Cu-Catalyzed Site-Selective C(sp^2)–H Radical Trifluoromethylation of Tryptophan Containing Peptides

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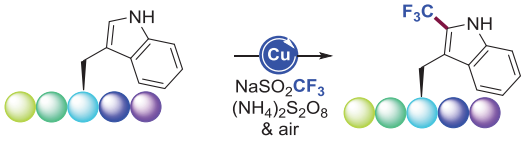


ABSTRACT: Site-selective functionalization of C–H bonds within a peptide framework poses a challenging task of paramount synthetic relevance. Herein, we report an operationally simple C(sp^2)–H trifluoromethylation of tryptophan (Trp) containing peptides. This fluorination technique is characterized by its chirality preservation, tolerance of functional groups, scalability, and exhibits chemoselectivity for Trp residues over other amino acid and heterocyclic units. As a result, it represents a sustainable tool toward the late-stage peptide modification and protein engineering.

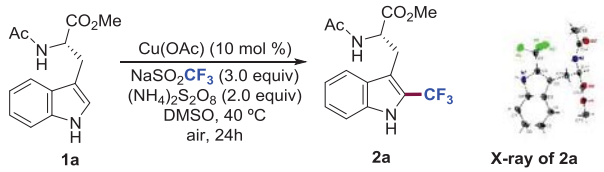
The straightforward chemical modification of biomolecules remains an unmet challenge that has profound implications in chemical biology, proteomics and drug discovery.[1] In this respect, the manipulation of native peptides in a tailored fashion has received a great deal of attention given the often improved biological activities and pharmacokinetics of the resulting engineered biomolecules.[2] The last decade has witnessed the development of cutting-edge methods toward the predictable activation of otherwise unreactive C–H bonds as latent functional groups within peptide settings.[3] The functionalization of C(sp^3)–H bonds has been extensively studied;[4] conversely, relatively few methods are available for the parent C(sp^2)–H functionalization of aromatic side chains of peptides.[5] As a result, the development of novel techniques for the rapid diversification of aromatic amino acid residues within a peptide framework constitutes a prime goal of utmost interest in the drug discovery space.

Despite its low natural abundance in native proteins, Trp featuring the indole motif represents an ideal platform for the design of post-synthetic transformations of peptides. Ackermman,[6] Fairlamb,[7] Albericio and Lavilla,[8] have elegantly introduced C2-arylation, alkynylation and alkylation reactions of Trp-containing peptides.[9] Although of great importance, they are restricted to a reduced set of reactions and mostly utilize expensive precious metals. In this light, Ackermann has recently introduced C–H directed allylation reactions of conveniently *N*-substituted-Trp derivatives featuring cost-efficient cobalt[10a] and manganese[10b] catalysis. Inspired by the emerging trends in sustainable development,[11] we envisioned that the use of earth-abundant copper catalysts could offer new vistas in the field and hence increase our synthetic toolbox for the introduction of other coupling partners into Trp-containing peptides.

The incorporation of a CF_3 group into a given biomolecule can dramatically modify its physical and biological properties, thereby resulting in the enhancement of the cellular membrane permeability and its robustness toward oxidative metabolism.[12] Although CF_3 cross-coupling technologies have lately undergone an impressive development, C–H trifluoromethylation reactions[13] of peptides are rare. Merck laboratories have disclosed the trifluoromethylation of tyrosine-containing peptides under photoredox catalysis,[14] and Li has used UV light irradiation[15] for the fluorination of a number of heterocycles, including a couple of examples of Trp derivatives. More recently, Langlois reagent ($NaSO_2CF_3$)[16] has been used for the modification of Trp-containing peptides under Ir-based catalysis; likewise, Davis and co-workers reported the trifluoromethylation of proteins such as melittin and myoglobin with huge excess of oxidant (up to 25 equiv).[17] Accordingly, we sought that trifluoromethylated oligopeptides could be within reach by a more practical functionalization event featuring base metal catalysis under mild reaction conditions. Driven by the major breakthroughs in the field by Baran[18] and MacMillan,[19] among others,[20] we envisioned a process harnessing the innate chemical reactivity[21] of electron-rich indole motif to undergo site-specific incorporation of *in situ* formed electrophilic trifluoromethyl radicals. As part of our interest in sustainable catalysis,[5a,22] we report herein the discovery of a new catalytic C–H trifluoromethylation protocol, which features a previously unrecognized opportunity in the field of sustainable late-stage peptide modifications.

We commenced our studies by exploring the radical trifluoromethylation of *N*-Ac-Trp-OMe (**1a**) with the Langlois reagent as the model reaction. The method developed by Baran[18c] featured the use of bench-stable $NaSO_2CF_3$ as surrogate for gaseous CF_3I and was found efficient for the innate trifluoromethylation of a vast array of heterocycles including melatonin, which contained the indole ring.

Table 1. Cu-catalyzed C−H trifluoromethylation of 1a[a]



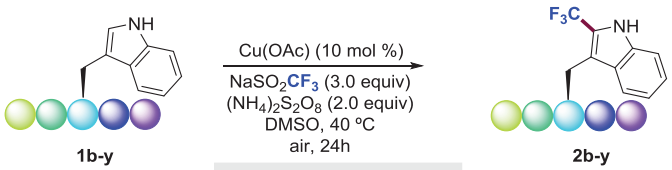
entry	change from standard conditions	**2a** (%)[b]
1	none	78 (75)[c]
2	without $(NH_4)_2S_2O_8$	0
3	without Cu(OAc) under Ar	52
4	without Cu(OAc)	30
5	$Cu(OAc)_2$ instead of Cu(OAc)	76
6	50 mol % of Cu(OAc)	78
7	$CoBr_2$ instead of Cu(OAc)	36
8	AgOTf instead of Cu(OAc)	30
9	$Na_2S_2O_8$ instead of $(NH_4)_2S_2O_8$	60
10	under Ar	79
11	at rt instead of 40 ºC	61
12	at rt instead of 40 ºC without Cu(OAc)	0
13	$NaSO_2CF_3$ (2.0 equiv)	49
14	$NaSO_2CF_3$ (1.0 equiv)	26

[a] Reaction conditions: **1a** (0.25 mmol), $NaSO_2CF_3$ (0.75 mmol), Cu(OAc) (10 mol %), $(NH_4)_2S_2O_8$ (0.50 mmol) in DMSO (0.125 M) at 40 ºC for 24 h under air. [b] Yield of isolated product after column chromatography. [c] Experiment performed with 1.0 g of **1a**.

However, its application[18c] to the functionalization of **1a** provided the target product **2a** in just 21% yield, hence showing the subtleties of the modification of the Trp residue. After considerable experimentation,[24] we found that the combination of Cu(OAc) (10 mol %), $NaSO_2CF_3$ as trifluoromethyl source, $(NH_4)_2S_2O_8$ as oxidant in DMSO as solvent at 40 ºC under air provided the best results, giving rise to **2a** in 78% yield (entry 1). Control experiments in the absence of either oxidant (entry 2) or copper catalyst (entries 3, 4 and 12) underpinned their critical role in the radical trifluoromethylation. Despite the crucial role of Cu(OAc) at room temperature, at 40 ºC the reaction can also occur to some extent in its absence (entries 11-12). Moreover, whereas the presence of air seemed to enhance the reactivity of the copper catalyst; the parent metal-free process took place in lower yields under an air atmosphere (entries 3-4). Intrigued by this experimental finding, we performed a number of experiments to critically analyze the role of the copper source. Increasing the catalyst loading did not result in higher yields of **2a** (entry 6); and while $Cu(OAc)_2$ proved to be equally efficient to Cu(OAc) (entry 5), other copper, cobalt (entry 7) or silver sources (entry 8) were shown comparatively less active catalysts.[24] Further experiments enabled a metal-free synthesis of **2a** in 65% yield,[24] although higher temperature and huge excess of oxidant were required. The nature of the solvent had a profound effect in the reaction outcome, and the best results were obtained in DMSO. Importantly, inexpensive $(NH_4)_2S_2O_8$ was the oxidant of choice and provided higher yields than commonly used *tert*-butyl hydroperoxide or related hazardous peroxides.[24] It is important to note that exclusion of air was not required and the reaction tube was simply sealed with a plastic cap to prevent solvent evaporation, which constitutes an additional bonus in terms of operational simplicity. HPLC analysis verified that the reaction took place with preservation of the α-center chirality,[24] and crystallographic analysis of **2a** confirmed that the absolute stereochemistry was identical to that of the starting Trp residue.[24] Notably, the process could be performed in gram-scale with a remarkable 75% yield, thus highlighting the synthetic utility and robustness of our radical functionalization method.

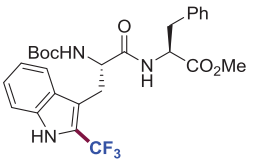
With the optimized conditions in hand, we next examined our oxidative alkylation in the challenging setting of peptides. Notably, a number of Trp-containing dipeptides were selectively trifluoromethylated in the C2 position of the Trp residue in the presence of Phe (**2b,l-m**), Gly (**2c,i**), Ser (**2d**), Thr (**2e**), Leu (**2f,j**), Asp (**2g**), Ala (**2h**), Val (**2k**), Pro (**2n**), Ile (**2o**), Sar (**2p**), Lys (**2q**), Met (**2r**) and Tyr (**2s**) units (Scheme 1). Of tremendous importance is the tolerance of oxidizable protic free-hydroxyl groups of Ser- and Thr-containing dipeptides (**2d** and **2e**, respectively) as well as thioether of Met-containing peptide **2r**.[25] Importantly, a wide range of *N*-protecting groups boded well, and peptides protected with Boc-, Ac-, Fmoc-, Cbz- and even Ts-groups smoothly underwent the corresponding radical trifluoromethylation reaction. The success of the method did not rely on a specific situation of the Trp along the peptide sequence, and was applicable to Trp residues located both at the N- and C-terminal positions. We next evaluated the robustness of the trifluoromethylation technique for the late-stage diversification of more complex oligopeptides. In this respect, it efficiently provided tripeptides **2t** and **2u** in 79% and 68% yields. Other related tripeptides (**2v,w**) were obtained in moderate yields. Remarkably, the innate trifluoromethylation of oligopeptides of high structural complexity was illustrated by the efficient assembly of trifluoromethylated tetra- and pentapeptides **2x** and **2y** in good yields. Our trifluoromethylation manifold could occur not only at Trp units located at N- and C-terminal positions, but also within peptides bearing Trp units in inner positions (**2w** and **2x**). It must be highlighted that the use of a copper catalyst did not result in the presence of significant amounts of metal impurities within the trifluoromethylated peptides and ICP-MS analysis of some representative samples verified that amounts lower than 4 ppb remained in certain samples.[24] In this regard, the metal-free reaction conditions which provided **2a** in 65% yield were applied for a number of Trp-containing peptides (Scheme 1); however, the Cu-catalyzed protocol afforded comparatively higher yields in all cases, thus illustrating the clear benefits derived from the use of a Cu catalyst in this transformation. The chemoselectivity of the method was further illustrated by the C2-selective trifluoromethylation of a wide range of diversely substituted Trp derivatives **3a-q**. As shown in Scheme 2, a variety of sensitive functional groups were accommodated such tetrahydrofuryl ring (**4d**), aliphatic carboxamides (**4j,k**) or alkyl cyano groups (**4h,i**). One of the most notable aspects of using ammonium persulfate as oxidant was the full tolerance to commonly oxidizable $C(sp^3)$–H in adjacent positions of oxygen[26] (**4d**) or nitrile groups[27] (**4h,i**). Likewise, the predictable nature of the present innate trifluoromethylation was underpinned by the inherent reactivity of the indole ring to undergo preferential C–H trifluoromethylation in the presence of 1,2,3-triazoles (**4f**) or pyridines (**4d,e**), which have been efficiently trifluoromethylated by related radical techniques.[18-20] Importantly, a primary amine (**4a**) or carboxylic acids (**4l-m**), which are prevalent motifs in native peptides could be also accommodated. Furthermore, the compatibility of the process in structurally more intricate contexts was demonstrated by using Trp derivatives bearing biologically relevant molecules and active pharmaceuticals, including those derived from fatty acids (palmitic and oleic acid, **4o** and **4p**, respectively), ibuprofen (**4n**) and aspirine (**4q**).

Scheme 1. Cu-catalyzed C(sp^2)−H trifluoromethylation of Trp-containing oligopeptides[a,b]

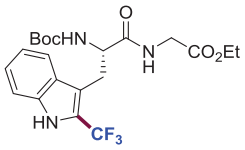


1b-y → **2b-y**

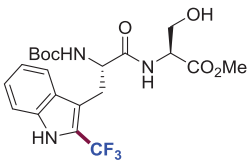
Trp-containing Dipeptides



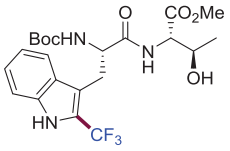
2b, 40% (16%)[d]
from Boc-Trp-Phe-OMe



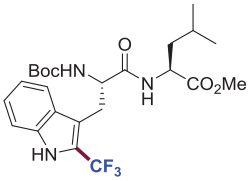
2c, 57% (16%)[d]
from Boc-Trp-Gly-OEt



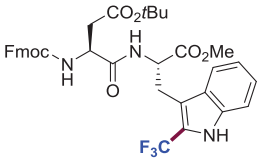
2d, 45%
from Boc-Trp-Ser-OMe



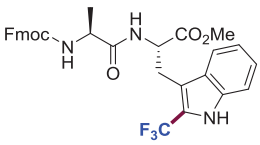
2e, 46%
from Boc-Trp-Thr-OMe



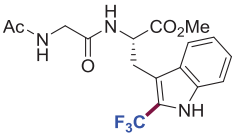
2f, 50%
from Boc-Trp-Leu-OMe



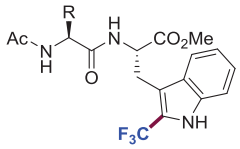
2g, 64%
from Fmoc-Asp(OtBu)-Trp-OMe



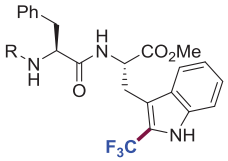
2h, 44%
from Fmoc-Ala-Trp-OMe



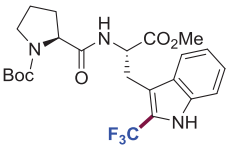
2i, 46%
from Ac-Gly-Trp-OMe



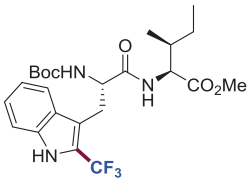
2j, 42%[c], *from Ac-Leu-Trp-OMe*
2k, 43% (27%)[d] *from Ac-Val-Trp-OMe*



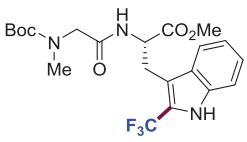
2l, 43%, *from Cbz-Phe-Trp-OMe*
2m, 31% (24%)[d], *from Ts-Phe-Trp-OMe*



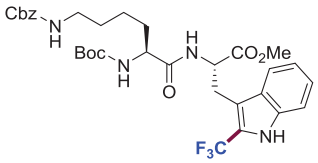
2n, 42% (11%)[d]
from Boc-Pro-Trp-OMe



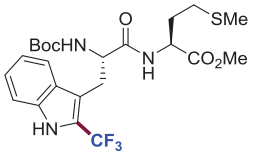
2o, 47%
from Boc-Trp-Ile-OMe



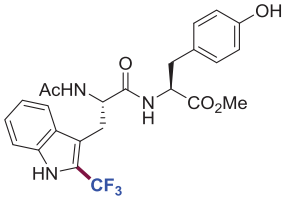
2p, 52%
from Boc-Sar-Trp-OMe



2q, 44%
from Boc-Lys(Cbz)-Trp-OMe

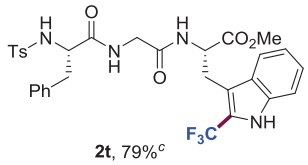


2r, 36%
from Boc-Trp-Met-OMe

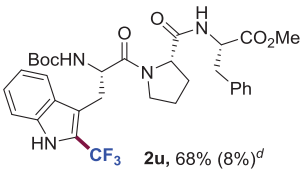


2s, 15%
from Boc-Trp-Tyr-OMe

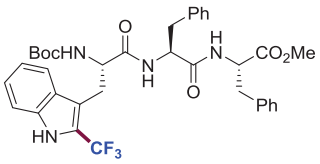
Trp-containing Tripeptides



2t, 79%[c]
from Ts-Phe-Gly-Trp-OMe

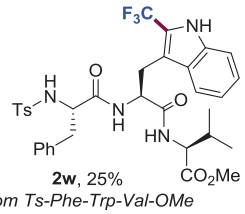


2u, 68% (8%)[d]
from Boc-Trp-Pro-Phe-OMe

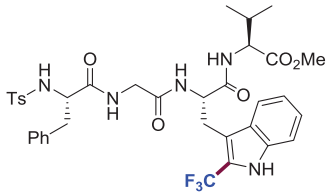


2v, 36%
from Boc-Trp-Phe-Phe-OMe

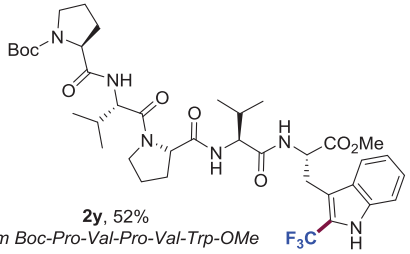
Trp-containing Tetra- and Pentapeptides



2w, 25%
from Ts-Phe-Trp-Val-OMe



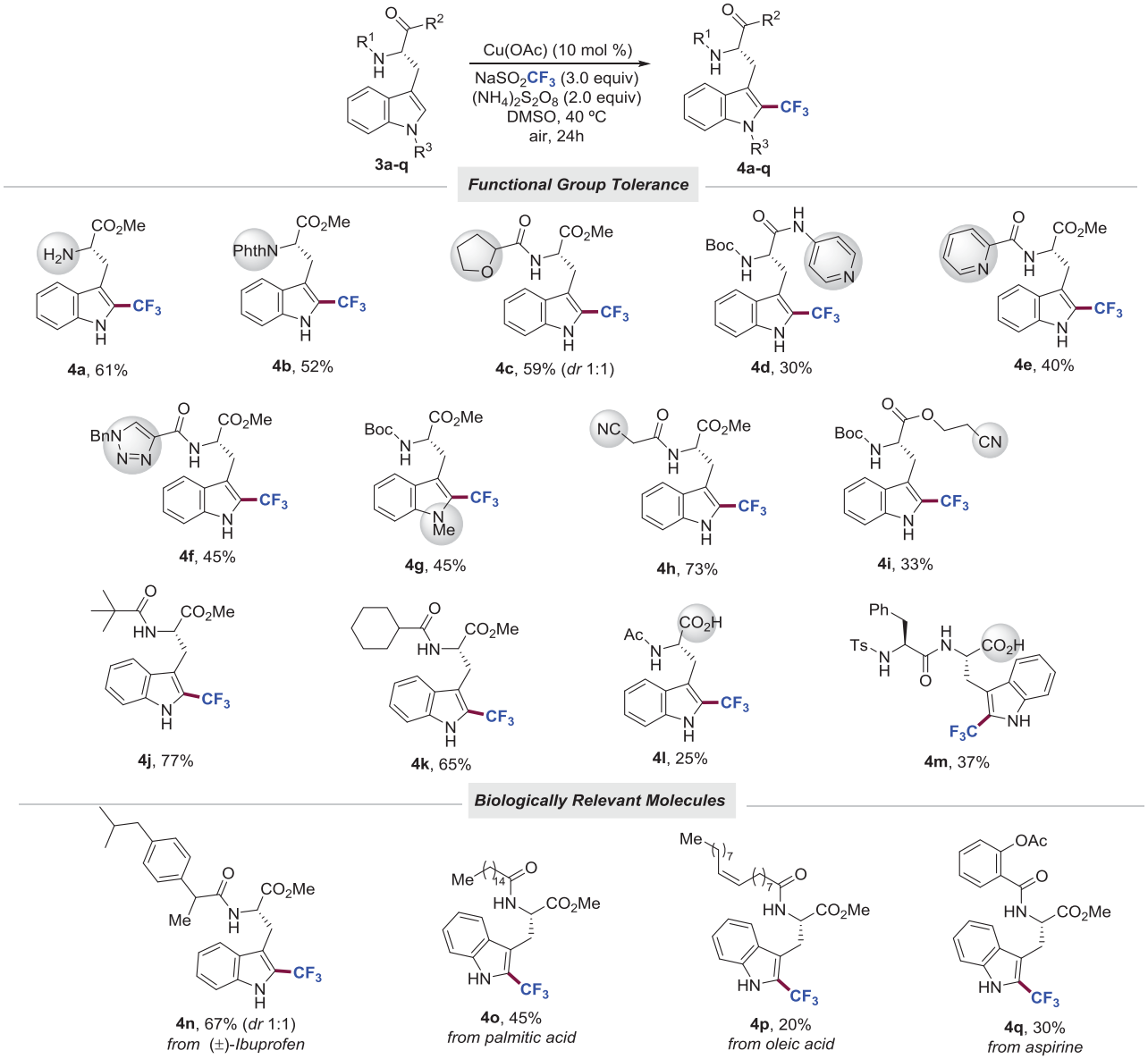
2x, 45%
from Ts-Phe-Gly-Trp-Val-OMe



2y, 52%
from Boc-Pro-Val-Pro-Val-Trp-OMe

[a] As for Table 1, entry 1.[b] Yield of isolated product after column chromatography, average of at least two independent runs. [c] 48h. [d] Reaction conditions: **1** (0.25 mmol), $NaSO_2CF_3$ (0.75 mmol), $(NH_4)_2S_2O_8$ (1.0 mmol) in DMSO (0.125 M) at 60 ºC for 24 h under air.

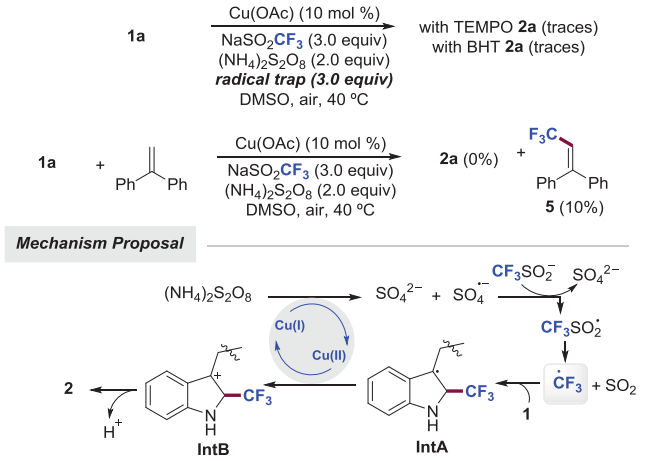
Scheme 2. Cu-catalyzed C(sp^2)–H trifluoromethylation of Trp derivatives[a,b]



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

Collectively, the Cu-catalyzed C–H trifluoromethylation of enantiomerically pure Trp-containing peptides proceeded with excellent site- and chemoselectivity and it represents a prototypical example of innate modification in which the incorporation of the electrophilic radical species is biased by the innate reactivity of the indole ring. In order to gain some insights into the reaction mechanism, we carried out several control experiments with **1a** as the model system. We found that the trifluoromethylation of **1a** was suppressed in the presence of radical traps such as TEMPO and BHT, which revealed that a radical pathway may be operative (Scheme 3). In particular, the performance of the process in the presence of diphenylethylene resulted in the isolation of compound **5** in 10% yield and not even traces of product **2a** were detected. Accordingly, the intermediacy of electrophilic trifluoromethyl radical species was reasonably assumed to be a plausible scenario. On the basis of the above results and previous reports,[17] a reaction mechanism is proposed in Scheme 3. The reaction would start with the Cu(I)-assisted redox decomposition of peroxydisulfate ion[28] to provide the sulfate radical anion $SO_4^{\cdot -}$, which is a very strong one-electron oxidant. The latter would react with $CF_3SO_2^-$ to deliver $CF_3SO_2^{\cdot}$, which would further release SO_2 and the active trifluoromethyl radical species. The indole ring of the Trp residue **1** would next undergo an electrophilic aromatic substitution at the C2 position, followed by re-oxidation of the resulting radical intermediate **IntA** to the corresponding carbocation **IntB**.[17-18] Eventually, aromatization of the indole moiety would afford the targeted product **2**. It must be commented that the group of Baran[18c] has observed that traces of metal impurities often remain in the commercially available Langlois reagent; the latter may initiate the corresponding persulfate cleavage toward the production of the transient trifluoromethyl radical species when performing the process in the absence of the copper catalyst.[29]

Scheme 3. Control experiments and mechanism proposal



In summary, we have developed a practical radical trifluoromethylation of Trp-containing oligopeptides with the readily available Langlois reagent. The mildness of the reaction conditions, advantageous use of non-precious first row copper catalyst, inexpensive persulfate oxidant, avoidance of chlorinated solvents, and performance under open-air conditions provide the method attractive features to greatly enhance the sustainability in late-stage drug development. Therefore, we anticipate that our Cu-catalyzed trifluoromethylation process could become a new platform for the introduction of metabolism blocking fluoroalkyl groups in a late-stage fashion of utmost importance in the field of bioconjugation, thus providing access to new peptide entities beyond those found in native proteins.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

Crystallographic information for compound **2a** (CIF)

Experimental procedures, syntheses and characterization of all new compounds, and tables with details of several optimization studies (PDF).

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