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Synthesis of Functionalized Polytriazoles via One-Pot Sequential Copper-Catalyzed Azide–Alkyne [3+2] Cycloaddition and Atom Transfer Radical Addition (ATRA)

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Dedicated to Prof. Krzysztof Matyjaszewski on occasion of receiving the 2011 Wolf Prize in Chemistry

Abstract: As a continuing effort of expanding the scope of catalyst regeneration in the presence of environmentally benign reducing agents, one-pot sequential azide–alkyne [3+2] cycloaddition and atom transfer radical addition (ATRA) reactions were performed via in situ reduction of copper(II) by ascorbic acid. The formation of functionalized triazoles was achieved utilizing a ligand-free catalytic system for the cycloaddition between tripropargylamine and vinylbenzyl azide and subsequent addition of tris(2-pyridyl)methylamine (TPMA) ligand in the ATRA step. With this strategy, reactions with carbon tetrachloride and carbon tetrabromide proceeded efficiently providing the desired triazoles in nearly quantitative yields (>90%) using 10 mol% of copper. Sequential azide–alkyne [3+2] cycloaddition and ATRA reactions were also extended to less active alkyl halides such as methyl trichloroacetate, methyl dichloroacetate and dichloroacetonitrile. The corresponding products were obtained in modest yields (50–80%). The presented methodology enables efficient synthesis of functionalized polytriazoles, which could have a potential use as chelating agents for a variety of transition metals.

Keywords: atom transfer radical addition · catalyst regeneration · click chemistry · copper · polytriazoles

1. Introduction and Background

The term "click chemistry", coined in 2001, serves as a guiding principle in the synthesis of compounds with desired functionality using "near perfect" reaction conditions.[1] Typically, reactions classified under the click chemistry umbrella are defined by a stringent set of criteria and among them, copper-catalyzed Huisgen [3+2] cycloaddition popularized by the Meldal[2] and Sharpless[3] groups was the first to achieve the "click status". To date, this reaction has dominated this area of research and has become synonymous with "click chemistry", mainly due to its reliability, robustness, functional group tolerance, ability to withstand a wide spectrum of solvents, and desirable properties of the resulting triazoles. Immense contributions have been made and wide arrays of applications found in various disciplines such as biology,[4,5] chemistry,[1,6–8] bioconjugation,[7,9] drug discovery[9–12] and materials/polymer science.[8,13–16]

The mechanism of copper-catalyzed azide–alkyne [3+2] cycloaddition has been widely investigated using computational[17–19] and experimental[3,20,21] techniques. Regardless of the starting copper salt or complex (either Cu^{I} or Cu^{II}), it has been established that Cu^{I} is the active catalytic species in the coupling of azide and alkyne.[6] The catalytic cycle begins with the coordination of the alkyne to the copper(I) center, resulting in the formation of a π-complex (Scheme 1). This step lowers the pK_a of terminal alkyne proton by approximately 10 units, enabling the conversion of the π-complex to a σ-acetylide copper(I) intermediate. Kinetic investigation[20] has revealed that the reaction rate is second-order with respect to the metal, suggesting the strong tendency of copper(I) acetylide species to form μ-coordinate bridged aggregates,[18,19] the formation of which is highly dependent on the nature of the complexing ligand. The next step in the catalytic cycle is the coordination of the organic azide, which consequently

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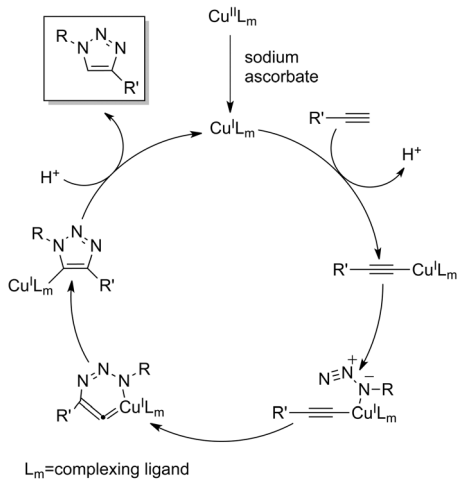
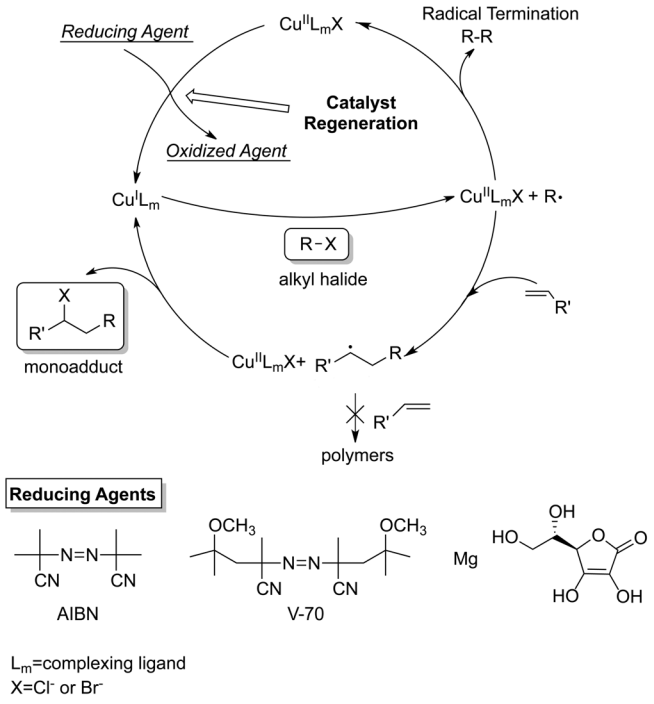


Scheme 1. Proposed mechanism for copper-catalyzed azide–alkyne [3+2] cycloaddition.

activates the *N*-terminus for nucleophilic attack to the acetylide. This results in the formation of vinylidine-like structure, which subsequently converts to a more stable copper(I) triazolide. Lastly the catalytic cycle is completed by protonolysis, which yields the desired 1,2,3-triazole and regenerates the active copper(I) species.

Other C–C forming reactions that are becoming more synthetically useful are the transition-metal-catalyzed atom transfer radical addition (ATRA) and the intramolecular counterpart, atom transfer radical cyclization (ATRC).[22–27] Traditionally, both were conducted in the presence of high catalyst loadings, therefore facing issues in product separation and catalyst recycling. A solution to these problems was found for the mechanistically similar atom transfer radical polymerization (ATRP)[28,29] in which reducing agents were utilized to continuously regenerate the activator or copper(I) complex (Scheme 2). The catalyst regeneration technique has also been shown to be highly efficient in ruthenium-[30] and copper-catalyzed ATRA and ATRC reactions.[26,31–34] The presence of the reducing agents (free-radical diazo initiators, magnesium or ascorbic acid) successfully allowed the reduction in the amount of transition-metal complex, and as a result, these reactions can now be conducted using very low amounts of the catalyst.[35–46] The synthetic usefulness of the methodology has also been demonstrated in sequential organic transformations involving ATRA/ATRC.[47–49]

The proposed mechanism[26,34] for 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 catalytic cycle starts with a homolytic cleavage of the alkyl halide bond by the copper(I) complex to produce an alkyl radical, which subse-



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

quently adds across a carbon–carbon double bond of an alkene. The generated secondary radical is then trapped by irreversible abstraction of 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 alkene to form oligomers/polymers.

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 then subsequently triazoles.[50,51] The methodology was also successfully extended to one-pot simultaneous reactions, in which propargyl methacrylate and alkyl azides were reacted to yield highly functionalized and well-defined polymeric materials.[52,53] Furthermore, our laboratory also initiated the study on sequential reactions involving copper(I)-catalyzed azide–alkyne [3+2] cycloaddition and mechanistically similar ATRA.[54] A wide variety of small organic molecules bearing triazole and halide functionalities have been synthesized.

Since we have demonstrated the efficiency of our catalytic system to mediate both organic transformations in a one-pot, two-step process, our focus has shifted towards functionalized polytriazoles. Such compounds are very ef-

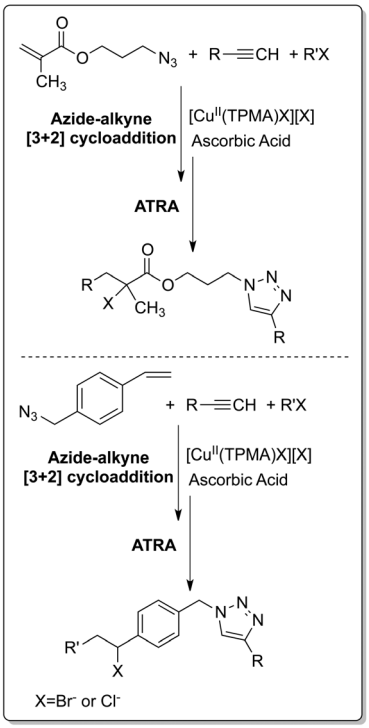
fective chelating agents and have found use in many different areas of catalysis.[55] A recent study has shown that the incorporation of polytriazole ligands enhanced the photophysical and electron-transfer properties of tripodal zinc porphyrins ($TPZn_3$).[56] In DNA and RNA chemistry, multiple alkynylation of nucleosides and oligonucleotides followed by functionalization via the copper(I)-catalyzed Huisgen cycloaddition with fluorophore-decorated organic azides resulted in the formation of modified DNA and RNA molecules that are highly fluorescent.[57]

In this article, we report on the synthesis of halogenated polytriazole derivatives employing sequential copper-catalyzed azide–alkyne [3+2] cycloaddition and atom transfer radical addition (ATRA). The presence of the halide functionality in the resulting molecule offers versatility towards further organic transformations involving reduction, elimination, conversion to a Grignard reagent, and/or free radical chemistry.

2. Results and Discussion

The motivation for the study of one-pot sequential reactions involving azide–alkyne [3+2] cycloaddition and atom transfer radical addition[54] catalyzed by [Cu^{II}-(TPMA)X][X] (TPMA = tris(2-pyridylmethyl)amine, X = Cl^-, Br^-) complexes in the presence of ascorbic acid as a reducing agent was primarily to demonstrate the synthetic usefulness of the catalyst regeneration technique originally developed for mechanistically similar ATRP. The pioneering work in our laboratory on copper-catalyzed ATRA in the presence of free-radical diazo initiator AIBN showed a significant reduction in the required catalyst loading with high turnover numbers (TONs).[31,32] Improved selectivity towards the desired monoadduct formation for alkenes that are prone to free-radical polymerization was demonstrated through the use of radical initiator that decomposes at ambient temperature (such as V-70)[58] or photoinitiated ATRA.[59] Very recently, copper-catalyzed ATRA and ATRC reactions have also been conducted in the presence of a more environmentally benign reducing agent such as ascorbic acid.[46] This reducing agent enabled not only high product yields and TONs, but also more superior selectivity towards monoadduct formation (particularly in the case of highly active acrylonitrile).

Based on literature reports, triazole formation via copper(I)-catalyzed [3+2] azide–alkyne cycloaddition is commonly conducted via in situ reduction of Cu^{II} to Cu^{I} complex by either sodium ascorbate or ascorbic acid.[3,6,21] Similarly, ATRA,[46] ATRC[46] and ATRP[60,61] reactions also utilize the same reducing agent to regenerate the copper(I) complex, which is needed to start the catalytic cycle by homolytically cleaving the carbon–halogen bond. Therefore, a logical step was taken in combining the two reactions in a one-pot sequential manner.[54] Indeed, reactions with azidopropyl methacrylate and 1-(azidomethyl)-4-vinylbenzene in the presence of a variety of alkynes and alkyl halides, catalyzed by as low as 0.5 mol% of [Cu^{II}(TPMA)X][X] (X = Br^-, Cl^-) complex, proceeded efficiently to yield highly functionalized (poly)halogenated esters and aryl compounds containing triazolyl group in almost quantitative yields (> 90%, Scheme 3).



Scheme 3. Sequential copper-catalyzed azide–alkyne [3+2] cycloaddition and atom transfer radical addition (ATRA).[54]

Encouraged by these results, we then applied the same methodology to azide–alkyne [3+2] cycloaddition between tripropargylamine and vinyl benzyl azide (VBA), followed by sequential ATRA of carbon tetrachloride. Surprisingly, reactions conducted in the presence of 1 mol% of [Cu^{II}(TPMA)Cl][Cl] complex and 20 mol% of ascorbic acid (relative to Cu^{II}) for 24 h at 60 °C yielded less than 10% of the desired product. Conducting reactions at elevated temperatures (80 °C) for longer reaction times (48 h) did not result in significant improvements. At the present time, it is unclear why the same catalytic system does not work efficiently for tripropargylamine. On the one hand, this substrate could inherently be less active in azide–alkyne cycloaddition. On the other, if the reaction requires multiple coordinations to the copper(I) center, such interactions will be efficiently blocked because of the tetradentate nature of TPMA ligand. We are presently exploring both possibilities.

Since one-pot sequential reactions catalyzed by [Cu^{II}-(TPMA)Cl][Cl] complex were not successful, we reverted

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to carrying out two-step, two-pot reactions. The first step involved the reaction between vinylbenzyl azide (VBA) and tripropargylamine at 60 °C in the presence of 10 mol% of $Cu^{II}SO_4$ and sodium ascorbate (1:10 molar ratio) in methylene chloride/water (50:50 by volume). After heating for 24 h, the desired tris(2-vinylbenzyl)triazole was isolated in 74% yield. Even better results were obtained when the solvent was changed to methanol and ascorbic acid utilized as a reducing agent (91% isolated yield). The resulting triazole was characterized using ^{1}H NMR and high resolution mass spectroscopy (HRMS). The corresponding spectra are shown in Figure 1. Positive ion mass spectrum indicates the presence of two molecular ion peaks, namely the protonated triazole (MH^+) and sodium ion (MNa^+).

For the second step, ATRA reactions of various alkyl halides were conducted in the presence of [Cu^{II}-(TPMA)X][X] (X = Br^- or Cl^-) and ascorbic acid. The results are summarized in Table 1. The addition of polyhalogenated methanes such as CCl_4 and CBr_4 provided nearly quantitative yields of $TBTA(CCl_4)_3$ (95%) and

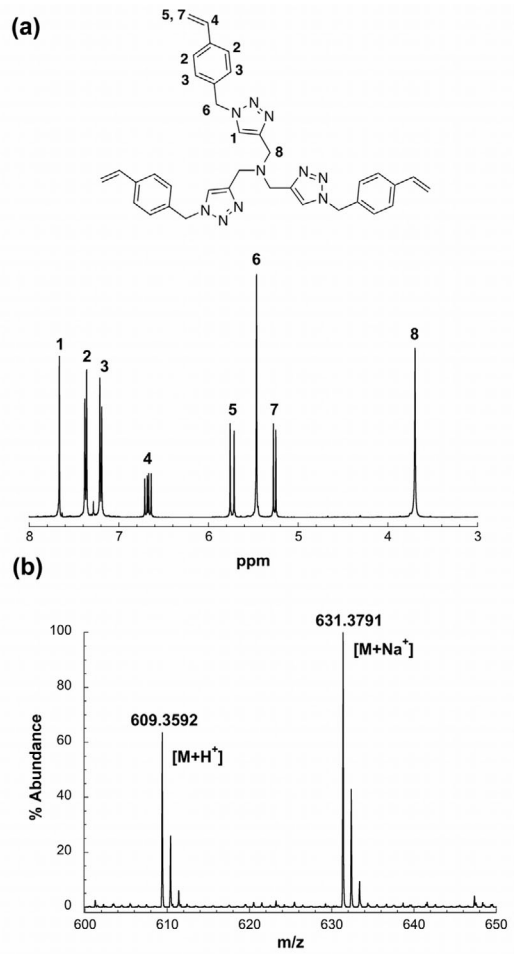
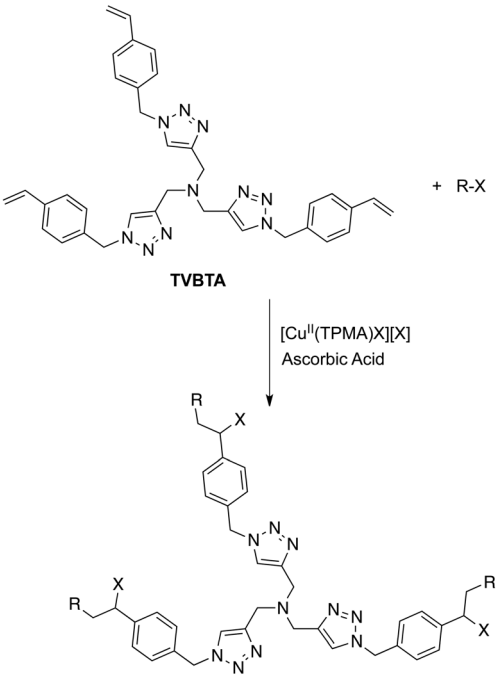


Figure 1. ^{1}H NMR (a) and HRMS (b) spectra of tris((1-(4-vinylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)amine (TVBTA).

Table 1. Copper-catalyzed ATRA of alkyl halides to TVBTA in the presence of ascorbic acid.



R–X[a]	[Cu^{II}][b]	*T* [°C]	Time [h]	Yield [%][c]
CCl_4	1.0	60	24	95
CCl_4	0.40	60	24	60(64)[d]
CCl_4	0.20	60	24	62
CBr_4	1.0	60	24	98(92)[d]
CBr_4	0.40	60	24	86
CBr_4	0.20	60	24	84
CCl_3CO_2Me	2.0	80	27	78(77)[d]
CCl_3CO_2Me	1.0	80	27	76
CCl_2HCN	2.0	80	27	70(67)[d]
CCl_2HCO_2Me	2.0	80	27	70(55)[d]
CCl_2HCO_2Me	1.0	80	27	64

[a] All reactions were performed in MeOH using $[TVBTA]_0/[CCl_4$ or $CBr_4]_0 = 1:3.75$, or $TVBTA]_0/[CCl_3CO_2Me$, $CHCl_2CN$, or $CCl_2HCO_2Me]_0 = 1:6$, $[TVBTA]_0 = 0.08$ M. The amount of ascorbic acid in each system ranged between 20 and 25 equiv relative to the copper(II) complex. [b] Mol% relative to [TVBTA]. [c] The yield is based on the formation of the triazole and was determined by ^{1}H NMR spectroscopy using *p*-dimethoxybenzene as internal standard (relative errors are ±15%). [d] Isolated yield after column chromatography.

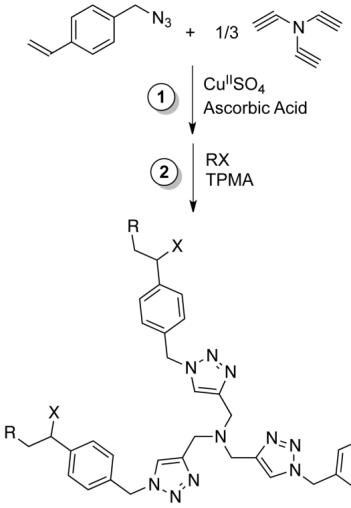
$TBTA(CBr_4)_3$ (98%) in the presence of as low as 1.0 mol% of the catalyst. Decreasing catalyst loadings to 0.4 and 0.2 mol% still resulted in reasonably high yields of the desired polytriazole monoadducts. The scope of ATRA was also extended to include trihalogenated (methyl trichloroacetate) and dihalogenated (methyl dichloroacetate and dichloroacetonitrile) alkyl halides. Since they are generally less active compared to CCl_4 and CBr_4, reactions were performed utilizing an excess of

alkyl halides (6.0 equivalents relative to TVBTA), elevated temperatures (80 °C), prolonged reaction times (27 h), and higher catalyst loadings (1.0–2.0 mol %). As indicated in Table 1, the results were clearly inferior to those of CCl_4 and CBr_4. Modest yield (78 %) was obtained in the addition of CCl_3CO_2Me in the presence of 2.0 mol % of $[Cu^{II}(TPMA)Cl][Cl]$ and ascorbic acid. For the case of CCl_2HCN and CCl_2HCO_2Me, the yields of the halogenated polytriazoles were approximately 70 % using the same catalyst loading (2.0 mol %). Further decrease in the amount of copper catalyst resulted in a decrease in the yield of the desired monoadduct.

We have already demonstrated that copper-catalyzed [3+2] azide–alkyne cycloaddition between vinylbenzyl azide and tripropargylamine in the presence of TPMA ligand can be problematic. However, TPMA is necessary for the ATRA step, and it is currently among the most active nitrogen-based ligands for such copper-catalyzed organic transformations.[26,33,34] With a strong determination to fulfill a one-pot synthesis of halogenated polytriazoles, a new strategy was devised. In the first step, [3+2] azide–alkyne cycloaddition between vinylbenzyl azide and tripropargylamine was conducted in a ligand-free catalytic system containing ascorbic acid. After completion of the reaction, free TPMA and alkyl halide were then added to the same reaction mixture and ATRA allowed to proceed. Indeed, with this protocol, the monoadduct in the case of CCl_4 was obtained in 91 % yield using 10 mol % of copper (Table 2, entry 1). Increasing the reaction time for ATRA from 8 to 19 h did not result in significant increase in the product yield (90 %, entry 2). Furthermore, decreasing catalyst loading to 1.0 mol % resulted in a significant decrease in the yield of the monoadduct (entry 3). The same trend was also observed in the case of CBr_4 (entries 4–6). As indicated in Table 2, sequential [3+2] azide–alkyne cycloaddition and ATRA proceeded reasonably well with less active methyl trichloroacetate (entry 7 and 8) and methyl dichloroacetate (entry 9 and 10). For both reactions, a large excess of alkyl halide was used (6.0 equivalents relative to vinyl benzyl azide).

Product characterization via spectroscopic techniques (^1H and ^{13}C NMR) and high resolution mass spectroscopy (HRMS) were carried out for all substrates to verify the formation of the monoadducts. Shown in Figure 2 are the ^1H NMR and HRMS spectra of the addition product involving CCl_4. In the HRMS spectrum, there are two observable molecular ion peaks corresponding to the protonated triazole (MH^+) and sodium ion (MNa^+).

Table 2. One-pot sequential copper-catalyzed [3+2] azide–alkyne cycloaddition and ATRA in the presence of ascorbic acid.



Entry[a]	R–X	$[Cu^{II}]$[b]	t_1 [h]/t_2 [h][c]	Yield [%][d]
1	CCl_4	10	1/8	91 (80)[e]
2	CCl_4	10	1/19	90
3	CCl_4	1.0	1/19	56
4	CBr_4	10	1/8	92 (86)[e]
5	CBr_4	10	1/19	99
6	CBr_4	1.0	1/19	60
7	CCl_3CO_2Me	10	1/24	75 (78)[e]
8	CCl_3CO_2Me	1.0	1/24	43
9	CCl_2HCO_2Me	10	1/24	66 (43)[e]
10	CCl_2HCO_2Me	1.0	1/24	50

[a] All reactions were performed at 60 °C in MeOH using $[VBA]_0$:$[tripropargylamine]_0$ = 3:1, $[VBA]_0$ = 0.1 M. The amount of ascorbic acid was 20 equiv relative to $Cu^{II}SO_4$. In the second step, 1.0 equiv of TPMA relative to $Cu^{II}SO_4$ and RX (CCl_4 or CBr_4 = 3.75 equiv, CCl_3CO_2Me or CCl_2HCO_2Me = 6.0 equiv relative to VBA) were added. [b] Mol % of $Cu^{II}SO_4$ relative to VBA. [c] t_1 = time for click reaction, t_2 = time for ATRA. [d] 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 %). [e] Isolated yield after column chromatography.

3. Conclusions

In summary, we reported an efficient synthesis of functionalized polytriazoles via one-pot sequential reactions involving copper-catalyzed [3+2] azide–alkyne cycloaddition and atom transfer radical addition (ATRA). In the first step, reactions were performed in a ligand-free catalytic system, composed of anhydrous $Cu^{II}SO_4$ and ascorbic acid. After completion of the click reaction, free TPMA and alkyl halide were then added to the same reaction mixture and ATRA allowed to proceed. It was observed that the reaction between vinyl benzyl azide, tripropargylamine and tetrahalogenated methanes (CCl_4 and CBr_4), proceeded efficiently in the presence of as low as 10.0 mol % of copper. Reactions with trihalogenated (methyl trichloroacetate) and dihalogenated (methyl dichloroacetate and dichloroacetonitrile) substrates were also successful, although the products were isolated in modest yields (50–80 %). The presented methodology enables efficient synthesis of functionalized polytriazoles,

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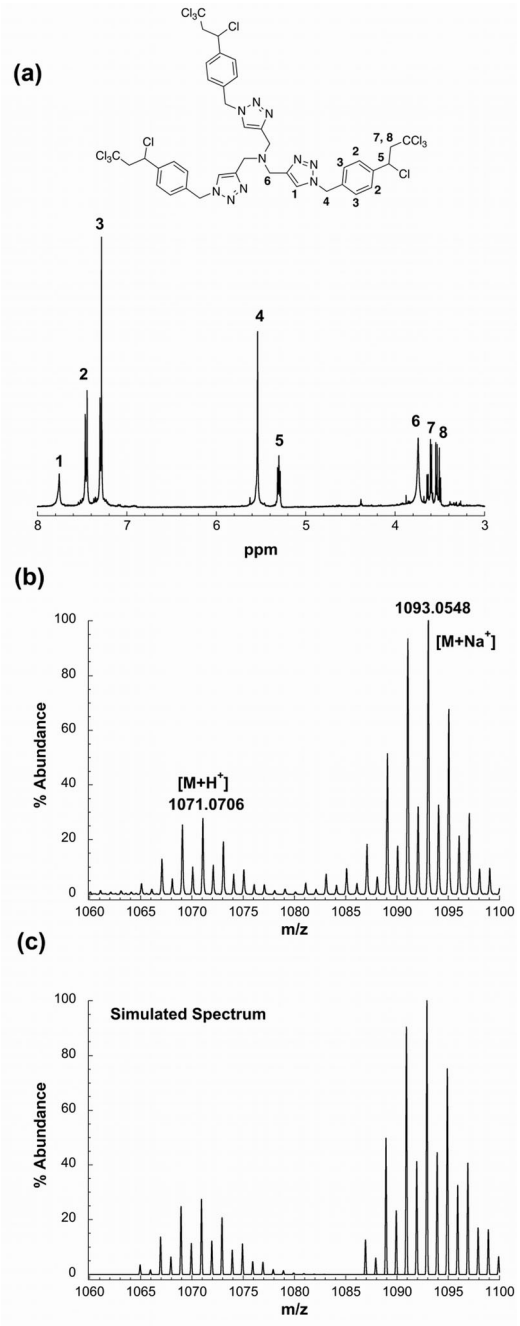

Figure 2. ^{1}H NMR (a) and experimental (b) and simulated (c) mass spectra of tris((1-(4-(1,3,3,3-tetrachloropropyl)benzyl)-1H-1,2,3-triazol-4-yl)methyl)amine.

which could have a potential use as chelating agents for a variety of transition metals.

4. Experimental Section

General procedures: Copper(II) sulfate (anhydrous), $CuSO_4{\cdot}5H_2O$, ascorbic acid, tripropargylamine, alkyl halides (carbon tetrachloride, carbon tetrabromide, methyl trichloroacetate, methyl dichloroacetate and dichloroacetonitrile) and methanol were purchased from commercial sources and used without further purification. Tris(2-pyridylmethyl)amine (TPMA)[62] and 4-vinylbenzyl azide (VBA)[63] were synthesized according to literature procedures. ^{1}H NMR and ^{13}C NMR spectra were obtained using Bruker Avance 400 MHz operating at room temperature. All chemical shifts are given in ppm relative to residual solvent peaks ($CDCl_3$, ^{1}H: $\delta = 7.26$ ppm and ^{13}C: $\delta = 77.2$ ppm). Mass spectroscopic analyses were performed using electrospray ionization time of flight mass spectrometry on a Bruker microTOF instrument. Simulated data for the molecular ion peaks and isotopic distributions were obtained using an Isotopic Distribution Simulator (IsoPro) v. 3.0.

Stock solutions: 0.01 M $[Cu^{II}(TPMA)X][X]$ ($X = Cl^-$ or Br^-) and anhydrous $Cu^{II}SO_4$ solutions were prepared in methanol. Ascorbic acid solution (0.25 M) was prepared in methanol immediately before use.

Copper-catalyzed [3+2] azide–alkyne cycloaddition between 4-vinylbenzyl azide and tripropargylamine: Into a 100 mL Schlenk flask equipped with a stirring bar were added 4-vinylbenzyl azide (VBA) (12.0 mmol, 1.8 mL), tripropargylamine (4.0 mmol, 564 μL), CH_2Cl_2/H_2O (50 mL, 1:1 mixture by volume), $CuSO_4{\cdot}5H_2O$ (0.30 g, 1.2 mmol) and sodium ascorbate (12.0 mmol, 2.377 g). The reaction flask was then capped with a rubber septum and stirred overnight at room temperature. The reaction was quenched by adding H_2O and ethylenediamine tetraacetic acid sodium salt dihydrate ($Na_4EDTA{\cdot}2H_2O$, 1.2 mmol, 0.499 g), stirred for approximately 1 h and poured into a separatory funnel. The product was extracted with CH_2Cl_2 (2×10 mL). The collected organic extract was dried over $MgSO_4$ and solvent was removed in vacuo to give yellow solid in 74% yield (2.98 mmol, 1.813 g). In another reaction flask, VBA (3.0 mmol, 450 μL), tripropargylamine (1.0 mmol, 141 μL), anhydrous $CuSO_4$ (0.3 mmol, 0.0479 g) and ascorbic acid (6.0 mmol, 1.0578 g dissolved in 24 mL MeOH) were mixed together. Aforementioned procedure was followed and after aqueous work-up and solvent removal, product was isolated in 91% yield (0.0913 mmol, 0.556 g).

General procedure for the ATRA of alkyl halides to TVBTA catalyzed by $[Cu^{II}(TPMA)X][X]$ ($X = Cl^-$ or Br^-) and ascorbic acid: TVBTA (0.1 mmol, 0.0609 g), alkyl halide (CCl_4 = 0.375 mmol, 36 μL; CBr_4 = 0.375 mmol, 0.1244 g; Cl_3CO_2Me = 0.6 mmol, 72 μL; Cl_2HCO_2Me = 0.6 mmol, 62 μL and $CHCl_2CN$ = 0.6 mmol, 48 μL), *p*-dimethoxybenzene, and the corresponding amount of $[Cu^{II}(TPMA)X][X]$ were added into a 5 mL Schlenk flask equipped with micro stirring bar. Methanol was then added in order to maintain constant volume and concentration of 0.08 M for TVBTA. Ascorbic acid solution was then added and immediately each reaction flask was secured with an airtight Teflon cap. The resulting reaction mixtures were immersed in an oil bath thermostated at 60 °C/80 °C for 24/27 h. The percent yield of the expected functionalized polytriazole ($TBTA(RX)_3$) was obtained using ^{1}H NMR spectroscopy relative to the internal standard. If necessary, the solvent was partially evaporated prior to ^{1}H NMR analysis.

General procedure for sequential copper-catalyzed [3+2] cycloaddition and atom transfer radical addition in the presence of ascorbic acid: In a typical experiment, a stock solution containing VBA (3.0 mmol, 450 μL), tripropargylamine (1.0 mmol, 141 μL), *p*-dimethoxybenzene and 2.4 mL MeOH was prepared to give a 1.0 M solution in VBA. Aliquots of the solution (0.5 mmol in VBA, 500 μL) were distributed into 5 mL Schlenk flasks containing a micro stirring bar. For each reaction mixture with $[VBA]_0$:-

$[Cu^{II}]_0$ ratio of 10:1, anhydrous $Cu^{II}SO_4$ (0.05 mmol, 0.0080 g) and ascorbic acid solution (1.0 mmol, 4.0 mL from 0.25 M solution) were added. For reactions utilizing $[VBA]_0:[Cu^{II}]_0$ ratio of 100:1, anhydrous $Cu^{II}SO_4$ (0.005 mmol, 500 μL from 0.01 M $CuSO_4$ solution) and ascorbic acid solution (0.1 mmol, 400 μL) were added. The volume of each reaction mixture was adjusted by adding MeOH in order to maintain constant concentration of VBA (0.10 M). Schlenk flasks were secured with an airtight Teflon cap and immersed in an oil bath thermostated at 60 °C for 1 h (10.0 mol% of $Cu^{II}SO_4$) or 20 h (1.0 mol% of $Cu^{II}SO_4$). Upon completion, each reaction mixture was taken inside the glovebox and uncapped. The corresponding amounts of TPMA (1.0 equiv relative to $Cu^{II}SO_4$) and alkyl halide (CCl_4 = 1.875 mmol, 181 μL; CBr_4 = 1.875 mmol, 0.622 g; Cl_3CO_2Me = 3.0 mmol, 360 μL; Cl_2HCO_2Me = 3.0 mmol, 310 μL or $CHCl_2CN$ = 3.0 mmol, 240 μL) were added. The resulting mixtures were then heated in an oil bath at 60 °C for 8 h (10.0 mol% of $Cu^{II}SO_4$) or 24 h (1.0 mol% of $Cu^{II}SO_4$). The percent yield of the expected functionalized polytriazole ($TBTA(RX)_3$) was obtained using ^{1}H NMR spectroscopy relative to the internal standard. If necessary, the solvent was partially evaporated prior to ^{1}H NMR analysis.

Product Characterization

Tris((1-(4-vinylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)amine (TVBTA): ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.69 (s, 3H), 7.41(d, J=8.4 Hz, 6H), 7.24 (d, J = 8 Hz, 6H), 6.71 (dd, J = 17.6, 10.9 Hz, 3H), 5.77 (d, J = 17.6 Hz, 3H), 5.50 (s, 6H), 5.30 (d, J = 10.9 Hz, 3H), 3.73 (s, 6H). ^{13}C NMR (100 MHz; $CDCl_3$): δ = 144.5, 138.0, 136.0, 134.1, 128.3, 126.8, 124.0, 114.9, 53.9, 47.1. HR-ESI-TOF for $C_{36}H_{37}N_{10}$ [M + H$^+$]: simulated: 609.3202, experimental: 609.3952. HR-ESI-TOF for $C_{36}H_{36}N_{10}Na$ [M + Na$^+$]: simulated: 631.3022, experimental: 631.3791.

Tris((1-(4-(1,3,3,3-tetrachloropropyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)amine ($TBTA(CCl_4)_3$): ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.76 (s, 3H), 7.46 (d, J = 8.4 Hz, 6H), 7.29 (d, J = 8.4 Hz, 6H), 5.54 (s, 6H), 5.32–5.29 (m, 3H), 3.74 (s, 6H), 3.59 (dd, J = 15.4, 5.4 Hz, 3H), 3.49 (dd, J = 15.4, 6.4 Hz, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ = 149.40, 141.24, 135.79, 128.53, 128.19, 124.68, 96.02, 62.57, 57.61, 53.68, 46.02, 62.57, 57.61, 53.68, 46.81. HR-ESI-TOF for $C_{36}H_{37}Cl_{12}N_{10}$ [M + H$^+$]: simulated: 1070.9358, experimental: 1071.0706. HR-ESI-TOF for $C_{36}H_{36}Cl_{12}N_{10}Na$ [M + Na$^+$]: simulated: 1092.9186, experimental: 1093.0548.

Tris((1-(4-(1,3,3,3-tetrabromopropyl)benzyl)-1*H*-1,2,3-triazol-4-yl)methyl)amine ($TBTA(CBr_4)_3$): ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.78 (s, 3H), 7.51 (d, J = 8.4 Hz, 6H), 7.27 (d, J = 8.4 Hz, 6H), 5.53 (s, 6H), 5.32 (dd, J = 7.6, 4.0 Hz, 3H), 4.12 (dd, J = 15.4, 4.0 Hz, 3H), 4.03 (dd, J = 15.4, 7.8 Hz, 3H), 3.75 (s, 6H). ^{13}C NMR (100 MHz; $CDCl_3$): δ = 143.35, 141.36, 135.48, 128.94, 128.45, 124.47, 82.90, 66.27, 56.90, 53.65, 49.14, 46.89. HR-ESI-TOF for $C_{36}H_{37}Br_{12}N_{10}$ [M + H$^+$]: simulated: 1604.3242, experimental: 1604.5386. HR-ESI-TOF for $C_{36}H_{36}Br_{12}N_{10}Na$ [M + Na$^+$]: simulated: 1626.3115, experimental: 1626.5079.

Trimethyl 4,4′,4″-(((4,4′,4″-(nitrilotris(methylene))tris(1*H*-1,2,3-triazole-4,1-diyl))tris(methylene))tris(benzene-4,1-diyl))tris(2,2,4-trichlorobutanoate) ($TBTA(Cl_3CCO_2Me)_3$): ^{1}H NMR (400 MHz; $CDCl_3$): δ = 8.10 (s, 3H), 7.44 (d, J = 8.4 Hz, 6H), 7.00 (d, J = 8.4 Hz, 6H), 5.56 (s, 6H), 5.24 (dd, J = 7.6, 5.8 Hz, 3H), 3.93 (s, 9H), 3.71 (s, 6H), 3.42 (dd, J = 15.0, 7.6 Hz, 3H), 3.18 (dd, J = 15.0, 5.8 Hz, 3H). ^{13}C NMR (101 MHz; $CDCl_3$): δ = 165.6, 143.8, 140.3, 135.6, 128.4, 128.1, 124.2, 81.9, 57.8, 54.5, 53.9, 53.6, 46.8, 43.6. HR-ESI-TOF for $C_{46}H_{50}N_{10}Cl_{12}O_6$ [M + H$^+$]: simulated: 1157.1051, experimental: 1160.9780.

4,4′,4″-(((4,4′,4″-(nitrilotris(methylene))tris(1*H*-1,2,3-triazole-4,1-diyl))tris(methylene))tris(benzene-4,1-diyl))tris(2,4-dichlorobutanenitrile)) ($TBTA(CHCl_2CN)_3$): ^{1}H NMR (400 MHz; $CDCl_3$): mixture of diastereomers δ = 7.76 (s, 3H), 7.75 (s, 3H), 7.42 (d, J = 8.4 Hz, 6H), 7.31 (d, J = 8.4 Hz, 6H), 5.54 (s, 6H), 5.13–5.05 (m, 3H), 4.79–4.75 (m, 3H), 4.55–4.51 (m, 3H), 3.72 (s, 6H), 2.85–2.77 (m, 3H), 2.73–2.66 (m, 3H), 2.66–2.56 (m, 3H). ^{13}C NMR (100 MHz; $CDCl_3$): δ = 144.15, 144.06; 139.40, 139.10; 136.09, 135.98; 128.79, 128.75; 127.77, 127.75; 124.10, 124.05; 116.29, 116.04; 57.85, 57.70; 53.54; 46.98, 46.96; 45.73, 45.40; 40.20, 39.91. HR-ESI-TOF for $C_{42}H_{40}Cl_6N_{13}$ [M + H$^+$]: simulated: 938.16275, experimental: 938.2882. HR-ESI-TOF for $C_{42}H_{39}Cl_6N_{13}Na$ [M + Na$^+$]: simulated: 960.1459, experimental: 960.2722.

Trimethyl 4,4′,4″-(((4,4′,4″-(nitrilotris(methylene))tris(1*H*-1,2,3-triazole-4,1-diyl))tris(methylene))tris(benzene-4,1-diyl))tris(2,4-dichlorobutanoate) ($TBTA(Cl_2HCCO_2Me)_3$): ^{1}H NMR (400 MHz; $CDCl_3$): mixture of diastereomers δ = 7.73 (s, 3H), 7.72 (s, 3H), 7.39 (d, J = 8.0 Hz, 6H), 7.29 (d, J = 8.4 Hz, 6H), 5.49 (s, 6H), 5.14 (dd, J = 5.9, 2.9 Hz, 3H), 5.12–5.02 (m, 3H), 4.71–4.62 (m, 6H), 3.77 (s, 9H), 3.67 (s, 6H), 3.66 (s, 6H), 2.76–2.61 (m, 6H), 2.43–2.31(m, 6H). ^{13}C NMR (100 MHz; $CDCl_3$): δ = 169.28, 168.99, 144.11, 144.03, 140.79, 135.45, 128.57, 127.84, 124.03, 124.0, 59.11, 57.1, 56.94, 54.84, 53.31, 46.97, 44.1. HR-ESI-TOF for $C_{46}H_{53}N_{10}Cl_6O_6$ [M + H$^+$]: simulated: 1053.2217, experimental: 1053.2524.

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