessitate the use of multiple equivalents of tetradecyllithium, and would thus be unacceptable when the organolithium reagent is expensive or difficult to prepare. Use of two equivalents of either n- or sec-butylmagnesium chloride, as a sacrificial base prior to the addition of tetradecyllithium, circumvented the excess use of the latter and furnished the desired ketone 230 in yields ranging from 63 to 78%. Unfortunately, despite the advantage that WA 228 is easily available from 224b, and its use for the same objective requires only one equivalent of sacrificial base, the obtained ketone 230 was contaminated with inseparable and unidentified impurity. Also, since 229 does not react with long-chain organometallic reagents, the approach starting from 224b is the most practical.

![Scheme 51](image)

Scheme 51

Given the importance of the fluoro analogues and in a bid to increase the potency of molecules important in biology, regioselective aldol reaction of fluoroacetone with aldehydes has been visualized as an effective technique, in principle, to introduce fluorine into the molecule (Scheme 52). The aldol reaction of fluoroacetone (231a) with aldehyde 232 under basic conditions using lithium diisopropylamide, or sodium or potassium hexamethyldisilazide, however, is not trivial and has failed to furnish any of the aldol product 233 or 234. In and indirect and interesting pathway, the carbanion obtained from α-fluoro WA 231b using lithium diisopropylamide reacted cleanly with 232, furnishing the intermediate 235 in high yields. Further addition of methylmagnesium bromide provided easy access to the aldol product 234. The other regioisomer, 233, was obtained through the addition of boron enolate of fluoroacetone (231a) onto aldehyde 232. The formation of boron enolate involved the use of dibutylboron triflate in the presence of Hüning’s base (diisopropylethylamine, DIPEA).

![Scheme 52](image)

Scheme 52

In an attempt to obtain pharmacologically important γ-alkyldenebutenolides 236 through an approach based on condensing dicarbanion of 1,3-dicarbonyl compounds with simple oxalic acid dielectrophiles (Scheme 53), the reactions of 237 with oxalyl chloride 238a, diethyl oxalate 238b and 1,4-dimethylpiperazine-2,3-dione 238d failed to furnish the desired product. However, the dianion 237 from ethyl acetoacetate reacted cleanly with the bis-WA of oxalic acid (238c) and afforded the desired product 236 in 75% yield. This clear success and the observed regioselectivity were rationalized through the possible formation of the chelated intermediate 239, which could be possible only with 238c.

![Scheme 53](image)

Scheme 53

The bromoalkanoic acid derived WAs represent yet another small building block capable of appending the WA functionality as part of a synthetic objective. The bromoacetic acid WA 240a, readily available from the α-bromoacetyl bromide, has been used by Palomo109a and others106 as a nucleophilic synthon, through a Reformatsky addition procedure under zinc-mediated conditions (Scheme 54). The β-hydroxy WA 241 and its β-trimethylsilyloxy counterpart are masked aldol products capable of further derivatization into β-hydroxy aldehydes and ketones. An attempt to obtain nonracemic aldol product 241, through the influence of chiral 1,2-amino alcohols as ligands un-
The 3-bromopropanoic acid, 5-bromopentanoic acid and 6-bromohexanoic acid derived WAs 240b–d have been used as electrophilic synthons. WA 240b was used in the synthesis of unsymmetrical 1,4-diketones 242\textsuperscript{109c} and β-(N,N-disubstituted)amino ketones 243\textsuperscript{109d} (Scheme 55). For the synthesis of the former, the key step involved alkylation of various aryl and heteroaryl α-aminonitriles with 240b followed by addition of the Grignard reagent to the alkylated product 244 and unmasking of the carbonyl group under acidic hydrolytic conditions. For the latter, various secondary amines were first alkylated with 240b, then subsequent Grignard addition onto 245 furnished the β-amino ketones 243.

The WAs 240c and 240d have served as valuable starting substrates enabling convenient synthesis of pyrimidinones 246a and 246b that contain the WA functionality (Scheme 56).

Alkylation of the potassium salt of ethyl cyanoacetate (247) with 240c and 240d and subsequent reaction with the free base of guanidine (248) under basic conditions gave the desired pyrimidinones 246a and 246b, respectively. The protection of the amine groups, followed by reaction with aryl- or heteroarylthiums, furnished a convenient access to a series of simplified α-keto heterocycles 249 for glycaminide ribonucleotide transformylase (GARTfase) inhibition studies.

One of the most extensively used building blocks containing the WA functionality is that derived from tartaric acid (Figure 10). The 2,3-O-isopropylidene-1,4-bis-WAs 250 and 251 are extremely important, particularly when the 1,4-carboxylate residues on the tartaric acid are to be differentiated.

The conveniently accessible diester, (−)-dialkyl 2,3-O-isopropylidene-L-tartrate 252\textsuperscript{110} and its enantiomer 253\textsuperscript{111} from D-(−)-tartaric acid have been converted into the corresponding bis-WAs 250\textsuperscript{112} and 251\textsuperscript{113} on treatment with DMHA hydrochloride in presence of trimethylaluminum.

Although convenient access to C\textsubscript{2}-symmetric 1,4-diketones was known to be possible through the addition of Grignard reagents onto WA 250\textsuperscript{112}, it was the systematic study by McNulty that unraveled the importance of experimental conditions and the potential of 250 for further synthetic exploitation (Scheme 57).\textsuperscript{114}

Mono-addition of simple alkyl groups through Grignard reagents furnished the ketoamide 254 in good isolated yields when the bis-amide 250 was treated with one equivalent of R'MgX at temperatures ranging from −78 to 22 °C. Use of large excess of R'MgX led to a straightfor-
ward synthesis of symmetrical diketone 255, and stepwise addition of Grignard reagents led to unsymmetrical diketone 256.

Using this precedence, various ketoamides 254 were recently prepared by Prasad and co-workers and these products were subjected to stereoselective reduction for an efficient entry into the synthesis of various classes of natural products. Representative examples of the ketoamides prepared and used, along with the targeted natural product, are depicted in Scheme 58. In the targeted syntheses, the first operation on the keto amide was the stereoselective reduction of the keto group in the ketoamide 254, followed by acetone removal and concomitant cyclization, has paved the way for an efficient strategy to γ-alkyl(aryl)-α,β-dihydroxybutyro lactones 263.\[115f\]

**Scheme 57** Use of ketoamide 254 in the synthesis of various natural products

Bruckner et al.\[116\] used the keto amide 258 (Scheme 59) on a multi-gram scale for Wittig olefinations with stabilized ylides 264 and 265 in their novel strategy towards the butenolide moiety of peridinin. The WA functionality apparently should afford direct access to the requisite aldehyde 266 and 267 needed for the synthetic endeavor, but the presence of the α,β-unsaturated ester probably deterred direct reduction with lithium aluminum hydride.

The authors used eight equivalents of sodium borohydride to selectively reduce the WA functionality in 268 and 269 to obtain the corresponding alcohols 270 and 271; these products were then re-oxidized under Swern conditions to arrive at 266 and 267. It is worth noting that reduction of the WA to the alcohol in the presence of the ester seems to be the first such observation.

In contrast to the formation of keto amides, the formation of C2-symmetric ketones 255 using excess amounts of RMgX or RLi was simple and straightforward (Scheme 60). Excellent use of various C2-symmetric 1,4-diketones 255 has been made in variety of synthetic endeavors and the most prominent and extensive among them originates from Prasad’s laboratory.\[117a–e\] A variety of C2-symmetric 1,4-diketones, obtained from building block 250, provided an efficient strategy for the enantioselective synthesis of α-O-benzylated aldehydes 272.

**Scheme 59**

**Scheme 60**

The highly stereoselective reduction of the Cγ-symmetric diketone 255 at low temperatures using L- or K-Selectride was the key reaction in the strategy for the synthesis of α-O-protected aldehydes. The α-O-benzylated aldehydes 272a–d (Scheme 61) have served as a building block for the synthesis of (+)-exo-brevicomin,\[117a\] (−)-muricatacin,\[117b\] the (−)-acid fragment of (−)-microcarpalide\[117c\] and (−)-disparlure.\[117d\] Stereoselective reduction of the diketo...
tone 273, followed by protection of the resulting hydroxy groups and functionalization of the alkenyl residues, led to a new strategy for preparing the tetrahydropyran framework of (–)-centrolobine (274; Scheme 62) through an iron(III) chloride mediated cyclization of the 1,5-diol unit.\textsuperscript{117c}

Scheme 61  Utility of C\textsubscript{2}-symmetric diketone 255

The symmetrical diketone 275, prepared by the addition of the magnesium salt of THP-protected propargylic alcohol to 250, has provided convenient access to the tetrahydroxy-substituted ten-membered cyclic enediyne structure 276\textsuperscript{118} (Scheme 63) through a series of functional group manipulations and a pinacol-type ring closure on the bis-aldehyde 277 using Pederson’s vanadium(II) reagent.

Strategies involving oxidative cleavage of the diol unit after synthetic operations on the carbonyl groups have also yielded valuable building blocks. C\textsubscript{2}-Symmetric 1,4-diaryl diketones 278 have been used for the synthesis of α-methoxyxylactic acids\textsuperscript{119a} α-methyl-α-methoxyxylactic acids\textsuperscript{119b} and TADDOL analogues\textsuperscript{119c} (Scheme 64). It is important to note that one can also use bis(N,N-dimethylamide) 279 instead of 250 for the convenient synthesis of 280 and 281.\textsuperscript{120}

Scheme 64

Scheme 65

Hydrolysis of the acetal unit in C\textsubscript{2}-symmetric 1,4-diketones 282, followed by dioxolane protection of the carbonyl groups and subsequent oxidative cleavage, provides a convenient route to protected α-keto aldehydes 283 (Scheme 65).\textsuperscript{121}
Finally, in our own research, we have developed several WA-based synthetic equivalents for specific objectives. Although the initial development of these was driven by a specific objective, their use is wide open to the imagination. Among those developed, two – 280 and 240b – have already been discussed; the others are shown in Figure 11.

![Figure 11](image)

**Figure 11** Various WA-based synthetic equivalents developed in our research program

N-Methoxy-N-methyl-2-phenylsulfonylacetamide (284), easily obtained by the reaction of the sodium salt of phenylsulfinic acid with α-chloro-N-methoxy-N-methylacetamide,122a was developed for use in the two-carbon homologation of alkyl halides.122b Successful alkylation of 284 with various alkyl halides under the mild conditions of potassium carbonate in N,N-dimethylformamide, followed by reductive desulfonylation with sodium amalgam and reduction of the WA to the aldehyde, renders 284 equivalent to an acetaldehyde carbanion. Given the fact that aldehydes with α-stereocenters do have the potential to epimerize while effecting two-carbon homologation with Wittig-based reagents, the approach with 284 is important and necessary in the domain of carbohydrates.

Two-carbon homologations of various iodides (Scheme 66) have been realized. That of the three-configured iodide 291 enabled the efficient synthesis of 4,5-O-isopropylidene-protected L-rhodinose,123 an important and necessary in the domain of carbohydrates. The erythro-configured iodides 293 and 294 have been used in the synthesis of another trideoxy sugar, D-amicetose.124

The dithiolane- and dithiane-based carboxamides 285 and 286 derived from glyoxylic acid represent novel synthetic equivalents for an α-dicarbonyl unit with opposing polarities (Scheme 67).125 They have been conveniently prepared on gram-scale as crystalline solids through an initial acid-catalyzed thiketalization of the aldehyde group in glyoxylic acid with ethane-1,2-dithiol or propane-1,3-dithiol and subsequent conversion of the carboxyl group into the WA. Nucleophilic addition onto the WA in 285 or 286 followed by alkylation provided a new strategy for the synthesis of the targeted mono-protected β-diketones in moderate to good yields. An interesting application of this new protocol was the successful synthesis of 6-(2-methyl-1,3-dithiolan-2-yl)-2,3,4,5-tetrahydropyridine (295), a dithioacetal-protected derivative of the important target molecule 296, a tautom of a compound responsible for the bread flavor. The requisite carbon skeleton to arrive at compound 295 was easily assembled in good yields by nucleophilic addition of 4-(2-tetrahydropyranoloxy)butylmagnesium bromide on 285 followed by methylation at C2 position to furnish 297. Further functional group interconversion gave convenient access to the azido ketone 298 as a key intermediate which underwent phosphine-mediated cyclization affording the target 299.

![Scheme 66](image)

**Scheme 66** Alkylation of sulfone 284 with various sugar halides

Recently, the development by our research group of the three synthetic equivalents 287, 288 and 289 using commercially available p-toluic acid was triggered by the importance of FTY-720 (299) as an immunosuppressant, currently in phase III clinical trials (Scheme 68).125 These synthetic equivalents for the central core of 299 have enabled incorporation of the polar head group through Julia, Wittig and Horner–Wadsworth–Emmons reactions and also provided an excellent handle, in the form of the WA functionality, for complete control over the length of the lipophilic side chain. All the reactions and conditions en route to the target molecule are simple.

![Scheme 67](image)

**Scheme 67**
and good-yielding and therefore hold significant promise for industrial application. The olefination of protected tris-aldehyde 300 with either 288 or 289 using three equivalents of potassium carbonate in a 1:3 mixture of N,N-dimethylformamide and tetrahydrofuran at 70 °C yielded product 301 as the E-isomer in 70 or 60% yield, respectively. The same reaction using Wittig salt 287 afforded the desired product 301 accompanied by its Z-isomer (E/Z = 1:3) in 70% yield. However, a simple hydrogenation of the E/Z-product mixture makes the formation of geometrical isomer with 287 inconsequential. The addition of n-heptylmagnesium bromide onto 301 and 302 furnished the ketones 303 and 304 in 70% yields, which on reduction using sodium borohydride and subsequent hydrogenolysis afforded the target compound 299 in good yields.

The reagent N-methoxy-N-methyl-N'-phenylsulfonylglycinamide 290, derived from glycine (305) in two steps is a crystalline solid with unlimited shelf-life. It has served as a useful template for the general synthesis of 4-aryl-1,2,3,4-tetrahydrosquinoine derivatives 306 (Scheme 69).126 N-Benzylation, followed by nucleophilic addition of ArMgX onto the WA group furnished the penultimate precursor 307 for derivatives 306. Although the N-phenylsulfonyl group in 290 offers a robust protection and also facilitates the desired alkylation, the use of other easily removable protecting groups on nitrogen should further enhance the significance and the potential of this glycine-derived WA building block.

4 Miscellaneous

The successful synthesis of resin-bound amines 308, 309, and 310 equivalent to DMHA (Figure 12) has made available all the convenience and advantages associated with solid-phase synthesis. In amine 308, the solid support is anchored to the oxygen, whereas in amines 309 and 310, the solid support is tethered to the nitrogen.

N-Acylation on amines 308–310 affords the corresponding solid-supported WAs 311–313 (Figure 13). These anchored WAs have enabled convenient access to N-Boc amino aldehydes 314, from α-amino acids, and α-acyl-amino-α,α-disubstituted ketones 315. Until the synthesis of 316 by Tanner et al., there were no examples in the literature of using lithiated alkenes and heterocyclic compounds as nucleophiles in the reaction with solid-supported WAs.

Very recently, an unusual and interesting product arising from the sequential treatment of the glycine-based WA 317a with lithium disopropylamide and phenylmagnesium bromide led to an efficient protocol for the α-arylation of glycine (Scheme 70).128 The observation of the...
demethoxylated product 318a is not surprising as it arises merely from an E2 elimination reaction, as observed by Graham.7a It was the formation of 318b that hinted towards the possibility of α-arylation. With the use of O-(tert-butyl) WA 317b, wherein the elimination reaction is completely circumvented, similar sequential treatment with lithium diisopropylamide and phenylmagnesium bromide furnished an α-arylated amide 319 as the exclusive product in 86% isolated yield. Expulsion of the tert-butoxide anion from the initially formed enolate 320 seems to be the key step which generates the iminium ion 321 and allows for the facile addition of various aryl residues as nucleophiles. This new chemistry of the WA functionality is likely to bring a new dimension to its further exploration.

Another important and interesting functional group interconversion effected using the WA functionality is its one-pot conversion into a terminal alkyne (Scheme 71) with the use of the Bestmann–Ohira reagent (322).129 The WA is first reduced to the aldehyde using disisobutylaluminum hydride, which in the same pot reacts with 322 under mild conditions (K,CO3, MeOH, r.t.). The reaction affords the corresponding terminal alkyne 323 in good yields, ranging from 71 to 88%, and with complete preservation of stereochemical integrity at the α-stereocenter.

From Pohl’s research group, the synthesis of (R)-3-hydroxyalkanoic acids 324, an important class of biologically active compounds, using (S)-3-hydroxy-β-butyrolactone as the starting building block, illustrates the only use of the WA functionality as a protecting group (Scheme 72).130 The benzyl-protected lactone ring 325b, when opened using DMHA, afforded WA 326 in 87% yield. The amide functionality served as masked carboxy group during the Parikh–Doering oxidation of the primary hydroxy, the Wittig reaction on the aldehyde, and finally the hydrogenation. Although the WA served as a rugged protection during these three steps, its hydrolysis and subsequent release of the free carboxy group was not all that straightforward. Conventional heating of 327 in aqueous methanol (1:1) in the presence of potassium hydroxide (2 N) failed to furnish the product; however, under microwave irradiation at 130 °C and 90 psi, the product was obtained in 20 minutes and in 87% yield.

5 Conclusion

The stability of the WA functionality, its ease of preparation, the scalability of its reactions and its predictable reactivity are the four main reasons for the increasing confidence that synthetic organic chemists have with regard to the use of the WA in various synthetic endeavors. The development of new building blocks and synthetic
equivalents based on the WA functionality will provide solutions to the existing problems or hurdles in synthetic schemes that aim at large and important objectives of great significance in any field of science. The use of the WA in functional materials has yet to be explored, but the four aspects mentioned above are bound to further inspire and motivate.

References

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(b) Hall, B. J.; Sutherland, J. D. Tetrahedron Lett. 1998, 39, 6593.
}
The hydrobromide salts of N-methoxy-N-methyl-α-aminocarboxamides were prepared from the corresponding Boc or CBz derivatives by deprotecting them using HBr/AcOH and precipitating their salts in diethyl ether; see reference 71a.

CBz derivatives by deprotecting them using HBr/AcOH and carboxamides were prepared from the corresponding Boc or CBz derivatives by deprotecting them using HBr/AcOH and precipitating their salts in diethyl ether; see reference 71a.

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CBz derivatives by deprotecting them using HBr/AcOH and carboxamides were prepared from the corresponding Boc or CBz derivatives by deprotecting them using HBr/AcOH and precipitating their salts in diethyl ether; see reference 71a.

CBz derivatives by deprotecting them using HBr/AcOH and carboxamides were prepared from the corresponding Boc or CBz derivatives by deprotecting them using HBr/AcOH and precipitating their salts in diethyl ether; see reference 71a.


