Site-selective Cu-catalyzed Alkylation of α-Amino Acids and Peptides toward the Assembly of Quaternary Centers

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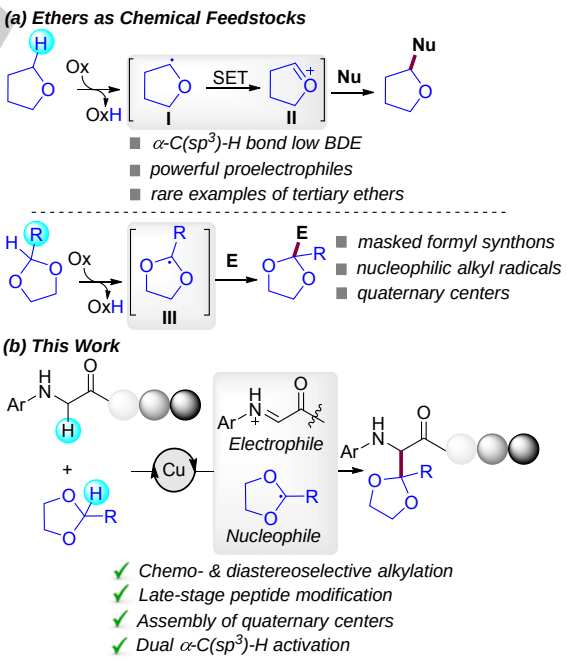
Abstract: A novel Cu(I)-catalyzed selective α-alkylation of α-amino acid and peptide derivatives with 2-alkyl-1,3-dioxolanes is reported. This oxidative coupling is distinguished by its site-specificity, high diastereoselectivity, chirality preservation and exhibits entire chemoselectivity for *N*-aryl glycine motifs over other amino acid units. Collectively, the method allows for the assembly of challenging quaternary centers as well as compounds derived from natural products of high structural complexity, which illustrates its ample opportunities toward the late-stage functionalization of peptides.

α-Amino acids constitute the core backbone of peptides and proteins and rank among the most widespread building-blocks in organic synthesis and chemical biology.[1] In fact, they are prevalent motifs in a sheer number of drugs with a broad spectrum of biomedical applications. Owing to the enhanced biological activities and often improved pharmacokinetic properties exhibited by unnatural amino acids and peptides derived thereof, the recent years have witnessed an increased interest in the site-specific chemical modification of peptides.[2] In this regard, transition-metal catalysis has recently unlocked new paradigms for the site-selective C–H functionalization of α-amino carbonyl compounds. Most of the latter relied on the modification (arylation and alkynylation) of specific side chain C–H bonds within cysteine, tryptophan or alanine containing-peptides via organometallic intermediates.[3] Despite the recent advances realized, the available C–H functionalization portfolio in these endeavors mostly use expensive Pd catalysts and toxic halide-derived coupling partners. A distinct approach relies on metal-catalyzed cross-dehydrogenative couplings (CDCs)[4] occurring between α-C(sp^3)–H bonds of glycine derivatives and nucleophilic C–H coupling partners, hence allowing the modification of the amino acid backbone in a more sustainable manner.[5] However, this straightforward and atom-economical technique is rarely applied to the challenging site-selective modification of structurally complex peptide compounds. In this light, we envisioned that the introduction of novel C–H counterparts could increase its utility for the late-stage[6] functionalization of glycine-containing peptides, thus streamlining the rapid assembly of high-value biomolecules featuring the use of less explored earth-abundat metal catalysts.

Due to their chemical inertness as well as high prevalence in a high number of U.S. Food and Drug Administration (FDA) approved pharmaceuticals[7], the direct functionalization of α-C(sp^3)–H of cyclic ethers represents a challenging task of prime synthetic importance.[8] In the last years, their powerful use as proelectrophiles in CDC reactions has received a great deal of attention;[8] as a result, tetrahydrofuran (THF) and related ethers have been efficiently coupled with a variety of nucleophiles (Scheme 1, *route a*). The generally accepted mechanism involves a first hydrogen atom abstraction step to produce α-carbon-centered radical **I** prone to undergo a subsequent oxidation to the corresponding electrophilic oxonium cation **II** via a SET step (Scheme 1, *route b*). In this respect, we surmised that the reactivity of the transient alkyl radical species **I** could be enhanced by starting from a tertiary alkyl ether, thus favoring the formation of a strongly stabilized tertiary radical intermediate.[9] The latter could be presumably triggered by a kinetically competent electrophile instead of undergoing further oxidation to species **II**. If successful, such a conceptually simple strategy would result in the virtually unexplored formation of a quaternary center. So far, the use of substituted ethers for the construction of quaternary carbon centers have been overlooked in organic synthesis and only scattered examples of oxidative functionalization of α-C(sp^3)–H of tertiary ethers with olefins have been reported.[10]



Scheme 1. CDCs with ethers and α-amino acid derivatives.

A particular class of oxygen heterocycles are 2-substituted-1,3-dioxolanes, which represent inexpensive formyl equivalents and offer an attractive avenue for the formal introduction of a carbonyl

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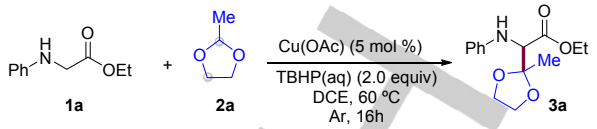
group into an organic compound. However, their conversion into the corresponding α,α-dioxy radicals **III** could be counterintuitive at first sight due to: (a) the sterical hindrance of the group in C2 and (b) the regioselectivity issues between C2 and C4 position of the dioxolane (Scheme 1, *route a*).[9] We anticipated that the judicious screening of the reaction parameters together with the rational selection of the C2-substituent could exploit the inherent stability of a transient tertiary radical *vs* the secondary one. Accordingly, we envisioned that the use of open-shell intermediates upon SET events could unlock new reaction pathways not yet accomplished via polar-type scenarios. Herein we report a practical Cu-catalyzed site-selective alkylation of α-amino acids and peptides with 2-alkyl-1,3-dioxolanes toward the assembly of new fully substituted carbon centers. This method features the advantageous use of a cost-efficient Cu catalyst along with an aqueous solution of *tert*-butyl hydroperoxide (TBHP) to assist a challenging *in situ* dual activation of both C–H coupling partners.[11] Remarkably, our catalytic manifold is endowed with a large scope, operational simplicity, reaction scalability, high diastereoselectivity and preservation of the α-center chirality. Accordingly, it clearly broadens the scope of CDCs to produce molecular diversity from inexpensive biomass devoid of prefunctionalization in a selective and rapid manner.

Following our dual catalyst activation design principle, we selected the alkylation of the benchmark amino ester **1a** with commercially available 2-methyl-1,3-dioxolane (**2a**) as the model reaction. After careful optimization,[12] we found that the desired transformation was feasible and α-alkylated glycinate **3a** was obtained in 79% yield when a combination of Cu(OAc) as catalyst, an aqueous solution of TBHP as oxidant, and 1,2-dichloroethane as solvent was used (Table 1, entry 1). Importantly, undesired functionalization on the C4 site of the dioxolane was never observed, which evidenced that the methyl group in C2 did not hamper the process and that electronic factors dominated over the sterics on the corresponding hydrogen atom abstraction step. As expected, control experiments verified the crucial role of both copper catalyst and oxidant as not even traces of **3a** were detected in their absence (entries 2 and 3, respectively). Notably, an aqueous solution of TBHP was found superior than its analogue in decane (entry 4), which constitutes a practical bonus in terms of economics and sustainability; other oxidants such as O_2 (entry 5) or related peroxides[12] afforded substantially lower yields of **3a**. A variety of copper sources were tested (entries 8−11), and Cu(OAc) and $Cu(OAc)_2$ provided the higher yields. Likewise, the performance of the process with other metal sources (entries 12-14) or at distinct temperatures did not improve the reaction outcome.[12] Importantly, the reaction was amenable to scale-up to gram quantities in similar yields (entry 1) and even a low Cu-catalyst loading (3 mol %) led to the formation of **3a** in 75% yield.[12]

Table 1. Cu-catalyzed alkylation of **1a** with 2-methyl-1,3-dioxolane[a]



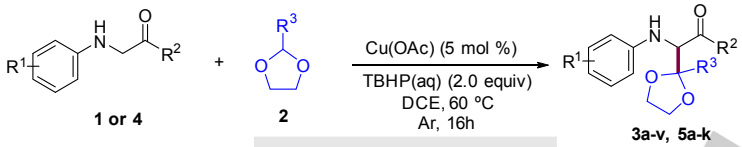
1a **2a** **3a**

entry	change from standard conditions	**3a** (%)[b]
1	none	79 (80)[c]
2	without Cu(OAc)	0
3	without TBHP(aq)	0
4	TBHP(dec) instead of TBHP(aq)	65
5	O_2 instead of TBHP(aq)	0
6	under air	68
7	without DCE	56
8	CuBr instead of Cu(OAc)	65
9	CuCl instead of Cu(OAc)	51
10	$Cu(OAc)_2$ instead of Cu(OAc)	79
11	$Cu(acac)_2$ instead of Cu(OAc)	69
12	$Fe(OAc)_2$ instead of Cu(OAc)	traces
13	$Co(OAc)_2$ instead of Cu(OAc)	traces
14	$Mn(OAc)_2$ instead of Cu(OAc)	traces

[a] Reaction conditions: **1a** (0.5 mmol), Cu(OAc) (5 mol %), TBHP(aq) (2.0 equiv), **2a** (0.5 mL), DCE (1.0 mL) at 60 ºC for 16 h under Ar. [b] Yield of isolated product after column chromatography. [c] Gram-scale reaction. TBHP (aq) = *t*BuOOH 70% in H_2O; TBHP (dec) = *t*BuOOH 5.0-6.0 M in decane.

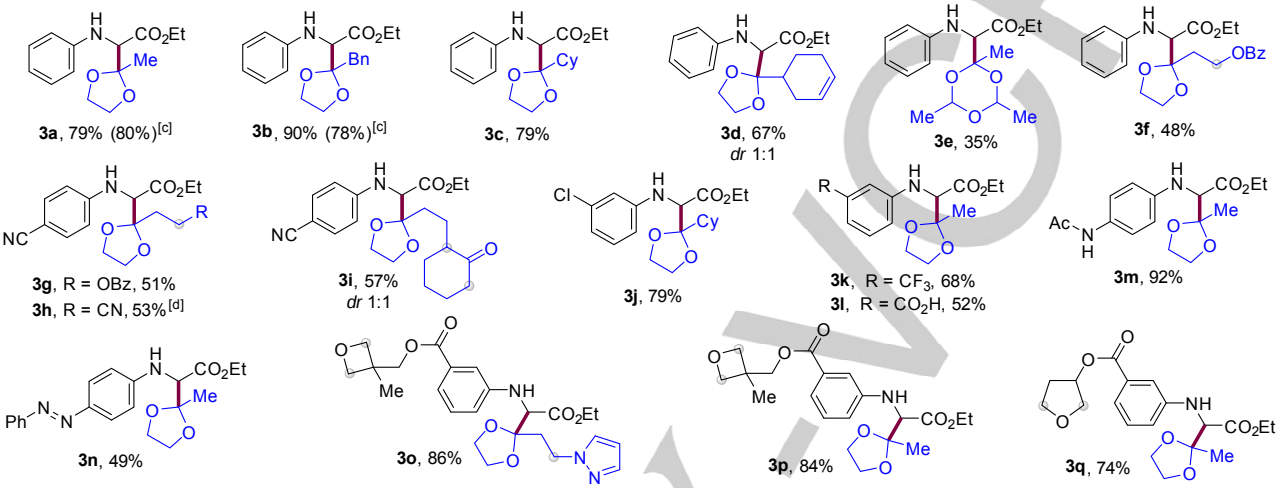
With the optimized conditions in hand, we next investigated the scope of the C(sp^3)–H alkylation protocol. With respect to the oxygen heterocycle, a wide variety of 2-alkyl substituted 1,3-dioxolanes smoothly underwent the target oxidative coupling in moderate to excellent yields.[13] Remarkably, dioxolanes bearing alkenes (**3d**) or oxidizable C(sp^3)–H bonds in adjacent position to benzylic positions (**3b**), ketones (**3i**), esters (**3f,g**), nitriles (**3h**)[14] or even a pharmaceutically relevant heterocyclic motif such as pyrazole (**3o**) were perfectly accommodated and were chemoselectively coupled by the C2 site of the dioxolane. Likewise, the alkylation was tolerant of a vast array of differently substituted *N*-aryl glycine esters with halides (**3j,k**), carboxylic acids (**3l**), esters (**3o-q**), ethers (**3o-q**), amides (**3m**)[15] and even sensitive azobenzenes (**3n**) being amenable to this oxidative alkylation. Of remarkable importance are **3o-q**, where high chemoselectivity was achieved toward the preferential activation of the dioxolane motif versus the C(sp^3)–H bonds adjacent to other biologically relevant cyclic ethers[7] such as oxetane (**3o,p**) and THF (**3q**). Not only glycine esters, but also other α-amino carbonyl compounds including α-amino ketones (**3t,u**) and amides (**3v**) could be selectively alkylated in moderate yields. Importantly, the alkylation of *N*-phenylglycinonitrile was also achieved; to the best of our knowledge, it represents the first example of a CDC with an α-amino nitrile compound (**3r,s**), which offers ample opportunities for further manipulation upon either hydrolysis or reduction reactions. The structure of **3r** was unambiguously assigned by X-Ray analysis.

Table 2. Cu-catalyzed C(sp^3)−H alkylation of α-amino carbonyl compounds[a,b]

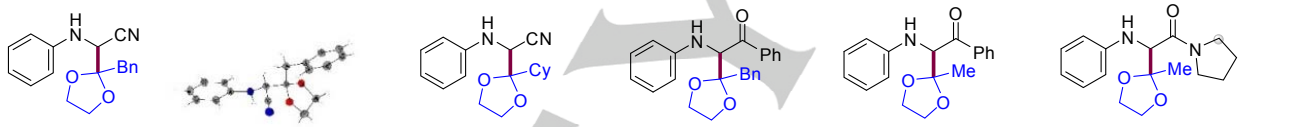


1 or 4 + 2 → 3a-v, 5a-k

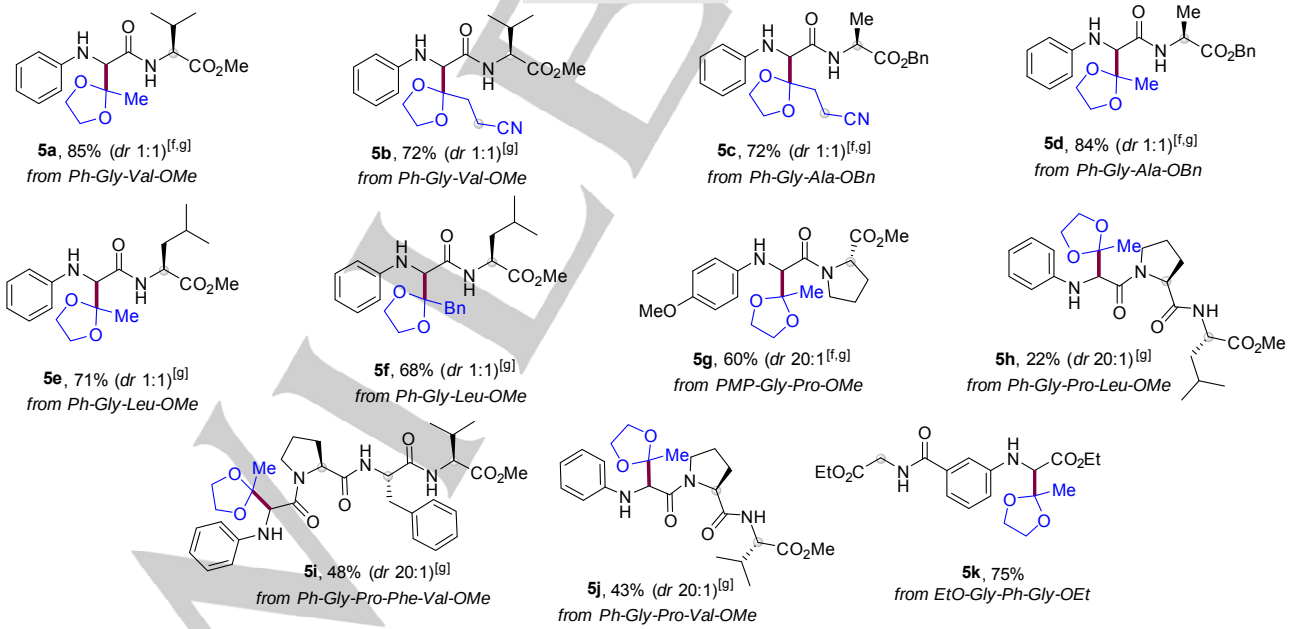
α-Amino Ester & Dioxolane Scope



α-Amino Carbonyl Derivative Scope



Short Peptide Scope



[a] As for Table 1, entry 1. [b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] Reaction performed at gram-scale. [d] Reaction performed at 80 °C. [e] Reaction performed with CuCl. [f] HPLC analysis verified the retention of the native chirality of the substrate. [g] *dr* value calculated by ^{1}H NMR.

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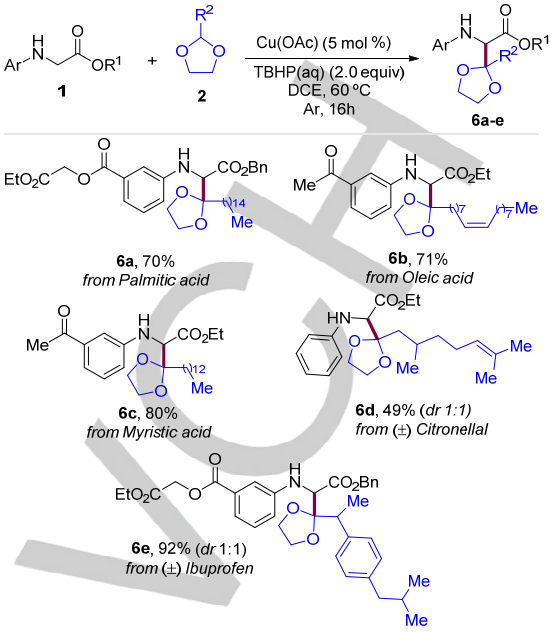
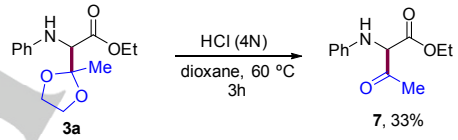
We subsequently examined our oxidative alkylation in the more complex setting of peptides, which are known to undergo oxidative fragmentations upon the formation of α-carbon radicals[16] and hence are often difficult to be selectively manipulated through oxidative processes. Notably, dipeptides containing Val (**5a,b**), Ala (**5c,d**), Leu (**5e,f**) and Pro (**5g**) units selectively underwent in good to high yields the alkylation on the terminal Gly unit, directed by the neighboring *N*-aryl group upon stabilization of the corresponding iminium-type intermediate. As verified by HPLC analysis, the oxidative alkylation proceeded with preservation of the α-center chirality.[12] Whereas dipeptides containing Val, Ala or Leu units afforded the corresponding products as diastereomeric mixtures (*dr* 1:1), the presence of a Pro residue resulted in a highly diastereoselective process (**5g**, *dr* 20:1). Although merely speculative, we hypothesized that owing to the rigidity of the Pro backbone, the alkyl radical species could attack the *in situ* formed iminium-type intermediate from its less sterically encumbered face, thus delivering stereochemically enriched derivatives.[17] The robustness of our method was further demonstrated by the site-selective functionalization of tri- and tetrapeptides in moderate to reasonable yields. It is worth noting that the presence of a Pro motif favored the alkylation to occur in a diastereoselective fashion (*dr* 20:1) in all cases (**5h-5j**), which underscores the high potential for Pro residues as key structural elements at the late-stage functionalization in complex peptides settings. Moreover, the oxidative alkylation exclusively occurred at the terminal Gly unit and other amino acid residues possessing oxidizable aliphatic chains with reactive secondary C–H bonds such as Leu (**5h**) and Val (**5i,j**) remained intact.[3i] Interestingly, the site-selective alkylation of dipeptide **5k** incorporating a phenyl unit as a linker between the Gly residues reinforced the directing role of the *N*-aryl moiety and verified that the process was not restricted to the functionalization of the terminal *N*-aryl Gly unit. Collectively, the small library of peptide-containing compounds rapidly assembled illustrates the high value of our C–H alkylation process to streamline the late-stage functionalization of complex molecules in a predictable and efficient manner, which resembles to an enzyme-type reactivity of utmost interest in the field of molecular recognition. Moreover, unlike previous alkylation methods,[11] our protocol allows for the introduction of cyclic ethers of high structural complexity resulting in heavily substituted peptide analogues containing heteroatom residues.

In order to evaluate the compatibility of the reaction in structurally more intricate contexts, several dioxolanes embedded in biologically significant molecules and active pharmaceuticals were tested, including those derived from fatty acids (palmitic, oleic and myristic acid), ibuprofen or citronellal (a key ingredient for perfumes). The use of the latter resulted in a selective alkylation to produce **6a-e** in moderate to excellent yields, which underscores the utility to introduce add-value moieties into α-amino carbonyl compounds. Although trivial at first sight, the cleavage of the introduced acetal group was not as simple as expected, and it was accomplished upon treatment with HCl, albeit the corresponding acetylated derivative **7** was obtained in low yields (Scheme 2).[18]

Table 4. Cu-catalyzed C(sp^3)−H alkylation of glycine esters with dioxolanes derived from natural products and drugs[a,b]



[a] As for Table 1, entry 1. [b] Yield of isolated product after column chromatography, average of at least two independent runs.

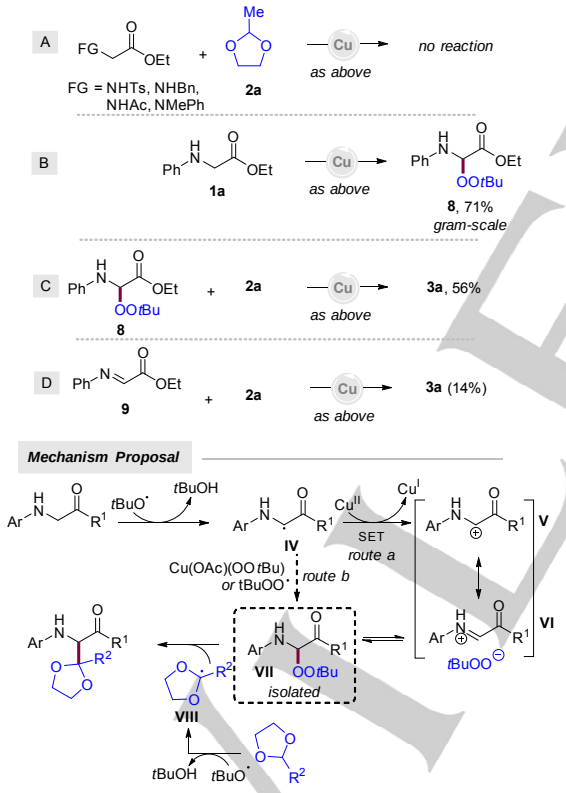


Scheme 2. Cleavage of the dioxolane moiety

In order to gain some insights into the reaction mechanism, we carried out several control experiments. Firstly, we found that the CDC of *N*-Ph-Gly-OEt **1a** with dioxolane **2a** was entirely inhibited in the presence of radical traps such as TEMPO and BHT, which indicated that a radical pathway may be operative.[19] Secondly, other *N*-substituted glycine derivatives including a tertiary amine remained unreactive under the standard conditions (Scheme 3, *path a*), thus highlighting the determinant role of the free-NH aryl group in the reaction outcome. Thirdly, α-*tert*butyldioxanyl intermediate **8** was easily prepared in a gram-scale and provided the alkylated product **3a** in 56% yield under the optimized conditions (Scheme 3, *path c*), hence evidencing its possible key role as a competent reaction intermediate within our catalytic cycle. Curiously, treatment of imine **9** furnished the corresponding coupling product **3a** in a comparatively lower 14% yield. On the basis of the above results and previous literature reports,[20] a plausible reaction mechanism is proposed in Scheme 3. The reaction would commence with the Cu(I)-assisted cleavage of *t*BuOOH[20b,e] to produce *tert*-butoxy radical species and a Cu(II) complex. The corresponding α-amino carbonyl compound would next undergo a hydrogen atom abstraction step by *t*BuO radical species[21] to furnish alkyl radical intermediate **IV**, which could be likely converted into the more stable carbocation **V** through a SET event assisted by Cu(II) (*route a*). Carbocation **V** could be further stabilized as the corresponding iminium ion **VI**. Based on experimental evidence, the latter could be reversibly trapped by a *tert*-butylperoxide anion to yield intermediate

VII,[12,22] which would ultimately react with *in situ* generated α-dioxy radical **VIII** to produce the coupling product.

In summary, we have developed a practical dual C(sp^3)−H functionalization reaction of α-amino carbonyl compounds and 2-alkyl-1,3-dioxolanes. From a fundamental point of view, this transformation represents a robust, yet unprecedented, means for the selective oxidation of 2-susbtituted dioxolane derivatives toward the challenging assembly of quaternary centers. Importantly, this Cu-catalyzed oxidative alkylation constitutes a powerful, yet sustainable, tool for building up structural diversity within a peptide framework and providing access to novel α-amino acids beyond those found in naturally occurring proteins. Important features of our strategy are the low-price of the copper catalyst, the retention of the chiral integrity of the existing stereocenters in peptide settings, the broad functional group tolerance, the site-seletivity toward the functionalization of *N*-aryl glycine unit and the high diastereoselectivity induced by proline-containing peptides. As a result, we anticipate that our Cu-catalyzed oxidative alkylation could become a versatile platform technology of tremendous importance in drug discovery and protein engineering.



Scheme 3. Control experiments and mechanism proposal

Acknowledgements ((optional))

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Keywords: sustainable C–H functionalization • quaternary center • copper catalysis • late-stage peptide modification • CDC

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[12] For more details, see the *Supporting Information*.

[13] The acyclic acetaldehyde dimethyl acetal or related acyclic derivatives remained unreactive under the optimized conditions, which revealed the subtleties of our system. Likewise, the use of 2-aryl-1,3-dioxolanes resulted in the obtention of complex mixtures of products. We hypothesized that the trapping of a strongly stabilized radical, being both tertiary and benzylic radical, might be slower than other side-reactions such as homo-coupling or even water-assisted acetal opening reactions: a) R. Mosca, M. Fagnoni, M. Mella, A. Albini, *Tetrahedron* **2001**, *57*, 10319; b) S. V. Ley, D. K. Baeschlin, D. J. Dixon, A. C. Foster, S. J. Ince, H. W. M. Priepke, D. J. Reynolds, *Chem. Rev.* **2001**, *101*, 53.

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[18] Such acetylated compound was unstable and rapidly decomposed. On the other hand, all attempts to perform the direct CDC of aldehydes and **1a** failed to provide the target acylation reaction, which reinforced the notion that dioxolanes did not act as merely protecting groups in our process and not only tamed the reactivity toward the formation of the corresponding tertiary alkyl radical but also resulted in a more stable product.

[19] The performance of the process under an oxygen atmosphere resulted in the formation of **3a** in a comparatively lower 44% yield, which supported the intermediacy of radical species. For the direct reaction of O_2 with a dioxolane-derived radical, see: H. Zeng, S. Yang, H. Li, D. Lu, Y. Gong, J.-T. Zhu, *J. Org. Chem.* **2018**, *83*, 5256.

[20] a) H. Bartling, A. Eisenhofer, B. König, R. M. Gschwind, *J. Am. Chem. Soc.* **2016**, *138*, 11860; b) E. Boess, L. M. Wolf, S. Malakar, M. Salamone, M. Bietti, W. Thiel, M. Klussmann, *ACS Catal.* **2016**, *6*, 3253; c) M. O. Ratnikov, M. P. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 1549; d) G.-J. Cheng, L.-J. Song, Y.-F. Yang, X. Zhang, O. Wiest, Y.-D. Wu, *ChemPlusChem* **2013**, *78*, 943; e) E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317; f) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. FarHs, M. Klussmann, *J. Am. Chem. Soc.* **2011**, *133*, 810.

[21] Cu(I)-catalyzed hydrogen abstraction reactions from the α-carbon of *N*-aryl glycine derivatives are well established; see for example: a) H. Zhi, S. P.-M. Ung, Y. Liu, L. Zhao, C.-J. Li, *Adv. Synth. Catal.* **2016**, *358*, 2553; b) J.-C. Wu, R.-J. Song, Z.-Q. Wang, X.-C. Huang, Y.-X. Xie, J.-H. Li, *Angew. Chem. Int. Ed.* **2012**, *51*, 3453; *Angew. Chem.* **2012**, *124*, 3509; c) L. Zhao, O. Baslé, C.-J. Li, *Proc. Natl. Acd. Sci. USA* **2009**, *106*, 4106.

[22] At this stage, the formation of species **VII** by direct reaction of radical species **IV** with *in situ* formed *t*BuOO radical species or Cu(OAc)(OO*t*Bu) cannot be entirely ruled out (Scheme 3, *route b*).

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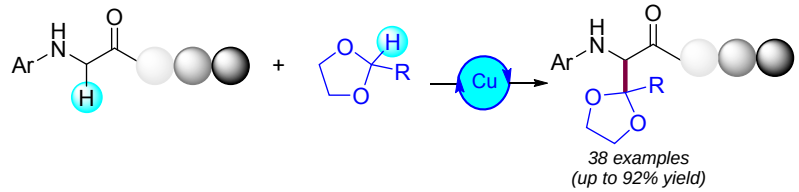

✓ *Chemo- & diastereoselective alkylation*
✓ *Assembly of quaternary centers*
✓ *Application to natural products*
✓ *Late-stage peptide modification*

*Marcos San Segundo and Arkaitz Correa**

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Site-selective Cu-catalyzed Alkylation of α-Amino Acids and Peptides toward the Assembly of Quaternary Centers

Just Glycine! A novel Cu-catalyzed selective α-alkylation of α-amino acid and peptide derivatives with 2-alkyl-1,3-dioxolanes is reported. This oxidative coupling is distinguished by its site-specificity, high diastereoselectivity, chirality preservation and exhibits entire chemoselectivity for *N*-aryl glycine motifs over other amino acid units. The method allows for the sustainable assembly of challenging quaternary centers as well as compounds derived from natural products of high structural complexity, which illustrates its ample opportunities toward the late-stage radical functionalization of peptides.