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Aromatic Nitrogen Donors for Efficient Copper(I)–NHC CuAAC under Reductant-Free Conditions

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Copper(I)-catalysed azide–alkyne cycloaddition (CuAAC) has been successfully conducted under reductant-free conditions. The catalytic system consisted of a combination of a copper(I)–N-heterocyclic carbene complex and aromatic N-donors. The catalyst is stable and can be stored, thus rendering the reaction valuable for routine use.

Introduction

The emergence of "click chemistry" as a new way of categorizing organic reactions involving simple, selective, modular, high-yielding and easily workable transformations has facilitated an extraordinary expansion in the number of molecules available for medicinal chemistry, biology and materials science.[1] Among these synthetic "click" tools, copper(I)-catalysed azide–alkyne cycloaddition (CuAAC) has received unrivalled attention.[2] The CuAAC procedure classically requires the presence of a sacrificial reducing agent such as ascorbic acid or TCEP [tris(2-carboxyethyl)-phosphane] to form the copper(I) species from a copper(II) source. The discovery of ligand-accelerating effects in CuAAC, despite increasing the reaction rate, has allowed both copper catalyst and reducing agent loadings to be dramatically reduced. The ligands (Figure 1) are usually aromatic N-donors, for example, triazole [**1**, TBTA: tris(benzyltriazolylmethyl)amine], benzimidazole [**2**, $(BimC_4A)_3$] and phenanthroline (**3**, bathophenanthrolinedisulfonic acid disodium salt).[3]

Nevertheless, few homogeneous catalytic systems giving rapid and efficient catalysis without the aid of a reducing reagent are available (Figure 2). This is important because ascorbic acid, dehydroascorbate and other byproducts have been reported to interact with azo amides, lysine and guanidine.[4] Also, in the case of lanthanide probes, ascorbic acid is known to act as a luminescence quencher.[5] In this context, the highly crowded [Cu(C18$_6$tren)]Br (**4**) introduced by

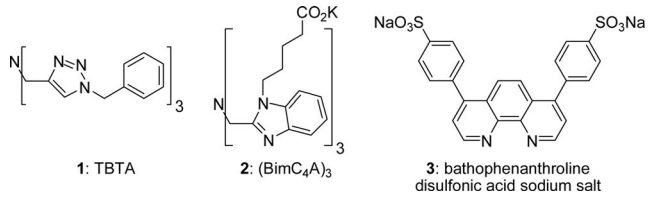

Figure 1. N-donor ligands that accelerate CuAAC.

Vincent and co-workers exhibits very good stability towards oxygen, thereby allowing a catalyst loading as low as 10^{-3} mol-% with an impressive turnover number.[6] On the other hand, this high catalytic efficiency is achieved at the expense of the high temperature needed for the reactions. Pericàs and co-workers recently reported a contracted version of the tripodal ligand **1**.[7] The stable complex **5** (0.5 mol-%) can be used in neat or "on water" conditions. (Aminoarenethiolato)copper(I) **6**, which exhibits excellent thermal stability, is also able to promote CuAAC at low loading (1 mol-%).[8] Unfortunately, the reactions cannot be conducted in water, and organic solvents such as dichloromethane are preferred. Finally, the seminal work of Nolan

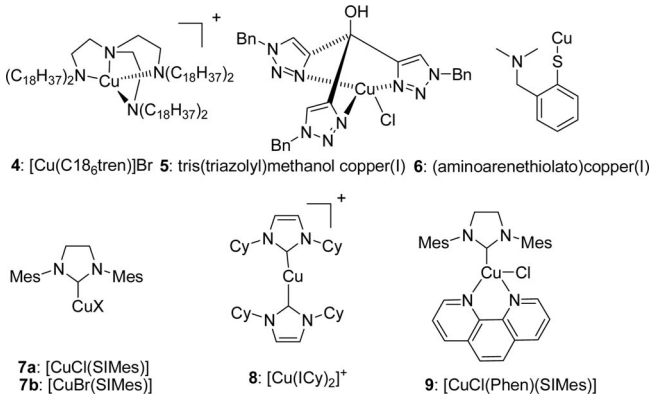

Figure 2. Oxygen-stable catalysts **4**–**9**.

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and co-workers on N-heterocyclic carbenes (NHC) has demonstrated the remarkable stability of neutral and cationic copper(I)–NHCs **7** and **8** towards moisture, heat and oxygen allowing CuAAC to occur, in some cases, at ppm catalyst loadings. Here again, the catalytic efficiency is achieved at the expense of neat or "on water" conditions.[9]

Inspired by these results, we recently reported that the combination of the Cu^{I}–NHCs [Cu(SIMes)Cl] [SIMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolidin-2-ylidene] with aromatic nitrogen donors such as 1,10-phenanthroline affords the well-defined copper(I)–NHC **9**.[10] The CuAAC reaction catalysed by **9** takes place efficiently in solution, at room temperature and in the total absence of a reducing agent. In this article we now report our complete experimental data concerning the advantages of combining Cu^{I}–NHCs with aromatic N-donors.

Results and Discussion

Copper(I)–NHC/Phenanthroline Equilibria

In our preliminary communication we reported the reversible association of 1,10-phenanthroline (**10**) with [CuCl(SIMes)]. Unexpectedly, the equilibrium constant was found to be rather low for a copper(I)–phenanthroline complex (K = 250 M^{-1}), and this was believed to be one of the key features of its catalytic efficiency.[10] Typical of ligand-exchange phenomena occurring on the NMR timescale, the ^{1}H and ^{13}C NMR spectra of a mixture of **7a** and phenanthroline (1:1) revealed an extreme broadening of the phenanthroline signals, whereas the carbene signature remained unchanged. Interestingly, a different picture emerges with the bulkier 2,9-dimethyl-1,10-phenanthroline (**11**) (neocuproine; Figure 3). The signals of **7a** and **11** are accompanied by signals corresponding to the [CuCl(neocuproine)(SIMes)] complex, which indicates a slower ligand exchange even though some enlargements of signals are still observed. Three other representative copper(I)–NHCs were examined: [CuCl(IMes)] [IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene, **12**], [CuCl(SIPr)] [SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene, **13**] and [CuCl(IPr)] [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2-ylidene, **14**]. In all cases, the observed exchange is slower than the NMR timescale, and separated signals are observed.

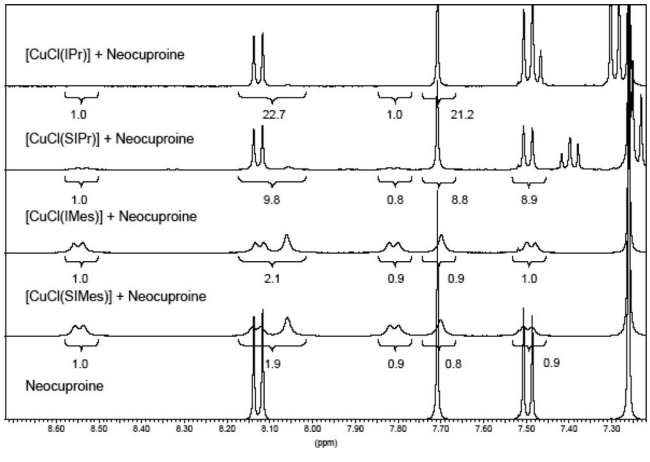
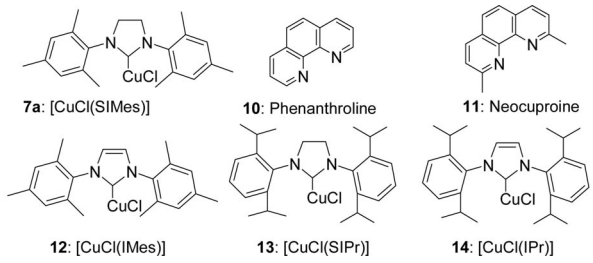
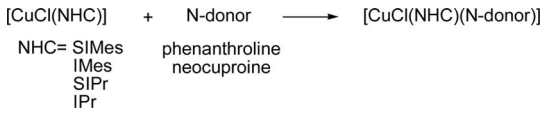


Figure 3. ^{1}H NMR spectra of copper(I)–NHCs and neocuproine ($CDCl_3$, 400 MHz, c = 0.017 M).



We then took advantage of the separated signals to estimate the values of the binding constant by using Equation (1) derived from reaction (2). The values are presented in Table 1.

$$K = [CuCl(NHC)(N\text{-donor})]/\{[CuCl(NHC)][N\text{-donor}]\} \quad (1)$$



(2)

Table 1. Equilibrium constants.

Entry	Copper(I)–NHC	Ligand	K [mol^{-1}]
1	[CuCl(SIMes)]	Phenanthroline	250
2	[CuCl(SIMes)]	Neocuproine	ca. 140
3	[CuCl(IMes)]	Neocuproine	ca. 120
4	[CuCl(SIPr)]	Neocuproine	ca. 6
5	[CuCl(IPr)]	Neocuproine	ca. 3

At first, the equilibrium constant appears to be strongly influenced by steric factors. Regarding the nature of the aromatic N-donor, the increase in the steric bulk (from **10** to **11**) results in a weaker association (Table 1, Entries 1 and 2). The same behaviour is observed for the NHC: the introduction of isopropyl groups at the 2- and 6-positions similarly results in a dramatic decrease in the association (Table 1, Entries 2 and 4, 3 and 5). We then considered the possibility of combining the steric factors (quantifiable by the $\%V_{bur}$ factor) with the binding energy. The $\%V_{bur}$ parameter has been proposed for metal–NHCs as a quantifier of part of the first coordination sphere (centred on the metal atom) occupied by the carbene ligand.[11] We then naturally attempted to correlate the values of $\%V_{bur}$ with the energy required to form the [CuCl(NHC)(N-donor)] complex. For that we selected the four NHCs studied (SIMes, IMes, SIPr and IPr) and added SIMet [SIMet = 1,3-dimethylimidazolidin-2-ylidene] and IMet [IMet = 1,3-dimethylimidazolin-2-ylidene], which are two carbenes with lower steric hindrance (Figure 4).

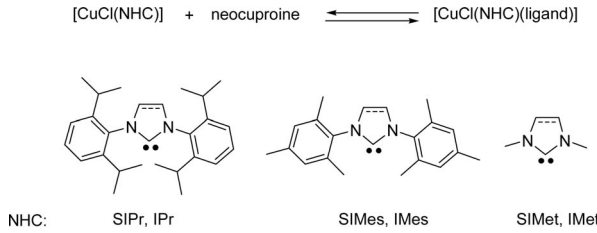


Figure 4. Equilibrium between the Cu–NHC and neocuproine and the carbenes selected for the study.

First of all, optimization performed on complex **9** with the Gaussian 03 package of software was found to give results similar to those of the corresponding X-ray analysis, which confirmed the ability of this program to reproduce the structures of our complexes.[12] The geometries of [CuCl(NHC)], [CuCl(NHC)(neocuproine)] and neocuproine were then freely optimized in the gas phase, and the binding energies were determined. These calculated energies include the association of the neocuproine with the copper(I) centre, the distortion of the complex from a linear to a tetrahedral geometry and the variation of bond lengths (especially for the chloride atom). The $\%V_{bur}$ values, which refer to the [Cu(NHC)] part of the complexes, are extracted from the optimized complexes and are compared, when possible, with X-ray data. The $\%V_{bur}$ values were calculated by using the SambVca program.[11c] To account only for the carbene–copper moiety, the chloride ion was excluded from the coordinate file, and a sphere of 3.5 Å was centred on the copper atom. Importantly, this implies that the metal–C distances are automatically adjusted to the values found in the calculations or X-ray analyses and are not fixed at a standard distance (usually 2.10 Å) as is done in regular calculations (Table 2).

Table 2. $\%V_{bur}$ values for [Cu(NHC)].

	$\%V_{bur}$					
	SIPr	IPr	SIMes	IMes	SIMet	IMet
Calcd.	53.4	50.3	43.2	41.5	29.2	28.8
X-ray	48.7	48.5	39.2			

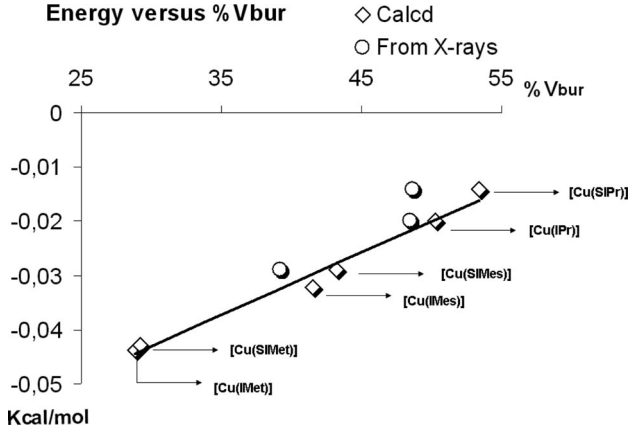


Figure 5. Correlation between the $\%V_{bur}$ values and the binding energies.

The energies were then plotted versus $\%V_{bur}$ for the different [Cu(NHC)]s as depicted in Figure 5. The energies correlate well with the $\%V_{bur}$ values calculated for each complex. The graph shows that neocuproine associates more easily with complexes in which NHCs are of low hindrance, in accord with experimental observations. Thus, for a fixed ligand, steric effects drive the equilibrium.

Copper(I)–NHC Screening

In our preliminary communication, we report that, among the few aromatic nitrogen donors added to [CuCl(SIMes)], phenanthroline provides one of the best catalytic activities.[10] Here, we also screen the effect of NHCs **12**–**14** with **10** on the model reaction of phenylacetylene (**15**) with benzyl azide (**16**) [reaction (3), Table 3]. The results presented in Table 3 show that only [CuCl(SIMes)] and [CuCl(IMes)] catalyse the formation of **17**.[9a] Here again, the addition of **10** greatly increases the isolated yields (Entries 1 vs. 2 and 3 vs. 4), **7a** being a better catalyst than **12**.

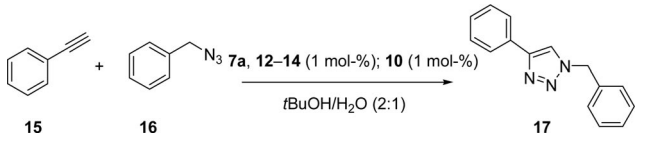


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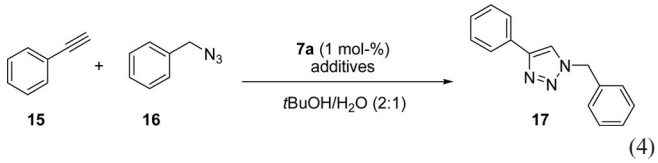
Table 3. Catalytic effect of copper(I)–NHCs in CuAAC.

Entry	Copper(I)–NHC	Additive	Yield [%]
1	[CuCl(SIMes)] (**7a**)	none	10
2	[CuCl(SIMes)] (**7a**)	phenanthroline (**10**)	78
3	[CuCl(IMes)] (**12**)	none	15
4	[CuCl(IMes)] (**12**)	phenanthroline (**10**)	49
5	[CuCl(SIPr)] (**13**)	none	0
6	[CuCl(SIPr)] (**13**)	phenanthroline (**10**)	<10
7	[CuCl(IPr)] (**14**)	none	0
8	[CuCl(IPr)] (**14**)	phenanthroline (**10**)	<10

Screening of Additives

Having selected **7a** as the best copper(I) precatalyst, we then screened a selection of 19 aromatic N-donors [reaction (4), Figure 6]. This collection of additives can be cast into two subsets: mono- and bidentates, derivatives of different pyridines and 1,10-phenanthrolines. Special attention was paid to the collection of pyridines, commercially available pyridines bearing electron-donating and -withdrawing groups.



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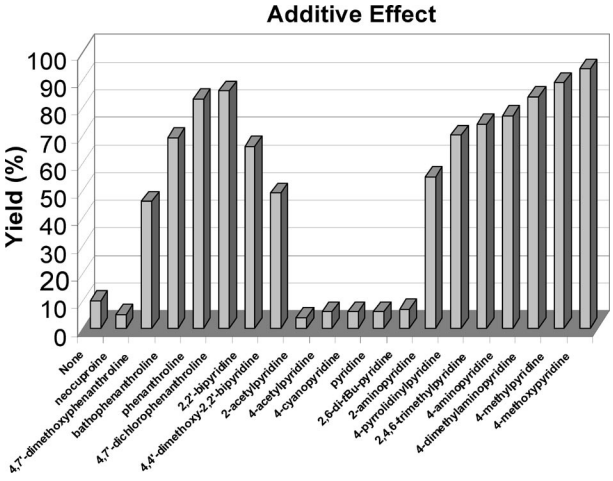
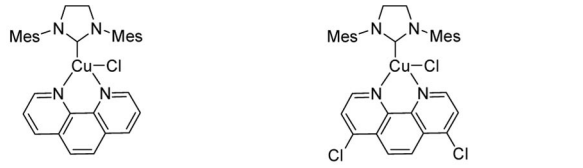


Figure 6. Screening of additives.

In the phenanthroline series, the hindered neocuproine exhibits nearly no activity with other additives of lower steric hindrance displaying better efficiencies. The efficiencies increase in roughly the following order: neocuproine < 4,7-dimethoxy-1,10-phenanthroline < bathophenanthroline < 1,10-phenanthroline < 4,7-dichloro-1,10-phenanthroline. Both 2,2′-bipyridine and 4,4′-dimethoxy-2,2′-bipyridine were also tested, but their contribution, albeit being beneficial, is poorer than that of the best phenanthroline. Interestingly, inspection of the pyridine derivatives revealed the existence of two subgroups. Pyridine and compounds possessing electron-withdrawing groups are inactive (2- and 4-acetyl-, 4-cyanopyridine). In contrast, the introduction of electron-donating substituents at the 2- and 4-positions results in a dramatic increase in the yield. For example, 2- and 4-aminopyridine as well as 4-pyrrolidinyl- and 4-methoxypyridine led to yields of 55, 77, 70 and 95%, respectively. Both 4-amino- and 4-(dimethylamino)pyridines gave good yields (77 and 84%, respectively), which demonstrates that catalysis can be enhanced regardless of the substitution pattern at the nitrogen atom.

Overall, [CuCl(SIMes)(Phen)] (**9**) and notably [CuCl(SIMes)(4,7-dichloro-1,10-phenanthroline)] (**18**) are well suited for the CuAAC reaction, the latter giving the best results (Scheme 1).



9: [CuCl(Phen)(SIMes)] **18**: [CuCl(SIMes)(4,7-dichloro-1,10-phenanthroline)]

Scheme 1. The two best catalysts resulting from CuAAC screening.

Synthesis of Complex 18

Complex **18** is easily accessible: addition of pentane to a dichloromethane solution containing equimolar quantities of [CuCl(SIMes)] and 4,7-dichloro-1,10-phenanthroline furnished the expected complex in 71% yield as a deep-purple microcrystalline solid. This material is stable for months at room temperature in the presence of air and light. Unfortunately, we were unable to grow crystals suitable for X-ray analysis. The ^{1}H and ^{13}C NMR spectra of **18** in $CDCl_3$ reveal an extreme broadening of the 4,7-dichloro-1,10-phenanthroline signals, evocative of the solution behaviour of **9** (Figure 7).

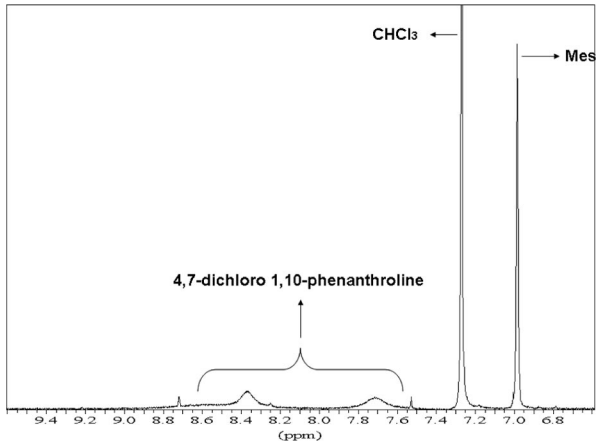


Figure 7. Aromatic part of the ^{1}H NMR spectrum of complex **18**.

Thus, although the signature of [CuCl(SIMes)] appears clearly, the signals of 4,7-dichloro-1,10-phenanthroline are considerably broadened. Importantly, **18** conserves its integrity in solution for days. This was not the case for **9**, which decomposes in solution exposed to air after several hours (in the solid state, the reddish crystals of **9** are stable for months). Also significant is that the addition of heterocycles containing electron-donating groups (i.e., 4,7-dimethoxy-1,10-phenanthroline, 4-methoxypridine) to [CuCl(SIMes)] solutions exposed to air results in a rapid decomposition of the complexes with concomitant formation of a reddish unidentified solid. The difference with **18** is probably a result of the lower electron-donating ability of the 4,7-dichloro-1,10-phenanthroline, which makes the complex less susceptible to oxidation, and thus it is more likely that the reaction goes to completion.

Quantum Studies of the Complexes

As we were unable to grow crystals of **18**, we used Gaussian quantum optimization [B3LYP at the 6-31g(d,p) level of theory] to reveal its structure. Structures of the complexes of **18** and [CuCl(SIMes)(4-DMAP)$_2$] (**19**) were optimized by this method (Figure 8 and Table 4).

The geometry of **7a** was determined by X-ray diffraction; an important feature of this complex is the linear copper geometry. When aromatic N-donors are added, the copper centre adopts a distorted tetrahedral environment, a consequence of the non-equivalent steric and/or electronic environment around the copper atom. This is not surprising as the tetrahedral geometry has been reported for many mixed σ-aromatic N-donor complexes. Elongation of the copper–

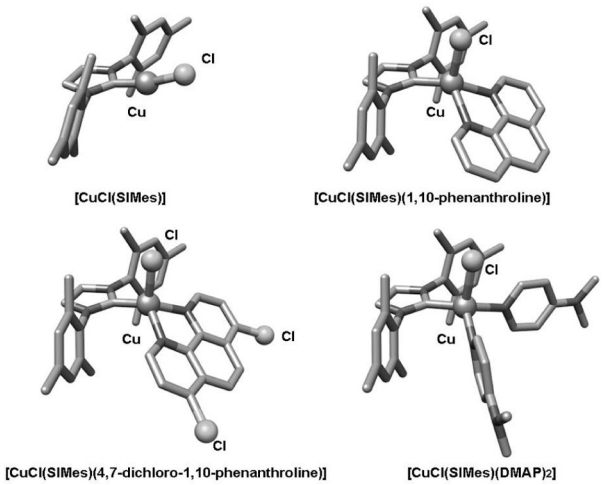


Figure 8. Optimized structures of **7a**, **9**, **18** and **19**.

Table 4. Bond lengths and angles of interest for complexes **7a**, **9**, **18** and **19**.

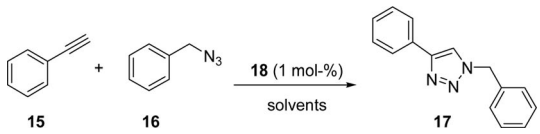
	Bond lengths [Å]			
	Cu–Cl	Cu–N	Cu–N	Cu–C
7a[a]	2.009	–	–	1.882
9[a]	2.347	2.114	2.128	1.916
9[b]	2.323	2.069	2.069	1.906
18[b]	2.316	2.064	2.064	1.906
19[b]	2.453	2.070	2.070	1.892
	Bond angles [°]			
	C–Cu–Cl	N–Cu–N	N–Cu–Cl	N–Cu–Cl
7a[a]	178.5	–	–	–
9[a]	120.5	77.4	99.9	102.0
9[b]	108.8	80.3	109.1	109.1
18[b]	108.6	79.7	109.3	109.3
19[b]	108.7	98.6	107.7	100.7

[a] X-ray data. [b] Quantum calculations.

chloride bond in the original [CuCl(SIMes)] is also a significant feature of the four-coordinate complexes of copper(I), the Cu–Cl bond length being between 2.32 and 2.45 Å. The switch from bidentate to monodentate ligands results in a decompression of the N–Cu–N angles (from ca. 80° for bidentate ligands to ca. 100° for monodentate ligands) and a rotation of the two heterocycles around the copper–nitrogen axis, which places the two 4-DMAP groups in a quasi-parallel position with the mesityl moieties.

Scope and Limitations

First of all the solvent effect was evaluated on the model reaction by using 1% loading of **18** after 18 h [reaction (5), Table 5]. As can be seen, **18** not only efficiently catalyses the CuAAC reaction in environmentally friendly alcoholic solvents (MeOH and EtOH), but the reaction can also be performed in dichloromethane. However, the efficiency is significantly reduced when using strong polar aprotic solvents such as DMF and DMSO.



(5)

Table 5. Solvent effect.

Entry	Solvent	Isolated yield [%]
1	MeOH	87
2	EtOH	92
3	CH_2Cl_2	82
4	DMF	40
5	DMSO	37

Next, the scope and limitations of the reaction were examined by using a representative collection of azides and alkynes in methanol (Figure 9). In agreement with our preliminary report, electron-rich (**20**) and -poor aromatic azides (**21**) are well tolerated. Propionic acid (**22**) is reluctant to react, probably because of protonation of the aromatic N-donor.[10] Propargylamine reacts well with alkyl azides to furnish **23**–**27** in good isolated yields, regardless of the length of the chain. Finally, **18** also catalyses the reaction with ammonium compound **28** to furnish the bis(triazole) **29**. We were also interested in the triazole moiety as a potential ligand for metals (Figure 10). We thus turned our attention to 2-(azidomethyl)pyridine (**30**), which reacts efficiently with **15** to furnish the potent "inverse click chelator" **31** in almost quantitative yield. Indeed, this compound has recently been published as a copper(II) and silver(I) clamp.[13] Because of our interest in potential ligands for other metals, we focused on dipicolinic acid (DPA) derivatives that are well known for their propensity to complex lanthanides.

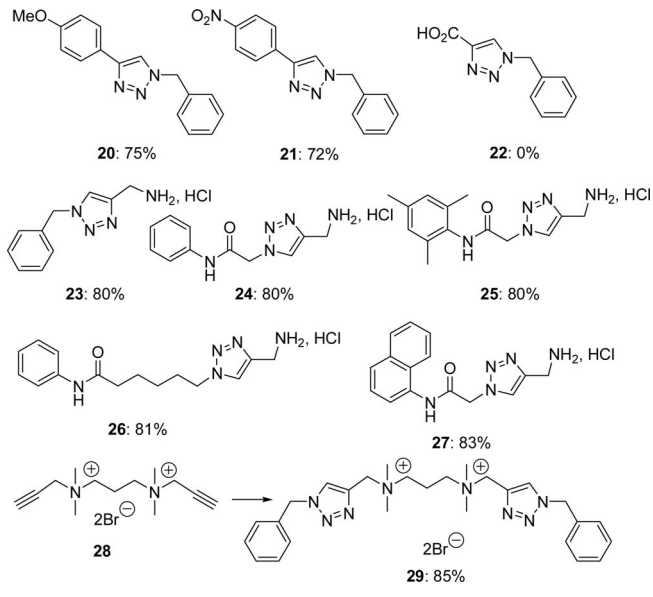


Figure 9. Some example of the CuAAC reaction catalysed by **18**.

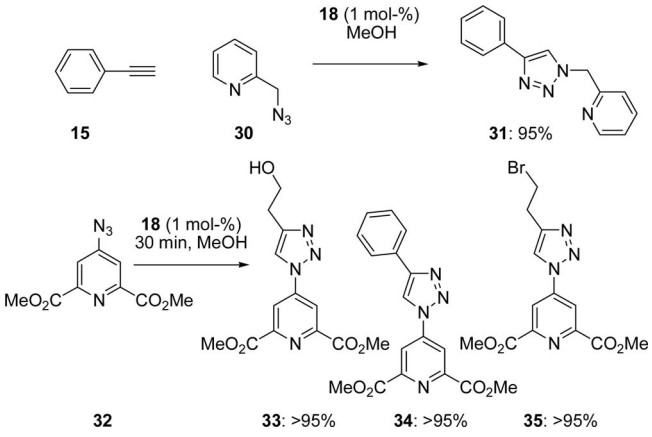


Figure 10. Synthesis of metal chelators.

Azide **32**, which can be synthesized on a multigram scale, exhibits unprecedented stability compared with aromatic azides, which are known to be sometimes photodegradable.[14] The reaction of **32** in methanol affords triazoles **33**–**35** in less than 30 min. The high reaction rate is probably caused by the presence of electron-withdrawing groups on the DPA moiety as electron-poor azides are known to react faster.

Finally, the ability of **18** to catalyse the [3+2] cycloaddition of carbohydrates was also tested (Figure 11). For this purpose, two protected ribopyranoses functionalized at the anomeric position were selected, one with a propargyl alcohol, the other with an azide group. In both cases, although the reactions require 18 h to reach completion, the CuAAC reaction occurs cleanly at 2 mol-% loading and affords good isolated yields for **37** and **39**. The efficiency of this slower reaction demonstrates the high stability of **18** in the presence of air.

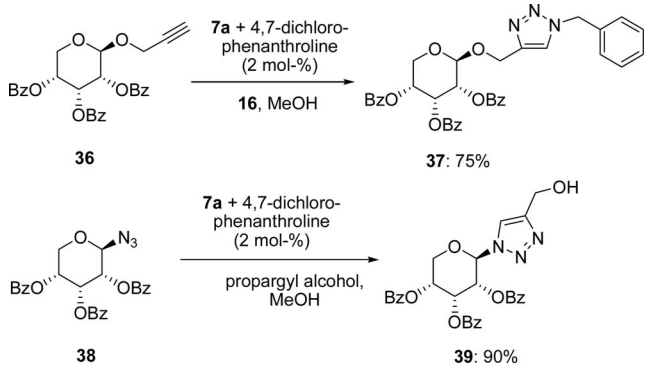


Figure 11. Synthesis of "clicked" D-ribopyranose derivatives.

Conclusions

We have reported herein that [CuCl(SIMes)(4,7-dichloro-1,10-phenanthroline)] (**18**) is an efficient catalyst for [2+3] azide–alkyne cycloaddition in the absence of a reducing agent. The CuAAC reaction can be applied to a large range of compounds, from basic alkynes and azides to more elaborate carbohydrates. Importantly, **18** can be stored and is easily synthesized from commercially available starting materials. We believe that this aspect renders its routine use very attractive.

Experimental Section

General: All commercially available reagents were used as received. TLC was performed with 250 μm silica gel 60 plates with a 254 nm fluorescent indicator. NMR spectra were recorded in the Fourier-transform mode with a Bruker Avance 400 (^{1}H at 400 MHz, ^{13}C at 100 MHz) spectrometer at 25 °C. Spin multiplicity is described by using the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet and br. = broad. Chemical shifts are given in ppm and coupling constants (*J*) in Hz. Standard carbohydrate numbering is used in the NMR assignment of compounds **36**–**39**. IR spectra were recorded with a Shimadzu FTIR-8400S spectrometer equipped with an ATR module (neat) or by using KBr pellets (KBr). High-resolution mass spectra were recorded with a Q-TOF micro spectrometer (Waters) in electrospray positive mode by using an internal (H_3PO_4) and external lock mass (leucine–enkephalin: $[M + H]^+$: *m*/*z* = 556.2766). All calculations were conducted by using density functional theory (DFT) as implemented in the Gaussian 03 program.[12] Geometry optimizations were performed by using the restricted B3LYP exchange and correlation functional with the double-ζ 6-31G(d,p) basis set. Harmonic frequency analysis based on analytical second derivatives was used to characterize the optimized geometries as local minima. The spectroscopic data for compounds **17**, **20**–**23**, **30**–**31** and the corresponding starting azides[15] have been reported in the literature. [CuCl(SIMes)], [CuCl(IMes)], [CuCl(SIPr)] and [CuCl(Pr)] were synthesized according to literature procedures.[16] 4,7-Dichloro-1,10-phenanthroline is commercially available or alternatively can be synthesized.[17]

NMR Estimation of Equilibrium Constants: A 0.033 M stock solution of neocuproine (12.5 mg, 0.06 mmol) in $CDCl_3$ (1.8 mL) and 0.033 M solutions of each complex [CuCl(NHC)] (SIMes: 4.0 mg; IMes: 4.0 mg; SIPr: 4.9 mg; IPr: 4.0 mg; 0.01 mmol) in $CDCl_3$ (1.8 mL) were prepared. A neocuproine solution (0.3 mL) was added to each [CuCl(NHC)] solution (0.3 mL), and the light- to dark-orange mixtures were transferred to 5 mm NMR tubes. Immediately after mixing, ^{1}H NMR spectra (16 scans) of each sample and the reference neocuproine (0.3 mL solution diluted with 0.3 mL of $CDCl_3$) were recorded. The spectra were calibrated with the solvent signal (δ = 7.26 ppm). Integrals were measured, and the signal of the highest chemical shift, which corresponds to the complex [CuCl(neocuproine)(NHC)], was normalized to 1. The ratio of [CuCl(neocuproine)(NHC)]/[free neocuproine], calculated from integral values, and the value of $[\text{neocuproine}]_{tot}$ = 0.017 M allowed each equilibrium constant to be estimated.

Screening of the Additives: Benzyl azide, phenylacetylene (2 mmol each), [(SIMes)CuCl] (0.02 mmol, 1 mol-%) and the additive (0.02 mmol, 1 mol-%) were mixed in *t*BuOH/water (1:1, 4 mL). The reaction mixture was stirred overnight, water (4 mL) was added, and the resulting solid was filtered, washed with pentane and dried in an oven at 85 °C.

[CuCl(SIMes)(4,7-dichloro-1,10-phenanthroline)] (18): [CuCl(SIMes)] (201 mg, 0.50 mmol, 1.0 equiv.) was dissolved in dichloromethane (5 mL). Under stirring, 4,7-dichloro-1,10-phenanthroline (174 mg, 0.70 mmol, 1.4 equiv.) was added portionwise. The solu-

tion turned immediately deep-red. Pentane (25 mL) was added slowly over 20 min, after which the solution was stirred for a further 30 min. The resulting suspension was filtered, the solid washed with pentane and dried under vacuum to furnish 230 mg (0.35 mmol, 71%) of a deep-purple solid. IR (KBr): $\tilde{\nu}$ = 3377, 3205, 2915, 1629, 1608, 1489, 1438, 1415, 1271, 850, 837, 732, 702, 574 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.4–8.2 (br., 4 H, H_{phen}), 7.7–7.5 (br., 2 H, H_{phen}), 6.90 (s, 4 H, H_{ArMes}), 3.85 (s, 4 H, CH_2), 2.27 (s, 6 H, CH_3), 2.22 (s, 12 H, CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 138.4, 136.6, 136.4, 129.9, 51.0, 21.3, 18.3 ppm (carbene C and 1,10-phenanthroline signals were not detected). HRMS (ESI+): calcd. for $C_{33}H_{32}Cl_2CuN_4$ 617.1300; found 617.1280.

General Procedure for the CuAAC Reaction: [CuCl(SIMes)] (1 mol-%) was added to a solution of 0.25 M azide (1 equiv.) and 0.25–0.5 M alkyne (1–2 equiv.) in methanol (total volume: 4 mL). 4,7-Dichloro-1,10-phenanthroline (1 mol-%) was added, the solution turned red-orange, and stirring was continued overnight. Alternatively, **18** (1 mol-%) was added. Unless indicated otherwise, the solution was stirred overnight, water (10 mL) was added, and the crude reaction mixtures were extracted with ethyl acetate, dried with $MgSO_4$ and concentrated to furnish pure products.

2-(4-Aminomethyl-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide Hydrochloride (24): Yield: 80%. IR (neat): $\tilde{\nu}$ = 3267, 3205, 3120, 3076, 3001, 1676, 1604, 1556, 1261, 866, 756 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.79 (s, 1 H, NH), 8.46 (s, 2 H, NH_2), 8.23 (s, 1 H, $H_{triazole}$), 7.62–7.02 (m, 5 H, H_{Ar}), 5.42 (s, 2 H, CH_2), 4.14 (s, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 164.0, 139.9, 138.5, 128.4, 126.0, 123.7, 119.2, 53.3, 33.9 ppm. HRMS (ESI+): calcd. for $C_{11}H_{14}N_5O$ 232.1198; found 232.1198.

2-(4-Aminomethyl-1*H*-1,2,3-triazol-1-yl)-*N*-(2,4,6-trimetylphenyl)-acetamide Hydrochloride (25): Yield: 80%. IR (neat): $\tilde{\nu}$ = 3281, 3130, 3014, 1670, 1529, 1236, 848 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 9.98 (s, 1 H, NH), 8.54 (br. s, 3 H, NH_3), 6.68 (s, 1 H, $H_{triazole}$), 5.45 (s, 2 H, H_{Ar}), 4.12 (s, 2 H, CH_2), 3.68 (s, 2 H, CH_2), 2.21 (s, 3 H, Me), 2.11 (s, 6 H, Me) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 163.9, 139.9, 135.6, 134.7, 131.6, 128.8, 125.9, 51.6, 33.8, 20.4, 18.30 ppm. HRMS (ESI$^+$): calcd. for $C_{14}H_{20}N_5O$ 274.1668; found. 274.1673.

6-(4-Aminomethyl-1*H*-1,2,3-triazol-1-yl)-*N*-phenylcaproamide Hydrochloride (26): Yield: 81%. IR (neat): $\tilde{\nu}$ = 3263, 2939, 1654, 1599, 1541, 1500, 1444, 1161, 844 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 10.00 (s, 1 H, NH), 8.44 (s, 3 H, NH_3), 8.18 (s, 1 H, $H_{triazole}$), 7.60 [d, ^3J(H,H) = 7.9 Hz, 2 H, H_{Ar}], 7.27 (t, $^3J_{H,H}$ = 7.7 Hz, 2 H, H_{Ar}), 7.00 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, H_{Ar}), 4.40 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_2), 4.08 (br., 2 H, CH_2), 2.30 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, CH_2), 1.83 (m, 2 H, CH_2), 1.65 (m, 2 H, CH_2), 1.25 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 171.0, 140.0, 139.3, 128.5, 124.3, 122.8, 119.0, 49.2, 36.0, 33.8, 29.5, 25.4, 24.4 ppm. HRMS (ESI$^+$): calcd. for $C_{15}H_{22}N_5O$ 288.1824; found. 288.1814.

2-(4-Aminomethyl-1*H*-1,2,3-triazol-1-yl)-*N*-naphthalen-1-ylacetamide Hydrochloride (27): Yield: 83%. IR (neat): $\tilde{\nu}$ = 3252, 3221, 3045, 1676, 1546, 1402, 1346, 1274, 1053, 802 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.69 (s, 1 H, NH), 8.32 (s, 1 H, $H_{triazole}$), 8.27 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, H_{Ar}), 7.95 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, H_{Ar}), 7.79 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, H_{Ar}), 7.70 (d, $^3J_{H,H}$ = 7.3 Hz, 1 H, H_{Ar}), 7.65–7.54 (m, 2 H, H_{Ar}), 7.50 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, H_{Ar}), 5.64 (s, 2 H, CH_2), 4.5–4.0 (br., 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 165.1, 140.4, 133.7, 132.8, 128.1, 127.6, 126.1, 126.0, 125.7, 125.5, 122.8, 121.5, 52.3, 34.0 ppm. HRMS (ESI$^+$): calcd. for $C_{15}H_{16}N_5O$ 282.1335; found 282.1365.

1,3-Bis(*N*,*N*-dimethylprop-2-ynylammonio)propane Dibromide (28): *N*,*N*,*N*′,*N*′-Tetramethyl-1,3-propanediamine (2.00 g, 15.4 mmol, 1.0 equiv.) and propargyl bromide (6.70 g, 46 mmol, 3.0 equiv., 80% w/w in toluene) were added sequentially to acetonitrile (30 mL). An exothermic reaction ensued, during which a white solid formed. The solution was stirred overnight, and the solid was filtered, washed with diethyl ether and dried in air to afford 3.40 g of a white solid (60%). IR (KBr): $\tilde{\nu}$ = 3427, 3184, 3014, 2968, 2918, 2119, 1475, 1448, 1386, 1176, 1004, 906, 887, 711 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 4.60 (d, $^4J_{H,H}$ = 2.4 Hz, 4 H, CH_2), 4.12 (t, $^3J_{H,H}$ = 4.2 Hz, 2 H, C≡C*H*), 3.48 (m, 4 H, CH_2), 3.20 (s, 12 H, Me), 2.32 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 82.5, 70.7, 60.1, 55.0, 51.1, 17.3 ppm. $C_{13}H_{22}Br_2N_2$ (368.15): calcd. C 42.65, H 6.06, N 7.65; found C 43.02, H 6.44, N 7.35.

1,3-Bis{*N*,*N*-dimethyl[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]-ammonio}propane Dibromide (29): The solvent was evaporated and the product was crystallized from a minimum amount of methanol. Yield: 85%. IR (KBr): $\tilde{\nu}$ = 3416, 3111, 3066, 1629, 1438, 1057, 896, 721 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.77 (s, 2 H, $H_{triazole}$), 7.3 (m, 10 H, H_{Ar}), 5.77, (m, 4 H, CH_2), 4.9 (m, 4 H, CH_2), 3.5 (m, 4 H, CH_2), 3.22 (s, 12 H, Me), 2.6 (m, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 135.6, 135.2, 128.8, 128.6, 128.2, 128.0, 59.1, 57.4, 53.0, 50.0, 17.1 ppm. $C_{27}H_{36}Br_2N_8$ (634.45): calcd. C 51.28, H 5.74, N 17.72; found C 51.43, H 6.02, N 17.51.

Dimethyl 4-Azidopyridine-2,6-dicarboxylate (32): A mixture of dimethyl 4-chloropyridine-2,6-dicarboxylate (2.2 g, 9.56 mmol) and sodium azide (6 g, 10 equiv.) in DMF (30 mL) was heated at 50 °C overnight. The yellow reaction mixture was allowed to cool to room temperature and poured into cold water (80 mL) under vigorous stirring. Compound **1** precipitated immediately from the solution, and filtration afforded 2.0 g (90%) of a pale-yellow solid. IR (neat): $\tilde{\nu}$ = 3075, 2960, 2122, 1753, 1718, 1594, 1445, 1351, 1273, 1250, 1190, 1158 cm^{-1}. ^{1}H (400 MHz, [D$_6$]DMSO): δ = 7.93 (s, 2 H, H_{Py}), 4.03 (s, 6 H, Me) ppm. ^{13}C NMR (400 MHz): δ = 164.4, 151.7, 149.9, 118.0, 53.4 ppm. $C_9H_8N_4O_4$ (236.18): calcd. C 45.77, H 3.41, N 23.72; found C 45.24, H 3.42, N 23.82.

Dimethyl 4-[4-(2-Hydroxyethyl)-1*H*-1,2,3-triazol-1-yl]pyridine-2,6-dicarboxylate (33): The product precipitated from solution and was isolated from the reaction mixture by simple filtration. White solid. Yield: >95%. IR (KBr): $\tilde{\nu}$ = 1759, 1726, 1599, 1438, 1246, 1058, 1053, 786, 758 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (s, 2 H, H_{Py}), 8.29 (s, 1 H, $H_{triazole}$), 3.99 (s, 6 H, Me), 3.90 (s, 2 H, CH_2), 3.01 (s, 2 H, CH_2) ppm. ^{13}C NMR (400 MHz, [D$_6$]DMSO): δ = 163.8, 149.6, 146.7, 144.8, 121.2, 116.7, 59.8, 52.9, 29.1 ppm. $C_{13}H_{14}N_4O_5$ (306.28): calcd. C 50.98, H 4.61, N 18.29; found C 50.99, H 4.42, N 18.29.

Dimethyl 4-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)pyridine-2,6-dicarboxylate (34): The product precipitated from solution and was isolated from the reaction mixture by simple filtration. Pale-yellow solid. Yield: >95%. IR (neat): $\tilde{\nu}$ = 3125, 2957, 1750, 1717, 1599, 1446, 1251, 1223, 1153, 1119, 1047, 1019, 987, 947, 892, 782, 756, 692 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.84 (s, 1 H, $H_{triazole}$), 8.81 (s, 2 H, H_{Py}), 7.99 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H, H_{Ar}), 7.53 (dd, $^3J_{H,H}$ = 7.3, 8.2 Hz, 2 H, H_{Ar}), 7.43 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, H_{Ar}), 3,99 (s, 6 H, Me) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 163.8, 149.6, 148.0, 144.7, 129.4, 129.0, 128.6, 125.3, 119.9, 116.8, 52.9 ppm. HRMS (ESI$^+$): calcd. for $C_{17}H_{14}N_4O_4Na$ 361.0913; found 361.0899.

Dimethyl 4-[4-(2-Bromoethyl)-1*H*-1,2,3-triazol-1-yl]pyridine-2,6-dicarboxylate (35): Pale-yellow solid. Yield: >95%. IR (neat): $\tilde{\nu}$ = 3508, 1737, 1591, 1446, 1292, 1265, 1238, 1045, 995 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.72 (s, 2 H, H_{Py}), 8.20 (s, 1 H, $H_{triazole}$), 4.05 (s, 6 H, Me), 3.74 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, CH_2), 3.41 (t, $^3J_{H,H}$ = 6.4 Hz, 2 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 149.7, 146.4, 144.8, 121.7, 116.9, 53.0, 32.0, 28.8 ppm. HRMS (ESI^+): calcd. for $C_{13}H_{13}BrN_4O_4Na$ 391.0018; found 391.0020.

Propargyl 2,3,4-Tri-*O*-benzoyl-β-D-ribopyranoside (36): 2,3,4-Tri-*O*-benzoyl-β-D-ribopyranosyl bromide (2.00 g, 3.80 mmol)[18] was suspended in propargyl alcohol (9.49 g, 10 mL, 169.3 mmol, 45 equiv.). This mixture was heated at 100 °C until complete dissolution occurred. Excess propargyl alcohol was evaporated under vacuum, and the resulting dark oil was taken up in CH_2Cl_2 (20 mL) and treated with activated charcoal to give 1.65 g of a viscous oil (87%). (NMR analysis revealed the presence of around 10% of a product with the opposite anomeric configuration.) IR (neat): $\tilde{\nu}$ = 1723, 1316, 1284, 1262, 1126, 1106, 1096, 1070, 1059, 1026, 709 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.05 (d, $^3J_{H,H}$ = 7.0 Hz, 2 H, H_{Ar}), 8.00 (d, $^3J_{H,H}$ = 7.0 Hz, 2 H, H_{Ar}), 7.85 (d, $^3J_{H,H}$ = 7.0 Hz, 2 H, H_{Ar}), 7.55–7.48 (m, 3 H, H_{Ar}), 7.33–7.26 (m, 6 H, H_{Ar}), 5.82 (dd, $^3J_{2,3}$ = 3.5, $^3J_{3,4}$ = 4.2 Hz, 1 H, 3-H), 5.62 (m, 1 H, 4-H), 5.55 (dd, $^3J_{2,3}$ = 3.5, $^3J_{1,2}$ = 2.3 Hz, 1 H, 2-H), 5.32 (d, $^3J_{1,2}$ = 2.3 Hz, 1 H, 1-H), 4.43–4.33 (m, 2 H, $OCH_2C{\equiv}CH$), 4.28 (dd, $^2J_{5a,5b}$ = 13.1, $^3J_{4,5a}$ = 2.0 Hz, 1 H, 5a-H), 4.12 (dd, $^2J_{5a,5b}$ = 13.1, $^3J_{4,5b}$ = 2.8 Hz, 1 H, 5b-H), 2.51 (t, $^4J_{H,H}$ = 2.5 Hz, 2 H, $C{\equiv}CH$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.2, 165.9, 165.2, 133.3, 133.3, 133.2, 130.1, 130.0, 129.8, 129.9, 129.6, 129.4, 128.4 (6 C), 97.1, 78.3, 77.4, 68.5, 67.7, 66.1, 61.6, 55.1 ppm. HRMS (ESI^+): calcd. for $C_{29}H_{24}O_8Na$ 523.1369; found 523.1377.

[4-(2,3,4-Tri-*O*-benzoyl-β-D-ribopyranosylmethyl)-1*H*-1,2,3-triazol-1-yl]methylbenzene (37): Propargyl 2,3,4-tri-*O*-benzoyl-β-D-ribopyranoside (300 mg, 0.60 mmol) and benzyl azide (**16**) (160 mg, 1.20 mmol, 2 equiv.) were dissolved in methanol. [CuCl(SIMes)] (2 mol-%) and 4,7-dichloro-1,10-phenanthroline (2 mol-%) were added, and the reaction mixture was stirred overnight. After evaporation of the solvent, the product was purified by SiO_2 column chromatography (CH_2Cl_2/AcOEt, 9:1, v/v) to give 283.5 mg (75% yield) of a white crystalline solid. IR (neat): $\tilde{\nu}$ = 1723, 1451, 1362, 1316, 1286, 1262, 1126, 1107, 1097, 1070, 1048, 1025 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.94 (d, $^3J_{H,H}$ = 7.4 Hz, 4 H), 7.78 (d, $^3J_{H,H}$ = 7.4 Hz, 2 H), 7.53–7.39 (m, 4 H), 7.34–7.27 (m, 3 H), 7.25–7.19 (m, 8 H) (H_{Ar}, $H_{triazole}$), 5.71 (dd, $^3J_{2,3} \approx {}^3J_{3,4} \approx 4$ Hz, 1 H, 3-H), 5.50 (m, 1 H, 4-H), 5.44 (AB system, $^2J_{H,H}$ = 15.0 Hz, 2 H, NCH_2), 5.41 (m, 1 H, 2-H), 5.15 (d, $^3J_{1,2}$ = 1.4 Hz, 1 H, 1-H), 4.85 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, $OCH_2C_{triazole}$), 4.69 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, $OCH_2C_{triazole}$), 4.23 (d, $^2J_{5a,5b}$ = 12.5 Hz, 1 H, 5a-H), 4.02 (dd, $^2J_{5a,5b}$ = 12.5, $^3J_{4,5b}$ = 2.3 Hz, 1 H, 5b-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.2, 165.9, 165.2, 134.4, 133.3 (2 C), 133.1, 130.0, 130.0, 129.8, 129.8, 129.6, 129.4, 129.2, 128.9, 126.2, 128.4 (6 C), 97.9, 68.6, 67.6, 66.3, 61.5, 61.4, 54.4 ppm; the signals of triazole and the phenyl quaternary carbon atoms overlap with other resonances. HRMS (ESI^+): calcd. for $C_{36}H_{31}N_3O_8Na$ 656.2009; found 656.1998.

2,3,4-Tri-*O*-benzoyl-β-D-ribopyranosyl Azide (38): Synthesized by starting from tri-*O*-benzoyl-β-D-ribopyranosyl bromide.[19] After workup, the crude product consisted essentially of a 4:1 mixture of anomers. The latter could be separated by SiO_2 column chromatography (elution with cyclohexane/AcOEt, 2:1, v/v) to give the major anomer in 63% yield. The pyranoid ring ^1H NMR coupling constants are consistent with a β-anomeric configuration and with a mixture of rapidly interconverting $^1C_4$ and $^4C_1$ chair conformations. IR (neat): $\tilde{\nu}$ = 2118, 1726, 1315, 1282, 1261, 1250, 1222, 1124, 1095, 1070, 1026, 710 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.89–7.81 (m, 6 H, H_{Ar}), 7.40 (t, $^3J_{H,H}$ = 7.5 Hz, 3 H, H_{Ar}), 7.24 (t, $^3J_{H,H}$ = 8.3 Hz, 2 H, H_{Ar}), 7.18 (t, $^3J_{H,H}$ = 7.2 Hz, 4 H, H_{Ar}), 5.80 (dd, $^3J_{2,3}$ = 4.0, $^3J_{3,4} \approx$ 3.5 Hz, 1 H, 3-H), 5.48 (m, 1 H, 4-H), 5.42 (d, $^3J_{1,2}$ = 4.6 Hz, 1 H, 1-H), 4.25 (dd, $^2J_{5a,5b}$ = 12.5, $^3J_{4,5a}$ = 3.2 Hz, 1 H, 5a-H), 4.08 (dd, $^2J_{5a,5b}$ = 12.5, $^3J_{4,5b}$ = 5.4 Hz, 1 H, 5b-H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 165.7, 165.5, 165.1, 133.5 (2 C), 133.4, 130.0, 129.9, 129.8, 129.5, 129.3, 129.2, 128.6, 128.5 (4 C), 87.8, 68.7, 67.2, 66.7, 63.2 ppm. HRMS (ESI^+): calcd. for $C_{26}H_{21}N_3O_7Na$ 510.1277; found 510.1268.

[1-(2,3,4-Tri-*O*-benzoyl-β-D-ribopyranosyl)-1*H*-1,2,3-triazol-4-yl]methanol (39): Tri-*O*-benzoyl-β-D-ribopyranosyl azide (168.5 mg, 0.33 mmol) and propargyl alcohol (37.4 mg, 0.66 mmol, 2 equiv.) were dissolved in methanol (1.2 mL). [CuCl(SIMes)] (2 mol-%) and 4,7-dichloro-1,10-phenanthroline (2 mol-%) were added to the reaction mixture, which was stirred overnight. After solvent evaporation, the product was filtered through a short SiO_2 plug, which was washed with acetone to give 182.1 mg of a crystalline solid (90% yield). IR (neat): $\tilde{\nu}$ = 1724, 1316, 1280, 1264, 1108, 1096, 1070, 1025, 710 cm^{-1}. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 8.27 (s, 1 H, $H_{triazole}$), 8.18 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H, H_{Ar}), 7.93 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H, H_{Ar}), 7.78 (d, $^3J_{H,H}$ = 7.2 Hz, 2 H, H_{Ar}), 7.70 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, H_{Ar}), 7.63–7.53 (m, 4 H, H_{Ar}), 7.45–7.32 (m, 4 H, H_{Ar}), 6.67 (d, $^3J_{1,2}$ = 8.5 Hz, 1-H), 6.49 (dd, $^3J_{2,3}$ = 3.1, $^3J_{3,4}$ = 3.0 Hz, 1 H, 3-H), 6.19 (dd, $^3J_{1,2}$ = 8.5, $^3J_{2,3}$ = 3.1 Hz, 1 H, 2-H), 5.80 (ddd, $^3J_{3,4}$ = 3.0, $^3J_{4,5a}$ = 8.1, $^3J_{4,5b}$ = 5.0 Hz, 1 H, 4-H), 4.68 (m, 2 H, CH_2OH), 4.54 (dd, $^2J_{5a,5b}$ = 11.2, $^3J_{4,5a}$ = 8.1 Hz, 1 H, 5a-H), 4.40 (dd, $^2J_{5a,5b}$ = 11.2, $^3J_{4,5b}$ = 5.0 Hz, 1 H, 5b-H), 4.29 (br., 1 H, OH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 166.1, 165.7, 165.2, 150.1, 134.7, 134.5, 134.4, 130.7, 130.4, 130.3, 129.8, 129.7, 128.5 (6 C), 122.5, 84.5, 70.0, 69.5, 67.9, 64.6, 56.8 ppm. HRMS (ESI^+): calcd. for $C_{29}H_{25}N_3O_8Na$ 566.1539; found 566.1539.

Supporting Information (see footnote on the first page of this article): Coordinate files for **18** and **19**, procedure for calculating $\%V_{bur}$ and NMR spectra of the previously unpublished compounds.

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