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One-Pot Sequential Azide–Alkyne [3+2] Cycloaddition and Atom Transfer Radical Addition (ATRA): Expanding the Scope of In Situ Copper(I) Regeneration in the Presence of Environmentally Benign Reducing Agent

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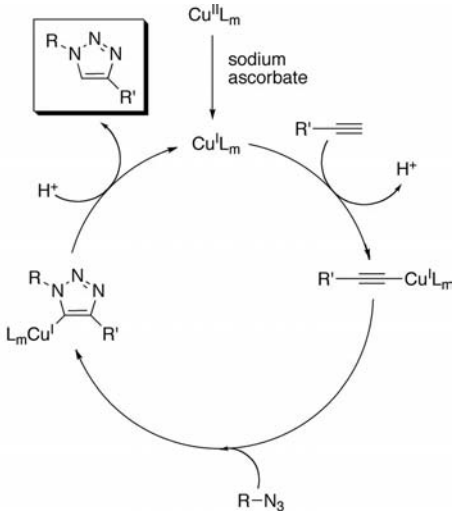
One-pot sequential reactions involving azide–alkyne [3+2] cycloaddition and atom transfer radical addition (ATRA) catalyzed by [Cu^{II}(TPMA)X][X] {X = Br^- or Cl^-, TPMA = tris(2-pyridylmethyl)amine} in the presence of ascorbic acid as a reducing agent are reported. Reactions with azidopropyl methacrylate and 1-(azidomethyl)-4-vinylbenzene in the presence of a variety of alkynes [phenylacetylene, (3,4-difluorophenyl)acetylene, propargyl alcohol, 2-methyl-3-butyn-2-ol, methyl propiolate and ethyl propiolate] and alkyl halides (carbon tetrachloride, carbon tetrabromide, ethyl trichloroacetate, methyl trichloroacetate, ethyl dichloroacetate, methyl dichloroacetate, dichloroacetonitrile and 2-bromopropionitrile) proceeded efficiently to yield highly functionalized (poly)halogenated esters and aryl compounds containing a triazolyl group in the presence of as low as 0.5 mol-% of the catalyst. It is envisioned that the presented methodology could have further implications in the organic synthesis of functionalized triazoles, which have recently been identified as the lead targets for the screening of potential pharmaceutical drugs.

Introduction and Background

In 2001, reinvigoration of an old style of organic synthesis was defined in response to the demands of modern chemistry.[1] This was coined as "click chemistry" describing a faster and modular style of synthesis. Among the reactions that met the stringent criteria, copper-catalyzed Huisgen [3+2] cycloaddition popularized by the Meldal[2] and Sharpless[3] laboratories was the first to achieve the "click status". To date, this reaction has emerged as the best example of click chemistry due to its reliability, robustness, functional-group tolerance, ability to withstand a wide spectrum of solvents, and desirable properties of the triazole.[1,2,4] Numerous applications of this type of chemistry have been found in all aspects of bioconjugation, drug discovery, and materials science.[4–6]

Mechanistically, the first step in the copper-catalyzed [3+2] cycloaddition involves the formation of copper(I) acetylides, which are formed from copper(I) [typically regenerated from copper(II) in the presence of sodium ascorbate], terminal alkynes, and a base (Scheme 1). The generated copper(I) acetylide species have a strong tendency to form μ-coordinate bridged aggregates, the formation of which is strongly dependent on the nature and type of complexing ligand.[7] The second step in the catalytic cycle is the reaction of copper(I) acetylides with organic azides to from triazolyl–copper intermediates,[8] which upon protonolysis yield the desired 1,2,3-triazole. This last step also regenerates the copper(I) catalyst.



Scheme 1. Proposed mechanism for the copper-catalyzed [3+2] cycloaddition.[9,10]

Other C–C bond-forming reactions that are becoming synthetically more useful are the transition-metal-catalyzed atom transfer radical addition (ATRA) and the intramolecular counterpart, atom transfer radical cyclization (ATRC).[11–16] Traditionally, both were conducted in the presence of high catalyst loadings, therefore facing issues in product separation and catalyst recycling. A solution to

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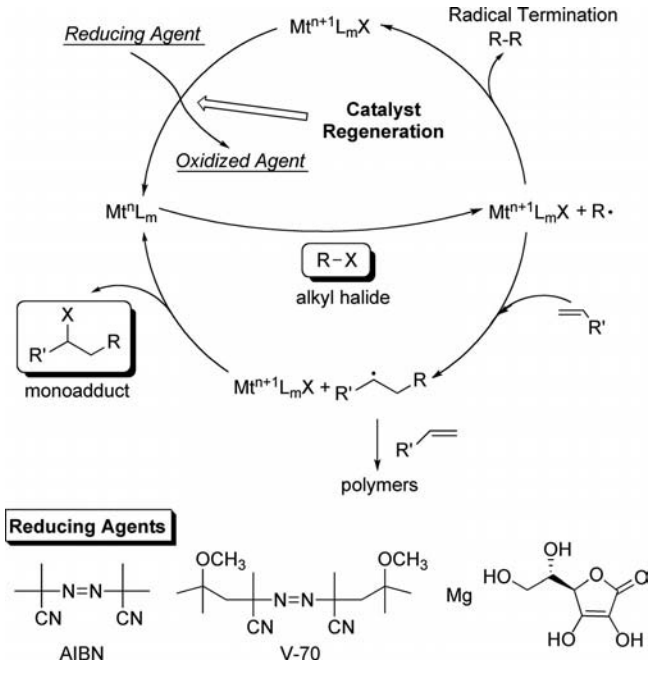
these problems was found for the mechanistically similar atom transfer radical polymerization (ATRP),[17,18] in which reducing agents were utilized to continuously regenerate the activator or copper(I) complex.[19–22] Catalyst-regeneration technique has also been shown to be highly efficient in ruthenium-[23] and copper-catalyzed[14,24–27] ATRA and ATRC reactions. The presence of the reducing agents (free-radical diazo initiators, magnesium or ascorbic acid) successfully allowed the reduction of the amount of the transition metal complex, and as a result, these reactions can now be conducted by using very low amounts of the catalyst.[28–40]

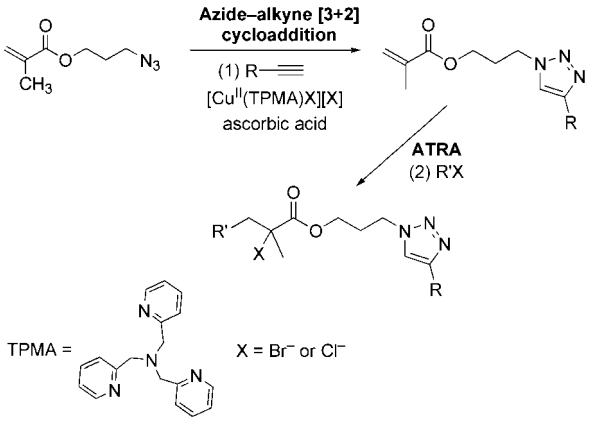
Additionally, the methodology was also extended to include sequential organic transformations involving ATRA/ATRC.[41–43]

The proposed mechanism for the copper-catalyzed ATRA in the presence of reducing agents is shown in Scheme 2. The role of the reducing agent is to continuously regenerate copper(I) from the copper(II) complex that accumulates in the reaction mixture as a result of unavoidable and often diffusion-controlled radical–radical termination reactions. The copper(I) complex starts a catalytic cycle by homolytically cleaving an alkyl–halide bond to produce an alkyl radical that adds across a carbon–carbon double bond of an alkene. The generated secondary radical then irreversibly abstracts a halogen atom from the copper(II) complex to form the desired monoadduct. This step regenerates the activator or copper(I) complex, completing the catalytic cycle. As indicated in Scheme 2, the competing side reactions in this process besides radical terminations by either coupling or disproportionation include repeating radical additions to the alkene to form oligomers/polymers.



Scheme 2. Proposed mechanism for the copper-catalyzed atom transfer radical addition (ATRA) in the presence of a reducing agent.

Since the azide–alkyne [3+2] cycloaddition (Scheme 1) [1,3,4] and ATRA (Scheme 2)[14,26,27] are both catalyzed by copper(I) complexes, our attention has focused on the possibility of mediating these reactions in a one-pot sequential manner (Scheme 3). Such a sequence would lead to the formation of compounds with both triazole and halogen functionalities. The latter one is particularly attractive, because it opens up the possibilities for numerous organic transformations such as elimination, displacement, conversion to a Grignard reagent, etc. Also, on the other hand, the halogen functionality could serve as further radical precursor. A combination of copper-catalyzed azide–alkyne [3+2] cycloaddition and mechanistically similar ATRP was first explored by the group of Matyjaszewski in a two-pot two-step manner consisting of converting the halogen end-groups in well-defined polymers to azides and subsequently to triazoles.[44,45] The methodology was also successfully extended to a one-pot simultaneous reaction in which propargyl methacrylate and alkyl azides were allowed to react to yield highly functionalized and well-defined polymeric materials.[46,47] However, to the best of our knowledge, the two reactions were never applied to small-molecule synthesis.



Scheme 3. Copper-catalyzed sequential azide–alkyne [3+2] cycloaddition and atom transfer radical addition (ATRA).

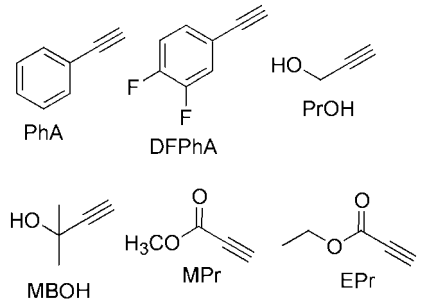
In this article, we report on one-pot sequential reactions involving azide–alkyne [3+2] cycloaddition and atom transfer radical addition (ATRA) catalyzed by $[Cu^{II}(TPMA)X][X]$ [X = Br^- or Cl^-, TPMA = tris(2-pyridylmethyl)amine] in the presence of ascorbic acid as a reducing agent.

Results and Discussion

Copper-Catalyzed Azide–Alkyne [3+2] Cycloaddition

In our previous reports we demonstrated that copper(II) complexes with the TPMA ligand {$[Cu^{II}(TPMA)X][X]$, X = Br^- or Cl^-} in the presence of reducing agents such as free-radical diazo initiators or ascorbic acid were highly active in ATRA, ATRC, and domino or cascade-type reactions.[24,25,30,40,41] The next logical step was to determine whether the same complexes could also catalyze azide–alkyne [3+2] cycloadditions, particularly taking into account

that the tetradentate nature of the TPMA[48] ligand could block the coordination of the alkyne to the copper(I) center, which is an important step in the reaction mechanism (Scheme 1).[6,49,50] Series of reactions involving azidopropyl methacrylate (AzPM) and various alkynes (Scheme 4 and Table 1) were performed in the presence of [Cu^{II}(TPMA)][Cl][Cl] and ascorbic acid as a reducing agent.



Scheme 4. Structures of alkynes used in the azide–alkyne [3+2] cycloaddition and atom transfer radical addition.

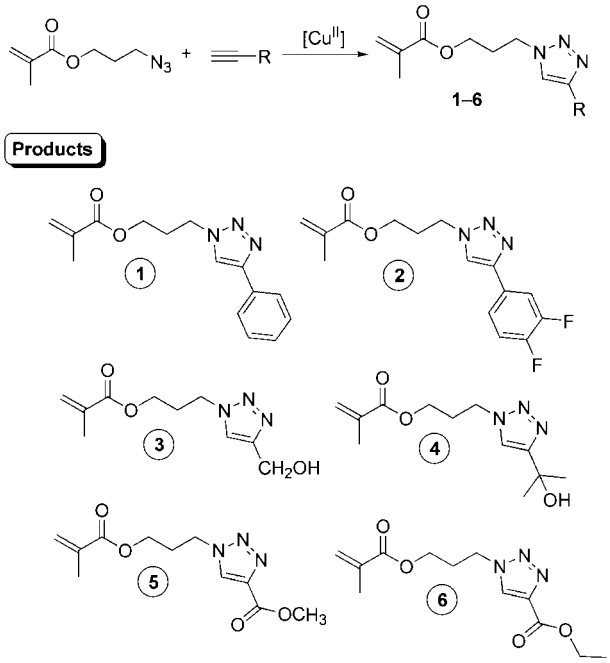
Although sodium ascorbate is widely used for in situ regeneration of Cu^{I} from Cu^{II} salts in azide–alkyne cycloaddition,[6] its insolubility in MeOH shifted our choice towards ascorbic acid.

As indicated in Table 1, cycloaddition reactions between AzPM and the alkynes phenylacetylene (PhA), (3,4-difluorophenyl)acetylene (DFPhA), propargyl alcohol (PrOH) 2-methyl-3-butyn-2-ol (MBOH), methyl propiolate (MPr) and ethyl propiolate (EPr) (Entries 1, 6, 11, 14, 17, and 21) in the presence of 1.0 mol-% of [Cu^{II}(TPMA)Cl][Cl] and 10–25 equiv. of ascorbic acid (relative to Cu^{II} complex) afforded the formation of the corresponding triazoles in nearly quantitative yields. Encouraged by these results, the extent of catalyst loading was further examined. In previous reports, azide–alkyne [3+2] cycloaddition reactions catalyzed by copper(I) in conjunction with the TPMA ligand required at least 10 mol-% of the complex relative to the azide.[44,49] Surprisingly, with DFPhA, MPr, and EPr triazoles were synthesized in 93%, 81%, and 86% yields (Table 1, Entries 10, 20 and 24), respectively, by using as low as 0.2 mol-% of the copper catalyst. An even lower catalyst loading (0.1 mol-%) was suffiecient for the reaction between AzPM and PhA (Entry 5). To the best of our knowledge, these are one of the lowest amounts of copper(II) complexes required to efficiently catalyze azide–alkyne [3+2] cycloaddition.

Sequential Azide–Alkyne [3+2] Cycloaddition and Atom Transfer Radical Addition (ATRA)

Having demonstrated the efficiency of [Cu^{II}(TPMA)Cl][Cl] to catalyze the azide–alkyne [3+2] cycloaddition in the presence of ascorbic acid as a reducing agent, optimization studies were conducted to maximize the yield of the monoadduct in the second sequential step involving ATRA of CCl_4. The results are summarized in Table 2. For all alkynes, nearly quantitative yields of the triazolyl haloalkyl esters were obtained by using 1.0 mol-% of the copper catalyst (Entries 1, 5, 8, 12, 16, and 20). Typical ^1H and ^{13}C NMR spectra of the reaction product (**6a**) are shown in

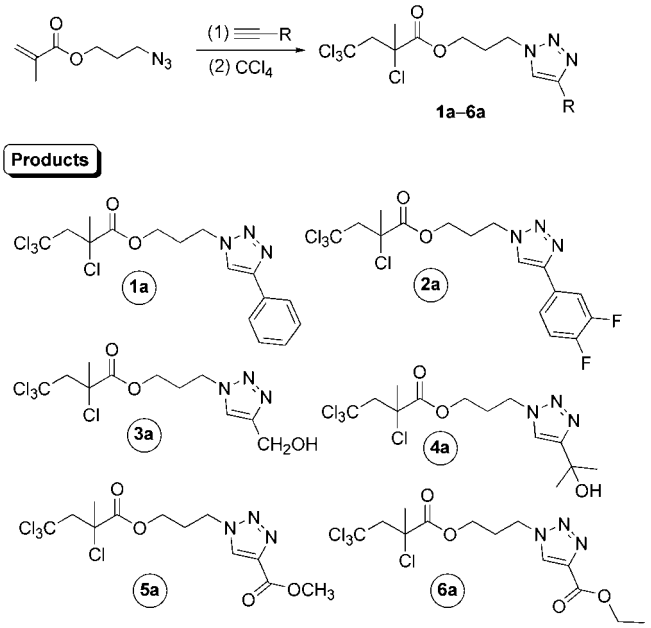
Table 1. [Cu^{II}(TPMA)Cl][Cl]-catalyzed azide–alkyne [3+2] cycloaddition in the presence of ascorbic acid as a reducing agent.



Entry[a]	Alkyne	Product	[Cu^{II}][b]	t [h]	Yield [%][c]
1	PhA	1	1.0	1	ca. 100
2			0.25	1	93
3			0.25	6	96
4			0.2	6	90
5			0.1	24	83
6	DFPhA	2	1.0	1	ca. 100
7			0.5	2	92
8			0.5	3	ca. 100
9			0.25	18	92
10			0.20	18	93
11	PrOH	3	1.0	3	ca. 100
12			0.50	3	90
13			0.25	6	76
14	MBOH	4	1.0	3	ca. 100
15			0.50	24	91
16			0.25	24	56
17	MPr	5	1.0	1	ca. 100
18			0.50	1	95
19			0.25	3	90
20			0.20	3	81
21	EPr	6	1.0	3	ca. 100
22			0.50	3	97
23			0.25	3	93
24			0.20	3	86

[a] All reactions were performed in CH_3OH at 60 °C by using $[AzPM]_0/[Alkyne]_0$ = 1:1, $[AzPM]_0$ = 0.50 M. The amount of ascorbic acid in each system ranged between 20 and 25 equiv. relative to that of the copper(II) complex. For alkyne structures, see Scheme 4. [b] mol-% relative to AzPM. [c] The yield is based on the formation of the triazole and was determined by ^1H NMR spectroscopy using *p*-dimethoxybenzene as internal standard (relative errors are ±15%).

Table 2. Sequential azide–alkyne [3+2] cycloaddition and atom transfer radical addition (ATRA) of carbon tetrachloride catalyzed by [Cu^{II}(TPMA)Cl][Cl] in the presence of ascorbic acid as a reducing agent.



Entry[a]	Alkyne	Product	[Cu^{II}][b]	t [h][c]	Yield [%][d]
1	PhA	1a	1.0	2	ca. 100 (91)[e]
2			0.50	3	90
3			0.25	3	78
4			0.20	3	70
5	DFPhA	2a	1.0	3	96
6			0.50	4	90
7			0.25	6	83
8	PrOH	3a	1.0	3	95 (86)[e]
9			0.50	3	86
10			0.25	3	83
11			0.20	3	73
12	MBOH	4a	1.0	3	ca. 100
13			0.50	3	86
14			0.25	3	74
15			0.20	3	72
16	MPr	5a	1.0	1	98
17			0.50	1	91
18			0.25	1	86
19			0.20	1	72
20	EPr	6a	1.0	3	ca. 100 (89)[e]
21			0.50	3	ca. 100
22			0.25	3	85
23			0.20	3	65

[a] All reactions were performed in CH_3OH at 60 °C by using $[AzPM]_0/[Alkyne]_0$ = 1:1, $[AzPM]_0$ = 0.50 M. The amount of ascorbic acid in each system ranged between 20 and 25 equiv. relative to that of the copper(II) complex. For alkyne structures, see Scheme 4. [b] mol-% relative to alkyne. [c] Reaction time for azide–alkyne cycloaddition [time for ATRA reaction was 8 h for all substrates with $(AzPM)_0/(CCl_4)_0$ = 1:1.25]. [d] The yield is based on the formation of the product and was determined by ^{1}H NMR spectroscopy by using *p*-dimethoxybenzene as internal standard (relative errors are ±15%). [e] Isolated yield for the large-scale reaction.

Figure 1. Further decrease in catalyst loading to 0.5 mol-% still resulted in very high yields of the desired monoadduct (Entries 2, 6, 9, 13, 17, and 21). It is particularly important to notice that the reaction mixtures containing as low as 0.25 mol-% of [Cu^{II}(TPMA)Cl][Cl] still proceeded efficiently to afford the final product in yields higher than 80% (Entries 7, 10, 18 and 22).

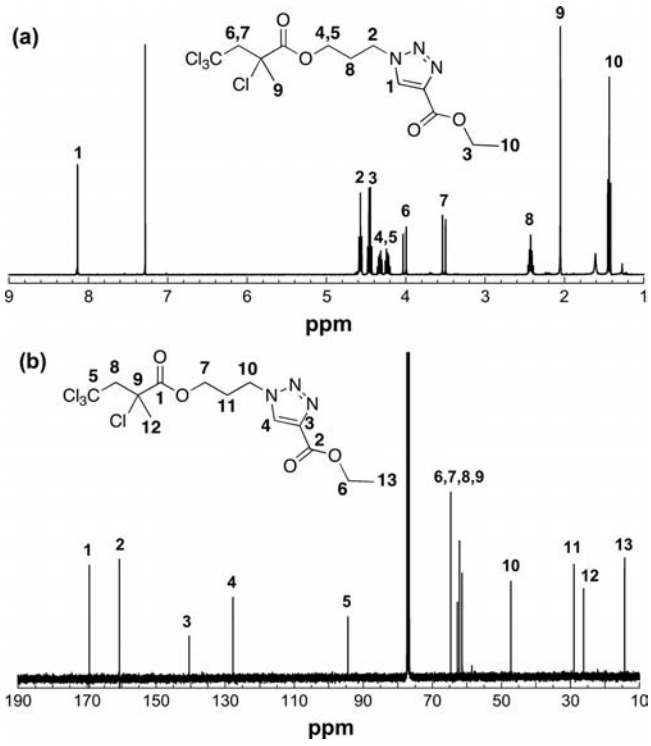
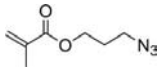
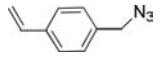


Figure 1. ^{1}H (a) and ^{13}C NMR ($CDCl_3$, 298 K) spectra of **6a**.

The results presented in Tables 1 and 2 clearly indicate that copper(II) complexes with the TPMA ligand, in conjunction with ascorbic acid, are very efficient catalysts for both azide–alkyne [3+2] cycloaddition and ATRA. In order to further demonstrate the synthetic usefulness of this sequential sequence of reactions, additional experiments were performed by using a variety of alkyl halides including carbon tetrabromide (CBr_4), ethyl trichloroacetate (CCl_3CO_2Et), methyl trichloroacetate (CCl_3CO_2Me), ethyl dichloroacetate (CCl_2HCO_2Et), methyl dichloroacetate (CCl_2HCO_2Me), dichloroacetonitrile (CCl_2HCN), and 2-bromopropionitrile [$CHBr(CH_3)CN$]. The results for azidopropyl methacrylate (AzPM) and 1-(azidomethyl)-4-vinylbenzene (AzMVB) are summarized in Table 3. As expected, for AzPM excellent yields of the final monoadduct were obtained by using CBr_4 and catalyst loadings as low as 0.50 mol-% (Entries 2 and 12). The corresponding molecular structure of the product in the case of methyl propiolate is shown in Figure 2. Sequential azide–alkyne [3+2] cycloaddition and ATRA also worked reasonably well for tri- and dihalogenated substrates by using 1.0 mol-% of the catalyst. The monohalogenated alkyl halide 2-bromopropionitrile yielded only 35 and 75% of the monoadduct in the case of phenylacetylene (Entry 10) and methyl propiolate (Entry 25), respectively. The decreased yield can be attributed to monoadduct reactivation resulting in the formation of oligomers/polymers. Furthermore, as indicated in

Table 3, the results for AzMVB were similar to AzPM. Generally, with 1.0 mol-% of the catalyst relative to azide, yields higher than 80% were obtained by using CCl_4 (Entries 27 and 32). Respectable yields of the monoadduct were still observed by using trihalogenated alkyl halides (Entries 30, 31, 35 and 37), but significantly decreased for dihalogenated ones (Entries 39, 40 and 41). Lastly, the monoadduct formed from the azide–alkyne [3+2] cycloaddition of methyl propiolate to AzMVB followed by sequential ATRA of 2-bromopropionitrile was attained in only 26% yield.

Table 3. Sequential azide–alkyne [3+2] cycloaddition and atom transfer radical addition (ATRA) of various alkyl halides catalyzed by $[Cu^{II}(TPMA)X][X]$ (X = Br^- or Cl^-) in the presence of ascorbic acid as a reducing agent.

Entry[a]	Alkyne	RX	$[Cu^{II}]$[b]	t_1 [h]/t_2 [h][c]	Product	Yield [%][d]
						
1	PhA	CBr_4	1.0	2/8	**7a**	99 (90)[e]
2			0.50	2/8		96
3			0.25	6/8		80
4		CCl_3CO_2Et	1.0	2/24	**8a**	82
5			0.50	2/24		72
6		CCl_2HCO_2Et	1.0	2/24	**9a**	80
7			0.50	2/24		65
8		CCl_2HCN	1.0	2/24	**10a**	85
9			0.50	2/24		70
10		$CHBr(CH_3)CN$	1.0	2/24	**11a**	35
11	MPr	CBr_4	1.0	2/8	**12a**	100 (86)[e]
12			0.50	2/8		94
13			0.25	6/8		78
14		CCl_3CO_2Et	1.0	1/24	**13a**	81
15			0.50	1/24		75
16		CCl_3CO_2Me	1.0	2/24	**14a**	91
17			0.50	2/24		81
18		CCl_2HCO_2Et	1.0	2/24	**15a**	80 (73)[e]
19			0.50	2/24		75
20			0.25	2/24		64
21		CCl_2HCO_2Me	1.0	2/24	**16a**	83
22			0.50	2/24		70
23		CCl_2HCN	1.0	2/24	**17a**	83
24			0.50	2/24		78
25		$CHBr(CH_3)CN$	1.0	2/24	**18a**	75
26			0.50	2/24		74
						
27	PhA	CCl_4	1.0	3/8	**19a**	85 (86)[e]
28			0.50	3/8		83
29			0.25	6/8		32
30		CCl_3CO_2Et	1.0	6/24	**20a**	45
31		CCl_3CO_2Me	1.0	6/24	**21a**	57
32	MPr	CCl_4	1.0	2/8	**22a**	92 (90)[e]
33			0.50	2/8		73
34			0.25	2/8		47
35		CCl_3CO_2Et	1.0	2/24	**23a**	87
36			0.50	2/24		83
37		CCl_3CO_2Me	1.0	2/24	**24a**	82 (84)[e]
38			0.50	2/24		78
39		CCl_2HCO_2Et	1.0	2/24	**25a**	43
40		CCl_2HCO_2Me	1.0	2/24	**26a**	48
41		CCl_2HCN	1.0	2/24	**27a**	46
42		$CHCl_3$	1.0	1/24	**28a**	42
43		$CHBr(CH_3)CN$	1.0	2/24	**29a**	26

[a] All reactions were performed in CH_3OH at 60 °C by using $[AzPM \text{ or } AzMVB]_0/[Alkyne]_0$ = 1:1, $[AzPM \text{ or } VBAz]_0$ = 0.50 M. The amount of ascorbic acid in each system ranged between 20 and 25 equiv. relative to that of the copper(II) complex. For alkyne structures, see Scheme 4. [b] mol-% relative to alkyne. [c] t_1 = reaction time for azide–alkyne cycloaddition, t_2 = reaction time for ATRA. For all alkyl halides 2 equiv. were used relative to AzPM or AzMVB, except for CCl_4 where only 1 equiv. was utilized. [d] The yield is based on the formation of the product and was determined by ^1H NMR spectroscopy by using *p*-dimethoxybenzene as internal standard (relative errors are ±15%). [e] Isolated yield for the large-scale reaction.

Certainly, from the point of view of further synthetic modifications of the resulting sequential product such as conversion to a Grignard reagent, monohalogenated alkyl halides are of particular interest. Future efforts in our laboratories are directed towards optimizing reaction conditions for such substrates and utilizing more active copper complexes.

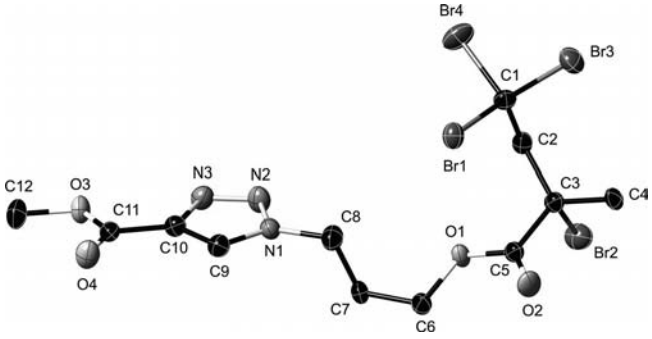


Figure 2. Molecular structure of (*S*)-monoadduct **12a** formed by the sequential azide–alkyne [3+2] cycloaddition between azidopropyl methacylate and methyl propiolate followed by ATRA of CBr_4 at 296 K, shown with 30% probability displacement ellipsoids. H atoms have been omitted for clarity.

Conclusions

We have reported the first examples of one-pot sequential reactions involving azide–alkyne [3+2] cycloaddition and atom transfer radical addition (ATRA). Both transformations are catalyzed by $[Cu^{II}(TPMA)X][X]$ (X = Br^- or Cl^-) complexes in conjunction with ascorbic acid as the reducing agent. Reactions with azidopropyl methacrylate and 1-(azidomethyl)-4-vinylbenzene in the presence of a variety of alkynes and alkyl halides proceeded efficiently to yield highly functionalized (poly)halogenated esters and aryl compounds containing a triazolyl group in the presence of as low as 0.5 mol-% of the catalyst. It is envisioned that the presented methodology could have further implications in organic synthesis of functionalized triazoles. Such compounds have recently been identified as the lead targets for the screening of potential pharmaceutical drugs. Additionally, our methodology incorporates a highly desirable halogen functionality, which is very versatile towards further organic transformations.

Experimental Section

General Procedures: All alkynes [phenylacetylene, (3,4-difluorophenyl)acetylene, propargyl alcohol, 2-methyl-3-butyn-2-ol, methyl propiolate and ethyl propiolate], 3-bromopropanol, methacryloyl chloride, and solvents (methanol, dichloromethane and pentane) were purchased from commercial sources and used as received. Tris(2-pyridylmethyl)amine,[51] azidopropyl methacrylate,[45] 1-(azidomethyl)-4-vinylbenzene,[52] and $[Cu^{II}(TPMA)X][X]$ (X = Br^- or Cl^-)[24,25] were synthesized according to literature procedures. ^1H and ^{13}C NMR spectra were obtained with Bruker Avance 400 MHz and 500 MHz spectrometers. All chemical shifts are given in ppm relative to residual solvent peaks (^1H: $CDCl_3$: δ = 7.26 ppm, CD_2Cl_2: δ = 5.32 ppm; ^{13}C: $CDCl_3$: δ = 77.2 ppm, CD_2Cl_2: δ = 54.0 ppm).

Stock Solutions: $[Cu^{II}(TPMA)Cl][Cl]$ solutions (0.04 M, 0.02 M and 0.01 M) were prepared by dissolving the corresponding copper(II) complex in methanol using volumetric flasks to accommodate various catalyst loadings. Azidopropyl methacrylate (320 μL, 2.0 mmol) was mixed with an equimolar amount of the alkyne {2.0 mmol: 220 μL (phenylacetylene), 240 μL [(3,4-difluorophenyl)-acetylene], 117 μL (propargyl alcohol), 194 μL (2-methyl-3-butyn-2-ol), 179 μL (methyl propopiolate), 203 μL (ethyl propopiolate)} and *p*-dimethoxybenzene added as internal standard (approximately 0.1 mol-% relative to azidopropyl methacrylate). Methanol was then added in order to make each stock solution 3.3 M in azidopropyl methacrylate.

General Procedure for Azide–Alkyne [3+2] Cycloaddition Catalyzed by $[Cu^{II}(TPMA)Cl][Cl]$ in the Presence of Ascorbic Acid: All reactions were performed in disposable 5.0 mm NMR tubes equipped with a plastic cap and Teflon tape. In a typical experiment, 60 μL of the stock solution [0.2 mmol of azidopropyl methacrylate (AzPM) and 0.2 mmol of alkyne] was added to the NMR tube, followed by the desired amount of the copper(II) catalyst {from 0.04 M $[Cu^{II}(TPMA)Cl][Cl]$ and for $[AzPM]_0/[Cu^{II}]_0$ = 100:1 (50 μL), from 0.02 M $[Cu^{II}(TPMA)Cl][Cl]$ and for $[AzPM]_0/[Cu^{II}]_0$ = 200:1 (50 μL), from 0.01 M $[Cu^{II}(TPMA)Cl][Cl]$ and for $[AzPM]_0/[Cu^{II}]_0$ = 400:1 and 500:1 (50 μL and 40 μL, respectively)} and 20–25 equiv. of 0.25 M ascorbic acid in methanol {relative to $[Cu^{II}(TPMA)Cl][Cl]$}. Methanol was then added in order to maintain a constant volume and a total concentration of 0.50 M in azidopropyl methacrylate. Each reaction mixture was immediately flushed with argon for at least 30 s and immersed in an oil bath thermostatted at 60 °C. The percent yield of the expected triazole was obtained by ^1H NMR spectroscopy relative to the internal standard. If necessary, solvent was partially evaporated prior to ^1H NMR analysis.

General Procedure for Sequential Azide–Alkyne [3+2] Cycloaddition/Atom Transfer Radical Addition Catalyzed by $[Cu^{II}(TPMA)Cl][Cl]$ in the Presence of Ascorbic Acid: The first step was performed as explained above. After completion of the azide–alkyne [3+2] cycloaddition, the reaction mixture was taken into a dry box (< 1.0 ppm O_2 and < 0.5 ppm H_2O), and carbon tetrachloride (24 μL, 2.5 mmol, 1.25 equiv. relative to AzPM) or (poly)halogenated alkyl halide (4.0 mmol, 2.0 equiv. relative to AzPM) was added. The NMR tube was then capped and sealed with Teflon tape and immersed in an oil bath thermostatted at 60 °C. The percent yield of the expected triazolyl halogenated alkyl ester was obtained by ^1H NMR spectroscopy relative to the internal standard. If necessary, solvent was partially evaporated prior to ^1H NMR analysis.

X-ray Crystal Structure Determination: The X-ray intensity data were collected with a Bruker Smart Apex II CCD diffractometer at 150 K by using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). Data reduction included absorption corrections by the multi-scan method using SADABS.[53] Structures were solved by direct methods and refined by full-matrix least-squares using the SHELXTL 6.1 bundled software package.[54] Hydrogen atoms were positioned geometrically (aromatic C–H 0.93 Å, methylene C–H 0.97 Å, methyl C–H 0.96 Å) and treated as riding atoms during subsequent refinement, with $U_{iso}(H) = 1.2U_{equiv}(C)$ or $1.5U_{equiv}$-(methyl C). The methyl groups were allowed to rotate about their local threefold axes. ORTEP-3 for Windows[55] and Crystal Maker 7.2 were used to generate molecular graphics. Further

details are given in Table 4. CCDC-805615 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 4. Crystal structure analysis data for methyl 1-[3-(2,4,4,4-tetrabromo-2-methylbutanoyloxy)propyl]-1*H*-1,2,3-triazole-4-carboxylate (**12a**).

Empirical formula	$C_{12}H_{15}Br_4N_3O_4$
Formula mass	584.91
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system, space group	monoclinic, *P*21/*n*
Unit cell dimensions:	
a	11.6637(4) Å
b	6.0493(2) Å
c	26.2815(9) Å
β	98.406(2)°
Volume	1834.43(11) Å^3
Z, calculated density	4, 2.118 Mg/m^3
Absorption coefficient	8.795 mm^{-1}
F(000)	1120
Crystal size	0.32× 0.09× 0.05 mm
θ range for data collection	1.57–26.19°
Limiting indices:	
h	–14 to 14
k	–7 to 7
l	–32 to 32
Reflections collected/unique	21440/3654 [*R*(int) = 0.0426]
Completeness to *θ*	99.0%
Absorption correction	semi-empirical from equivalents
Max./min. transmission	0.6930/0.1676
Refinement method	full-matrix least squares on F^2
Data/restraints/parameters	3654/0/210
Goodness of fit on F^2	1.363
Final *R* indices [$I>2\sigma(I)$]	R_1 = 0.0587, wR_2 = 0.1796
R indices (all data)	R_1 = 0.0785, wR_2 = 0.1947
Largest difference peak/hole	2.685/–1.162 e Å^{-3}

Product Characterization

For detailed ^{1}H and ^{13}C NMR assignments, see the Supporting Information.

3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)propyl Methacrylate (1): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.82–7.80 (m, 2 H), 7.77 (s, 1 H), 7.41 (t, *J* = 7.5 Hz, 2 H), 7.32 (t, *J* = 7.5 Hz, 1 H), 6.10 (s, 1 H), 5.60 (s, 1 H), 4.53 (t, *J* = 7.0 Hz, 2 H), 4.24 (t, *J* = 7.0 Hz, 2 H), 4.02 (d, *J* = 15 Hz, 1 H), 3.50 (d, *J* = 15 Hz, 1 H), 2.36 (quint, *J* = 6.0 Hz, 2 H), 1.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.19, 147.94, 135.95, 130.52, 128.87, 128.23, 126.10, 125.75, 119.79, 61.25, 47.39, 29.58, 18.33 ppm.

3-[4-(3,4-Difluorophenyl)-1*H*-1,2,3-triazol-1-yl]propyl Methacrylate (2): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.75 (s, 1 H), 7.67–7.62 (m, 1 H), 7.52–7.49 (m, 1 H), 7.19 (q, *J* = 10 Hz, 1 H), 6.10 (s, 1 H), 5.60 (s, 1 H), 4.51 (t, *J* = 7.0 Hz, 2 H), 4.23 (t, *J* = 6.0 Hz, 1 H), 2.38–2.30 (m, 2 H), 1.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.18, 151.74, 149.27, 146.08, 135.92, 126.13, 121.78, 119.98, 117.79, 114.48, 61.16, 47.5, 29.34, 18.32 ppm.

3-[4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]propyl Methacrylate (3): ^{1}H NMR (500 MHz. $CDCl_3$): δ = 7.58 (s, 1 H), 6.13 (s, 1 H), 5.63 (s, 1 H), 4.83 (s, 2 H), 4.50 (t, *J* = 7.0 Hz, 2 H), 4.20 (t, *J* = 6.0 Hz, 2 H), 2.38–2.32 (m, 2 H), 1.97 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 161.13, 140.23, 136.00, 127.79, 126.21, 60.85, 52.39, 47.63, 29.10, 18.26 ppm.

3-[4-(2-Hydroxyprop-2-yl)-1*H*-1,2,3-triazol-1-yl]propyl Methacrylate (4): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.49 (s, 1 H), 6.11 (s, 1 H), 5.60 (s, 1 H), 4.46 (t, *J* = 7.0 Hz, 2 H), 4.20 (t, *J* = 6.0 Hz, 2 H), 2.35–2.29 (m, 2 H), 1.95 (s, 3 H), 1.64 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.32, 15.79, 135.95, 127.79, 126.03, 119.59, 68.38, 61.41, 47.19, 30.57, 29.50, 18.23 ppm.

Methyl 1-[3-(Methacryloyloxy)propyl]-1*H*-1,2,3-triazole-4-carboxylate (5): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.11 (s, 1 H), 6.08 (s, 1 H), 5.60 (s, 1 H), 4.52 (t, *J* = 7.0 Hz, 2 H), 4.20 (t, *J* = 6.0 Hz, 2 H), 3.95 (s, 3 H), 2.37–2.31 (m, 2 H), 1.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.03, 167.22, 147.64, 136.26, 126.21, 121.97, 61.38, 56.62, 47.36, 29.63, 18.26 ppm.

Ethyl 1-[3-(Methacryloyloxy)propyl]-1*H*-1,2,3-triazole-4-carboxylate (6): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.11 (s, 1 H), 6.07 (s, 1 H), 5.59 (s, 1 H), 4.52 (t, *J* = 7.0 Hz, 2 H), 4.41 (q, *J* = 7.1 Hz, 3 H), 4.20 (t, *J* = 6.0 Hz, 2 H), 2.37–2.31 (m, 2 H), 1.92 (s, 3 H), 1.39 (t, *J* = 7.1 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 167.01 160.68, 140.36, 135.84, 127.65, 126.17, 61.35, 60.96, 47.71, 29.42, 18.29, 14.32 ppm.

3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)propyl 2,4,4,4-Tetrachloro-2-methylbutanoate (1a): Isolated yield = 620 mg (91%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.82–7.80 (m, 2 H), 7.77 (s, 1 H), δ7.43–7.40 (m, 2 H), 7.34–7.31 (m, 1 H), 4.53 (t, *J* = 7.0 Hz, 2 H), 4.36–4.32 (m, 1 H), 4.27–4.22 (m, 1 H), 4.02 (d, *J* = 15 Hz, 1 H), 3.50 (d, *J* = 15 Hz, 1 H), 2.36 (quint, *J* = 6.5 Hz, 2 H), 1.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.33, 130.44, 128.92, 128.32, 125.81, 119.99, 94.59, 64.76, 63.10, 62.18, 46.90, 29.17, 26.13 ppm.

3-[4-(3,4-Difluorophenyl)-1*H*-1,2,3-triazol-1-yl]propyl-2,4,4,4-tetrachloro-2-methylbutanoate (2a): ^{1}H NMR (500 MHz, CD_2Cl_2, 25 °C): δ = 7.80 (s, 1 H), 7.69 (ddd, *J* = 11.5, 7.7, 2.1 Hz, 1 H), 7.56–7.53 (m, 1 H), 7.25 (dt, *J* = 10.3, 8.4 Hz, 1 H), 4.53 (t, *J* = 6.9 Hz, 2 H), 4.30 (m, 1 H), 4.24 (m, 1 H), 3.99 (d, *J* = 15.4 Hz, 1 H), 3.53 (d, *J* = 15.4 Hz, 1 H), 2.39 (quint, *J* = 6.5 Hz, 2 H), 2.02 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ = 169.33, 121.83, 121.76, 121.71, 117.82, 117.63, 114.66, 114.47, 94.67, 64.82, 63.24, 61.91, 47.10, 26.10, 26.19 ppm.

3-[4-(Hydroxymethyl)-1*H*-1,2,3-triazol-1-yl]propyl 2,4,4,4-Tetrachloro-2-methylbutanoate (3a): Isolated yield 550 mg (86%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.59 (s, 1 H), 4.82 (s, 2 H), 4.50 (t, *J* = 7.0 Hz, 2 H), 4.32 (dt, *J* = 11.6, 5.9 Hz, 1 H), 4.23 (dt, *J* = 11.6, 5.8 Hz, 1 H), 4.34–4.3 (m, 1 H), 4.25–4.2 (m, 1 H), 4.02 (d, *J* = 15.4 Hz, 1 H), 3.52 (d, *J* = 15.4 Hz, 1 H), 2.39 (quint, *J* = 6.4 Hz, 2 H), 2.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.60, 148.17, 121.20, 94.72, 64.82, 62.97, 47.10, 29.37, 26.46 ppm.

3-[4-(2-Hydroxyprop-2-yl)-1*H*-1,2,3-triazol-1-yl]propyl 2,4,4,4-Tetrachloro-2-methylbutanoate (4a): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.11 (s, 1 H), 4.56 (t, *J* = 7.0 Hz, 2 H), 4.35–4.31 (m, 1 H), 4.26–4.22 (m, 1 H), 4.02 (d, *J* = 15.4 Hz, 1 H), 3.12 (d, *J* = 15.4 Hz, 1 H), 2.72 (s, 3 H), 2.41 (quint, *J* = 6.4 Hz, 2 H), 2.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.47, 148.29, 125.76, 94.39, 64.62, 62.75, 62.75, 47.20, 28.96, 27.35, 26.28 ppm.

Methyl-1-[3-(2,4,4,4-tetrachloro-2-methylbutanoyloxy)propyl]-1*H*-1,2,3-triazole-4-carboxylate (5a): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.15 (s, 1 H), 4.57 (t, *J* = 7.0 Hz, 2 H), 4.36–4.3 (m, 1 H), 4.26–4.20 (m, 1 H), 4.01 (d, *J* = 15.4 Hz, 1 H), 3.98 (s, 3 H), 3.52 (d, *J* = 15.4 Hz, 1 H), 2.43 (quint, *J* = 6.4 Hz, 2 H), 2.05 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.33, 161.13, 140.23, 94.19, 64.56, 62.71, 62.13, 52.39, 47.36, 29.10, 26.19 ppm.

Ethyl 1-[3-(2,4,4,4-Tetrachloro-2-methylbutanoyloxy)propyl]-1*H*-1,2,3-triazole-4-carboxylate (6a): Isolated yield 610 mg (89%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.11 (s, 1 H), 4.55 (t, J = 6.9 Hz, 2 H), 4.43 (q, J = 7.1 Hz, 3 H), 4.33–4.3 (m, 1 H), 4.26–4.17 (m, 1 H), 3.99 (d, J = 15.4 Hz, 1 H), 3.49 (d, J = 15.4 Hz, 1 H), 2.43–2.37 (m, 2 H), 2.02 (s, 3 H), 1.41 (t, J = 7.1 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.38, 160.63, 140.46, 127.77, 94.48, 64.70, 62.74, 62.14, 61.41, 47.28, 29.01, 26.19, 14.34 ppm.

3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)propyl 2,4,4,4-Tetrabromo-2-methylbutanoate (7a): Isolated yield 870 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.85 (d, J = 8.2 Hz, 2 H), 7.84 (s, 1 H), 7.45 (t, J = 7.4 Hz, 3 H), 7.36 (t, J = 7.4 Hz, 1 H), 4.73 (d, J = 15.6 Hz, 1 H), 4.59 (t, J = 6.8 Hz, 3 H), 4.42–4.36 (m, 1 H), 4.30–4.24 (s, 1 H), 3.99 (d, J = 15.6 Hz, 1 H), 2.45 (quint, J = 6.4 Hz, 3 H), 2.33 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.8, 147.9, 130.4, 128.9, 128.3, 125.8, 65.8, 62.9, 57.8, 47.0, 31.2, 29.1, 26.0 ppm.

1-Ethyl 5-[3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)propyl] 2,2,4-Trichloro-4-methylpentanedioate (8a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.85 (d, J = 8.2 Hz, 2 H), 7.84 (s, 1 H), 7.45 (t, J = 7.4 Hz, 3 H), 7.36 (t, J = 7.4 Hz, 1 H), 4.56 (t, J = 7 Hz, 2 H), 4.36 (q, J = 7 Hz, 2 H), 4.29–4.23 (m, 2 H), 3.61 (d, J = 15.2 Hz, 1 H), 3.47 (d, J = 15.2 Hz, 1 H), 2.45–2.35 (m, 2 H), 1.86 (s, 3 H), 1.41 (t, J = 15.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.0, 165.3, 147.8, 130.5, 128.9, 128.2, 125.7, 120.2 80.9, 65.3, 64.4, 63.3, 53.8, 53.3, 48.0, 29.1, 27.8, 13.7 ppm.

5-Ethyl 1-[3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)propyl] 2,4-Dichloro-2-methylpentanedioate (9a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C; approx. 50:50 mixture of diastereomers): δ = 7.85 (d, J = 8.2 Hz, 2 H), 7.84 (s, 1 H), 7.42 (t, J = 7.4 Hz, 3 H), 7.33 (t, J = 7.4 Hz, 1 H), 4.57–4.51 (m, 1 H), 4.54 (t, J = 7 Hz, 2 H), 4.33 (q, J = 7.2 Hz, 2 H), 4.26–4.19 (m, 2 H), 3.01–2.96 (m, 1 H), 2.85–2.74 (m, 1 H), 2.68–2.63 (m, 1 H), 2.40–2.33 (m, 2 H), 1.84 (s, 3 H), 1.82 (s, 3 H), 1.30 (t, J = 15.2 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 169.9, 169.3, 147.7, 130.5, 128.8, 128.2, 125.7, 120.1, 66.7, 63.5, 53.3, 52.5, 48.0, 45.8, 29.3, 29.1, 13.9 ppm.

3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)propyl 2,4-Dichloro-4-cyano-2-methylbutanoate (10a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C; approx. 50:50 mixture of diastereomers): δ = 7.84 (d, J = 6.0 Hz, 2 H), 7.82 (s, 1 H), 7.47–7.43 (m, 2 H), 7.39–7.34 (m, 1 H), 4.86–4.79 (m, 1 H), 4.62–4.55 (m, 1 H), 4.38–4.28 (m, 1 H), 3.04 (ddd, J = 14.8, 8.8, 0.6 Hz), 2.95–2.89 (m, 1 H), 2.83–2.78 (m, 1 H), 2.68–2.63 (m, 1 H), 2.46–2.39 (m, 2 H), 1.90 (s, 3 H), 1.89 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 169.5, 148, 130.4, 128.9, 128.3, 125.7, 120, 116.6, 65.9, 63.8, 47.6, 38.7, 29, 28.8 ppm.

3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)propyl 2-Bromo-4-cyano-2-methylpentanoate (11a): ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers): δ = 7.88 (s, 1 H), 7.86 (d, J = 6.8 Hz, 2 H), 7.47–7.44 (m, 2 H), 7.38–7.35 (m, 1 H), 4.59 (t, J = 6.8 Hz, 2 H), 4.38–4.29 (m, 2 H), 2.99–2.82 (m, 1 H), 2.64–2.53 (m, 1 H), 2.49–2.41 (m, 1 H), 2.31–2.32 (m, 1 H), 2.06 (s, 3 H), 2.05 (s, 3 H), 1.45 (d, J = 7.2 Hz, 3 H), 1.42 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.2, 161.3, 140.0, 130.5, 128.9, 128.2, 125.7, 120.2, 118.2, 63.4, 57.9, 48.0, 45.2, 29.1, 27.8, 22.7, 19.5 ppm.

Methyl 1-[3-(2,4,4,4-Tetrabromo-2-methylbutanoyloxy)propyl]-1*H*-1,2,3-triazole-4-carboxylate (12a): Isolated yield 850 mg (86%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.18 (s, 1 H), 4.68 (d, J = 15.5 Hz, 1 H), 4.59 (t, J = 6.9 Hz, 2 H), 4.37–4.31 (m, 1 H), 4.25–4.19 (m, 1 H), 3.97 (d, J = 15.6 Hz, 1 H), 3.96 (s, 3 H), 2.43 (quint, J = 6.4 Hz, 2 H), 2.30 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 169.84, 161.06, 127.92, 65.79, 62.59, 57.69, 52.33. 47.40, 31.06, 29.00, 25.99 ppm.

1-Ethyl 5-{3-[4-(Methoxycarbonyl)-1*H*-1,2,3-triazol-1-yl]propyl} 2,2,4-Trichloro-4-methylpentanedioate (13a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.18 (s, 1 H), 4.58 (t, J = 6.9 Hz, 2 H), 4.38 (q, J = 7.1 Hz, 2 H), 4.29–4.21 (m, 2 H), 3.97 (s, 3 H), 3.61 (d, J = 15.2 Hz, 1 H), 3.47 (d, J = 15.2 Hz, 1 H), 2.45–2.38 (quint, J = 6.2 Hz, 2 H), 1.86 (s, 3 H), 1.39 (t, J = 15.2 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 170.1, 165.3, 161.2, 140.12, 127.8, 80.7, 65.4, 64.3, 62.6, 53.3, 52.3, 47.3, 29.1, 27.6, 13.3 ppm.

5-{3-[4-(Methoxycarbonyl)-1*H*-1,2,3-triazol-1-yl]propyl} 1-Methyl 2,2,4-Trichloro-4-methylpentanedioate (14a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.20 (s, 1 H), 4.57 (t, J = 6.9 Hz, 2 H), 4.28–4.22 (m, 2 H), 3.95 (s, 3 H), 3.56 (d, J = 15.0 Hz, 1 H), 3.44 (d, J = 15.0 Hz, 1 H), 2.39 (quint, J = 6.2 Hz, 2 H), 1.82 (s, 3 H) ppm.

5-Ethyl 1-{3-[4-(Methoxycarbonyl)-1*H*-1,2,3-triazol-1-yl]propyl} 2,4-Dichloro-2-methylpentanedioate (15a): Isolated yield 670 mg (73%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C; approx. 50:50 mixture of diastereomers): δ = 8.02 (s, 1 H), 8.16 (s, 1 H), 4.86–4.79 (m, 1 H), 4.57–4.54 (m, 1 H), 4.58 (t, J = 7.0 Hz, 2 H), 4.27–4.16 (m, 2 H), 3.95 (s, 3 H), 2.96 (dd, J = 15.1, 6.9 Hz, 1 H), 2.78 (qd, J = 16.4, 6.6 Hz, 1 H), 2.65 (dd, J = 15.1, 6.2 Hz, 1 H), 2.41–2.35 (m, 2 H), 1.84 (s, 3 H), 1.81 (s, 3 H), 1.31 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 170.0, 168.9, 161.1, 140.0, 128.0, 66.7, 66.1, 62.6, 52.6, 52.3, 47.3, 45.8, 29.0, 27.7, 13.9 ppm.

1-{3-[4-(Methoxycarbonyl)-1*H*-1,2,3-triazol-1-yl]propyl} 5-Methyl 2,4-Dichloro-2-methylpentanedioate (16a): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C; approx. 50:50 mixture of diastereomers): δ = 8.20 (s, 1 H), 8.19 (s, 1 H), 4.54–4.61 (m, 2 H), 4.25–4.18 (m, 1 H), 4.27–4.16 (m, 2 H), 3.95 (s, 3 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 2.99 (dd, J = 15.1, 7.0 Hz, 1 H), 2.80 (qd, J = 13.8, 6.6 Hz, 2 H), 2.65 (dd, J = 15.1, 6.1 Hz, 1 H), 2.43–2.36 (m, 2 H), 1.85 (s, 3 H), 1.83 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 169.9, 169.4, 161.1, 140.0 128.1, 66.7, 66.1, 62.8, 62.7, 53.4, 52.9, 52.3, 47.3, 46.2, 46.0, 29.4, 28.9, 27.8 ppm.

Methyl 1-[3-(2,4-Dichloro-4-cyano-2-methylbutanoyloxy)propyl]-1*H*-1,2,3-triazole-4-carboxylate (17a): ^{1}H NMR (400 MHz. $CDCl_3$, 25 °C; approx. 50:50 mixture of diastereomers): δ = 8.18 (s, 1 H), 8.16 (s, 1 H), 4.87–4.79 (m, 1 H), 4.58 (t, J = 7.0 Hz, 2 H), 4.30–4.23 (m, 2 H), 3.97 (s, 3 H), 3.83 (s, 3 H), 3.07–3.01 (m, 1 H), 2.94–2.88 (m, 1 H), 2.83–2.78 (m, 1 H), 2.70–2.63 (m, 1 H), 2.48–2.39 (m, 2 H), 1.90 (s, 3 H), 1.89 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 169.5, 140.2, 127.6, 116.1, 66.0, 63.7, 58.6, 52.2, 47.2, 38.3, 32.3, 29.3, 28.9 ppm.

Methyl 1-[3-(2-Bromo-4-cyano-2-methylpentanoyloxy)propyl]-1*H*-1,2,3-triazole-4-carboxylate (18a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C; approx. 50:50 mixture of diastereomers): δ = 8.19 (s, 1 H), 8.12 (s, 1 H), 4.60 (t, J = 7.0 Hz, 2 H), 4.34–4.21 (m, 2 H), 3.97 (s, 3 H), 3.83 (s, 3 H), 2.95–2.88 (m, 1 H), 2.65–2.55 (m, 1 H), 2.59–2.55 (m, 1 H), 2.70–2.63 (m, 1 H), 2.61–2.54 (m, 1 H), 2.45–2.39 (m, 1 H), 2.07 (s, 3 H), 2.04 (s, 3 H), 1.46 (d, J = 7.1 Hz, 3 H), 1.43 (d, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 170.3, 161.3, 140.0, 128.1, 114.7, 63.0, 55.8, 46.5, 45.3, 29.7, 27.2, 21.0, 19.5 ppm.

4-Phenyl-1-[4-(1,3,3,3-tetrachloropropyl)benzyl]-1*H*-1,2,3-triazole (19a): Isolated yield 600 mg (86%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.83 (d, J = 7.2 Hz, 2 H), 7.47 (d, J = 8.0 Hz, 2 H), 7.44–7.41 (m, 2 H), 7.36–7.32 (m, 1 H), 7.33 (d, J = 8.0 Hz, 2 H), 5.59 (s, 2 H), 5.31 (dd, J = 6.3, 5.6 Hz, 1 H), 3.63 (dd, J = 15.3, 5.3 Hz, 1 H), 3.52 (dd, J = 15.3, 6.5 Hz, 1 H) ppm. ^{13}C NMR

(101 MHz, $CDCl_3$, 25 °C): δ = 148.3, 140.9, 135.6, 130.5, 128.9, 128.50, 128.31, 128.25, 125.7, 119.8, 96.1, 62.5, 57.7, 53.6 ppm.

Ethyl 2,2,4-Trichloro-4-{4-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]-phenyl}butanoate (20a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.05 (s, 1 H), 7.46 (d, J = 8.2 Hz, 2 H), 7.32 (d, J = 8.2 Hz, 2 H), 5.60 (d, J = 4.2 Hz, 2 H), 5.26–5.22 (m, 1 H), 4.35 (q, J = 7.2 Hz, 2 H), 3.44 (dd, J = 15.0, 7.2 Hz, 1 H), 3.20 (dd, J = 15.0, 6.0 Hz, 1 H), 1.27 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 165.5, 148.3, 140.2, 135.7, 130.4, 128.9, 128.7, 128.4, 128.2, 125.6, 81.9, 64.1, 57.8, 54.5, 53.7, 13.8 ppm.

Methyl 2,2,4-Trichloro-4-{4-[(4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl]phenyl}butanoate (21a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.81 (d, J = 7.2 Hz, 2 H), 7.79 (s, 1 H), 7.42–7.38 (m, 4 H), 7.35–7.28 (m, 3 H), 5.55 (s, 2 H), 5.22 (dd, J = 7.5, 6.0 Hz, 1 H), 3.87 (s, 3 H), 3.42 (dd, J = 15.0, 7.6 Hz, 1 H), 3.17 (dd, J = 15.0, 5.9 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 165.5, 148.3, 140.2, 135.7, 130.4, 128.4, 128.3, 128.2, 125.7, 81.9, 57.8, 54.5, 53.9, 53.8 ppm.

Methyl 1-[4-(1,3,3,3-Tetrachloropropyl)benzyl]-1*H*-1,2,3-triazole-4-carboxylate (22a): Isolated yield 570 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.04 (s, 1 H), 7.49–7.45 (m, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 5.60 (s, 2 H), 5.30–5.27 (m, 1 H), 3.93 (s, 3 H), 3.60 (dd, J = 15.3, 5.3 Hz, 1 H), 3.50 (dd, J = 15.3, 6.6 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 161.0, 141.4, 134.6, 128.7, 128.4, 127.5, 96.0, 62.5, 57.5, 53.9, 52.3 ppm.

Methyl 1-[4-(1,3,3-Trichloro-4-ethoxy-4-oxobutyl)benzyl]-1*H*-1,2,3-triazole-4-carboxylate (23a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.05 (s, 1 H), 7.46 (d, J = 8.2 Hz, 2 H), 7.32 (d, J = 8.2 Hz, 2 H), 5.60 (d, J = 4.2 Hz, 2 H), 5.26–5.22 (m, 1 H), 4.19–4.07 (m, 2 H), 3.95–3.94 (m, 3 H), 3.43 (dd, J = 15.0, 7.6 Hz, 1 H), 3.17 (dd, J = 15.0, 5.8 Hz, 1 H), 1.30 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 165.5, 161.0, 140.8, 140.4, 134.5, 128.6, 128.4, 127.5, 81.8, 57.7, 54.5, 53.95, 53.80, 52.3, 13.7 ppm.

Methyl 1-[4-(1,3,3-Trichloro-4-methoxy-4-oxobutyl)benzyl]-1*H*-1,2,3-triazole-4-carboxylate (24a): Isolated yield 610 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.04 (s, 1 H), 7.45 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 5.60 (s, 2 H), 5.23 (dd, J = 7.6, 5.8 Hz, 1 H), 3.94 (s, 3 H), 3.72 (s, 3 H), 3.43 (dd, J = 15.0, 7.7 Hz, 1 H), 3.17 (dd, J = 15.0, 5.8 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 165.5, 161.0, 134.5, 128.7, 128.4, 127.5, 81.8, 57.7, 54.5, 53.8, 52.3 ppm.

Methyl 1-[4-(1,3-Dichloro-4-ethoxy-4-oxobutyl)benzyl]-1*H*-1,2,3-triazole-4-carboxylate (25a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C; approx. 50:50 mixture of diastereomers): δ = 8.04 (s, 1 H), 8.01 (s, 1 H), 7.44 (d, J = 8.2 Hz, 2 H), 7.23 (d, J = 8.2 Hz, 2 H), 5.61 (s, 2 H), 4.68 (dd, J = 17.0, 3.7 Hz, 1 H), 4.33 (q, J = 7.2 Hz, 2 H), 4.28–4.2 (m, 1 H), 4.14 (dd, J = 17.0, 6.0 Hz, 1 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 2.79–2.67 (m, 2 H), 1.36 (t, J = 7.4 Hz, 3 H) ppm.

Methyl 1-[4-(1,3-Dichloro-4-methoxy-4-oxobutyl)benzyl]-1*H*-1,2,3-triazole-4-carboxylate (26a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C; approx. 50:50 mixture of diastereomers): δ = 8.06 (s, 1 H), 8.03 (s, 1 H), 7.37 (d, J = 8.2 Hz, 2 H), 7.25 (d, J = 8.2 Hz, 2 H), 5.53 (s, 2 H), 4.68 (dd, J = 17.0, 3.7 Hz, 1 H), 4.33 (q, J = 7.2 Hz, 2 H), 4.28–4.20 (m, 1 H), 4.14 (dd, J = 17.0, 6.0 Hz, 1 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 2.79–2.67 (m, 2 H), 1.36 (t, J = 7.4 Hz, 3 H) ppm.

Methyl 1-[4-(1,3-Dichloro-3-cyanopropyl)benzyl]-1*H*-1,2,3-triazole-4-carboxylate (27a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C; approx. 50:50 mixture of diastereomers): δ = 8.05 (s, 1 H), 8.04 (s, 1 H), 7.41 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.2 Hz, 2 H), 5.58 (s, 2 H), 4.75 (dd, J = 10.0, 4.4 Hz, 1 H), 4.54–4.50 (m, 1 H), 3.86 (s, 3 H), 2.81–2.73 (m, 1 H), 2.69–2.63 (m, 1 H), 2.60–2.52 (m, 1 H) ppm.

Methyl 1-[4-(1,3,3-Trichloropropyl)benzyl]-1*H*-1,2,3-triazole-4-carboxylate (28a): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C; approx. 50:50 mixture of enantiomers): δ = 8.04 (s, 1 H), 8.00 (s, 1 H), 7.46 (d, J = 8.2 Hz, 2 H), 7.33 (d, J = 8.2 Hz, 2 H), 6.72 (dd, J = 17.6, 10.9 Hz, 1 H), 5.84–5.81 (m, 1 H), 5.61 (s, 2 H), 5.58 (s, 2 H), 5.09 (dd, J = 9.6, 4.8 Hz, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 2.96 (ddd, J = 14.6, 9.7, 4.8 Hz, 1 H), 2.76 (ddd, J = 14.7, 8.5, 4.8 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C): δ = 161.2, 140.5, 135.8, 134.7, 128.9, 128.0, 127.1, 70.1, 58.6, 57.0, 54.3, 52.3 ppm.

Supporting Information (see footnote on the first page of this article): Details of spectroscopic data for isolated compounds.

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