RESEARCH ARTICLE doi.org/10.1002/adsc.202100964

Advanced Synthesis & Catalysis

Single Electron Transfer-Induced Selective α-Oxygenation of Glycine Derivatives

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Manuscript received: August 3, 2021; Revised manuscript received: October 13, 2021;
Version of record online: October 27, 2021

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202100964

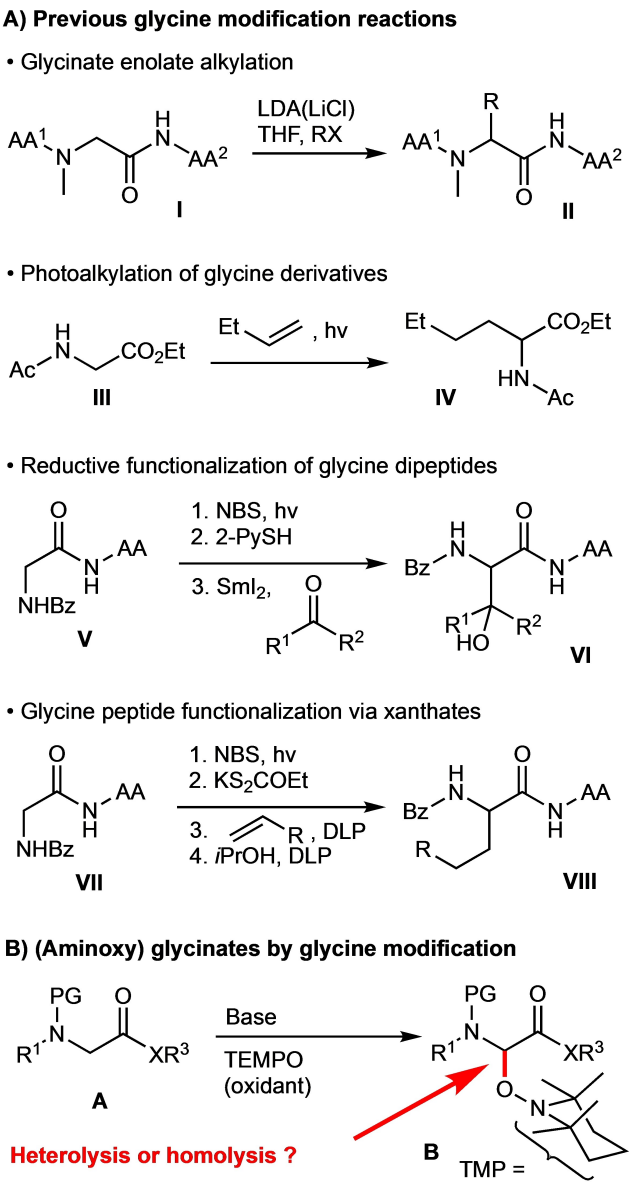
Abstract: Modification of amino acids is an important strategy in organic and bioorganic chemistry. In contrast to common side-chain functionalization, backbone modification is much less explored. Especially glycine units seem to be attractive and versatile since a wide range of functionality can be potentially introduced. We report here oxidative modification of glycinates that are stable and enable further functionalization. Selective glycinate enolate oxidation by TEMPO or a $FeCp_2PF_6$/TEMPO reagent combination provides stable alkoxyamines in good to excellent yields. The methodology is expanded to glycine-containing dipeptides demonstrating selective oxygenation at the glycine unit. The orthogonal reactivity potential of oxygenated glycines for transformation to other amino acid derivatives is explored.

Keywords: Oxygenation; Glycine; Single electron oxidation; TEMPO; Alkoxyamines

Introduction

Proteins are vital biopolymers for sustaining life. Nature uses a conserved set of amino acids to provide a vast space of protein structures. Further optimization for function can occur by directed evolution,[1] by chemical modification of existing peptidic structures[2] or by de novo peptide synthesis using modified precursors leading to foldamers and related structures.[3] Chemical modifications of peptides and proteins help to understand the crucial structural factors determining their function or may lead to new functional roles. Specifically, modification of natural amino acids can be classified into two basic strategies: (i) modification at the side chain and (ii) modification at the peptide backbone by selective introduction of side chains. Side-chain functionalization has been well explored by a multitude of typical reactions for most heteroatom-bearing amino acids; for inert aliphatic and aromatic amino acids, metal-catalyzed cross-coupling reactions are currently actively explored.[2,4]

Backbone modification is a promising strategy, since variable functionality can be introduced and the structural changes are profound. Especially glycine modification is attractive and therefore, various methodologies to achieve selective side-chain introduction have been developed in the past (Scheme 1.A). Seebach and coworkers pioneered glycine enolate chemistry and applied it extensively,[5] culminating in the site-selective alkylation of the immunosuppressive cyclic undecapeptide, cyclosporine A, at a sarcosine subunit **I**,[5c] whereas Kazmaier and colleagues targeted glycine enolates via the enolate-Claisen rearrangement and palladium-catalyzed cross-coupling reactions.[2e,6] Radical-based methodology was more rarely applied, but gained recently more importance.[7] The UV light-



Scheme 1. A) Modification of glycine derivatives for introduction of side chains in peptides. B) Proposed oxygenation of glycine derivatives as tool for peptide modification. Py = 2-pyridyl.

mediated alkylation of *N*-acetylglycine ethyl ester **III** or derived peptides with terminal alkenes or toluene to obtain norleucine derivatives **IV** constituted one of the first methods for radical amino acid modification, but selectivities were moderate.[8] Easton and colleagues studied the relative stability of amino acid radicals and found that secondary glycyl radicals are more stable than tertiary radicals, formed from valine or alanine,[9] which is attributed to their particular geometry as well as the captodative effect. This selectivity for glycine derivatives was applied in photobromination reactions with NBS to obtain bromoglycine derivatives. An important application of this method was reported by Skrydstrup *et al.* who employed glycine photobromination in peptides **V** as a handle for nucleophilic substitution reactions as well as reductive transformations with samarium diiodide generating glycine enolates, which served as nucleophiles toward carbonyl compounds providing β-hydroxy-α-amino acid-containing peptides **VI**.[10a] Since halo glycine derivatives are not stable, the Hiemstra/Speckamp[10b] and Skrydstrup[10c] groups used more stable glycinyl xanthates **VII**, which serve as precursors for thermal radical addition reactions providing diverse substituted amino acids or dipeptides **VIII**. However, the efficiencies drop significantly for tripeptides. Recently, N-arylglycinates also gained importance as glycinyl radical[2d] or formally cationic glyoxylate imine precursors,[11] but these compounds are not applicable in peptides.

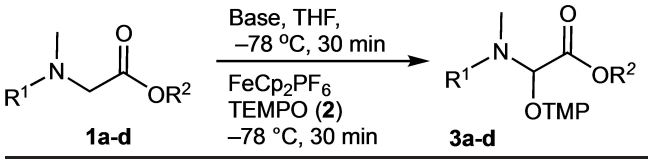
We hypothesized that appropriately protected (aminoxy) glycine derivatives **B** may be valuable precursors for protein backbone modification (Scheme 1.B). We envisaged to approach them by developing anion-radical crossover methodology using enolates derived from glycine derivatives **A** and couple them by photocatalyzed[12] or thermal oxidative electron transfer[13] with persistent radical TEMPO. Unknown oxygenated glycine derivatives **B** constitute at the same time glycinyl radical as well as glycinyl cation surrogates, since the C–O bond might be homolytically or heterolytically cleaved and thus may serve as precursors for radical or polar reactions by choosing proper conditions. Indeed, we demonstrated recently that diketopiperazine-derived alkoxyamines homolyse at temperatures as low as 70 °C.[14]

Herein, we report a single-step approach to diverse oxygenated glycine and sarcosine derivatives by single electron transfer-induced enolate oxygenation. The conditions are applicable to epimerization-free oxygenation reactions of dipeptides. Orienting investigations toward radical or polar transformations as well as cycloadditions are presented.

Results and Discussion

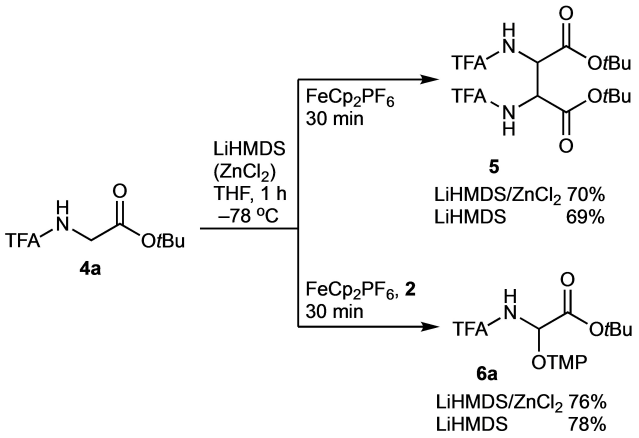
Initially N-protected sarcosine derivatives **1 a–c**, which were synthesized from sarcosine methyl ester hydrochloride, were briefly investigated. Deprotonation by hindered amide bases, subsequent single electron oxidation by ferrocenium hexafluorophosphate and oxygenation with persistent radical TEMPO (**2**) at −78 °C provided aminoxy sarcosinates (**3 a–c**) (Table 1, entries 1–5). The reaction is little if at all dependent on the counter ion and lithium enolates (entries 1,2,4) as well as potassium enolates (entries 2,5) are applicable with similar efficiency. A number of common nitrogen protecting groups can also be used. The methodology was extended to L-valine-sarcosine dipeptide **1 d**, synthesized by coupling

Table 1. Oxygenation of sarcosine derivatives **1**.[a]



Entry	1	R^1	R^2	Base	3	Yield
1	**a**	Boc	Me	LiHMDS	**a**	82%
2	**a**	Boc	Me	LDA	**a**	79%
3	**a**	Boc	Me	KHMDS	**a**	82%
4	**b**	Bz	Me	LiHMDS	**b**	82%
5	**c**	Cbz	Me	KHMDS	**c**	65%
6	**d**	*N'*-Boc-L-Val	*t*Bu	KHMDS	**d**	76%[b]

[a] General conditions: Base (1.2 equiv.), **1** (1.1 equiv.), THF, −78 °C, 30 min, **2** (1 equiv.), Cp_2FePF_6, 30 min.
[b] Isolated as a 2 : 1 *syn/anti* diasteromeric mixture (*vide infra*).



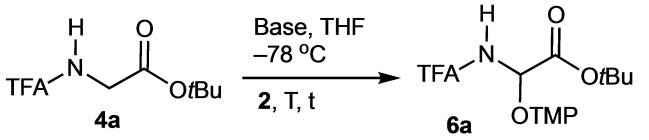
Scheme 2. Dimerization and oxygenation of glycine ester **4a** with $FeCp_2PF_6$ as single electron oxidant.

N-Boc-L-valine and sarcosine *tert*-butyl ester hydrochloride (see the SI), and oxygenated dipeptide **3d** was obtained in 76% yield as 2 : 1 diastereomeric mixture (Table 1, entry 6). Significantly, the valine unit had a free NH function, which was deprotonated but not oxygenated, and the stereocenter at the valine unit was not compromised.

The applicability of a N–H-containing function in dipeptide **1d**, raised the question whether glycine derivatives can also be directly oxygenated via their enolates and whether the stoichiometric oxidant ferrocenium hexafluorophosphate can be replaced by photocatalytic oxidative conditions. Initially the redox potential of the zinc enolate of *N*-trifluoroacetyl glycine *tert*-butyl ester (**4a**) generated by deprotonation under Kazmaier's conditions by LiHMDS in the presence of anhydrous zinc chloride[15] was determined by cyclic voltammetry to +0.34 V (irreversible) vs. the saturated calomel electrode, indicating facile oxidation by most photocatalysts. Subjecting the zinc enolate of **4a** to a variety of oxidative photocatalytic conditions did not lead to radical-derived products (see the SI for a survey). To learn the reasons for this failure and whether SET oxidation is possible at all, ferrocenium hexafluorophosphate was applied as oxidant, which triggered smooth single electron oxidation at −78 °C and dimerization of the resulting radicals providing a 1:1 diastereomeric mixture of amino aspartate derivative **5** (Scheme 2). The corresponding N,C-dilithium amide enolate also underwent the oxidative coupling reaction smoothly in 69% yield. Performing the oxygenation in the presence of TEMPO (**2**) under similar conditions resulted in clean formation of alkoxyamine **6a**.

However, much to our surprise a control experiment in the absence of the ferrocenium salt or a photocatalyst showed that the zinc enolate of **4a** was oxidized and oxygenated directly by TEMPO to give the alkoxyamine **6a** albeit only in 52% yield at 0 °C. (Table 2, entry 1). Increasing the amount of **2** to 2.2 equivalents led to an increase of the yield to 97% (entry 2). Lowering the temperature to −78 °C under these conditions led only to a very slow reaction. The corresponding dilithium amide enolate was equally applicable with similar rate providing oxygenated glycinate in almost quantitative yield (entry 3). The more reactive disodium or dipotassium enolates can also be used with similar outcome (entries 4,5), but 0 °C remains optimal as the oxygenation is slow at −78 °C as shown for the dipotassium amide enolate (entry 6). For practicality reasons, KHMDS solution was used subsequently for all further experiments. It must be mentioned that sarcosine derivatives **1a** and **1b** were unreactive under these conditions and the starting material was recovered after quenching (not shown).

Table 2. Optimization of α-aminooxygenation of **4a** using **2** as oxidant and oxygenating reagent.[a]



Entry	Base	**2** (equiv.)	T (°C)	t (h)	**6a**
1	$ZnCl_2$, LiHMDS	1.1	0	1	52%
2	$ZnCl_2$, LiHMDS	2.2	0	1	97%
3	LiHMDS	2.2	0	1	97%
4	NaHMDS	2.2	0	1	92%
5	KHMDS	2.2	0	1	92%
6	KHMDS	2.2	−78	4	30%

[a] General conditions: Base (2.5 equiv.), THF, −78 °C, 30 min, **2**, 0 °C, 1 h.

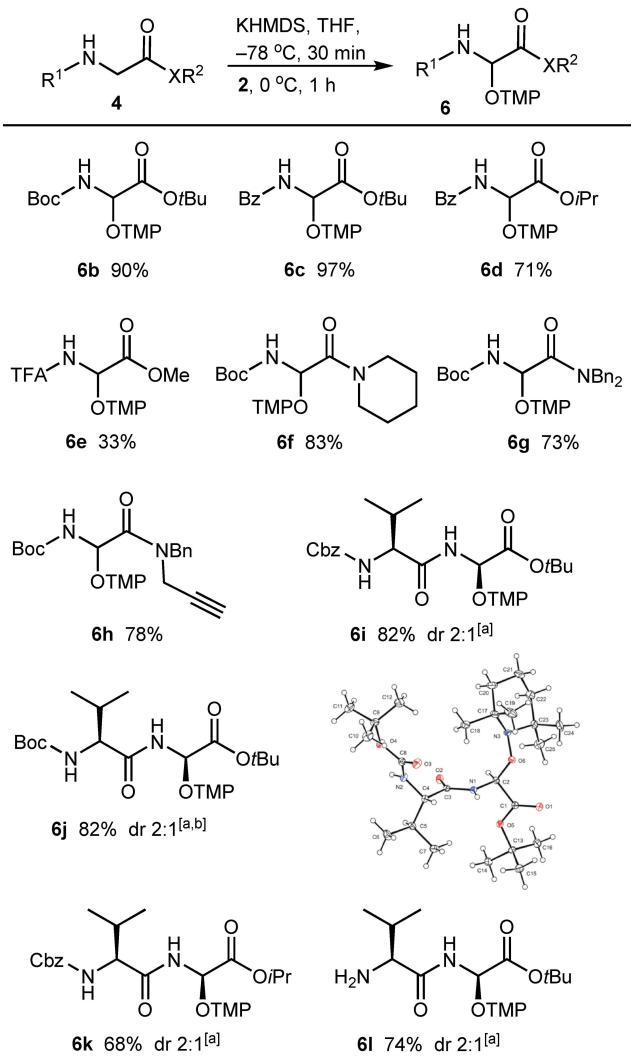


Chart 1. α-Oxygenation of glycine derivatives **4**. General conditions: KHMDS (2.5 equiv.) for **4b–h**, (3.3 equiv.) for **4i–l**, –78 °C, 30 min, **2** (2.2 equiv.), 0 °C, 1 h. [a] Major (S^{Val},R^{Gly}) diastereomer shown. [b] X-ray crystal structure of minor (S^{Val},S^{Gly})-**6j**. Displacement ellipsoids are drawn at 30% probability level.

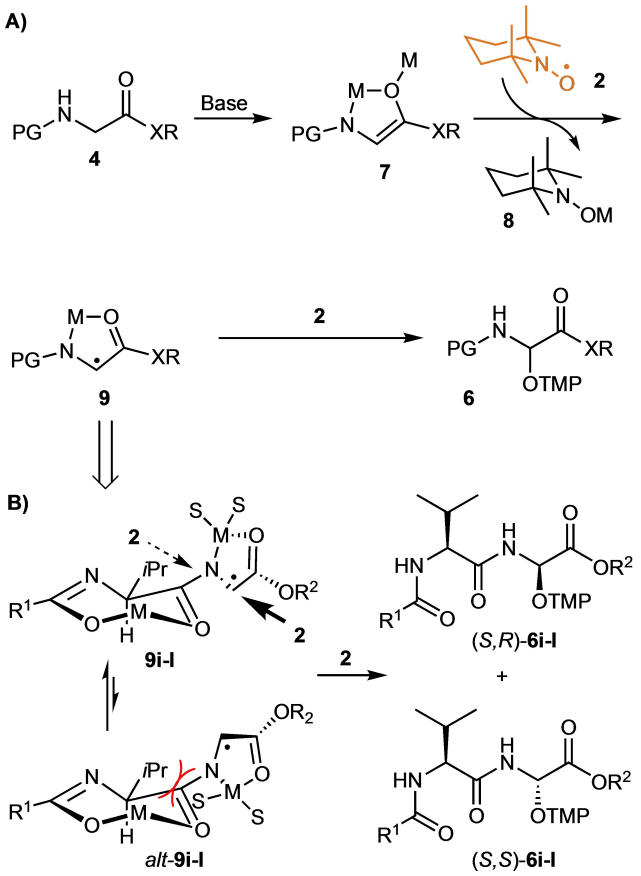
The scope of the oxygenation reactions is wide (Chart 1). Glycine *tert*-butyl esters **4a–c** and isopropyl ester **4d** provided oxygenated glycinates **6a–d** in very good yields, but methyl esters are not well suited for the oxygenation reactions as exemplified for oxygenation product **6e** since enolate decomposition was observed. Glycine amides afforded oxygenated derivatives **6f–h**, which are suitable starting materials for further functionalization reactions (*vide infra*). L-Valine-containing dipeptides **4i–l** with C-terminal *tert*-butyl or isopropyl glycinate units (synthesis see the SI[16]) required a third equivalent of base for deprotonation of the N–H function at valine, but furnished good yields of oxygenated dipeptides **6i–l** as partially separable 2:1 (S^{Val},R^{Gly})/(S^{Val},S^{Gly}) diastereomeric mixtures. α-Oxygenation of the zinc and titanium enolates of dipeptide **4i** was also investigated because potential chelation of the metal ions may change the diastereoselectivity. The zinc enolate of dipeptide **4i** reacted reproducibly much more sluggishly than that of glycinate **4a** (*cf.* Table 2, entry 2) and oxygenated product **6i** was isolated in 42% yield (35% recovered starting material). The titanium enolate was oxygenated at even slower rate accompanied by significant decomposition and gave 35% yield (10% recovered starting material). The 2:1 (S^{Val},R^{Gly})/(S^{Val},S^{Gly}) diastereoselectivity of both reactions was very similar to that of the lithium or potassium enolates.

Typical N-protecting groups, such as Boc, Cbz, benzoyl or trifluoroacetyl were applicable in the oxygenation reactions providing derivatives **6a–k** in very good yields. However, the Fmoc group was cleaved under the basic reaction conditions, giving dipeptide **6l**. Thus, Fmoc-protected peptides may be used if oxygenated peptides with free N-terminal amino groups are desired for further functionalization. The dipeptide *N'*-Boc-Val-Gly-OMe **4n**, analogous to **4j** (see the SI), decomposed under the reaction conditions further demonstrating that methyl esters are not applicable under the reaction conditions. It is noteworthy that a secondary glycinamide **4m** failed to undergo the oxygenation reaction because enolization did not take place (See the SI for details).

The minor (*S,S*) diastereomer of **6j** crystallized and its configuration was unequivocally established by X-ray crystallography. Investigation of oxygenated dipeptide **6j** by HPLC at a chiral stationary phase with reference to racemic standard confirmed that no epimerization occurred during deprotonation/oxygenation (See the SI). The configurations of **6i,k,l** as well as that of oxygenated dipeptide **3d** (*vide supra*) were assigned by analogy.

Aminoxy glycinates **6** display remarkable stability under ordinary conditions. Despite being hemiaminals, they can be purified by chromatography without losses. The aminoxy dipeptides **6** do not show tendencies to epimerization neither during the oxygenation reaction nor during purification or storage. To verify stability against epimerization at the valine α-carbon during deprotonation and oxygenation under the basic reaction conditions dipeptide **4j** was deprotonated by a larger excess of KHMDS (4.4 equiv.) at −78 °C and subjected to oxidation by **2**. The product displayed the same specific optical rotation thus suggesting that deprotonation at the valine α-carbon did not take place.

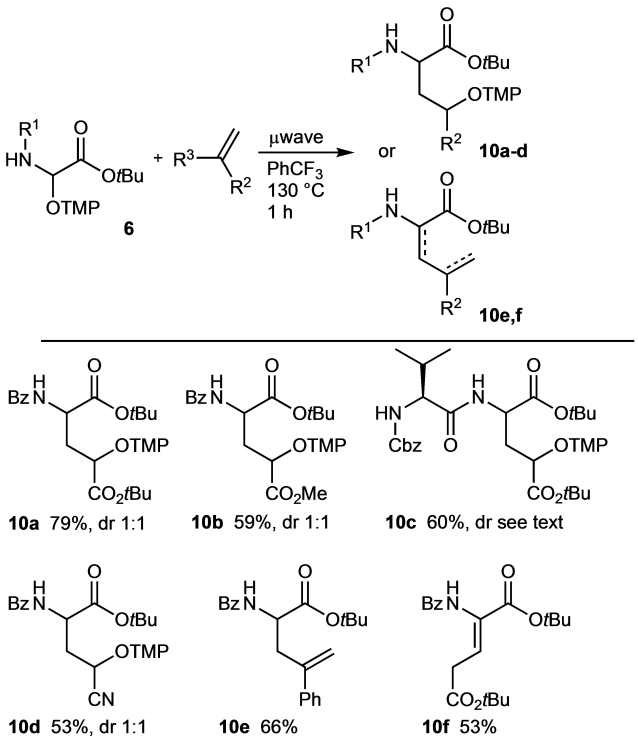
The results for oxygenation of glycine derivatives **4** vs. those of sarcosine **1** differ significantly in that for sarcosine oxygenation an external oxidant, ferrocenium hexafluorophosphate, is mandatory as observed before for most major carbonyl classes,[13] whereas for glycinates **4** TEMPO (**2**) has a dual function as very mild oxidant and oxygenating reagent (Scheme 3.A). The decisive factor for TEMPO serving as oxidant is the additional negative charge on the nitrogen atom



Scheme 3. A) Mechanism for the formation of aminoxy glycinates **6**; B) Rationalization of the oxygenation diastereoselectivity in dipeptides **6i–l**. S = coordinated solvent THF.

after deprotonation to amide enolate dianions **7**. These chelated extremely electron-rich species have in contrast to other enolates a significantly lower redox potential (*vide supra*) and are thus prone to donate an electron to the weak electron acceptor **2** leading to piperidine N-oxide **8** and chelated radical anions **9**, which smoothly couple with excess **2** providing aminoxy glycinates **6**. The diastereoselectivity of the oxygenated dipeptides **6i–l** can be rationalized by assuming chelated glycinate radical anions **9i–l**, which are connected to a chelated seven-membered amide unit at the neighboring valine unit resulting from deprotonation of the N–H function by a third equivalent of base (Scheme 3.B). The chair conformation places the bulky isopropyl substituent in an equatorial orientation thus shielding the α-face of the glycinate radical anion **9i–l**. Therefore, radical coupling with TEMPO (**2**) will proceed predominately from the more accessible β-face. The conformer *alt*-**9i–l** with inverted five-membered chelate should not play a significant role since it suffers from steric interactions between the solvated metal center and the isopropyl group; moreover, dipole moments are better aligned in intermediates **9i–l** than *alt*-**9i–l**.

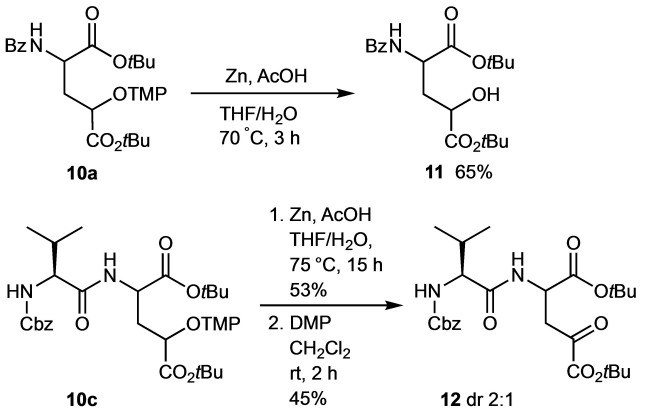
Aminoxy glycinates **6** are versatile precursors for further transformations. Intermolecular radical addition of alkoxyamines **6c,i** to methyl or *tert*-butyl acrylates as well as acrylonitrile based on the persistent radical effect[17] succeeded under microwave conditions in α,α,α-trifluorotoluene at 130 °C providing protected modified amino diacid derivatives **10a–d** (Scheme 4). Oxygenated glutamate derivatives **10a,b,d** were obtained as 1:1 diastereomeric mixtures. They were accompanied by small amounts of thermal elimination products, such as **10f**. Dipeptide **10c** was formed as an inseparable mixture of four diastereomers in an approximately 2:2:1:1 ratio, which indicated that radical addition takes place with similar diastereoselectivity as oxygenation and that coupling of the adduct radical is unselective (*vide infra*). If the resulting alkoxyamine is thermally labile as in the addition to α-methylstyrene selective elimination took place furnishing allylglycinate **10e**. If the temperature of the radical addition of glycinate **6c** to *tert*-butyl acrylate was raised to 150 °C, dehydroglutamate derivative **10f** was selectively obtained in 53% yield as a single (*Z*)-diastereomer as determined by a ROESY experiment. These results indicate that alkoxyamine derivatives **6** might serve as precursors for nitroxide-mediated living radical polymerization reactions providing chain end amino acid-functionalized polymers. In contrast, sarco-



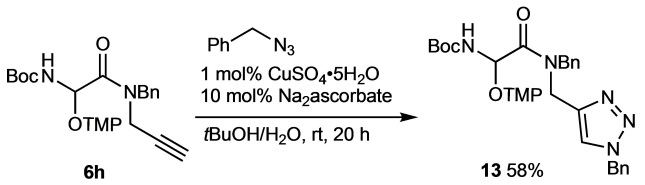
Scheme 4. Thermal intermolecular radical addition reactions of glycine alkoxyamines **6**.

sine alkoxyamines **3a,b** were unreactive under these conditions and not unexpectedly 1-octene did not react with alkoxyamines **6** (not shown).

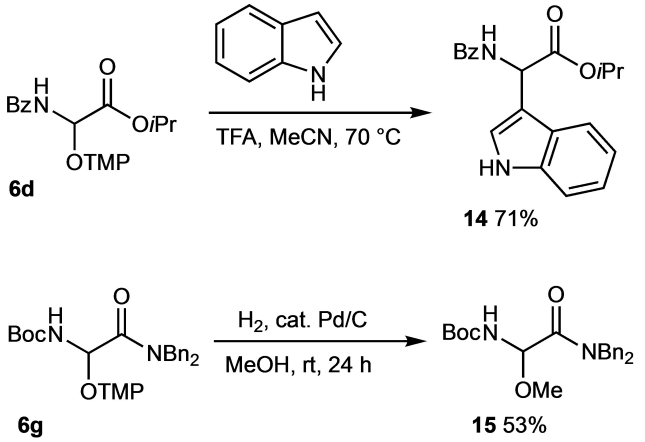
The protected alcohol function in compound **10a** was liberated by reductive cleavage of TEMPO with zinc in acetic acid yielding alcohol **11** in 65% yield as 1:1 diastereomeric mixture (Scheme 5). Deprotection of the alkoxyamine function in dipeptide **10c** and subsequent Dess-Martin oxidation provided a 2:1 diastereomeric mixture of valine-4-oxoglutamate di-



Scheme 5. Removal of the alkoxyamine unit in compounds **10a,c**.



Scheme 6. Click reaction of N-propargyl alkoxyamine **6h** with benzyl azide.



Scheme 7. Heterolytic reactions of aminoxy glycinates **6d** or **6g**.

peptide **12** in unoptimized 24% yield over the two steps.

Aminoxy glycinates **6** are also applicable in cycloaddition or polar reactions. Huisgen-Sharpless click reactions of N-propargylamide **6h** with benzyl azide in the presence of Cu(I) furnished triazole derivative **13** (Scheme 6). Such reactions may serve to couple various biomolecules with alkoxyamine-functionalized amino acids.

Aminoxy glycinates **6** represent hemiaminal derivatives, which are glycine cation surrogates. Indeed, a Friedel-Crafts-type reaction of **6d** with indole proceeded smoothly in the presence of stoichiometric amounts of trifluoroacetic acid providing nor-tryptophan derivative **14** in 71% yield (Scheme 7). However, *tert*-butyl esters are not applicable in this reaction because of competitive ester cleavage (See the SI). Moreover, the exchange of the tetramethylpiperidinyloxy group for a methoxy group was unintentionally observed during attempted hydrogenolysis of glycine *N,N*-dibenzylamide **6g** in methanol affording methoxy glycinate **15** in moderate yield; *N,N*-dibenzylglycine amide **4g** was, however, also formed in 10–20% yield indicating that hemiaminal reduction competes to some extent with alkoxide exchange, but both processes are faster than intended benzyl group hydrogenolysis. The exchange reaction works similarly if the reaction was performed under a nitrogen atmosphere in the absence of dihydrogen (See the SI).[18] Thus, polar coupling reactions are attractive by exchange of the alkoxyamine unit by C–C and C–O bond formation reactions.

Conclusion

In summary, we have accomplished high-yielding α-oxygenation reactions of glycine and sarcosine derivatives by single electron enolate oxidation and coupling with persistent radical TEMPO. The electron rich amide enolate dianions generated by deprotonation of glycinates or glycinamides are oxidized even by very weak single-electron oxidant TEMPO, thus stronger external oxidants are not necessary. The oxygenation reactions were extended to C-terminal glycine dipeptides. The glycine unit was selectively oxygenated without compromising the stereochemistry at the N-terminal amino acid residue. The obtained aminoxy glycine derivatives **6** proved to be stable under ordinary conditions. Moreover, they are polyfunctional and the individual functionalities can be selectively and orthogonally addressed in radical, polar or cycloaddition reactions, which results in non-natural amino acid derivatives. The results bear many implications for applications of these oxygenated amino acids, since modifications of peptides, coupling with biomolecules and polymers may be envisaged, which might lead to

new functions or materials. Investigations along these lines are underway in these laboratories.

Experimental Section

General procedure for α-oxygenation of glycine derivatives: KHMDS solution (1.1 mL, 1.1 mmol, 1 M in THF) was added dropwise to a solution of glycine derivative **4** (0.44 mmol) in THF (3 mL) at −78 °C and the mixture was stirred for 30 min. TEMPO (151 mg, 0.98 mmol) was added, the solution was warmed to 0 °C and stirred for 1 h. The reaction was quenched by addition of a few drops of sat. NH_4Cl solution, the mixture was filtered through a short pad of Celite®, which was washed with EtOAc. The solvent was removed at reduced pressure and the crude product was purified by column chromatography (10% EtOAc/cyclohexane) to obtain the α-oxygenated glycinates (**6a**–**6l**).

CCDC 2047587 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

*This work was generously funded by the Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences (RVO: 61388963), the Gilead Sciences & IOCB research center and the European Regional Development Fund; OP RDE; Project: Chemical biology for drugging undruggable targets (ChemBioDrug) (No. CZ.02.1.01/0.0/0.0/16_019/0000729). I.C. thanks the Ministry of Education, Youth and Sports of the Czech Republic (MSM0021620857) for financial support. We thank Dr. Radek Pohl for performing the ROESY experiment on **10f**. N.V. thanks Charles University in Prague for a stipend. The reported results are part of her projected PhD thesis.*

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