ORGANOMETALLICS
Article
pubs.acs.org/Organometallics

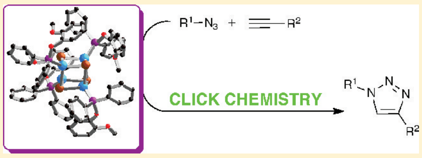
Novel Phosphinite and Phosphonite Copper(I) Complexes: Efficient Catalysts for Click Azide–Alkyne Cycloaddition Reactions

Steven Lal, Jayne McNally, Andrew J. P. White, and Silvia Díez-González*

Department of Chemistry, Imperial College London, Exhibition Road, South Kensington, London SW7 2AZ, U.K.

S *Supporting Information*

ABSTRACT: The preparation of novel phosphinite- and phosphonite-bearing copper(I) complexes of the general formula [CuX(L)] is reported. These compounds, which remain scarce in the literature, could be prepared using readily available starting materials and were spectroscopically and structurally characterized. These complexes, together with their known phosphine and phosphite analogues, were then applied to the 1,3-dipolar cycloaddition of azides and alkynes, to find that the new complexes displayed the best activities. Full optimization of the reaction conditions resulted in a noteworthy Click catalytic system, active under very mild reaction conditions in the absence of any additive and using low metal loadings.



1. INTRODUCTION

Phosphorus(III) compounds, and phosphines and phosphites in particular, are ubiquitous ligands in modern organometallic chemistry. The related phosphinite and phosphonite derivatives, however, are far less popular and their applications in catalysis remain limited. Accordingly, copper(I) halogen complexes bearing tertiary phosphines are widely known in the literature and compounds with 1:3, 2:3, 1:2, and 1:1 Cu/L ratios can be prepared under different reaction conditions.[1] Phosphite-containing complexes are also relatively common; known since the beginning of the 20th century, both 1:1 and 1:2 Cu/L adducts can be easily prepared. In contrast, only a few reports concerning the preparation of phosphinite-[2] or phosphonite-containing[3] Cu^I complexes can be found in the literature.

Similarly, only a few applications of these ligands can be found in the literature for copper(I)-mediated transformations. We could only find one example with D-xylose-derived phosphinite ligands for the asymmetric conjugate addition of organometallic fragments onto enones.[4] Likewise, taddol- or biphenol-based phosphonite ligands have almost exclusively been applied to conjugate additions,[5] but also have been used for the dehydrogenative coupling of hydrosilanes and alcohols.[6] It is important to note that in all examples the active species were generated *in situ* upon mixing of a copper source and the phosphi(o)nite ligand and that, to the best of our knowledge, no well-defined copper system with these ligands has been applied to catalysis to date.

Consequently, we were interested in the preparation of novel copper(I) complexes bearing simple phosphinite and phosphonite ligands and in their application in catalysis. Among the plethora of existing copper-catalyzed reactions, the [3 + 2] cycloaddition of organic azides and terminal alkynes has recently attracted enormous interest due to its status of best "Click" reaction to date.[7] In this extremely efficient preparation of 1,4-disubstituted [1,2,3]-triazoles,[8] the use of pre-formed copper(I) complexes avoids the need for any reducing agent in the reaction mixture. Furthermore, ligands in this transformation are key to both protecting and activating copper(I) centers, allowing for milder reaction conditions and broader scopes.[9] Hence, the use of ligands/additives in this cycloaddition reaction has definitely helped to increase its impact, but still, this cycloaddition process remains a victim of its own success and only few efforts have been focused on developing efficient catalytic systems, particularly in comparison with the reports on the diverse applications of this process.

Phosphorus-based ligands were among the first ones applied to the cycloaddition of azides and alkynes. In 2003, the previously reported $[CuBr(PPh_3)_3]$ and $\{CuI[P(OEt)_3]\}$ complexes were applied to the preparation of various glyco-derived triazoles in good yields.[10] We recently reported the optimized conditions for using such catalytic systems under strict Click conditions.[11]

Despite the popularity of these ligands in modern chemistry, only three other methodology studies have been available so far in this context. The related $[Cu(NO_3)(PPh_3)_2]$ was reported as an efficient catalyst at room temperature under neat conditions.[12] Alternatively, Elsinga and Feringa screened a number of phosphoramidite ligands for this reaction, although they generated the active copper(I) species *in situ* from $CuSO_4{\cdot}5H_2O$ and sodium ascorbate.[13] Soon after, triphenylphosphine was shown to greatly improve the catalytic activity of various copper carboxylates, much better than the more expensive PCy_3, BINAP, and dppe ligands.[14] However, in all these studies the reaction products had to be purified on silica gel, a technique precluded by Click postulates.

This prompted us to closely examine the potential of a related series of phosphorus-containing ligands in the copper-catalyzed cycloaddition of azides and alkynes. Herein, we report the preparation of phosphine, phosphinite, phosphonite, and

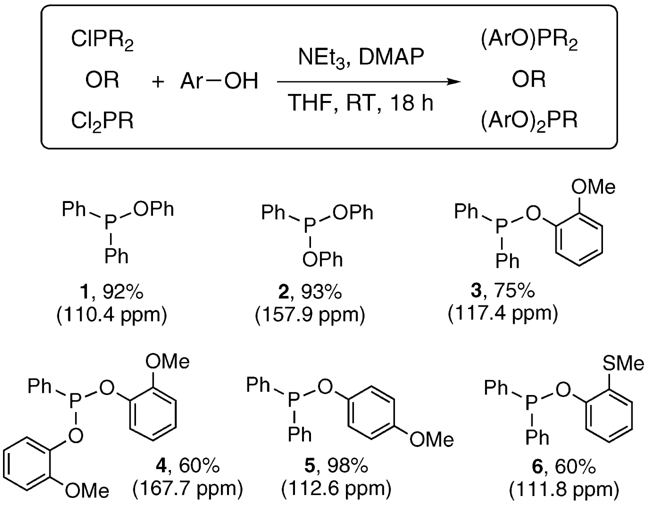
Received: August 24, 2011
Published: November 2, 2011

phosphite-bearing copper complexes and their application in cycloaddition reactions under Click-suitable conditions.

RESULTS AND DISCUSSION

Preparation of Copper(I) Complexes. In order to carry out a thorough methodological study, we synthesized four series of copper(I) complexes bearing phosphine, phosphinite, phosphonite, and phosphite ligands. Thus, different phosphinite and phosphonite ligands were prepared from the corresponding phenols and chlorophosphines (Scheme 1).[15]

Scheme 1. Preparation and ^{31}P NMR Signals for Phosphinite and Phosphonite Ligands



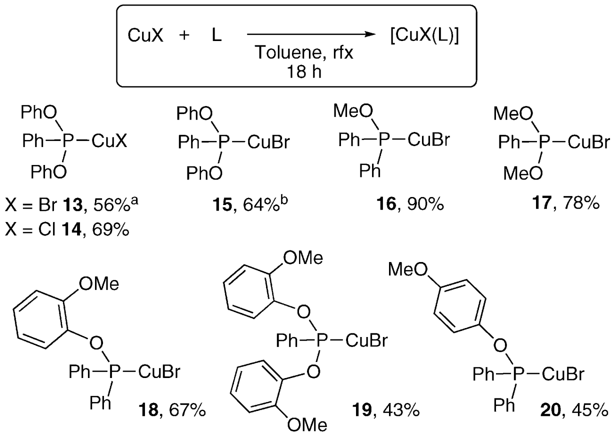
In all cases the expected compounds were isolated as pure products after filtration on alumina/Celite in air. However, ligand **5** was particularly unstable and had to be used promptly after isolation to avoid its decomposition.

The introduction of other functional groups on the phenyl rings of these ligands, such as nitro, cyano, and amino groups, was also attempted. However, either the formation of complex mixtures of products or the fast decomposition of the expected compounds was observed, even when alternative procedures were used.[16] Actually, these compounds are known to be sensitive to hydrolysis,[17] which has certainly hampered their more widespread use in catalysis.

Following procedures described in the literature, we prepared the phosphine-based complexes [CuX(PPh$_3$)] (X = Cl, **7**; X = Br, **8**; X = I, **9**), and phosphite-containing compounds {CuX[P(OPh)$_3$]} (X = Cl, **10**; X = Br, **11**). All attempts to synthesize the iodo analogue from triphenyl phosphite were unsuccessful, resulting instead in the related {CuI[P(OPh)$_3$]$_2$} (**12**).[18]

On the other hand, [CuX(L)] complexes bearing ligands **1**–**5** were generally prepared in refluxing anhydrous toluene in fair to excellent yields after recrystallization (Scheme 2). Commercially available methyl diphenylphosphinite and dimethyl phenylphosphonite were also employed. Reactions in DCM, DCE, and MeCN led to the isolation of the corresponding hydrolyzed ligands, with only traces (at the most) of the expected coordination complexes. Also, reactions with the thioether derivative **6** led to complex mixtures insoluble in all solvents tested. Furthermore, the *in situ* reduction of CuBr$_2$ salts by phosphinite **1** in boiling methanol also did not produce any copper(I) complex.[19]

Scheme 2. Preparation of Phosphinite and Phosphonite Copper(I) Complexes



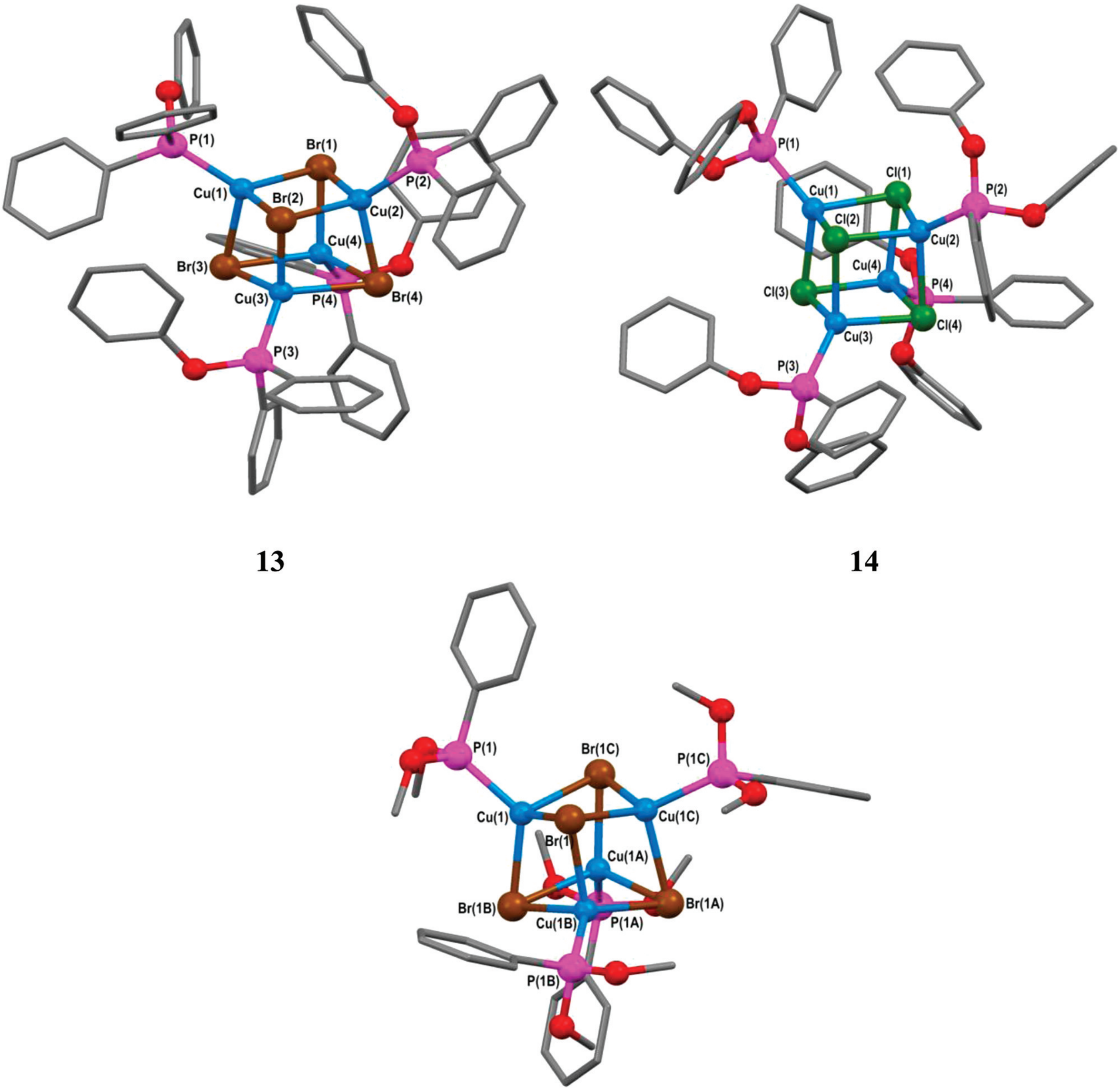
[a]Conditions: toluene, reflux, 2 h. [b]Conditions: toluene, room temperature, 3 days.

It is important to note that, regardless of the stoichiometry of the reactions, only the Cu/L 1:1 complexes were obtained.[20] This is in great contrast with the more usual phosphine and phosphite copper(I) complexes.

Crystallographic Studies. In an effort to establish the stoichiometry of the newly prepared complexes, mass spectrometry studies were carried out, but unfortunately in each case the results were inconclusive. However, material suitable for single-crystal X-ray analysis was obtained for complexes **13**, **14**, **17**, **18**, and **20** by slow diffusion of hexane in warm toluene solutions. Ball and stick representations are given in Figures 1 and 2, and selected bond lengths are provided in Table 1 and in the captions of these figures.

All five structures have a cubane-like [Cu$_4$X$_4$] core, with each copper center having a tetrahedral environment comprised of three bridging halogens and a neutral phosphine ligand. This confirmed the originally assumed stoichiometry for these complexes. As expected for a complex containing a smaller halogen atom, the copper core is less distorted in **14** (X = Cl) than in **13**, **17**, **18**, or **20** (X = Br), as shown by the X–Cu–X angles. These range between 93.56(4) and 98.12(4)° for the chloro species **14**, while for the bromo species **13**, **17**, **18**, and **20** they lie in the ranges 93.256(10)–105.903(12), 98.656(13)–107.119(15), 94.835(18)–101.760(18), and 98.544(12)–103.409(12)°, respectively.[21] This same effect is seen for the Cu–X bond lengths (Table 1), which vary between 2.3534(11) and 2.4430(11) Å for the chloro species **14** and in the ranges 2.4773(4)–2.5822(4), 2.4572(5)–2.6096(6), 2.4683(4)–2.6102(4), and 2.4945(3)–2.5584(4) Å for the bromo species **13**, **17**, **18**, and **20**, respectively.[21] The shortest intracube Cu···Cu distances are 3.0295(4), 3.1760(9), 3.0039(7), 3.1643(6), and 3.0979(6) Å in **13**, **14**, **17**, **18**, and **20**, respectively. All of these distances are significantly longer than the sum of the van der Waals radii (2.80 Å).

These cubane-like solid structures are well-known for copper(I) complexes. For the related complexes [CuX(PR$_3$)], it has been unambiguously shown that their structure in the solid state depends not only on the complex itself but also on the solvent used for growing the crystal.[22] In particular, the use of polar solvents has been reported to favor step-like rather than cubane-like structures in the solid state. In our case, all



13

14

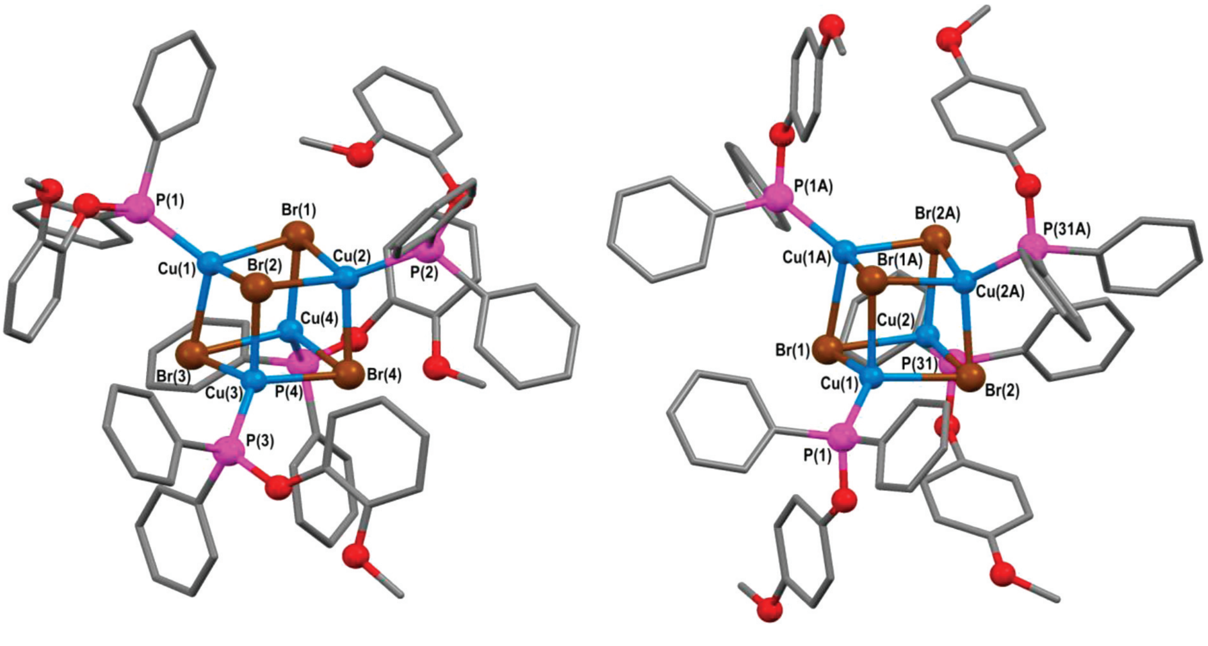
17

Figure 1. Ball and stick representations of {CuBr[PPh$_2$(OPh)]} **13**, {CuCl[PPh(OPh)$_2$]} **14**, and the S_4-symmetric {CuBr[PPh(OMe)$_2$]} **17**. Hydrogen atoms have been omitted for clarity. Selected bond lengths for **17** (Å): Cu(1)−Br(1) = 2.5396(4), Cu(1)−Br(1B) = 2.4683(4), Cu(1)−Br(1C) = 2.6102(4), Cu(1)−P(1) = 2.1835(6), Br(1)−Cu(1B) = 2.6102(4), Br(1)−Cu(1C) = 2.4683(4).

attempts to grow suitable crystals from chloroform or dichloromethane failed.

Catalytic Studies: [3 + 2] Cycloaddition of Azides and Alkynes. We screened all the prepared copper complexes for the preparation of [1,2,3]-triazoles in air. The obtained results for the cycloaddition of benzyl azide with phenylacetylene under standard cycloaddition conditions are shown in Table 2. In a first stage, we tested the ligands bearing only phenyl/phenoxy groups in order to determine the most promising series. Phosphinite- and phosphonite-bearing complexes, and **15** in particular, clearly displayed the best catalytic activities, with complete conversions after 5−8 h of stirring. In contrast, only modest conversions were obtained with known phosphine- or phosphite-containing catalysts **7**−**9** and **10** and **11**. Interestingly, for the latter series no ligand effect was observed on comparison of chloro analogues **7** and **10** or bromo derivatives **8** and **11**. The observed differences in reactivity could not be linked to the relative stability of the complexes, and actually these catalysts were still active after 48 h of stirring under ambient conditions.[23]

It is important to note that we did not observe any bright yellow color in the reaction mixtures with any of these complexes. This color has previously been related to the formation of copper acetylide derivatives[24] and also to the use of related tris-phosphine copper complexes,[11] but not with a 1:1 Cu/L ratio. In addition, it is important to note that no green-blue color—indicating metal oxidation to copper(II)—was observed during the complex screening, nor did the disproportionation of any of the catalysts result in copper(0) precipitation. These results clearly show the good potential of



18 **20**

Figure 2. Ball and stick representations of {CuBr[PPh_2(OPh-2-OMe)]} (**18**) and the C_2-symmetric {CuBr[PPh_2(OPh-4-OMe)]} **20**. Hydrogen atoms have been omitted for clarity. Selected bond lengths for **20** (Å): Cu(1)−Br(1) = 2.4737(7), Cu(1)−Br(2) = 2.5162(11), Cu(1)−Br(1A) = 2.692(3), Cu(1)−P(1) = 2.1955(8), Cu(2)−Br(1) = 2.5584(4), Cu(2)−Br(2) = 2.5407(3), Cu(2)−Br(2A) = 2.4945(3), Cu(2)−P(31) = 2.1796(6).

Table 1. Selected Bond Lengths (Å) for Complexes (13), (14), and (18)

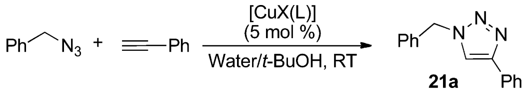
	13 (X = Br)	**14** (X = Cl)	**18** (X = Br)
Cu(1)−X(1)	2.5043(3)	2.4500(10)	2.5709(6)
Cu(1)−X(2)	2.5159(3)	2.3534(11)	2.4572(5)
Cu(1)−X(3)	2.5822(4)	2.4083(13)	2.5371(5)
Cu(1)−P(1)	2.1934(7)	2.1320(11)	2.1745(10)
Cu(2)−X(1)	2.5051(3)	2.3657(10)	2.4873(5)
Cu(2)−X(2)	2.4926(3)	2.4304(11)	2.6096(6)
Cu(2)−X(4)	2.5692(4)	2.4037(11)	2.5302(5)
Cu(2)−P(2)	2.1866(6)	2.1522(10)	2.1848(10)
Cu(3)−X(2)	2.4773(4)	2.4158(13)	2.6070(5)
Cu(3)−X(3)	2.5483(3)	2.4086(14)	2.5439(5)
Cu(3)−X(4)	2.5745(3)	2.4430(11)	2.4723(6)
Cu(3)−P(3)	2.1829(6)	2.211(3)	2.1859(9)
Cu(4)−X(1)	2.5289(3)	2.4029(11)	2.4686(5)
Cu(4)−X(3)	2.5265(3)	2.3649(12)	2.5644(6)
Cu(4)−X(4)	2.5439(3)	2.4304(13)	2.5588(5)
Cu(4)−P(4)	2.1818(6)	2.1453(13)	2.1758(10)

phosphinite and phosphonite derivatives as ancillary ligands for this cycloaddition reaction.

Among these series, phosphite ligands are probably the least promising (Table 2). In particular, complex **12**, bearing two phosphite ligands, led to even more disappointing conversions after 24 h of stirring than the monophosphite complexes **10** and **11**. This is not, however, a general trend, and significant increases in the reaction rate were observed when 5 mol % of free ligand was added to the reaction mixtures containing 5 mol % of **7** or **13** (Table 3). Further enhancements were observed with 10 mol % of ligand, but not with higher loadings. Of note, the preformed tris-phosphine complex [CuCl(PPh_3)$_3$] provided the best catalytic results in that series, showing the advantage of using preformed catalysts over in situ generated species.[25,26] It is worth mentioning that, in these reactions, the addition of extra phosphorus ligand led to bright yellow reaction mixtures.

Following our optimization studies, we next screened different solvents using {CuBr[PPh$(OPh)_2$]} **15** as catalyst to

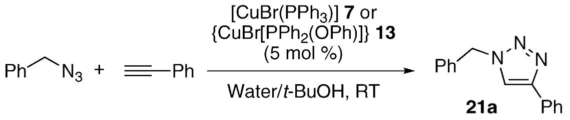
Table 2. Catalyst Screening for the Preparation of [1,2,3]-Triazoles



[CuX(L)]	time (h)	conversn (%)[a]	[CuX(L)]	time (h)	conversn (%)[a]
[CuCl(PPh_3)] **7**	24	47	{CuI[P$(OPh)_3$]$_2$} **12**	24	∼5
[CuBr(PPh_3)] **8**	24	42	{CuBr[PPh_2(OPh)]} **13**	8	>95
[CuI(PPh_3)] **9**	24	14	{CuCl[PPh$(OPh)_2$]} **14**	8	>95
{CuCl[P$(OPh)_3$]} **10**	24	56	{CuBr[PPh$(OPh)_2$]} **15**	5	>95
{CuBr[P$(OPh)_3$]} **11**	24	36			

[a] ^1H NMR conversions are the average of at least two independent runs.

Table 3. Phosphine and Phosphinite Effects in the Model Reaction

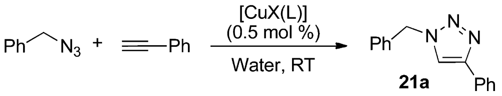


7 + PPh_3 (mol %)	time (h)	conversn (%)[a]	13 + $PPh_2(OPh)$ (mol %)	time (h)	conversn (%)[a]
0	24	47	0	8	>95
5	6	>95	5	5.5	74
10, 15, or 20	5	>95	10, 15, or 20	4.5	>95
5[b]	2.5	>95			

[a] ^1H NMR conversions are the average of at least two independent runs. [b] $[CuCl(PPh_3)_3]$ was used in this instance.

find that pure water was the best-performing media. It is important to note that only sluggish reactions were observed in the absence of solvent, and 2 days of reaction was required in order to obtain high conversion into triazole **21a** even with 5 mol % of **15**. Taking into consideration the high activity displayed by copper(I) species in this cycloaddition reaction, one might think that any catalyst could provide shorter reaction times when used neat. However, these results clearly show that not all copper complexes are suitable to be used neat.[27] Under aqueous conditions, the catalyst loading could be lowered to 0.5 mol % while keeping convenient reaction times (under 6 h for the model reaction). Next, we screened all the other phosphi(o)nite complexes **16**−**20** under these optimized conditions (Table 4).

Table 4. Phosphi(o)nite-Based Catalyst Screening for the Preparation of [1,2,3]-Triazoles



[CuX(L)]	time (h)	conv (%)[a]
$\{CuBr[PPh(OPh)_2]\}$ **15**	5.5	>95
$\{CuBr[PPh_2(OMe)]\}$ **16**	5	>95
$\{CuBr[PPh(OMe)_2]\}$ **17**	5	>95
$\{CuBr[PPh_2(OPh\text{-}2\text{-}OMe)]\}$ **18**	3	>95
$\{CuBr[PPh(OPh\text{-}2\text{-}OMe)_2]\}$ **19**	6	>95
$\{CuBr[PPh_2(OPh\text{-}4\text{-}OMe)]\}$ **20**	5	>95

[a] ^1H NMR conversions are the average of at least two independent runs.

No significant differences between related phosphinite and phosphonite complexes were observed. Furthermore, independently of the ligand on the copper center, all these catalysts showed remarkably similar activities under such conditions, with complete conversions in 5−6 h. The only exception was observed with phosphinite complex **18**, which reduced the required reaction time by half. We think this might be due to the beneficial effect of the oxygen coordination to the copper center (Figure 3). Even though such an interaction was not observed in the solid state (see Figure 2), the tetrameric structure of **18** is unlikely to be kept in solution, which would enable the postulated interaction. A similar interaction in phosphonite complex **19**, now bearing two *o*-methoxy groups *per* copper center, might be deleterious for the catalytic activity, since no enhancement of the reaction rate was observed with this catalyst.

With an optimized catalytic system in hand, we next investigated the scope of the reaction. The results are presented in Scheme 3. In most cases, the triazole products precipitated out of the reaction mixture and could be isolated in excellent yields by simple filtration and washing with water and pentane. Oily triazoles were isolated from the reaction mixture by extraction with ethyl acetate, and in no case was purification on silica gel necessary. Different functional groups were well tolerated, such as esters, alcohols, amines, halogen atoms, and alkenes. Interestingly, when a propargylamine was used as starting material (**21c**,**i**), the reaction mixtures turned blue-grey, probably due to nitrogen binding to the copper center. Gratifyingly, this had no negative effect on the catalytic ability and good conversions into triazoles were observed in both cases.[28]

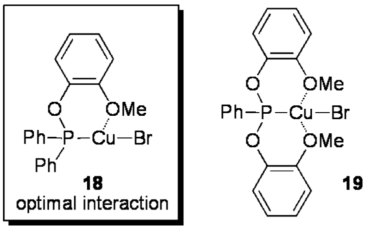


Figure 3. Postulated interactions in catalysts **18** and **19**.

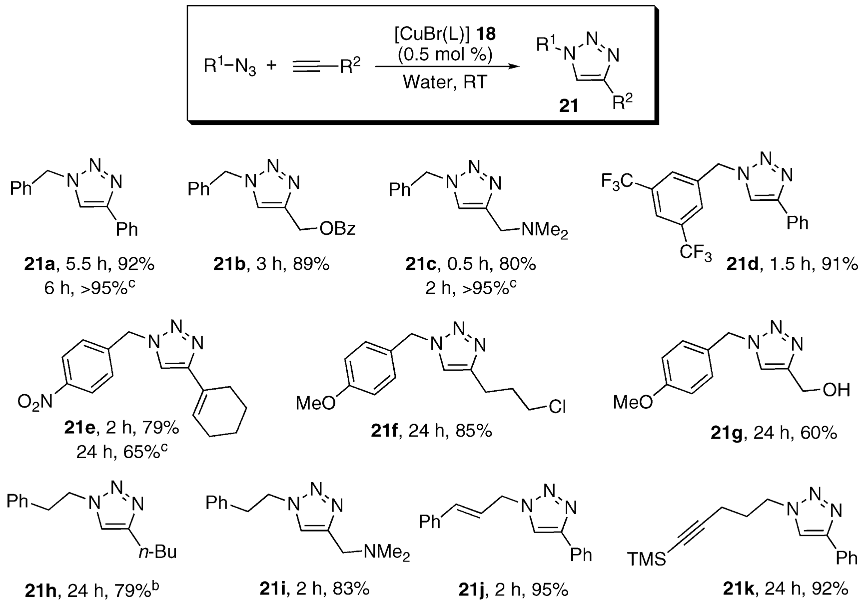
We also attempted some reactions using the phosphinite−copper complex **16**. Even if this catalyst did not display the best catalytic activity during the optimization studies (see Table 4), it has the advantage of being prepared from commercially available starting materials in very high yields. As shown in Scheme 3, $\{CuBr[PPh_2(OMe)]\}$ **16** displayed a remarkable activity in the reactions tested, providing a new convenient Click catalyst for this cycloaddition reaction.

■ CONCLUSIONS

Four series of copper complexes bearing phosphine, phosphinite, phosphonite, and phosphite ligands have been investigated in the present study. In particular, we have synthesized and fully characterized eight novel phosphinite- and phosphonite-bearing complexes with copper(I) halogen precursors, species that are surprisingly scarce in the literature. Gratifyingly, all complexes prepared could be handled in air without any particular precautions.

Catalytic studies on the [3 + 2] cycloaddition of azides and alkynes showed that, for a 1:1 Cu/L ratio, these phosphinite and phosphonite complexes were the most efficient ones. Careful optimization of the reaction conditions allowed for the use of $\{CuBr[PPh_2(OPh\text{-}2\text{-}OMe)]$ **18** in the preparation of diverse 1,2,3-triazoles under very mild reaction conditions and low catalytic loadings.[29]

Scheme 3. Preparation of 1,2,3-Triazoles[a]



[a]Isolated yields are the average of at least two independent runs. [b]Reactions run with 1 mol % [Cu]. [c]Reactions run with 0.5 mol % of **16**.

These results also highlight the fact that, despite the sudden and huge popularity of this transformation, most efforts have mainly been concentrated on its applications rather than in the development of better performing catalytic systems, therefore overlooking the true potential of well-defined copper species.

■ EXPERIMENTAL SECTION

General Considerations. All reagents were used as received. Unless otherwise stated, all reactions were carried out in air and using technical solvents without any particular precautions to exclude moisture or oxygen. Anhydrous solvents were dried by passing them through columns of molecular sieves in a solvent purification system. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer at room temperature. Chemical shifts (δ) are reported in ppm with respect to tetramethylsilane (^{1}H NMR) or H_3PO_4 (^{31}P NMR) as internal standard. Mass spectra (MS) were recorded on a Micromass Autospec Premier, Micromass LCT Premier, or VG Platform II spectometer using EI or ESI techniques at the Mass Spectroscopy Service of Imperial College London. Elemental analyses were performed at London Metropolitan University (U.K.). All reported yields are isolated yields and in the catalytic studies are the average of at least two independent runs.

The non commercially available ligands were prepared by following the reported procedure by Mukaiyama.[15a] It is important to note that in all cases we needed to use DMAP as additive in order to achieve full conversions. Monophosphine complexes **7** and **8**[30] were prepared from the corresponding CuX_2 salts following the literature procedures, whereas the iodo analogue **9**[31] was prepared from CuI. Phosphite complexes **10**−**12** were prepared by following the conditions reported by Nishizawa using toluene instead of benzene as solvent.[18]

Synthesis of [CuX(L)] Complexes. *{CuBr[PPh$_2$(OPh)]}* ***13.*** Copper(I) bromide (0.143 g, 1 mmol) was added to a solution of phosphinite **1** (0.326 g, 1 mmol) in dry toluene (20 mL) under a nitrogen atmosphere. The reaction mixture was then heated at reflux for 2 h and filtered over a sintered glass while still hot. The obtained filtrate was concentrated to yield an off-white viscous oil. Methanol addition resulted in the formation of a white solid, which was recrystallized from a toluene/hexane mixture and dried under vacuum (0.23 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87−7.72 (m, 4H), 7.45−7.35 (m, 2H), 7.34−7.26 (m, 4H), 7.14−7.06 (m, 2H), 7.03−6.93 (m, 2H), 6.87−6.78 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5 (C^{Ar}), 135.9 (d, J = 33.4 Hz, C^{Ar}), 131.7 (d, J = 17.5 Hz, CH^{Ar}), 130.8 (CH^{Ar}), 129.3 (CH^{Ar}), 128.5 (d, J = 10.2, CH^{Ar}), 123.6 (CH^{Ar}), 120.3 (CH^{Ar}). ^{31}P NMR (162 MHz, $CDCl_3$): δ 89.4 (s, broad). Anal. Calcd for $C_{18}H_{15}OPBrCu$ (419.94): C, 51.26; H, 3.58. Found: C, 51.21; H, 3.67.

{CuCl[PPh(OPh)$_2$]} ***14.*** Phenylphosphonite **2** (0.294 g, 1 mmol) was added to a stirred suspension of CuCl (0.099 g, 1 mmol) in dry toluene (20 mL) under a nitrogen atmosphere. The reaction mixture was then refluxed overnight to give a clear solution, which yielded a viscous yellow oil upon concentration. Methanol addition resulted in the formation of a white precipitate, which was filtered, washed with methanol, and dried under vacuum (0.27 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04−7.87 (m, 2H), 7.56−7.45 (m, 1H), 7.45−7.33 (m, 2H), 7.22−7.12 (m, 4H), 7.11−7.05 (m, 2H), 7.04−6.97 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.6 (C^{Ar}), 132.2 (CH^{Ar}), 130.5 (d, J = 20.4 Hz, C^{Ar}), 129.9 (CH^{Ar}), 129.7 (CH^{Ar}), 128.5 (d, J = 10.3 Hz, CH^{Ar}), 124.5 (CH^{Ar}), 120.5 (d, J = 6.3 Hz, CH^{Ar}). ^{31}P NMR (162 MHz, $CDCl_3$): δ 127.2 (s, broad). Anal. Calcd for $C_{18}H_{15}O_2ClPCu$ (393.28): C, 54.97; H, 3.84. Found: C, 55.06; H, 3.76.

{CuBr[PPh(OPh)$_2$]} ***15.*** Copper(I) bromide (0.143 g, 1 mmol) was added to a stirred solution of phenylphosphonite **2** (0.294 g, 1 mmol) in toluene (1 mL) in air. The reaction mixture was stirred for 3 days at room temperature and then concentrated under reduced pressure to give an off-white precipitate, which was washed with methanol to give the title complex as an off-white solid (0.279 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97−7.87 (m, 2H), 7.51−7.42 (m, 1H), 7.39−7.30 (m, 2H), 7.17−7.02 (m, 8H), 7.02−6.94 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 152.7 (d, J = 2.2 Hz, C^{Ar}), 135.6 (d, J = 39.9 Hz, (CH^{Ar}), 132.3 (CH^{Ar}), 130.6 (d, J = 20.3 Hz, CH^{Ar}), 129.8 (CH^{Ar}), 128.6 (d, J = 10.4 Hz, CH^{Ar}), 124.6 (CH^{Ar}), 120.7 (d, J = 6.3 Hz, CH^{Ar}). ^{31}P NMR (162 MHz, $CDCl_3$): δ 122.8 (s, broad). HRMS: calcd for $C_{20}H_{18}NO_2PCu$ 398.0371, found 398.0241 ([M − Cl + MeCN]$^+$). Anal. Calcd for $C_{18}H_{15}O_2BrPCu$ (435.93): C, 49.39; H, 3.45. Found: C, 49.61; H, 3.29.

{CuBr[PPh$_2$(OMe)]} ***16.*** Methyl diphenylphosphinite (0.40 mL, 2 mmol) was added to CuBr (0.28 g, 2 mmol) in dry toluene (20 mL) under a nitrogen atmosphere. The reaction mixture was then refluxed for 18 h before being concentrated under reduced pressure. The resulting residue was recrystallized from toluene/hexane to give the title complex as an off-white solid (0.79 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86−7.66 (m, 4H, H^{Ar}), 7.43−7.28 (m, 6H, H^{Ar}), 3.75 (d, J = 14.6 Hz, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.5 (d, J

= 33.0 Hz, C^{Ar}), 131.3 (d, *J* = 92.6 Hz, CH^{Ar}), 130.5 (CH^{Ar}), 128.4 (d, *J* = 9.9 Hz, CH^{Ar}), 56.4 (d, *J* = 6.9 Hz, CH$_3$). ^{31}P NMR (162 MHz, DMSO-d_6): δ 94.9 (s, broad). HRMS (ESI): calcd for $C_{15}H_{16}NOPCu$ 320.0266, found 320.0265 ([M − Br + MeCN]$^+$). Anal. Calcd for $C_{13}H_{13}OPBrCu$ (357.9183): C, 43.41; H, 3.64. Found: C, 43.59; H, 3.79.

{CuBr[PPh(OMe)$_2$]} ***17***. From dimethyl phenylphosphonite (0.32 mL, 2 mmol), following the procedure described for the preparation of **16**, the title complex was isolated as an off-white solid (0.49 g, 1.6 mmol, 78%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.82−7.74 (m, 2H, H^{Ar}), 7.47−7.40 (m, 1H, H^{Ar}), 7.40−7.34 (m, 2H, H^{Ar}), 3.73 (d, *J* = 13.0 Hz, 6H, CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ 135.8 (d, *J* = 42.1 Hz, C^{Ar}), 131.2 (CH^{Ar}), 130.5 (d, *J* = 18.0 Hz, CH^{Ar}), 128.2 (d, *J* = 9.8 Hz, CH^{Ar}), 54.6 (CH$_3$). ^{31}P NMR (162 MHz, DMSO-d_6): δ 135.3 (s, broad). HRMS (ESI): calcd for $C_{10}H_{14}NO_2PCu$ 274.0058, found 273.9976 ([M − Br + MeCN]$^+$). Anal. Calcd for $C_8H_{11}BrO_2PCu$ (311.8976): C, 30.64; H, 3.54. Found: C, 30.66; H, 3.53.

{CuBr[PPh$_2$(OPh-2-OMe)]} ***18***. From phosphinite **3** (0.308 g, 1 mmol), following the procedure described for the preparation of **16**, the title complex was isolated as an off-white solid (0.31 g, 0.67 mmol, 67%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.89−7.73 (m, 4H, H^{Ar}), 7.46−7.33 (m, 6H, H^{Ar}), 7.04−6.97 (m, 1H, H^{Ar}), 6.97−6.88 (m, 1H, H^{Ar}), 6.83−6.74 (m, 1H, H^{Ar}), 6.73−6.64 (m, 1H, H^{Ar}), 3.68 (s, 3H, CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ 150.5 (C^{Ar}), 143.4 (CH^{Ar}), 136.6 (d, *J* = 33.0 Hz, CH^{Ar}), 130.8 (d, *J* = 17.8 Hz, CH^{Ar}), 128.5 (d, *J* = 10.1 Hz, CH^{Ar}), 124.3 (CH^{Ar}), 120.2 CH^{Ar}), 112.7 (CH^{Ar}), 55.5 (CH$_3$). ^{31}P NMR (162 MHz, DMSO-d_6): δ 95.2 (s, broad). HRMS (ESI): calcd for $C_{21}H_{20}NO_2PCu$ 412.0528, found 412.0533 ([M − Br + MeCN]$^+$). Anal. Calcd for $C_{19}H_{17}O_2BrPCu$ (449.94): C, 50.51; H, 3.79. Found: C, 50.70; H, 3.83.

{CuBr[PPh(OPh-2-OMe)$_2$]} ***19***. From phosphonite **4** (1.00 g, 2 mmol), following the procedure described for the preparation of **16**, the title complex was isolated as an off-white solid (0.21 g, 0.86 mmol, 43%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.85−7.70 (m, 2H, H^{Ar}), 7.43−7.31 (m, 3H, H^{Ar}), 7.03−6.95 (m, 2H, H^{Ar}), 6.94−6.84 (m, 2H, H^{Ar}), 6.83−6.73 (m, 2H, H^{Ar}), 6.72−6.62 (m, 2H, H^{Ar}), 3.72 (s, 6H, CH$_3$). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.3 (C^{Ar}), 141.6 (C^{Ar}), 136.2 (C^{Ar}), 131.7 (CH^{Ar}), 130.2 (d, *J* = 20.0 Hz, CH^{Ar}), 127.8 (d, *J* = 8.9 Hz, CH^{Ar}), 125.1 (CH^{Ar}), 121.2 (d, *J* = 7.0 Hz, CH^{Ar}), 120.2 (CH^{Ar}), 112.5 (CH^{Ar}), 55.3 (CH$_3$). ^{31}P NMR (162 MHz, DMSO-d_6): δ 133.4 (s, broad). HRMS (ESI): calcd for $C_{22}H_{22}NO_4PCu$ 458.0582, found 458.0580 ([M − Br + MeCN]$^+$). Anal. Calcd for $C_{20}H_{19}O_4BrPCu$ (495.95): C, 48.26; H, 3.85. Found: C, 48.35; H, 3.97.

{CuBr[PPh$_2$(OPh-4-OMe)]} ***20***. From phosphinite **5** (0.62 g, 2 mmol), following the procedure described for the preparation of **16**, the title complex was isolated as an off-white solid (0.40 g, 0.9 mmol, 45%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.86−7.72 (m, 4H, H^{Ar}), 7.45−7.33 (m, 6H, H^{Ar}), 7.03−6.97 (m, 1H, H^{Ar}), 6.97−6.87 (m, 1H, H^{Ar}), 6.84−6.75 (m, 1H, H^{Ar}), 6.75−6.65 (m, 1H, H^{Ar}), 3.59 (s, 3H, CH$_3$). ^{13}C NMR (100 MHz, CDCl$_3$): δ 131.7 (d, *J* = 17.3 Hz, C^{Ar}), 130.9 (C^{Ar}), 129.0 (C^{Ar}), 128.5 (d, *J* = 10.0 Hz, CH^{Ar}), 128.2 (CH^{Ar}), 125.3 (CH^{Ar}), 121.2 (d, *J* = 6.3 Hz, CH^{Ar}), 114.4 (CH^{Ar}), 55.4 (CH$_3$). ^{31}P NMR (162 MHz, DMSO-d_6): δ 93.5 (s, broad). HRMS (ESI): calcd for $C_{21}H_{20}NO_2PCu$ 412.0528, found 412.0534 ([M − Br + MeCN]$^+$). Anal. Calcd for $C_{19}H_{17}O_2PBrCu$ (449.94): C, 50.51; H, 3.79. Found: C, 50.60; H, 3.65.

X-ray Crystallography. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 791881 (**13**), 791882 (**14**), 837020 (**17**), 837021 (**18**), and 837022 (**20**). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax, (internat.) + 44 1223/336-033; e-mail, deposit@ccdc.cam.ac.uk).

Catalytic Studies: General Procedure for the Copper-Catalyzed [3 + 2] Cycloaddition of Azides and Alkynes. In a vial fitted with a screw cap, a freshly prepared 0.025 M solution of [CuBr(L)] in MeCN (0.1 mL, 0.5 mol %) was introduced. After the solvent was evaporated, water (0.5 mL), azide (0.5 mmol), and alkyne (0.5 mmol) were added. The reaction was allowed to proceed at room temperature and monitored by ^{1}H NMR analysis of aliquots. After total consumption of the starting azide or no further conversion, the reaction product was extracted with EtOAc (oily triazoles) or, alternatively, collected by filtration and washed with pentane (solid triazoles). In all examples, the crude products were estimated to be greater than 95% pure by ^{1}H NMR. Reported yields are isolated yields and are the average of at least two independent runs.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, tables, and figures giving experimental procedures, product characterization, crystallographic data and CIF files giving crystallographic data for **13**, **14**, **17**, **18**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: s.diez-gonzalez@imperial.ac.uk.

ACKNOWLEDGMENTS

Imperial College London and the EPSRC are gratefully acknowledged for financial support of this work. We sincerely thank Dr. King Kuok (Mimi) Hii for her generous sponsorship over the last year.

REFERENCES

(1) Fife, D. J.; Moore, W. M.; Morse, K. W. *Inorg. Chem.* **1984**, *23*, 1684−1691, and references therein.

(2) (a) Couch, D. A.; Robinson, S. D. *Inorg. Chem.* **1974**, *13*, 456−461. (b) Snatzke, G.; Raza, Z.; Habus, I.; Sunjic, V. *Carbohydr. Res.* **1980**, *182*, 179−196. (c) Bayler, A.; Schier, A.; Schmidbaur, H. *Inorg. Chem.* **1998**, *37*, 4353−4359. (d) Arena, C. G.; Drommi, D.; Faraone, F.; Graiff, C.; Tiripicchio, A. *Eur. J. Inorg. Chem.* **2001**, 247−255. (e) Punji, B.; Mague, J. T.; Balakrishna, M. S. *J. Organomet. Chem.* **2006**, *691*, 4265−4272.

(3) (a) Xu, W.; Vittal, J. J.; Puddephatt, R. J. *J. Am. Chem. Soc.* **1995**, *117*, 8362−8371. (b) Punji, B.; Mague, J. T.; Balakrishna, M. S. *Inorg. Chem.* **2007**, *46*, 10268−10275. (c) Hung-Low, F.; Renz, A.; Klausmeter, K. K.; Wur., J. *Eur. J. Inorg. Chem.* **2009**, 2994−3002.

(4) Guimet, E.; Diégez, Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **2005**, *16*, 2161−2165.

(5) (a) Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; van den Henvel, A.; Levêque, J.-M.; Mazé, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011−4027. (b) Martorell, A.; Naasz, R.; Feringa, B. L.; Pringle, P. G. *Tetrahedron: Asymmetry* **2001**, *12*, 2497−2499. (c) Reetz, M. T.; Maiwald, P. *C. R. Chim.* **2002**, *5*, 341−344. (d) Reetz, M. T.; Gosberg, A.; Moulin, D. *Tetrahedron Lett.* **2002**, *43*, 1189−1191. (e) Kop-Weiershausen, T.; Lex, J.; Neudörfl, J.-M.; Goldfuss, B. *Beilstein J. Org. Chem.* **2005**, 1, DOI: 10.1186/1860-5397-1-6.

(6) Weickgenannt, A.; Mewald, M.; Muesmann, T. W. T.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2223−2226.

(7) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.

(8) For a comprehensive review, see: (a) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952−3015. For the first report on a copper(I)-catalyzed [3 + 2] cycloaddition reaction, see: (b) L'abbé, G. *Bull. Soc. Chem. Belg.* **1984**, *93*, 579−592.

(9) Díez-González, S. *Catal. Sci Technol.* **2011**, *1*, 144−178.

(10) Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asín, J. A.; Isac-García, J.; Santoyo-González, F. *Org. Lett.* **2003**, *5*, 1951−1954.

(11) Lal, S.; Díez-González, S. *J. Org. Chem.* **2011**, *76*, 2367−2373.

(12) Wang, D.; Li, N.; Zhao, M.; Shi, W.; Ma, C; Chen, B. *Green Chem.* **2010**, *12*, 2120−2123.

(13) Campbell-Verduyn, L. S.; Mirfeizi, L.; Dierckx, R. A.; Elsinga, P. H.; Feringa, B. L. *Chem. Commun.* **2009**, 2139−2141.

(14) Gonda, Z.; Novák, Z. *Dalton Trans.* **2010**, *39*, 726−729.

(15) (a) Kuroda, K.; Maruyama, Y.; Hayashi, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 381−392. For a base-free synthesis, see: (b) Chauzov, V. A.; Studnev, Y. N.; Ragulin, L. I.; Fokin, A. V. *Zh. Obshch. Khim.* **1989**, *59*, 1294−1296.

(16) (a) Shintou, T.; Fukumoto, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1569−1579. (b) Yan, Y. Y.; RajanBabu, T. V. *J. Org. Chem.* **2000**, *65*, 900−906. (c) Collins, D. J.; Drygala, P. F.; Swan, J. M. *Aust. J. Chem.* **1983**, *36*, 2095−2110. (d) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7346−7349.

(17) (a) Pryjomska, I.; Bartosz-Bechowski, H.; Ciunik, Z.; Trzeciak, A. M.; Ziółkowski, J. J. *Dalton Trans.* **2006**, 213−220. (b) Mikhel, I. S.; Garland, M.; Hopewell, J.; Mastroianni, S.; McMullin, C. L.; Orpen, A. G.; Pringle, P. G. *Organometallics* **2011**, *30*, 974−985.

(18) Nishizawa, Y. *Bull. Chem. Soc. Jpn.* **1961**, *35*, 1170−1178.

(19) Orio, A. A.; Chastain, B. B.; Gray, H. B. *Inorg. Chim. Acta* **1969**, *3*, 8−10.

(20) For a similar observation, see ref 2e. For examples of Cu/L 1:4 phosphonite complexes, see ref 19.

(21) The Cu(1) site in the structure of **20** was found to be disordered; therefore, bond lengths and angles involving this site have been omitted from the quoted ranges.

(22) (a) Churchill, M. R.; Kalra, K. L. *Inorg. Chem.* **1974**, *13*, 1065−1071. (b) Churchill, M. R.; Kalra, K. L. *Inorg. Chem.* **1974**, *13*, 1427−1434. (c) Churchill, M. R.; DeBoer, B. G.; Donovan, D. J. *Inorg. Chem.* **1975**, *14*, 617−623. (d) Barron, P. F.; Dayson, J. C.; Engelhardt, L. M.; Healy, P. C.; White, A. H. *Inorg. Chem.* **1984**, *23*, 3766−3769.

(23) For instance, with 5 mol % of **7**, 47% conversion was observed after 24 h and 68% after 48 h.

(24) (a) Owsley, D. C.; Castro, C. E. *Org. Synth.* **1972**, *52*, 128−131. (b) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038−2039. (c) Shao, C.; Cheng, G.; Su, D.; Xu, J.; Wang, X.; Hu, H. *Adv. Synth. Catal.* **2010**, *352*, 1587−1592.

(25) (a) Rasappan, R.; Hager, M.; Gissibi, A.; Reiser, O. *Org. Lett.* **2006**, *8*, 6099−6102. (b) Díez-González, S.; Escudero-Adán, E. C.; Benet-Buchholz, J.; Stevens, E. D.; Slawin, A. M. Z.; Nolan, S. P. *Dalton Trans.* **2010**, *39*, 7595−7606.

(26) For an example of enhanced catalytic activity of $[\mathrm{CuBr(PPh_3)_3}]$ in the presence of free $\mathrm{PPh_3}$, see: Nakamura, I.; Zhang, D.; Terada, M. *J. Am. Chem. Soc.* **2010**, *132*, 7884−7886.

(27) For examples of catalysts used neat in this transformation, see: Candelon, N.; Lastécouères, D.; Diallo, A. K.; Ruiz Aranzaes, J.; Astruc, D.; Vincent, J.-M. *Chem. Commun.* **2008**, 741−743. See also refs 11, 12, and 25b.

(28) For a discussion on catalyst deactivation in the presence of free amines, see: Özçubukçu, S.; Ozkal, E.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2009**, *11*, 4680−4683.

(29) For a comparison of different catalysts for this cycloaddition reaction, see the Supporting Information.

(30) Jardine, F. H.; Rule, L.; Vohra, A. G. *J. Chem. Soc. A* **1970**, 238−240.

(31) Casado, A. L.; Espinet, P. *Organometallics* **2003**, *22*, 1305−1309.