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FULL PAPER

Double Cu-Catalyzed Direct Csp^3-H Azidation / CuAAC Reaction: A Direct Approach towards Demanding Triazole Conjugates

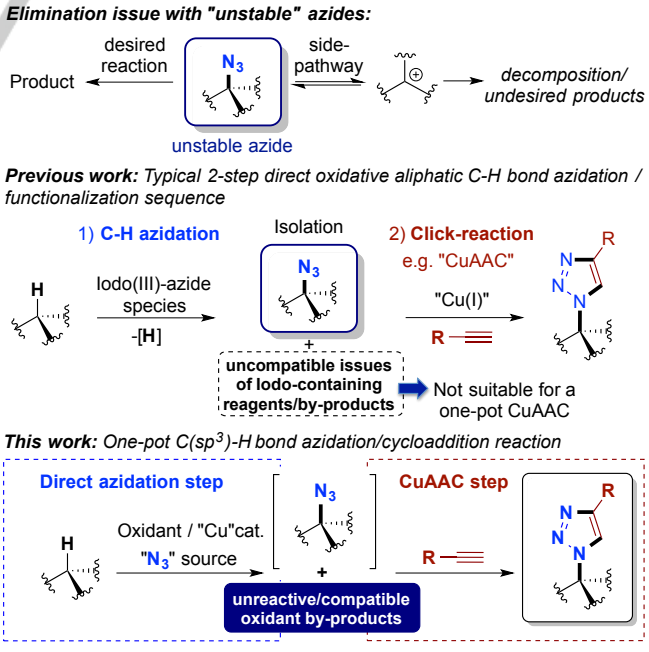
Tobias Brandhofer,[a][b] Aysegül Özdemir,[b] Andrea Gini,*[b] Olga García Mancheño*[a]

Dedication ((optional))

Abstract: The first one-pot procedure for the double copper(I)-catalyzed oxidative Csp^3-H azidation – CuAAC process, implying unstable azide intermediates and easy-to-remove reagents under water-tolerant conditions, is presented. The combination of TBHP as oxidant and $TMSN_3$ as azide source for the C-H bond azidation, which produces harmless side-products such as *t*BuOH and H_2O, probed to be perfectly compatible with the following cycloaddition step. Highly demanding 1,2,3-triazoles could be then directly obtained in good overall yields by extraction or simple crystallization, thus avoiding chromatography purifications. The potential of this methodology, has also being highlighted by the successful reaction of alkynes presenting interesting complex biological moieties based for example on Biotin, DNA base or cinchona alkaloid units.

Introduction

The 1,2,3-triazole heterocycle[1] has become in the past years an essential artificial amide bio-isosteric[2] core for the development of novel lead-target biological active molecules for pharmacological and agrochemical applications.[3,4] 1,2,3-Triazole-containing molecules present hence important biological activities,[3,4] while their synthesis can be easily achieved.[1,5] In this regard, the copper catalyzed azide-alkyne cycloaddition (CuAAC) reaction,[6] discovered independently by the groups of Fokin and Sharpless, and Meldal,[7] was elevated as the most prominent approach for the straightforward, highly efficient and selective synthesis of 1,4-substituted 1,2,3-triazoles.[5-6,8] Moreover, the introduction of the CuAAC reaction has also revolutionized the area of biochemistry, since it tolerates aqueous media and allows the orthogonal, fast generation of a large variety of bio-conjugates upon reaction of the appropriate alkyne and organic azide coupling partners.[3,9] However, an important aspect to be considered is the accessibility of the azide reagent. Although the insertion of an azide moiety into organic molecules may appear an established procedure,[10] on a number of occasions the synthesis and handling of organic azides might become a real synthetic limitation. While most of simple aliphatic azides are particularly stable toward various reaction and storage conditions, such as the presence of water or dioxygen,[1,4,8-9] in the cases in which a stable radical or carbocation can be generated, the azide unit of the C(sp^3)-N_3 species is promptly cleaved (Scheme 1, top). Indeed, certain azides are sensitive to elimination under standard functionalization reactions, such as the CuAAC, which would led to degradation or undesired side-reactions.[10] Therefore, the in situ generation and trapping of the azide would be essential when the target is difficult to handle in the required environment for the work-up, purification and following synthetic step. However, the one-pot procedures reported in literature are essentially limited to nucleophilic substitutions,[11] diazo transfers[12] or addition to epoxides,[13] which required a pre-functionalization (e.g. use of an alkyl halide, etc) on the molecule where the azide has to be installed. Conversely, the one-pot combination of the more convenient direct C-H bond azidation[14-16] of organic molecules with CuAAC remains fundamentally unexplored.[17-18] This restraint might be the result of the interaction between the copper catalyst and the standard hypervalent iodine(III)-containing reagents used for C-H bond azidation reactions (Scheme 1, middle).[14] In fact, such iodine reagents and their by-products have the potential to deactivate the copper species involved in the CuAAC catalytic cycle.[19]



Scheme 1. Common oxidative C-H azidation sequence reactions and our double Cu-catalyzed one-pot approach.

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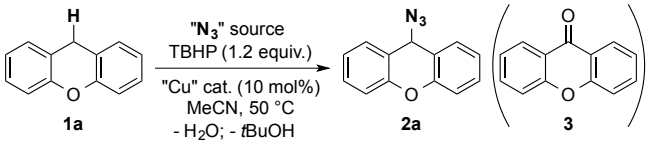
To solve the current limitations, expand the application field of direct azidation and develop a general and robust one-pot methodology, we envisioned a mild and facile double copper-catalyzed approach for the oxidative Csp^3-H azidation – trapping of unstable azides by CuAAC, implying common and easy-to-remove compatible reagents (Scheme 1, bottom).

Results and Discussion

Based on the experience on Csp^3-H bond functionalization of xanthene and acridane moieties acquired in our laboratory,[20] we decided to start our investigations with the optimization of the reaction involving the commercially available, cheap and bench-stable xanthene (**1a**) as model substrate and precursor of the unstable azide intermediate.[18,21] To ensure the highest conversion into the desire azide **2a**[18-20] and avoiding unwanted side-products such as xanthone (**3**) by over-oxidation of the substrate, the azidation step was first investigated (Table 1).

Table 1. Optimization of the C-H bond azidation step.[a]

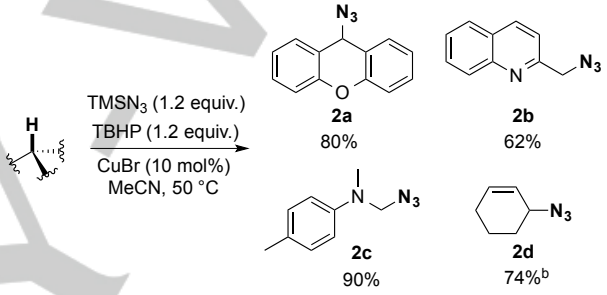


Ent.	"Cu" cat.	Oxidant	"N_3" (equiv.)	t (h)	Conv. (%)[b]
1	CuBr	TBHP	$TMSN_3$ (2.0)	2	99(86)[c]
2	CuBr	DDQ	$TMSN_3$ (2.0)	18	---[d,e]
3	CuBr	PIDA	$TMSN_3$ (2.0)	18	90
4	Cu_2O	TBHP	NaN_3 (2.0)	24	40
5	CuI	TBHP	NaN_3 (2.0)	24[4]	99[70]
6	$CuSO_4 \cdot 5H_2O$	TBHP	$TMSN_3$ (2.0)	24	92
7	CuBr	TBHP	NaN_3 (2.0)	24	20
8	CuBr	TBHP	$TMSN_3$ (1.2)	2	99(80)[c]
9	CuBr	TBHP	$TMSN_3$ (1.2)	2	99[e,f]

[a] **1a** (0.4 mmol, 1 equiv.), $TMSN_3$ (2 equiv.), *t*BuOOH 70% in H_2O (1.2 equiv.) and catalyst (10 mol%) were reacted in MeCN (0.4 M) at 50 °C. [b] Conversion determined by ^{1}H-NMR analysis. [c] Yield of **2a** after work-up and extraction in brackets. [d] A mixture complex was observed. [e] Xanthone (**3**) was obtained as major product after work-up. [f] *t*BuOOH 3M in isooctane was used.

Initially, *tert*-butyl hydroperoxide (TBHP) 70% in water was employed in the presence of copper bromide as catalyst[22] and $TMSN_3$ as azide source. A full conversion into the desired product was observed after 2 hours at 50 °C (entry 1). Other standard oxidants in cross-dehydrogenative coupling (CDC)[23] of C(sp^3)-H bonds such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and phenyliodine diacetate (PIDA) were also explored (entries 2-3). While the formation of the product **2a** could not be observed with DDQ, a good 90% conversion over a prolonged reaction time (18 vs. 2 h) was achieved with PIDA (entry 3). Next, various Cu(I) species such as Cu_2O and CuI, and $CuSO_4$, as one of the most employed Cu-catalyst in CuAAC reactions, were tested (entries 4-6). However, all of those catalysts required longer reaction times (24 vs. 2 h) for achieving an acceptable conversion, being CuI among them the most competitive species (99% vs. 40 and 92% with Cu_2O and $CuSO_4$, respectively). Alternatively, NaN_3 was used as azide source, displaying a notably lower reactivity (20% conversion, entry 7). Moreover, the decrease of the equivalents of azide reagent $TMSN_3$ from 2 to 1.2 did not show a significant effect on the performance of the reaction, providing similar good results (entry 8). Finally, we were pleased to observe a superior reactivity of the standard aqueous TBHP solution compared to anhydrous TBHP (3M in isooctane), which mainly led to the overoxidation to xanthone (entry 9).

Although the main focus was the development of the one-pot azidation/CuAAC reaction, the applicability of the first azidation step was also shortly explored with a few different types of representative substrates (Scheme 2). Thus, besides xanthene, other benzylic, alpha to an heteroatom and even the more difficult to oxidize allylic substrates, such as 2-methylquinoline (**1b**), N,N-dimethyl toluidine (**1c**) and cyclohexene (**1d**), could be directly transformed into the corresponding azides **2** in good yields.



[a] Yields after work-up and extraction (see S.I.).
[b] Reaction at 100 °C for 4 h using 1 equiv. of $TMSN_3$ and 5 equiv. of **1d**.

Scheme 2. Oxidative C-H bond azidation step with some selected representative substrates

After having optimized the azidation step (TBHP 70% in H_2O, CuBr (10 mol%), $TMSN_3$ (1.2 equiv.) in MeCN for 2 h at 50 °C), the one-pot process was studied (Table 2). Thus, after the azidation reaction, the mixture was initially allowed to cool down to room temperature, and the phenyl acetylene (**4a**) and sodium ascorbate were added. Unfortunately, only traces of the desired triazole product **5aa** could be then observed (entry 1). To our delight, the simple addition of *tert*-butyl alcohol as co-solvent to improve the solubility of the reaction mixture was enough to achieve full conversion in 24 h at room temperature, providing the desire product in a satisfying 62% yield (entry 2). The one-pot reaction with the PIDA/$TMSN_3$ system (for the first step see Table 1, entry 3) was also carried out as control experiment (entry 3). However, as we anticipated, it only led to a low 14% yield of **5aa**, showing the already mentioned incompatibility issues of the iodo-based oxidants within the second step. Moreover, the addition of standard ligands utilized in CuAAC processes, such as tris(benzyltriazolylmethyl)amine (TBTA), glycol or 2,2'-bipyridine (bpy), decreased the reactivity (entries 4-6). On the contrary, the use of 50 °C for both steps led to an increased 68% overall yield after 24 h (entry 7).

The main issue regarding the formation of the triazole ring is the intrinsic instability of the azide intermediate **2a**. Indeed, the decomposition pathway to the corresponding xanthone (**3**) become predominant as the reaction time increases. However, under the same conditions, the reaction at 50 °C after 4 h showed

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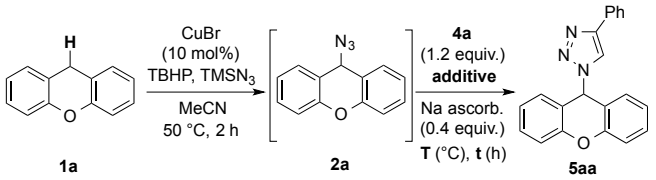
no full conversion (entry 8). In general, the rate determining-step for the CuAAC reaction comprises a Cu-acetylide, which formation is influenced by the nature of the alkyne and the presence of a base.[6,24] Therefore, in order to accelerate the process, several bases were next investigated (entries 9-12). As expected, all the tested bases led to a faster overall reaction and better yields (72-82%). Diisopropylethyl amine (DIPEA) provided the best results in term of yield and reaction time, leading to **5aa** in a good 82% yield in only 4 h (entry 9). It is interesting to note that 2,6-lutidine gave a similar yield than DIPEA but provided a significant higher amount of decomposition products (entry 12).

Table 2. Optimization of the one-pot sequence.[a]



Entry	Additive (eq.)	co-solvent	T (°C)	t (h)	Yield (%)[b]
1	-	--	r.t.	24	traces
2	-	*t*BuOH	r.t.	24	62
3	-	*t*BuOH	r.t.	24	14[c]
4	TBTA (0.3)	*t*BuOH	r.t.	24	48
5	--	glycol	r.t.	24	17[d]
6	bpy (0.3)	*t*BuOH	r.t.	24	traces
7	-	*t*BuOH	50	24	68
8	-	*t*BuOH	50	4	42[e]
9	DIPEA (1.5)	*t*BuOH	50	4	82
10	Et_3N (1.5)	*t*BuOH	50	4	78
11	K_2CO_3 (1.5)	*t*BuOH	50	18	72
12	2,6-lutidine (1.5)	*t*BuOH	50	4	80

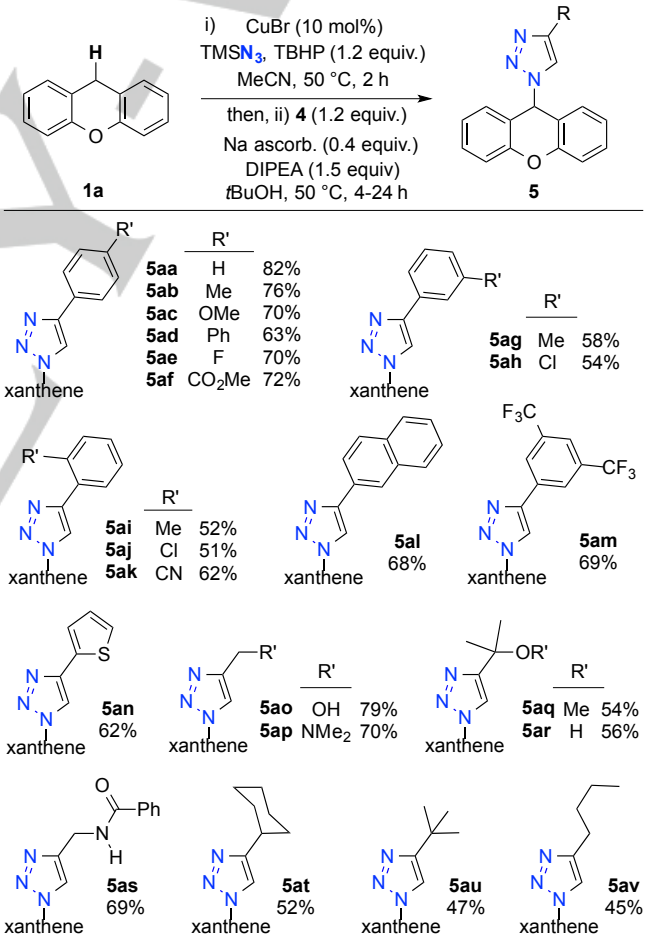
[a] **1a** (0.4 mmol, 1 equiv.), $TMSN_3$ (2 equiv.), TBHP 70% in H_2O (1.2 equiv.) and CuBr (10 mol%) in MeCN (0.4 M) at 50 °C for 2 h; then alkyne **4a** (1.2 equiv.), Na ascorbate (0.4 equiv.), the additive and *t*BuOH (2.5 mL/mmol) as co-solvent were added to the mixture and stirred at the corresponding temperature. [b] Isolated yields. [c] The PIDA/$TMSN_3$ system was used for the azidation step. [d] Glycol was used instead of *t*BuOH as co-solvent. [e] No full conversion.

Next, various alkynes were screened in the reaction (Table 3). Firstly, several aryl-substituted acetylenes bearing electron-withdrawing and donating groups, as well as substituents in the *ortho*-, *para*- and *meta*-position, were tested. The method showed a good steric and electronic functional group tolerance, providing in all cases the substituted products **5aa-5am** in good yields (up to 82%). Even heteroarene-containing acetylenes such as thiophene, gave the desire product **5an** in a satisfactory 62% yield. Although no clear electronic effects could be observed, the reaction was slightly influenced by steric hindrance on the alkyne. Hence, *ortho*-substituted phenyl acetylenes provided the products (**5ai-k**) in lower yields than the related regioisomers (e.g. 4-MeC_6H_4 **5ab**, 76% *vs* 3-MeC_6H_4 **5ag**, 58% *vs* 2-MeC_6H_4 **5ai**, 52%).

Additionally, this methodology tolerates substrates bearing demanding functional groups such as a hydroxyl (**4o**, **4r**), methoxide (**4q**), tertiary amine (**4p**) or amide (**4s**) in α to the acetylene moiety, leading to the corresponding products **5** in moderate to good yields (54%-79%). To our delight, alkyl acetylenes, which are known to react slower in CuAAC processes,[4] were active under the optimized condition. Thus, the products **5at-v** were achieved in moderate but synthetically practical yields (45-52%). However, no steric influence was observed between *n*-butyl (**5at**, 45%), cyclohexyl (**5au**, 52%) and *t*-butyl (**5av**, 47%) derivatives.

Noteworthy, the procedure proved to be very robust, providing a similar high 85% yield of **5aa** when conducting on a one-gram scale (Scheme 3, top). Moreover, in the reaction with bis-terminal alkynes, a controlled and complete selectivity between the mono and bis-cyclization was obtained by a careful choice of the stoichiometry (Scheme 3, bottom). Hence, the desire bis-click product **6** was obtained as only product in almost quantitative yield in the presence of 0.46 equiv. of bis-alkyne **4w** as limiting reagent (Scheme 3, entry A). Alternatively, the sole formation of the mono cyclization product **5aw** was observed when using **4w** in excess (2.4 equiv.; Scheme 3, entry B).

Table 3. Scope of the reaction of **1a** with various alkynes **4**[a][b]



[a] **1a** (0.4 mmol, 1 equiv.), $TMSN_3$ (2 equiv.), TBHP 70% in H_2O (1.2 equiv.) and CuBr (10 mol%) in MeCN (0.4 M) at 50 °C for 2 h; then **4** (1.2 equiv.), Na ascorbate (0.4 equiv.), DIPEA (1.2 equiv.) and *t*BuOH (2.5 mL/mmol) were added and stirred at 50 °C. [b] Isolated yield.

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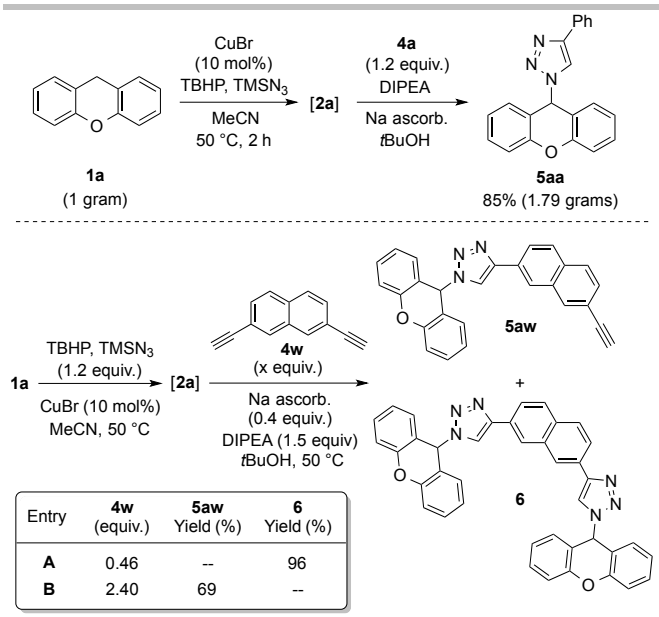


Entry	4w (equiv.)	5aw Yield (%)	6 Yield (%)
A	0.46	--	96
B	2.40	69	--

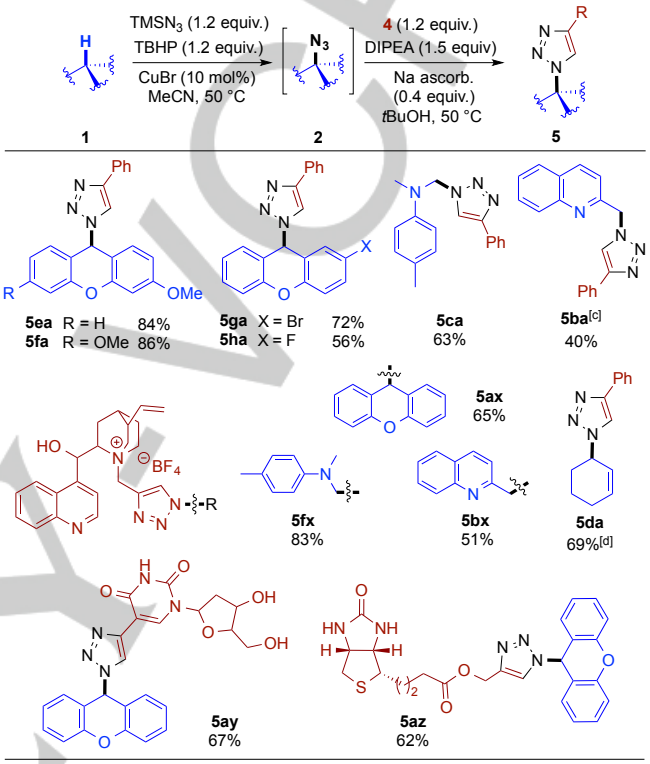
Scheme 3. Gram-scale, and mono- vs. bis-cycloaddition selectivity

The scope of the methodology was next investigated with different type of substrates (Table 4). Whereas xanthene derivatives **1e-h** presenting electron rich groups gave the desire products in high yields (84-86%; **5ea**, **5fa**), the reaction with electron poor derivatives was slightly less efficient (56-72%; **5ga**, **5ha**). Furthermore, N,N-dimethylanilines could also be enrolled in the reaction.[20] Thus, the *p*-toluidine derivative **1c** gave the product in a good overall 63% yield. Noteworthy, the developed strategy allowed the transformation of the highly demanding 2-methyl quinoline **1b**,[25,26] a previously unexplored substrate in direct azidation reactions. However, in this case the addition of a double amount of sodium ascorbate (0.8 *vs.* 0.4 equiv.) was required. In addition, the one-pot reaction with cyclohexene as representative allylic substrate was also possible upon carrying out the first azidation step at 100 °C (see Scheme 2), leading to the triazole conjugate **5da** in a good 69% yield. To our delight, the reaction was also suitable for alkyne derivatives of important bioactive compounds such as cinchona alkaloid derivatives (**5ax**, 65%; **5cx**, 83%; and **5bx**, 51%), nucleosides (**5ay**, 67%) or biotin (**5az**, 62%).

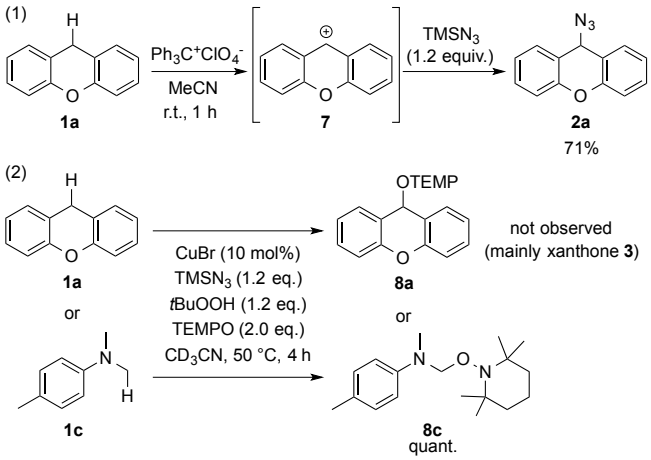
At this stage, it is important to point out that this methodology allows a facile isolation of the final products.[27] Thus, purification by column chromatography could be avoided,[28] since the evaporation and extraction or a simple precipitation of the crude mixture provided pure products in good to excellent yields.

Motivated by these results, we subsequently carried out some mechanistic studies for the azidation step (Scheme 4). In order to analyze the radical or cationic character of the key intermediates in this reaction, the xanthene carbocation **7** was initially synthesized by hydrogen abstraction of **1a** with a trityl salt (Ph_3CClO_4) (Scheme 4, eq. 1). This cationic species **7** was then reacted with $TMSN_3$, providing the product **2a** in a good 71%. This result indicates an ionic mechanism via **7** as electrophilic key intermediate. Furthermore, radical trapping experiments with 2,2,6,6-tetramethyl-piperidinyloxyl radical (TEMPO) were performed with both xanthene (**1a**) and the N,N-dimethylaniline **1c** in MeCN-D3 (Scheme 4, eq. 2). Although the corresponding trapping adduct of **1a** could not be detected by NMR due to a fast oxidation to xanthone **3**, the formation of the more stable adduct **8c** was quantitatively observed. This suggests a first radical formation followed by a further oxidation to the corresponding carbocation (or iminium) species, which finally react with the nucleophilic azide reagent to form the observed products.

Table 4. Scope: Different targets & anchoring of bio-probes[a,b]



[a] **1a** (0.4 mmol, 1 equiv.), $TMSN_3$ (2 equiv.), TBHP 70% in H_2O (1.2 equiv.) and CuBr (10 mol%) in MeCN (0.4 M) at 50 °C for 2 h; then **4** (1.2 equiv.), Na ascorbate (0.4 equiv.), DIPEA (1.2 equiv.) and *t*BuOH (2.5 mL/mmol) were added to the mixture and then stirred for 4-24 h at 50 °C. [b] Isolated yield. [c] 0.8 equiv. of Na ascorbate was used. [d] First-step reaction with **1d** (5 equiv.), $TMSN_3$ (1 equiv.) and TBHP (5.5M in decane) at 100 °C for 4 h.



Scheme 4. Key intermediates analysis: Isolation of a cationic species and radical trapping studies.

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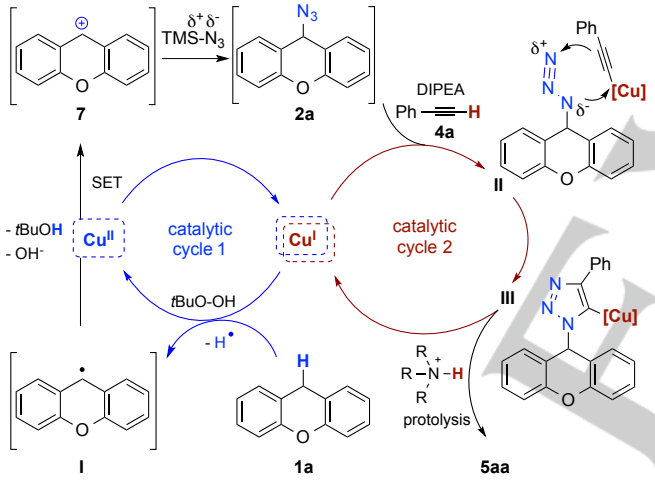
With this information, and based on related isolated Cu-catalyzed TBHP-mediated C-H functionalization and the well-known CuAAC processes reported in the literature,[24,29] the postulated reaction mechanism for the double Cu-catalyzed one-pot process is outlined in Scheme 5. Accordingly, in the first step the Cu(I) catalyst promote the homolytic cleavage of the organic peroxide TBHP, leading to the *tert*-butoxy radical (*t*BuO•) and Cu(II)-OH species. The formed *t*BuO• is then able to abstract a hydrogen radical from the substrate **1a** to form *t*BuOH and the C-centered radical intermediate **I**. The radical **I** subsequently undergoes a SET process with the Cu(II) complex present in the media, leading to the carbocation **7**. In this step, a Cu(I) species is also generated, closing hence the first Cu-catalytic cycle. Next, the electrophilic intermediate **7** reacts with the $TMSN_3$ nucleophile to form in situ the organic azide **2a**. After addition of the rest of the reagents required for the CuAAC reaction, the Cu(I) species interacts with the terminal acetylene **4a**, giving the active Cu-acetylide. This species undergoes a 1,3-dipolar cycloaddition reaction with the previously formed azide **2a**, providing the 1,2,3-triazolyl cuprate **III**. Finally, a protolysis of **III** to give the product **5aa** and liberation of the active Cu(I) species closes the second Cu-catalytic cycle.



Scheme 5. Proposed double Cu-catalyzed mechanism.

Conclusions

In conclusion, a practical and efficient one-pot double Cu(I)-catalyzed the direct oxidative Csp^3-H bond azidation / CuAAC reaction implying unstable azides has been developed. Thus, the combination of TBHP as oxidant and $TMSN_3$ as simple, iodine-free azide source for the C-H bond functionalization, which produces harmless side-products such as *t*BuOH and H_2O, probed to be perfectly compatible with the next cycloaddition step. In this manner, highly demanding 1,2,3-triazole derivatives were directly obtained in good overall yields from a variety of substrates presenting dibenzylic (xanthenes) or alpha to nitrogen C-H bonds (N,N-dimethyl anilines), as well as difficult oxidizing compounds such as 2-methyl quinolines and allylic substrates. Moreover, the isolation of the products could be normally achieved by evaporation and extraction or by simple crystallization/ precipitation from the crude mixture. To further highlight the potential of this approach, not only simple but also more complex biological interesting alkynes based for example on Biotin, a DNA base or cinchona alkaloids were successfully implemented. Finally, due to its simplicity and the good overall yields considering the involved sensitive intermediates, this methodology presents a great potential for the preparation of challenging bioconjugates.

Experimental Section

General information and materials:

^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$, CD_3CN and DMSO-D6 (reference signals: ^1H = 7.26 ppm, ^{13}C = 77.16 ppm, $CDCl_3$) on a Bruker ARX-300, a Bruker ARX-400, Bruker Avance II 300, Bruker Avance II 400 or a Jeol JNM-ECS 400 MHz. Chemical shifts (d) are given in ppm and spin-spin coupling constants (J) are given in Hz. Analytical thin layer chromatography was performed using silica gel 60 F254 and I2 served as staining agent. Column chromatography was performed on silica gel 60 (0.040-0.063 mm). Exact masses (HRMS) were recorded on an Agilent Q-TOF 6540 UHD or Bruker MicrOTof ESI spectrometer using electrospray ionization (ESI) techniques or on an Finnigan MAT SSQ 710 A spectrometer using electron impact (EI) techniques.
The starting materials **3e**,[20a, 29] **3f**,[30] **3g** and **3h**,[20a, 29] **4q**,[31] **4s**,[32] **4w**,[33] **4x**[34] and **4z**[35] were prepared following known literature procedures. Alternatively, xanthenes **1** were synthetized from the corresponding xanthones **3** in a sequential manner.[20a] CH_3CN was distilled over CaH_2. Other solvents and commercially available reagents were used without further purification.

Standard procedure for the tandem azidation-click-reaction:

CuBr (5.7 mg, 0.04 mmol, 10 mol%) and the substrate **1** (0.4 mmol, 1.0 eq) were dissolved in 1 mL CH_3CN. $TMSN_3$ (63.7 µL, 0.48 mmol, 1.2 eq) and *t*BuOOH (70% in H_2O; 65.7 µL, 0.48 mmol, 1.2 eq) were added and the solution was stirred at 50 °C for 2-2.5 h. Then, sodium ascorbate (31.7 mg, 0.4 mmol, 0.4 eq), 1 mL *t*BuOH, DIPEA (95.2 µL, 0.3 mmol, 1.5 eq) and the acetylene **4** (0.48 mmol, 1.2 eq) were successively added. After stirring the mixture at 50 °C for 18 h, H_2O (10 mL) and DCM (10 mL) were added. The two phases were separated and the aqueous phase was extracted with DCM (3x10mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and the solvent was removed under vacuum. The crude product was further purified by recrystallization or flash column chromatography.

Analytical data of the products:

4-Phenyl-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5aa): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5aa** (107 mg, 0.33 mmol, 82 %) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.72 (m, 2H), 7.47 – 7.38 (m, 5H), 7.36 (d, *J* = 3.0 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 3H), 7.26 (s, 1H), 7.19 – 7.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 130.7, 130.5, 129.7, 128.8, 128.3, 125.7, 124.3, 118.2, 118.0, 117.7, 117.4, 56.3; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{21}H_{15}N_3O$ + Na: 348.1107; found: 348.1105.

4-(*p*-Tolyl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5ab): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5ab** (103 mg, 0.30 mmol, 76 %) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.33 (m, 4H), 7.27 (d, *J* = 1.0 Hz, 2H), 7.25 (d, *J* = 1.0 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.11 – 7.07 (m, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 138.5, 132.0, 130.2, 129.6, 129.3, 129.3, 127.6, 126.0, 123.6, 118.1, 117.4, 60.5, 21.5; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{22}H_{17}N_3O$ + Na: 362.1264; found: 362.1260.

4-(4-Methoxyphenyl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5ac): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5ac** (100 mg, 0.28 mmol, 70 %) as a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 2H), 7.39 (ddd, *J* = 7.8, 7.1, 4.3 Hz, 4H), 7.28 (d, *J* = 1.1 Hz, 1H), 7.25 (d, *J* = 2.2 Hz, 2H), 7.21 (s, 1H), 7.16 – 7.09 (m, 2H), 6.89 – 6.84 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 150.9, 130.7, 130.1, 129.7, 127.0, 124.2, 123.3, 117.7, 117.4, 117.2, 114.2, 56.2, 55.4; HRMS (ESI): m/z [M + K]$^+$ calcd. for $C_{22}H_{17}N_3O_2$ + K: 394.0952; found: 394.0950.

4-([1,1'-Biphenyl]-4-yl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5ad): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5ad** (101 mg, 0.25 mmol, 63 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.84 (m, 3H), 7.69 – 7.62 (m, 4H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 8.6 Hz, 4H), 7.32 – 7.27 (m, 3H), 7.14 (dd, *J* = 15.6, 8.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 141.3, 140.7, 130.8, 130.3, 129.7, 129.4, 129.3, 128.9, 127.6, 127.1, 126.5, 124.3, 123.6, 118.1, 117.4, 60.7; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{27}H_{19}N_3NaO$ + Na: 424.1420; found: 424.1420.

4-(4-Fluorophenyl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5ae): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5ae** (96 mg, 0.28 mmol, 70 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 2H), 7.74 – 7.69 (m, 5H), 7.41 – 7.32 (m, 11H), 7.28 (d, *J* = 1.1 Hz, 3H), 7.11 (dd, *J* = 5.7, 2.1 Hz, 7H), 7.08 – 7.06 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 (d, *J* = 273.9 Hz), 151.5, 147.1, 131.8, 130.3, 129.3, 127.9 (d, *J* = 8.2 Hz), 126.7 (d, *J* = 3.2 Hz), 123.6, 118.0, 117.4, 115.9 (d, *J* = 21.7 Hz), 60.7; 19F NMR (280 MHz, $CDCl_3$) δ -113.04 (tt, J_{F-H} = 8.6, 5.3 Hz); HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{21}H_{14}FN_3O$ + Na: 366.1013; found: 366.1009.

Methyl 4-(1-(9H-xanthen-9-yl)-1H-1,2,3-triazol-4-yl) benzoate (5af): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5af** (110 mg, 0.29 mmol, 72 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.03 (m, 2H), 7.86 (s, 1H), 7.84 – 7.80 (m, 2H), 7.37 (ddd, *J* = 10.2, 7.7, 6.1 Hz, 4H), 7.29 – 7.26 (m, 2H), 7.13 – 7.08 (m, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 151.5, 146.8, 134.8, 132.6, 130.4, 130.3, 129.9, 129.3, 125.9, 123.7, 117.8, 117.5, 60.9, 52.3; HRMS (ESI): m/z [M + K]$^+$ calcd for $C_2_3H_{17}N_3O_3$ + Na: 406.1168; found: 406.1158.

4-(*m*-Tolyl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5ag): According to the standard procedure, the crude was recrystallized from hexane/EtOAc (9:1) to obtain the product **5ag** (79 mg, 0.23 mmol, 58 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.63 (s, 1H), 7.60 – 7.55 (m, 1H), 7.43 – 7.36 (m, 4H), 7.31 (dd, *J* = 4.3, 3.3 Hz, 2H), 7.29 (s, 1H), 7.19 – 7.16 (m, 1H), 7.16 – 7.10 (m, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 147.9, 138.7, 132.2, 130.3, 130.2, 129.4, 129.3, 128.8, 126.7, 123.6, 123.3, 118.1, 117.4, 60.6, 21.6; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{22}H_{17}N_3O$ + Na: 362.1264; found: 362.1257.

4-(3-Chlorophenyl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5ah): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5ah** (78 mg, 0.22 mmol, 54 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.79 (d, *J* = 1.7 Hz, 1H), 7.63 (dt, *J* = 7.3, 1.5 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.36 (dd, *J* = 7.9, 4.5 Hz, 3H), 7.32 (dd, *J* = 4.1, 2.3 Hz, 2H), 7.29 (d, J = 2.9 Hz, 2H), 7.14 (dd, *J* = 5.2, 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 134.9, 132.2, 132.2, 130.9, 130.4, 130.2, 129.3, 128.6, 126.2, 124.2, 123.7, 117.9, 117.5, 60.9; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{21}H_{14}ClN_3O$ + Na: 382.0718; found: 382.0712.

4-(*o*-Tolyl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5ai): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5ai** (71 mg, 0.21 mmol, 52 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.56 (dd, *J* = 5.8, 2.2 Hz, 1H), 7.39 (dd, *J* = 12.5, 4.5 Hz, 4H), 7.29 (s, 1H), 7.27 – 7.23 (m, 4H), 7.11 (dd, *J* = 10.8, 3.8 Hz, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 147.9, 138.6, 132.2, 130.3, 130.2, 129.4, 129.3, 128.8, 126.7, 123.6, 123.3, 118.1, 117.4, 60.6, 21.6; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{22}H_{17}N_3O$ + Na: 362.1264; found: 362.1264.

4-(2-Chlorophenyl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5aj): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5aj** (73 mg, 0.20 mmol, 51 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.66 (s, 1H), 7.34 – 7.26 (m, 4H), 7.20 (ddd, *J* = 6.2, 3.3, 2.1 Hz, 3H), 7.16 – 7.14 (m, 2H), 7.14 – 7.07 (m, 1H), 7.06 – 7.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 144.9, 134.9, 131.2, 130.7, 130.2, 129.78, 129.5, 129.1, 127.1, 124.2, 121.64, 117.5, 117.4, 56.4; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{21}H_{14}ClN_3O$ + Na: 382.0718; found: 382.0729.

2-(1-(9H-Xanthen-9-yl)-1H-1,2,3-triazol-4-yl)benzonitrile (5ak): According to the standard procedure, the crude was recrystallized from Et_2O to obtain the product **5ak** (87 mg, 0.25 mmol, 62 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.89 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.73 (dt, *J* = 7.7, 1.6 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.41 (t, *J* = 1.5 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 4H), 7.30 – 7.27 (m, 2H), 7.17 (s, 1H), 7.14 – 7.10 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 144.5, 133.7, 133.6, 133.3, 130.9, 129.4, 128.3, 128.1, 124.2, 120.9, 118.8, 117.6, 117.2, 108.7, 56.8; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{22}H_{14}N_4O$ + Na: 373.1060; found: 373.1061.

4-(Naphthalen-2-yl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5al): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5al** (102 mg, 0.27 mmol, 68 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, *J* = 0.8 Hz, 1H), 7.95 (s, 1H), 7.91 (d, *J* = 1.5 Hz, 2H), 7.86 (ddd, *J* = 7.3, 4.0, 2.5 Hz, 2H), 7.53 – 7.49 (m, 2H), 7.41 (ddd, *J* = 5.7, 1.9, 1.1 Hz, 4H), 7.33 – 7.28 (m, 2H), 7.18 (s, 1H), 7.16 – 7.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 133.5, 133.3, 132.4, 130.2, 129.2, 128.6, 128.2, 127.8, 127.7, 126.5, 126.3, 124.8, 124.0, 123.6, 117.9, 117.3, 117.2, 60.6; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{25}H_{17}N_3O$ + Na: 398.1264; found: 398.1265.

4-(3,5-Bis(trifluoromethyl)phenyl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5am): According to the standard procedure, the crude was purified by flash column chromatography (hexane/EtOAc, 4:1) to obtain the product **5am** (127 mg, 0.28 mmol, 69 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 2H), 7.90 (s, 1H), 7.82 (s, 1H), 7.41 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 2H), 7.33 (ddd, *J* = 16.0, 8.0, 1.3 Hz, 4H), 7.17 – 7.09 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 145.3, 132.7, 132.4 (q, *J* = 33.5 Hz), 130.6, 129.2, 126.0, 125.1, 123.3 (q, *J* = 278.8 Hz), 121.9 (q, *J* = 2.3 Hz), 121.5, 117.5, 117.4, 61.3; ^{19}F NMR (280 MHz, $CDCl_3$) δ -62.90 (m); HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{23}H_{13}F_6N_3O$ + H: 462.1036; found: 462.0988.

4-(Thiophen-2-yl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5an): According to the standard procedure, the crude was recrystallized from Et_2O to obtain the product **5an** (82 mg, 0.25 mmol, 62 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.63 – 7.61 (m, 1H), 7.45 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.43 – 7.38 (m, 3H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.31 – 7.29 (m, 2H), 7.15 – 7.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 144.0, 132.3, 131.8, 130.3, 129.3, 126.5, 126.1, 123.6, 121.8, 118.1, 117.4, 60.6; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{13}N_3OS$ + Na: 354.0672; found: 354.0665.

(1-(9H-Xanthen-9-yl)-1H-1,2,3-triazol-4-yl)methanol (5ao): According to the standard procedure, the crude was recrystallized from Et_2O to obtain the product **5ao** (87 mg, 0.32 mmol, 79 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.42 – 7.36 (m, 2H), 7.32 – 7.29 (m, 2H), 7.29 – 7.28 (m, 1H), 7.26 (d, *J* = 1.1 Hz, 1H), 7.14 – 7.08 (m, 2H), 7.07 (s, 1H), 4.73 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 148.6, 130.8, 129.7, 126.9, 124.2, 120.2, 117.4, 56.7, 56.4; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{13}N_3O_2$ + Na: 302.0900; found: 302.0896.

1-(1-(9H-Xanthen-9-yl)-1H-1,2,3-triazol-4-yl)-N,N-dimethylmethanamine (5ap): According to the standard procedure, the crude was recrystallized from hexane/CH_3CN (9:1) to obtain the product **5ap** (86 mg, 0.28 mmol, 70 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.13 – 7.05 (m, 4H), 3.49 (s, 2H), 2.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 130.6, 129.6, 124.1, 120.9, 117.6, 117.5, 117.3, 56.2, 54.6, 45.3; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{19}N_4O$ + H: 307.1553; found: 307.1554.

4-(2-Methoxypropan-2-yl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5aq): According to the standard procedure, the crude was recrystallized from Et_2O to obtain the product **5aq** (68 mg, 0.22 mmol, 54 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 9.0 Hz, 2H), 7.17 (s, 1H), 7.12 (dd, *J* = 10.5, 4.4 Hz, 2H), 7.01 (s, 1H), 3.00 (s, 3H), 1.50 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 130.6, 129.7, 129.6, 124.2, 118.9, 117.7, 117.4, 72.9, 56.2, 50.5, 26.4; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{19}N_3O_2$ + Na: 344.1369; found: 344.1369.

2-(1-(9H-Xanthen-9-yl)-1H-1,2,3-triazol-4-yl)propan-2-ol (5ar): According to the standard procedure, the crude was recrystallized from Et_2O to obtain the product **5ar** (69 mg, 0.22 mmol, 56 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.38 – 7.33 (m, 3H), 7.29 – 7.22 (m, 6H), 7.10 – 7.05 (m, 3H), 7.02 (s, 1H), 1.57 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 137.9, 130.2, 129.2, 123.6, 118.5, 118.1, 117.4, 68.7, 60.4, 30.6; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{18}H_{17}N_3NaO_2$ + Na: 330.1213; found: 330.1212.

N-((1-(9H-Xanthen-9-yl)-1H-1,2,3-triazol-4-yl)methyl)benzamide (5as): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5as** (78 mg, 0.20 mmol, 51 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.6 Hz, 2H), 7.56 (s, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.35 (m, 4H), 7.28 (d, *J* = 7.7 Hz, 2H), 7.24 (s, 1H), 7.08 (t, *J* = 7.5 Hz, 2H), 7.03 (s, 1H), 6.56 (s, 1H), 4.62 (d, *J* = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 151.4, 134.2, 133.7, 131.8,

130.3, 129.3, 128.7, 128.7, 127.1, 123.7, 117.9, 117.4, 60.6, 35.5; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{23}H_{18}N_4O_2$ + Na: 405.1322; found: 405.1321.

4-Cyclohexyl-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5at): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5at** (69 mg, 0.21 mmol, 52 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 3H), 7.26 (d, *J* = 1.5 Hz, 1H), 7.25 – 7.21 (m, 3H), 7.11 – 7.04 (m, 2H), 7.00 (s, 1H), 2.74 – 2.63 (tt, *J* = 11.3, 3.5 Hz, 1H), 2.02 – 1.94 (m, 2H), 1.85 – 1.66 (m, 4H), 1.44 – 1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 130.1, 129.7, 129.2, 124.2, 123.5, 118.3, 117.3, 60.0, 35.3, 33.0, 26.2, 26.1; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{21}H_{21}N_3O$+ Na: 354.1577; found: 354.1579.

4-(*tert*-Butyl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5au): According to the standard procedure, the crude was recrystallized from hexane/Et_2O (1:1) to obtain the product **5au** (57 mg, 0.19 mmol, 47 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 6.8 Hz, 2H), 7.16 – 7.09 (m, 3H), 6.80 (s, 1H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 130.4, 129.6, 125.8, 124.0, 117.9, 117.2, 116.5, 55.8, 30.8, 30.3; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{19}N_3O$ + Na: 328.1420; found: 328.1414

4-Butyl-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5av): According to the standard procedure, the crude was recrystallized from Et_2O to obtain the product **5av** (55 mg, 0.18 mmol, 45 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.33 (m, 3H), 7.26 – 7.22 (m, 4H), 7.10 – 7.05 (m, 2H), 7.01 (s, 1H), 2.65 – 2.60 (m, 2H), 1.59 (ddd, *J* = 11.5, 7.7, 6.5 Hz, 2H), 1.33 (tt, *J* = 14.0, 7.1 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 133.7, 130.1, 129.2, 129.1, 123.5, 118.3, 117.4, 60.0, 31.4, 25.3, 22.5, 13.9; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{19}H_{19}N_3O$ + Na: 328.1420; found: 328.1423.

4-(7-Ethynylnaphthalen-2-yl)-1-(9H-xanthen-9-yl)-1H-1,2,3-triazole (5aw): The standard procedure was differed only in the amount of the alkyne: 2.4 equivalent of 2,7-diethynylnaphthalene **4w** was used. Then the crude was recrystallized from CH_3CN to obtain the product **5aw** (110 mg, 0.28 mmol, 69 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.97 (s, 1H), 7.83 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.48 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.45 (s, 1H), 7.44 – 7.39 (m, 4H), 7.31 – 7.27 (m, 3H), 7.15 (ddd, *J* = 8.2, 5.3, 1.2 Hz, 2H), 3.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 148.5, 133.0, 132.8, 132.5, 130.8, 129.7, 128.9, 128.7, 128.5, 128.0, 124.9, 124.3, 124.2, 120.1, 118.5, 117.6, 117.5, 84.0, 77.8, 56.5; HRMS (EI): m/z [M]$^+$ calcd for $C_{16}H_{16}N_4$: 264,1375; found: 264.1362.

2,7-Bis(1-(9H-xanthen-9-yl)-1H-1,2,3-triazol-4-yl)naphthalene (6): The standard procedure was differed only in the amount of the alkyne: 0.48 equivalents of 2,7-diethynylnaphthalene **4w** were used. Then the crude was recrystallized from CH_3CN to obtain the product **6** (114 mg, 0.19 mmol, 96 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 2H), 7.81 – 7.79 (m, 3H), 7.47 – 7.43 (m, 8H), 7.34 (d, *J* = 1.1 Hz, 2H), 7.32 – 7.29 (m, 6H), 7.18 (tdd, *J* = 7.1, 3.5, 1.2 Hz, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 148.5, 134.3, 133.5, 132.8, 130.7, 129.6, 128.3, 124.5, 124.2, 124.0, 118.3, 117.5, 117.3, 56.3; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{40}H_{26}N_6O_2$ + Na: 646.2015; found: 645.2003.

1-(3-Methoxy-9H-xanthen-9-yl)-4-phenyl-1H-1,2,3-triazole (5ea): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5ba** (119 mg, 0.34 mmol, 84 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.82 – 7.78 (m, 2H), 7.42 (dddd, *J* = 7.9, 7.2, 4.7, 2.0 Hz, 5H), 7.30 (ddd, *J* = 7.8, 4.2, 2.3 Hz, 2H), 7.16 – 7.09 (m, 2H), 6.82 (t, *J* = 2.2 Hz, 1H), 6.72 (dd, *J* = 8.6, 2.5 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 152.5, 151.4, 147.7, 132.1, 130.5, 130.2, 130.1, 129.4, 129.3, 128.9, 128.5, 126.08, 123.6, 117.3, 111.3, 110.3, 101.4, 60.5, 55.6; HRMS (EI): m/z [M]$^+$ calcd for $C_{22}H_{17}N_3O_2$: 355,1321; found 355.1312.

1-(3,6-Dimethoxy-9H-xanthen-9-yl)-4-phenyl-1H-1,2,3-triazole (5fa): According to the standard procedure, the crude was recrystallized from Et_2O to obtain the product **5ca** (133 mg, 0.35 mmol, 86 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.75 – 7.73 (m, 2H), 7.39 (dd, *J* = 10.3, 4.7 Hz, 2H), 7.33 – 7.28 (m, 1H), 7.26 – 7.23 (m, 2H), 6.98 (s, 1H), 6.75 (d, *J* = 2.5 Hz, 2H), 6.66 (dd, *J* = 8.6, 2.6 Hz, 2H), 3.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 150.9, 130.7, 130.1, 129.7, 127.0, 124.2, 123.3, 117.7, 117.4, 117.2, 114.2, 56.2, 55.4; HRMS (ESI): m/z [M]$^+$ calcd for $C_{23}H_{19}N_3O_3$: 385,1426; found: 385,1388.

1-(2-Bromo-9H-xanthen-9-yl)-4-phenyl-1H-1,2,3-triazole (5ga): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5da** (116 mg, 0.29 mmol, 72 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.1 Hz, 2H), 7.45 (s, 1H), 7.43 – 7.31 (m, 2H), 7.27 (d, *J* = 6.2 Hz, 3H), 7.22 (d, *J* = 6.4 Hz, 1H), 7.19 (s, 1H), 7.13 – 7.05 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 150.7, 133.9, 132.2, 131.0, 130.4, 129.6, 128.9, 128.5, 127.5, 125.8, 124.6, 119.6, 119.3, 117.9, 117.5, 117.0, 116.4, 55.8; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{21}H_{14}BrN_3O$ + Na: 426.0218; found: 426.0204.

1-(2-Fluoro-9H-xanthen-9-yl)-4-phenyl-1H-1,2,3-triazole (5ha): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5ea** (75 mg, 0.22 mmol, 56 %) as a white solid.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.9 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.28 (dd, *J* = 9.8, 1.2 Hz, 3H), 7.23 – 7.15 (m, 4H), 7.12 (s, 1H), 7.10 – 6.99 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7 (d, *J* = 243.9 Hz), 150.9, 148.9, 147.1 (d, *J* = 2.2 Hz), 130.9, 130.4, 129.6, 128.9, 128.4, 125.8, 124.5, 118.9 (d, *J* = 8.2 Hz), 118.7 (d, *J* = 7.6 Hz), 118.3 (d, *J* = 23.7 Hz), 117.9, 117.4, 116.6, 115.3 (d, *J* = 23.8 Hz), 56.3 (d, J = 1.2 Hz); ^{19}F NMR (280 MHz, $CDCl_3$) δ -117.80 (m); HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{21}H_{14}FN_3O$ + Na: 366.1019; found: 366.1013.

2-((4-Phenyl-1H-1,2,3-triazol-1-yl)methyl)quinoline (5ba):[28] According to the standard procedure, the crude was purified by flash column chromatography (20% EtOAc/hexane) to obtain the product **5ga** (36 % NMR yield; CH_2Br_2 as internal standard). The analytical data is in accordance with the literature.[35] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 20.4, 8.4 Hz, 2H), 7.88 (s, 1H), 7.77 (dd, *J* = 4.5, 2.3 Hz, 2H), 7.70 (dd, *J* = 5.6, 4.1 Hz, 1H), 7.57 – 7.49 (m, 1H), 7.37 – 7.32 (m, 5H), 7.28 (dd, *J* = 5.0, 3.6 Hz, 2H), 5.84 (s, 2H); HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{14}N_4$ + H: 287.1297; found: 287.1296.

N,4-Dimethyl-N-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)aniline (5ca): According to the standard procedure, the product **5fa** (70 mg, 0.25 mmol, 63 %) was obtained as yellow oil after extraction and removal of the solvent under vacuum. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.77 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.44 – 7.35 (m, 3H), 7.09 (d, *J* = 8.3 Hz, 2H), 7.00 – 6.96 (m, 2H), 5.87 (s, 2H), 3.21 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 145.1, 131.2, 130.4, 129.7, 128.8, 128.4, 128.3, 125.9, 114.1, 71.4, 38.6, 20.4; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{18}N_4$ + H: 279.1610; found: 279.1608.

1-(Cyclohex-2-en-1-yl)-4-phenyl-1H-1,2,3-triazole (5da): According to a modified standard procedure (first-step reaction with **1d** (5 equiv.), $TMSN_3$ (1 equiv.) and TBHP (5.5M in decane) at 100 °C for 4 h), the crude was purified by flash column chromatography (hexane/EtOAc, 5:1) to obtain the product **5da** (62.3 mg, 0.28 mmol, 69 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 2H), 7.80 (s, 1H), 7.45 – 7.39 (m, 2H), 7.35 – 7.29 (m, 1H), 6.18 (dtd, *J* = 9.7, 3.8, 1.9 Hz, 1H), 5.85 (ddt, *J* = 10.0, 3.8, 2.2 Hz, 1H), 5.32 (dtq, *J* = 7.9, 4.2, 2.2 Hz, 1H), 2.27 – 2.14 (m, 3H), 2.07 – 1.98 (m, 1H), 1.78 – 1.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 134.1, 131.0, 128.9, 128.1, 125.8, 124.3, 118.5, 56.1, 30.8, 24.8, 19.2; HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{14}H1_5N_3$ + Na: 248.1164; found: 248.1169.

(2*S*)-1-((1-(9H-Xanthen-9-yl)-1H-1,2,3-triazol-4-yl)methyl)-2-((*R*)-hydroxy(quinolin-4-yl)methyl)-5-vinylquinuclidin-1-ium tetrafluoroborate (5ax):[28] According to the standard procedure, the crude was recrystallized from Et_2O/CH_3CN (99:1) to obtain the product **5ax** (167 mg, 0.26 mmol, 65 %) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, *J* = 4.0 Hz, 1H), 8.59 (bs, 1H), 8.31 (d, *J* = 7.3 Hz, 1H), 8.24 – 8.14 (m, 1H), 7.88 (bd, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 4.1 Hz, 1H), 7.76 – 7.70 (m, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.45 – 7.36 (m, 2H), 7.30 (bs, 1H), 7.25 – 7.18 (m, 2H), 7.10 – 7.04 (m, 2H), 7.02 – 6.93 (m, 1H), 6.41 (bs, 1H), 6.12 (d, *J* = 13.3 Hz, 1H), 5.92 – 5.78 (m, 1H), 5.23 (bs, 1H), 5.18 (d, *J* = 4.7 Hz, 1H), 5.08 (d, *J* = 13.2 Hz, 1H), 4.73 – 4.53 (m, 1H), 4.05 – 3.96 (m, 1H), 3.90 – 3.83 (m, 1H), 3.55 – 3.40 (m, 1H), 3.02 – 2.91 (m, 1H), 2.86 – 2.72 (m, 1H), 2.55 – 2.42 (m, 1H), 2.21 – 2.09 (m, 1H), 1.79 (bs, 1H), 1.65 – 1.56 (m, 1H), 1.35 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 156.1, 151.5, 151.4, 149.7, 147.3, 144.7, 136.4, 135.3, 134.9, 130.8, 129.6, 128.7, 127.1, 126.6, 124.0, 123.9, 122.9, 121.8, 119.8, 118.0, 117.6, 117.5, 117.3, 116.8, 66.5, 65.5, 57.1, 56.6, 53.4, 38.1, 31.2, 27.1, 23.8, 21.3; HRMS (ESI): m/z [M]$^+$ calcd for $C_{35}H_{34}N_5O_2$: 556.2707; found: 556.2714.

(2*S*)-2-((*R*)-Hydroxy(quinolin-4-yl)methyl)-1-((1-((methyl(*p*-tolyl)amino)methyl)-1H-1,2,3-triazol-4-yl)methyl)-5-vinylquinuclidin-1-ium tetrafluoroborate (5cx):[28] According to the standard procedure, the product **5fx** (197 mg, 0.33 mmol, 83 %) was obtained as a brown solid after extraction and removal of the solvent under vacuum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 – 8.64 (m, 1H), 8.17 – 8.05 (m, 1H), 7.90 – 7.50 (m,

2H), 7.20 – 7.01 (m, 2H), 6.98 – 6.83 (m, 3H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.67 – 6.51 (m, 1H), 6.43 – 6.31 (m, 1H), 6.26 – 6.06 (m, 1H), 5.84 – 5.52 (m, 2H), 5.32 (d, *J* = 12.9 Hz, 1H), 5.19 – 4.95 (m, 2H), 4.59 – 4.39 (m, 1H), 3.93 – 3.71 (m, 2H), 3.66 – 3.48 (m, 1H), 3.18 – 3.08 (m, 1H), 3.01 (bs, 2H), 2.78 – 2.60 (m, 2H), 2.62 – 2.53 (m, 1H), 2.37 – 2.20 (m, 1H), 2.15 – 1.94 (m, 6H), 1. 6 – 1.59 (m, 1H), 1.46 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 148.8, 147.2, 147.1, 144.8, 135.3, 130.1, 129.7, 129.6, 129.5, 127.0, 126.3, 122.9, 122.5, 118.7, 116.7, 115.4, 114.5, 114.1, 113.2, 112.5, 73.0, 71.8, 71.4, 69.0, 66.7, 65.6, 65.0, 60.4, 56.8, 52.4, 48.7, 41.0, 37.9, 36.6, 31.2, 31.0, 29.7, 27.8, 27.1, 20.4, 20.3, 18.6; HRMS (ESI): m/z $[M]^+$ calcd for $C_{31}H_{37}N_6O$: 509.3023; found: 509.3018.

(2*S*)-2-((*R*)-Hydroxy(quinolin-4-yl)methyl)-1-((1-(quinolin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)methyl)-5-vinylquinuclidin-1-ium tetrafluoroborate (5bx):[28] According to the standard procedure, the crude was recrystallized from Et_2O/CH_3CN (1:1) to obtain the product **5gx** (121 mg, 0.20 mmol, 51 %) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (bs, 1H), 8.05 – 7.87 (m, 3H), 7.80 – 7.68 (m, 2H), 7.63 (bs, 1H), 7.52 – 7.35 (m, 2H), 7.25 – 7.15 (m, 1H), 6.55 – 6.39 (m, 1H), 6.10 (bs, 1H), 6.07 – 5.95 (m, 1H), 5.83 (bs, 2H), 5.17 (bs, 1H), 5.12 – 5.05 (m, 1H), 4.49 (bs, 2H), 3.78 (bs, 2H), 3.15 – 3.00 (m, 2H), 2.92 – 2.80 (m, 1H), 2.70 (s, 1H), 2.37 – 2.29 (m, 1H), 2.23 – 2.12 (m, 1H), 1.96 (s, 1H), 1.79 (bs, 1H), 1.63 (bs, 1H), 1.57 – 1.45 (m, 2H), 1.23 – 1.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 150.1, 150.0, 148.1, 147.9, 138.8, 136.3, 135.4, 130.1, 129.7, 129.5, 129.0, 128.6, 127.6, 127.1, 126.9, 125.7, 125.3, 122.9, 122.1, 118.6, 116.0, 69.4, 60.3, 49.8, 49.1, 39.0, 31.3, 28.0, 25.4, 25.1, 19.8; HRMS (ESI): m/z $[M]^+$ calcd for $C_{32}H_{33}N_6O$: 517,2710; found: 517.2701.

5-(1-(9H-Xanthen-9-yl)-1H-1,2,3-triazol-4-yl)-1-((2*R*,4*S*,5*R*)-4-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (5ay):[28] According to the standard procedure, the crude was recrystallized from Et_2O to obtain the product **5ay** (127 mg, 0.27 mmol, 67 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 1.7 Hz, 1H), 7.79 – 7.75 (m, 3H), 7.60 (bs, 1H), 7.42 – 7.38 (m, 2H), 7.38 – 7.34 (m, 2H), 7.10 – 7.05 (m, 2H), 5.90 (d, *J* = 1.2 Hz, 1H), 5.47 (d, *J* = 3.5 Hz, 1H), 3.26 (d, *J* = 3.5 Hz, 2H), 2.98 – 2.96 (m, 1H), 1.65 – 1.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 169.7, 164.3, 140.6, 133.9, 130.5, 130.3, 129.1, 127.9, 126.5, 125.7, 125.3, 68.9, 53.8, 45.4, 39.4, 37.3, 22.0, 21.9; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{24}H_{21}N_5O_6$ + Na: 498.1390; found: 498.1378.

(1-(9H-Xanthen-9-yl)-1H-1,2,3-triazol-4-yl)methyl5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoate (5az): According to the standard procedure, the crude was recrystallized from CH_3CN to obtain the product **5az** (125 mg, 0.25 mmol, 62 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.41 (m, 2H), 7.41-7.32 (m, 2H), 7.28 (bs, 1H), 7.21 – 7.07 (m, 4H), 5.78 (bs, 1H), 5.20 (bs, 1H), 5.14-5.07 (m, 2H), 4.49 (bs, 1H), 4.29 (bs, 1H), 3.11 (bs, 1H), 2.90-2.85 (m, 1H), 2.75-2.65 (m, 1H), 2.40 – 2.22 (m, 2H), 1.75-1.25 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 150.9, 143.6, 130.7, 130.3, 129.6, 129.2, 124.1, 123.6, 117.4, 61.9, 60.1, 57.4, 57.3, 56.4, 55.4, 40.5, 33.6, 28.2, 24.6; HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{26}H_{27}N_5O_4S$ + Na: 528.1681; found: 528.1674.

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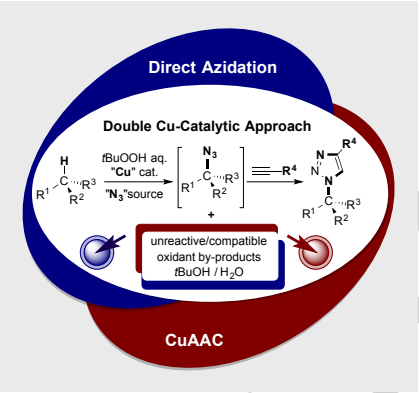

Tobias Brandhofer, Aysegül Özdemir, Andrea Gini, Olga García Mancheño**

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