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Reaction Mechanisms

Reaction of Alkynes and Azides: Not Triazoles Through Copper–Acetylides but Oxazoles Through Copper–Nitrene Intermediates

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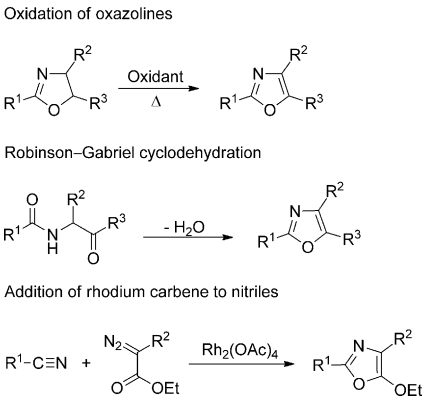
Abstract: Well-defined copper(I) complexes of composition $[Tpm^{*,Br}Cu(NCMe)]BF_4$ ($Tpm^{*,Br}$ = tris(3,5-dimethyl-4-bromopyrazolyl)methane) or $[Tpa^{*}Cu]PF_6$ (Tpa^{*} = tris(3,5-dimethylpyrazolylmethyl)amine) catalyze the formation of 2,5-disubstituted oxazoles from carbonyl azides and terminal alkynes in a direct manner. This process represents a novel procedure for the synthesis of this valuable heterocycle from readily available starting materials, leading exclusively to the 2,5-isomer, attesting to a completely regioselective transformation. Experimental evidence and computational studies have allowed the proposal of a reaction mechanism based on the initial formation of a copper–acyl nitrene species, in contrast to the well-known mechanism for the copper-catalyzed alkyne and azide cycloaddition reactions (CuAAC) that is triggered by the formation of a copper–acetylide complex.

Introduction

Oxazole is an interesting heteroaromatic compound belonging to the 1,3-azole family.[1] This heterocycle constitutes an important structural unit of a variety of natural products[2] and compounds with remarkable biological properties,[3] such as antibacterial,[4] antifungal,[5] or cytotoxic[6] activities. It also serves as a scaffold for the construction of peptides, macrocycles, and polymers.[7] Moreover, oxazole derivatives, particularly chiral oxazolines, have been employed as ligands in coordination chemistry and asymmetric catalysis.[8] Due to their valuable applications, there has been a great deal of interest in their syntheses. Classical strategies for the preparation of substituted oxazoles involve oxidation of oxazolines,[9] the Robinson–Gabriel cyclodehydration[10] of α-acylamino ketones, or rhodium-catalyzed reaction of diazocarbonyl compounds[11] (Scheme 1).



Scheme 1. Classical procedures for the synthesis of substituted oxazoles.

A different approach to substituted oxazole derivatives involves transition-metal functionalization of the parent oxazole ring. This strategy has been achieved through the application of palladium cross-coupling chemistry[12] or, more recently, by transition-metal-catalyzed direct functionalization of the heterocyclic compound.[13] Although reliable and high yielding, most of those procedures suffer from drawbacks such as difficulties in gaining access to appropriate prefunctionalized synthetic precursors or the need for harsh reaction conditions, which constrain the functional group tolerance of these reactions. In recent years, milder routes that can be used to convert different acyclic precursors into oxazoles have appeared in the literature.[14]

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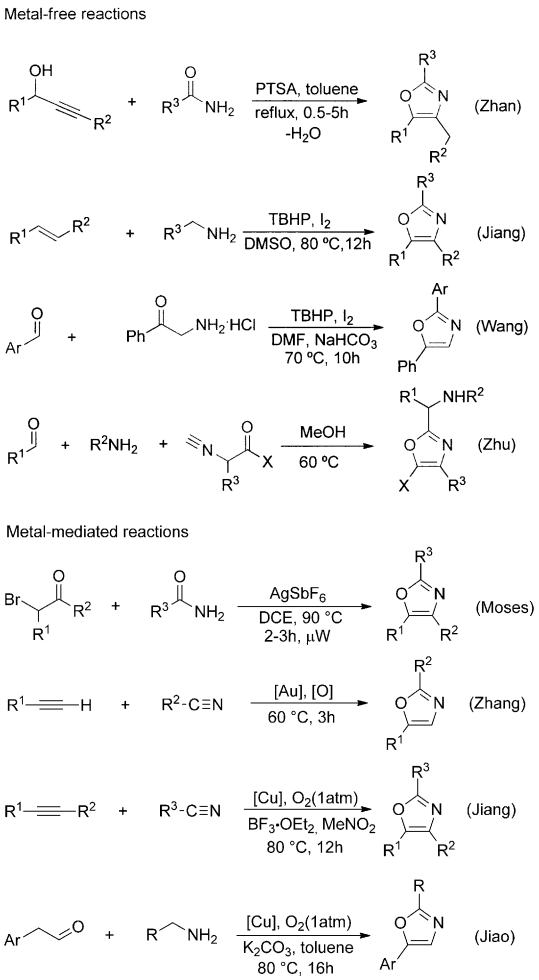
Despite the plethora of synthetic procedures available for the synthesis of this heterocycle, the development of methods that can be used to prepare substituted oxazoles in a one-pot fashion, under mild reaction conditions and from readily available starting materials remains highly desirable. In the last few years some interesting contributions have been made in this respect (Scheme 2). In 2009, Zhan and co-workers[15] reported



Scheme 2. One-step protocols for the synthesis of substituted oxazoles.

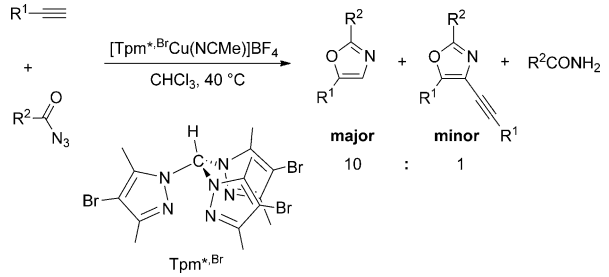
a catalytic one-pot propargylation/cycloisomerization tandem reaction for the synthesis of fully substituted oxazoles, with amides and propargylic alcohols being employed as starting materials and *p*-toluenesulfonic acid monohydrate (*p*-TSA) used as a bifunctional catalyst. The groups of Wang[16] and Jiang[17] independently developed a similar methodology based on the use of TBHP/I_2-mediated tandem oxidative cyclization. 2-Amino-1-phenylethanone hydrochloride and commercially available aromatic aldehydes were employed as reaction substrates in the former case, whereas aryl alkenes and benzyl amines were used as the reactants in the latter. Zhu and co-workers have also demonstrated the use of multicomponent reactions for the synthesis of oxazoles.[18] Recently, metal-mediated one-step protocols have emerged. The group of Moses[19] has shown a silver-mediated approach to di- and tri-substituted oxazoles from primary amides and activated β-bromo-α-ketones. Zhang and co-workers[20] described an elegant [2+2+1] annulation of a terminal alkyne, a nitrile and an oxygen atom from pyridine/quinoline *N*-oxides for the preparation of 2,5-disubstituted oxazoles through gold-catalyzed alkyne oxidation. A copper-mediated aerobic [2+2+1] cycloaddition of internal alkynes and nitriles to fully substituted oxazoles has been devised by the group of Jiang.[21] In a very recent contribution, Jiao and co-workers[22] have shown an impressive copper-catalyzed aerobic oxidative dehydrogenative annulation of ready available aldehydes, amines and molecular oxygen for the synthesis of 2,5-disubstituted oxazoles.

A few years ago, we began to examine the catalytic activity of a family of cationic copper(I) complexes of general formulae [Tpm*Cu(NCMe)]BF_4 (Tpm* = tris(pyrazolyl)methane ligand) in the copper-catalyzed alkyne–azide cycloaddition reaction (CuAAC), employing sulfonyl azides as reactants. We found that the compound bearing the $Tpm^{*,Br}$ ligand ($Tpm^{*,Br}$ = tris(3,5-dimethyl-4-bromo-pyrazolyl)methane) effectively catalyzed this reaction, providing, in a selective manner, the expected *N*-sulfonyl-triazole derivatives in high yields.[23] As a follow-up to this research project, we wanted to test another type of electron-deficient azide, that is, carbonyl azides, a substrate never applied in the CuAAC reaction.[24] In this contribution we report the results of our studies on the reaction of carbonyl azides and terminal alkynes catalyzed by well-defined copper(I) complexes. This catalytic transformation constitutes a novel procedure for the direct and selective synthesis of 2,5-disubstituted oxazoles from easily accessible starting materials and using a copper complex as the catalytic precursor. Two families of catalysts bearing the above $Tpm^{*,Br}$ as well as Tpa* ligands have been developed for this transformation. The reaction mechanism has been also investigated on the basis of experimental evidence and theoretical calculations, leading to an unprecedented reaction pathway involving the initial formation of an acyl nitrene–copper species and not a copper–acetylide. A portion of this work has been previously communicated.[25]

Results and Discussion

Reaction of carbonyl azides and terminal alkynes catalyzed by [$Tpm^{*,Br}$Cu(NCMe)]BF_4

Our interest on the CuAAC reaction focused on the use of electron-deficient azides as substrates. These reactants have been found to be problematic and, in most cases, furnished products other than the expected triazole.[26] We succeeded in preparing *N*-sulfonyl triazoles selectively in very high yields from the reaction of sulfonyl azides and terminal alkynes by using [$Tpm^{*,Br}$Cu(NCMe)]BF_4 as the catalytic system.[23] We then focused on carbonyl azides, a substrate that was previously unknown for this transformation. Under the same experimental conditions developed for the synthesis of *N*-sulfonyl triazoles, the reaction of benzoyl azide and phenylacetylene (Scheme 3) afforded a mixture of two heteroaromatic products in a 10:1

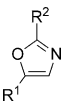
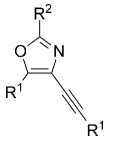


Scheme 3. Formation of oxazoles through the reaction of 1-alkynes and carbonyl azides catalyzed by $[Tpm^{*,Br}Cu(NCMe)]BF_4$.

ratio, together with a small amount of benzamide as a by-product. FTIR and NMR studies revealed the lack of any carbonyl functionality in either products and both displayed all the NMR signals within the typical range for triazole rings. However, unambiguous identification was achieved by means of X-ray diffraction studies, which showed the formation of a 2,5-disubstituted oxazole and a trisubstituted oxazole (Scheme 3),[25] as the major and minor derivatives, respectively.

By using this protocol an array of 2,5-disubstituted oxazoles, with yields in the range of 17–82%, were prepared by combining a variety of carbonyl azides with 1-alkynes (Table 1). It is interesting to note that there was no evidence for the formation of the 2,4-disubstituted regioisomer in any of the experiments, attesting to the excellent regioselection of this transformation. As shown in Table 1, the reaction was observed for a range of alkynes and carbonyl azides bearing aryl-, alkyl- or heteroaromatic substituents, in variable yields. In most cases, the trisubstituted oxazoles, which incorporate two molecules of the alkyne, were formed in 2–7% yield. Furthermore, amides derived from decomposition of the carbonyl azides were also detected. Among the reactants employed, alkylacetylenes showed the lowest conversions (Table 1, entries 13–15 and 19). It is worth noting the role of the $Tpm^{*,Br}$ ligand because the use of CuI as the catalyst precursor gave no reaction.[25]

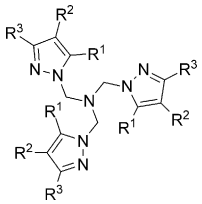
Table 1. Reaction scope with $[Tpm^{*,Br}Cu(NCMe)]BF_4$ as the catalyst.[a]

Entry	R^1	R^2	 Yield [%][b]	 Yield [%][b,c]
1	Ph	Ph	60	6
2	Ph	*p*-MeC_6H_4	77	4
3	Ph	*p*-$MeOC_6H_4$	82	<2
4	Ph	*p*-$NO_2C_6H_4$	14	<2
5	*p*-MeC_6H_4	Ph	61	6
6	*p*-MeC_6H_4	*p*-MeC_6H_4	56	5
7	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	63	6
8	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	43	<2
9	*p*-BrC_6H_4	*p*-$MeOC_6H_4$	52	<2
10	3-thienyl	Ph	49	7
11	3-thienyl	*p*-MeC_6H_4	46	4
12	3-thienyl	*p*-$MeOC_6H_4$	59	<2
13	1-propyl	Ph	18[d]	<2
14	1-butyl	Ph	17[d]	<2
15	cyclopropyl	*p*-$MeOC_6H_4$	24[d]	4
16	Ph	2-thienyl	41	<2
17	*p*-MeC_6H_4	2-thienyl	38	<2
18	*p*-$MeOC_6H_4$	2-thienyl	36	<2
19	cyclopropyl	2-thienyl	18[d]	3

[a] Reaction conditions: 1-alkyne (1.2 mmol), carbonyl azide (1.0 mmol), catalyst (0.05 mmol), $CHCl_3$ (1 mL), 24 h, 40 °C. Either BF_4 or PF_6 can be employed as counterions without any effect on the reaction outcome. [b] Isolated yield based on azide (average of two runs). The remaining initial azide was converted into $RCONH_2$ and/or recovered unreacted. [c] Yields of compounds <2% correspond to products that could not be isolated due to the extremely low conversion. [d] Reaction performed at 60 °C.

Complexes bearing tris(pyrazolylmethyl)amine (Tpa*) ligands and their catalytic activity in the reaction of alkynes and carbonyl azides

With the aim of improving both the catalytic activity and the reaction scope observed with the $Tpm^{*,Br}$-containing copper complex, we targeted the development of new catalysts that could surpass the drawbacks of formation of by-products (trisubstituted oxazoles, amides) or the low yields for alkyl-substituted alkynes. We learned from the somewhat related CuAAC reaction that the use of tertiary amine-based ligands, such as tris(heterocyclic)methylamines, induced a certain acceleration in these cycloaddition reactions.[27] Inspired by this work and on the basis of our own experience with pyrazolyl-containing ligands, we decided to prepare a series of cationic Cu^I complexes of general formulae $[Tpa^*Cu]PF_6$, bearing tris(pyrazolylmethyl)amine ligands (Tpa*; Figure 1) as potential catalysts for this transformation.[28,29]



Tpa*	R^1	R^2	R^3
Tpa	H	H	H
Tpa*	Me	H	Me
Tpa^{Me_3}	Me	Me	Me
$Tpa^{*,Br}$	Me	Br	Me

Figure 1. Tris(pyrazolylmethyl)amine (Tpa*) ligands used in this work.

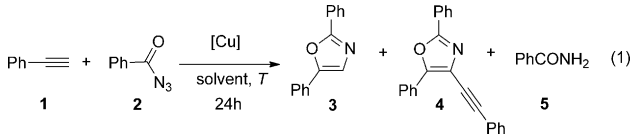
Once the above complexes were prepared, we focused on their activity as catalysts in the model reaction of phenylacetylene with benzoyl azide [Equation (1)]. To compare their performance to that of $[Tpm^{*,Br}Cu(NCMe)]BF_4$, reactions were carried out by using the optimal reaction conditions previously established for the latter. Thus, substrates phenylacetylene (**1**; 1.2 mmol) and benzoyl azide (**2**; 1.0 mmol) were heated in chloroform at 40 °C for 24 h in the presence of 5 mol% copper catalyst (Table 2, entries 1–5). Under these conditions, the parent Tpa copper adduct showed no catalytic activity (Table 2, entry 2), the best performance in the series of Tpa* complexes being achieved with $[Tpa^*Cu]PF_6$, (entry 3). As a first improvement of this catalytic system, it should be noted that benzamide was not observed as a by-product in any reaction catalyzed by the Tpa* species. However, the selectivity of

Table 2. Optimization of conditions for the reaction of phenylacetylene and benzoyl azide catalyzed by [Tpa*Cu]PF_6 complexes.[a]

Entry	Catalyst	Solvent	T [°C]	Yield **3**/**4**/**5** [%][b]
1	[Tpm*,^{Br}Cu(NCMe)]BF_4	$CHCl_3$	40	60:6:29
2	[TpaCu]PF_6	$CHCl_3$	40	n.r.[c]
3	[Tpa*Cu]PF_6	$CHCl_3$	40	71:22:0
4	[Tpa^{Me3}Cu]PF_6	$CHCl_3$	40	18:5:0
5	[Tpa*,^{Br}Cu]PF_6	$CHCl_3$	40	53:5:0
6	[Tpa*Cu]PF_6	$CHCl_3$	60	33:6:0
7	[Tpa*Cu]PF_6	CH_2Cl_2	40	70:1:0
8	[Tpa*Cu]PF_6	DCE	40	60:5:0
9	[Tpa*Cu]PF_6	THF	40	50:0:0
10	[Tpa*Cu]PF_6	–	40	95:0:0
11	–	$CHCl_3$	40	n.r.[c]

[a] Reactions conditions: phenylacetylene (1.2 mmol), benzoyl azide (1 mmol), catalyst (0.05 mmol), solvent (1 mL). Either BF_4 or PF_6 can be employed as counterions without any effect on the reaction outcome [b] Isolated yield. [c] n.r. = no reaction.

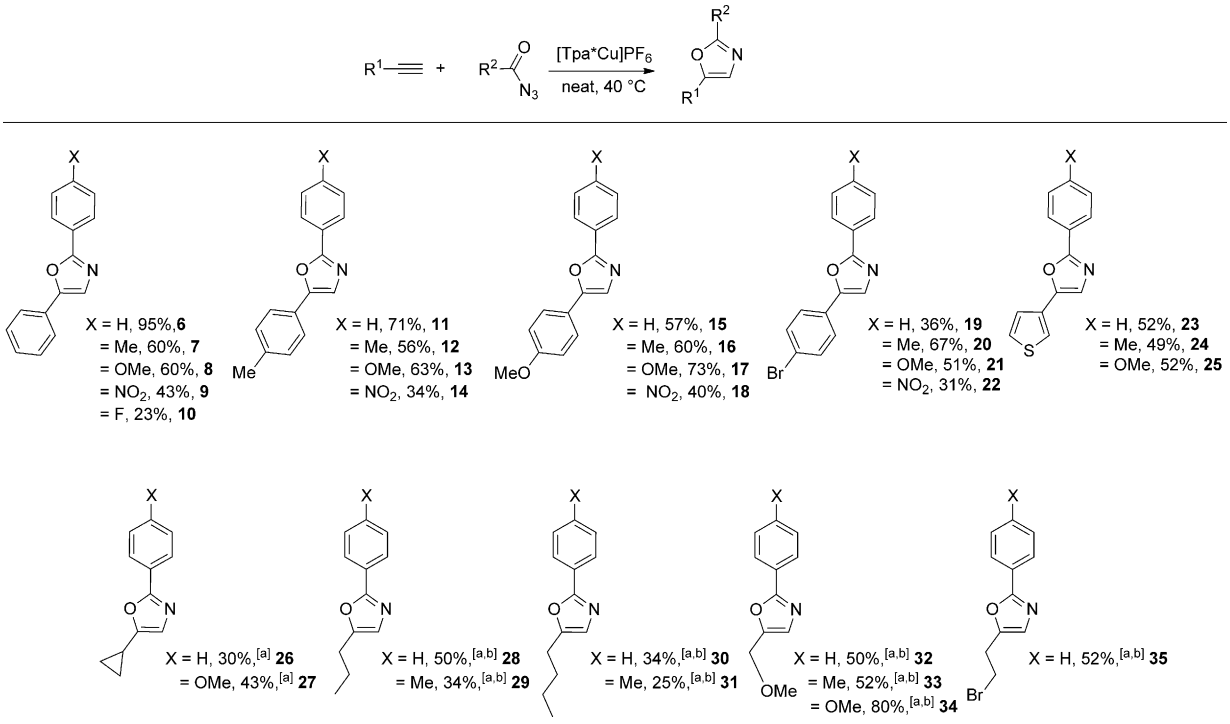
the reaction, i.e., the ratio of 2,5-disubstituted oxazole vs. trisubstituted product, dropped from 10:1 found for the Tpm*,^{Br}Cu complex to 3:1 observed for the Tpa*Cu analogue (Table 2, entries 1 vs. 3).



In an effort to enhance the selectivity, we examined other reaction conditions with [Tpa*Cu]PF_6 as the catalyst (Table 2, entries 6–10). Increasing the temperature to 60 °C negatively affected the overall yield of products (Table 2, entry 6). However, the use of CH_2Cl_2 as solvent substantially improved the selectivity (Table 2, entry 7). Other solvents such as 1,2-dichloroethane (DCE) or THF were less effective in this regard (Table 2, entries 8 and 9). The removal of all solvents, i.e., the use of the alkyne-azide mixture as the reaction medium, provided the highest yield (95%), with the transformation being completely selective toward the 2,5-disubstituted oxazole (Table 2, entry 10). It is worth noting that, under the same conditions, the reaction of benzoyl azide and phenylacetylene catalyzed by the Tpm*,^{Br}Cu complex afforded a mixture of the disubstituted (33% yield) and the trisubstituted (9% yield) oxazole derivatives. Finally, no reaction was observed in the absence of any copper species (Table 2, entry 11).

This first screening demonstrated that the Tpa*Cu-based system is more active and selective than that based on the Tpm*,^{Br}Cu complex, because the former avoids formation of the trisubstituted oxazole derivatives as well as the formation of amides as by-products. With these results in hand, we further explored the scope of the reaction by employing an array of terminal alkynes and carbonyl azides (30 examples; Scheme 4).

In a general manner, the [Tpa*Cu]PF_6 complex catalyzed the reaction between 1-alkynes and carbonyl azides with the formation of the disubstituted oxazole *as the sole product* in moderate to good yields. The effect of the nature of the substitu-



Scheme 4. Synthesis of 2,5-disubstituted oxazoles through [Tpa*Cu]PF_6-catalyzed reaction of 1-alkynes and carbonyl azides. Reagents and conditions: 1-alkyne (1.2 mmol), carbonyl azide (1 mmol), catalyst (0.05 mmol). Isolated yields based on azide (average of two runs). The remaining initial azide was recovered unreacted. [a] Reactions performed at 60 °C in DCE (1 mL). [b] Bisoxazole derivatives were isolated as minor by-products in 3–9% (see the Experimental Section for details).

ents R^1 and R^2 in the reactants deserve some comments. When phenylacetylene was used as the substrate, the highest yield was observed with the neutral benzoyl azide (Scheme 4, **6**). However, when either electron-rich or electron-poor benzoyl azides were employed instead, the yield diminished, with the decrease being more pronounced with the latter (**7**–**8** vs. **9**–**10**). A similar behavior was noticed with respect to the nature of the substituents on the aromatic ring of alkynes. When unsubstituted benzoyl azide was applied, phenylacetylene provided the best performance, whereas the electron-poor aryl acetylenes gave the lowest yield (**6** vs. **11**, **15**, **19**). However, these trends were not clear when electron-rich ($R^2 = p$-Me-C_6H_4, p-OMe-C_6H_4) or electron-poor ($R^2 = p$-NO_2) benzoyl azides were used as the reactants. In such cases, the electronic nature of the aryl alkyne seemed to have no significant influence on the reaction outcome and both electron-rich and electron-poor systems could be successfully employed (**7**–**9** vs. **12**–**14**, **16**–**18**, and **20**–**22**). The presence of a heterocycle on the alkyne, as in 3-ethynylthiophene, was also well-tolerated (**23**–**25**). Finally, when alkyl-substituted alkynes were applied, the reaction had to be carried out at higher temperatures (60 °C) to reach good conversions, a feature also observed in related CuAAC reactions.[30] With these reactants, the product yields appeared to be affected by steric rather than electronic effects on the alkynes (cf. **26**–**31**). Methyl propargyl ether and 4-bromobutyne underwent the reaction efficiently with better isolated yields than those obtained with nonfunctionalized aliphatic alkynes (cf. **32**–**35**). It should be pointed out that in any reaction carried out with aliphatic alkynes, small amounts of a bisoxazole derivative (a product derived by the coupling of two molecules of oxazoles) was isolated as a by-product. Related bistriazoles have also been observed as by-products in CuAAC reactions catalyzed by Cu^I salts in the absence of a reducing agent.[24e,25,31]

So far, it appears that there is no clear relationship between the reaction yield and the electronic properties of either the alkyne or the carbonyl azide. This observation seems to indicate that the reaction follows a complex mechanistic pathway in which the positive or negative electronic effects induced by substrates could match in one step and mismatch in another.

A comparison between the catalytic performance of both complexes, $[Tpm^{*,Br}Cu(NCMe)]BF_4$ and $[Tpa^*Cu]PF_6$ in this transformation is shown in Figure 2. It can clearly be seen that the results achieved with the Tpa*–Cu system are better than those obtained with the $Tpm^{*,Br}$–Cu species, given the former catalyst did not lead to the formation of trisubstituted oxazoles or amides as by-products. Worthy of note is the substantial yield improvement with aliphatic alkynes as substrates in the $[Tpa^*Cu]PF_6$-catalyzed reactions. Overall, the complex $[Tpa^*Cu]PF_6$ has been shown to upgrade the catalytic activity, the selectivity, and also the scope for this direct procedure toward the synthesis of 2,5-disubstituted oxazoles, when compared with the $Tpm^{*,Br}$-containing catalyst.

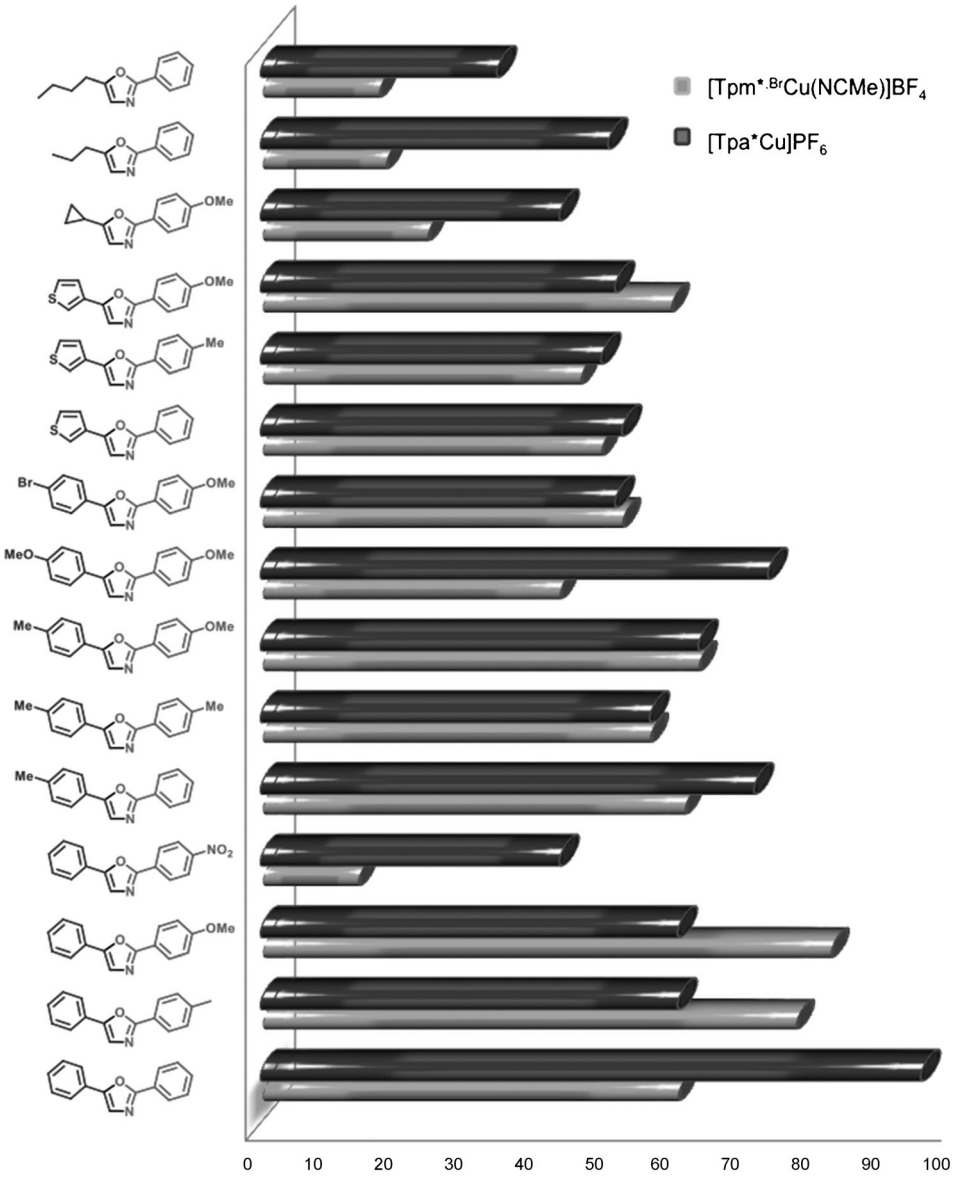
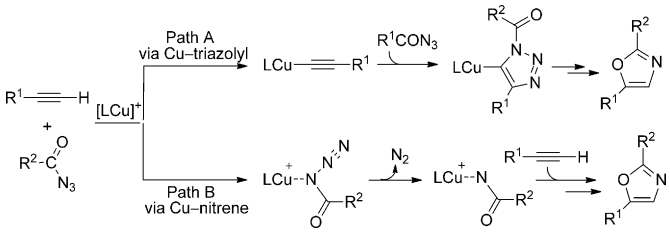


Figure 2. Comparison of the catalytic performance of complexes $[Tpa^*Cu]PF_6$ and $[Tpm^{*,Br}Cu(NCMe)]BF_4$ (data from Table 1 and Scheme 4).

Mechanistic studies: experimental data

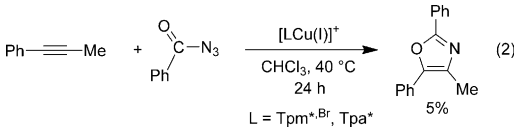
In our previous contribution,[25] we proposed a mechanistic picture for this transformation based on the mechanistic studies described to date for the related CuAAC reaction.[24a,e–f,26f,32] Now we have collected some specific information on this novel transformation to explore the mechanism through which the reaction between carbonyl azides and alkynes takes place in the presence of catalytic amounts of these Cu^{I} complexes. Two different pathways could be invoked for the reaction to initiate. As shown in Scheme 5, pathway A involves reaction of



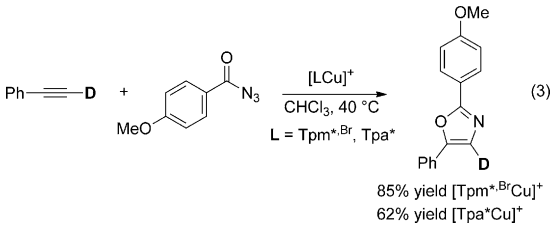
Scheme 5. Possible pathways for the reaction of alkynes and carbonyl azides catalyzed by Cu^{I} complexes.

the copper center with the terminal alkyne to form a Cu–acetylide species, which could coordinate the azide, leading to the formation of a Cu–triazolyl intermediate. This route would be similar to that proposed for the related CuAAC reaction.[24a,e–f] On the other hand, the copper catalyst could react with the carbonyl azide to form a copper–azide species from which N_2 extrusion would generate a Cu–acyl nitrene intermediate. Further interaction with the alkyne in subsequent steps would lead to the observed oxazole derivative. This pathway finds support in the well-known tendency of acyl azides to eliminate N_2, under thermal or photochemical conditions, to form nitrene species,[33] although it has not yet been proposed for copper-catalyzed cycloaddition reactions. In this sense, very recently, Davies and co-workers[34] reported the synthesis of 2,4,5-trisubstituted oxazoles by a gold-catalyzed intermolecular [3+2] cycloaddition of alkynes and *N*-ylides, which is a potential *N*-acyl nitrene equivalent.

To distinguish between both pathways, we carried out a number of experiments. Should the reaction initiate with the formation of a Cu–acetylide species (path A), it would be reasonable to expect that an internal alkyne could not take part in this transformation. However, when benzoyl azide was treated with an internal alkyne (1-phenyl-1-propyne; [Eq. (2)]), a small amount oxazole was isolated at the end of the reaction with both $[Tpm^{*,Br}Cu(NCMe)]BF_4$ and $[Tpa^{*}Cu]PF_6$ as the catalysts. Some benzamide was observed as by-product with the former, whereas, with the latter, the remaining initial azide was recovered unreacted. Therefore the reaction, albeit slow, took place in a selective manner.

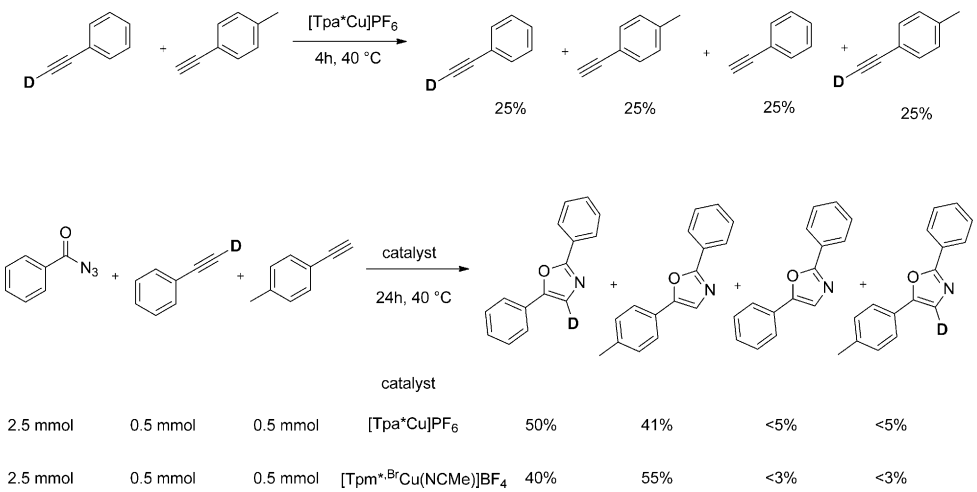


However, the observed low yields did not convince us to rule out the intermediacy of a Cu–acetylide in this process, so we conducted a second experiment using deuterated-phenylacetylene as the substrate [Eq. (3)]. The expected deuterated oxazole derivative was isolated in high yield (85% for the $Tpm^{*,Br}$–Cu system and 62% for the Tpa*–Cu catalyst) as the sole product.



For further confirmation, crossover experiments involving PhC≡CD and *p*-$MeOC_6H_4C{\equiv}CH$ were planned. As an initial test, an equimolar mixture of the two alkynes was treated with $[Tpa^{*}Cu]PF_6$ (Scheme 6, top). It could be shown in this way that the copper complex catalyzed the H/D exchange, reaching 25% in only 15 min and being completed after 4 h. According to this result, the $[Tpa^{*}Cu]PF_6$ catalyst seems to promote the formation of Cu–acetylides, which are the most likely intermediates in this exchange.[35]

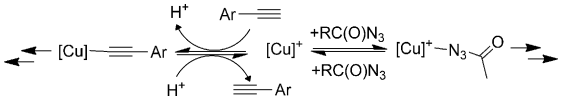
Following this indication, the crossover experiments were performed by addition of an equimolar mixture of the two al-



			catalyst				
2.5 mmol	0.5 mmol	0.5 mmol	$[Tpa^{*}Cu]PF_6$	50%	41%	<5%	<5%
2.5 mmol	0.5 mmol	0.5 mmol	$[Tpm^{*,Br}Cu(NCMe)]BF_4$	40%	55%	<3%	<3%

Scheme 6. Crossover experiments involving deuterated alkynes.

kynes to an excess of benzoyl azide (1:2.5) in the presence of either $[Tpm^{*,Br}Cu(NCMe)]BF_4$ or $[Tpa^{*}Cu]PF_6$. Very interestingly, the levels of scrambling remained very low with both catalysts (Scheme 6, bottom). Thus, in spite of the potential ability of the considered catalytic species for Cu–acetylide generation, the results of the scrambling experiments strongly suggest that the reaction pathway leading to the formation of 1,3-oxazoles from terminal alkynes and acyl azides does not involve a copper–acetylide as an intermediate (Scheme 7).



Scheme 7. Plausible equilibria of the copper complexes employed as pre-catalysts with azide and alkyne reactants.

Computational studies

Calculations were carried out by using two different systems: a model system with $[TpmCu]^+$ as the catalyst, HC≡CMe as the alkyne, and $N_3C(=O)CH_3$ as the carbonyl azide, and the real system using $[Tpm^{*,Br}Cu]^+$, HC≡CPh and $N_3C(=O)Ph$ as the catalyst and reactants, respectively. The model system was employed to screen all mechanistic possibilities, and once the different possible pathways were defined, key calculations with the real system were performed. First, the two major pathways A and B, depicted in Scheme 5 were investigated on the model system.

Pathway A: Cu–triazolyl

According to the generally accepted mechanism for the click reaction, the process starts with the formation of a copper–acetylide species.[36] The formation of this copper–acetylide requires cleavage of the terminal alkynyl–H bond, and the proton has to be taken by some species with base properties. The problem of the nature of this base has not been analyzed in detail in previous computational studies,[36] but has to be explicitly considered here because we are discussing the competition with mechanisms for which this copper–acetylide species is not formed. According to the calculations detailed in the Supporting Information, we have found that the use of reaction product oxazole as base provides a lower-limit estimation for the free energy cost of this proton abstraction. In this optimal case, the transformation from the starting complex **^{1}C1** (C for computed, superscript 1 for singlet electronic state) to the copper–acetylide intermediate **^{1}C2** has a free energy cost of 8.8 kcal mol^{-1} (see Figure 3, pathway A). Further interaction with the azide and formation of the first C–N bond proceeds through transition state **^{1}TS2–3** located at 30.7 kcal mol^{-1} above the reactants. Figure 4 presents the geometry of **^{1}TS2–3**. From here it has been postulated[36] that the formation of the second C–N bond takes place through a second transition state, which we could not locate at the M06 level. However, its eventual existence is in any case not relevant to the current discussion (see below). Further details on these technical aspects are provided in the Supporting Information. Alternative mechanisms with participation of dinuclear copper intermediates have been proposed for the Cu^I-catalyzed cycloaddition of azides and alkynes.[37] We did not consider this option here because mononuclear species were sufficient to explain the observed experimental behavior.

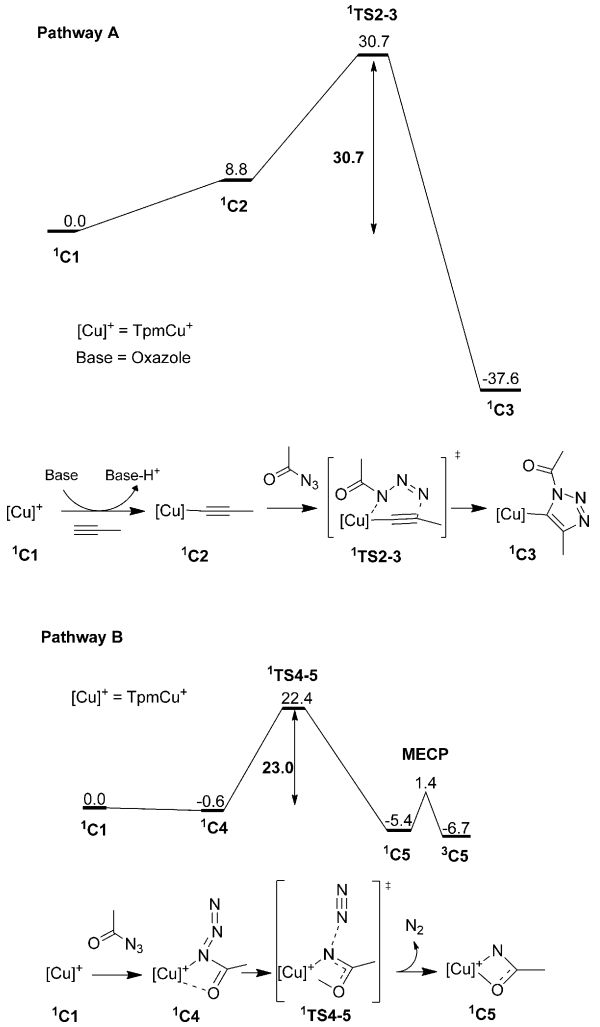


Figure 3. Reaction pathways A and B. Relative free energies in kcal mol^{-1}.

Pathway B: Cu–nitrene

This pathway starts by coordination of the azide through both the nitrogen and the oxygen atoms (see Figure 3, pathway B). This species evolves to the acyl nitrene intermediate by N_2 extrusion, through **^{1}TS4–5** located at 22.4 kcal mol^{-1} above reactants (geometry presented in Figure 4). The acyl nitrene remains coordinated through both the nitrogen and oxygen atoms, at −5.4 kcal mol^{-1} below the starting materials. Once the acyl nitrene is formed, the reaction is not expected to revert towards reactants due to N_2 elimination. The triplet and singlet potential energy surfaces remain close in energy in this region of the potential energy surface. In fact, the ground state of the acyl nitrene is a triplet **^{3}C5** in which the nitrene is coordinated through only the nitrogen atom. Crossing be-

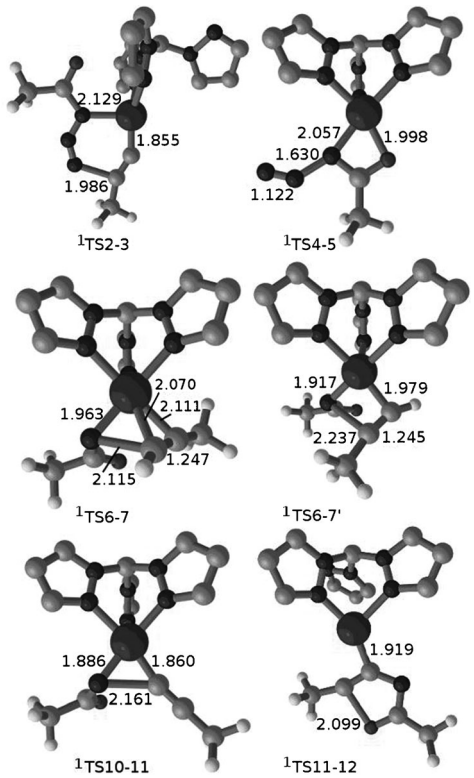


Figure 4. Structures, including selected bond distances (in Å), of the key transition states. The hydrogen atoms of the Tpm ligand have been removed for clarity.

tween surfaces takes place through a Minimum Energy Crossing Point (MECP)[38] with a relative energy of 1.4 kcal mol^{-1}, also shown in the profile in Figure 3. The triplet species is introduced here for the sake of completion, although, as will be seen below, the same qualitative conclusions could be obtained by considering only the single electronic state. The N_2 extrusion is thus expected to take place with a barrier of 23.0 kcal mol^{-1}, which corresponds to the energy difference between **^{1}C4** and **^{1}TS4–5**. Formation of the Cu–nitrene complex (pathway B) is preferred over formation of the Cu–triazolyl complex (pathway A), because the barrier for the former is 7.7 kcal mol^{-1} lower in energy. Thus, we should expect the formation of acyl nitrene intermediate **^{3}C5**. This finding rules out the mechanism previously hypothesized,[25] and is fully consistent with the observed complete deuteration at the fourth position of the oxazole ring.

Once the Cu–nitrene complex **^{3}C5** is formed, we can envision different mechanistic possibilities, of which the two lowest in energy are presented here: 1) B1, the direct formation of the C–N bond with the alkyne, and 2) B2, the formation of the C–N bond through a copper–acetylide intermediate. A third possibility, B3, is presented in the Supporting Information. Because all these pathways occur mostly in the singlet PES, they start with crossing from triplet to singlet PES through the same MECP mentioned above. Path B1 starts with coordination of the alkyne to the Cu–nitrene species, forming a π-complex **^{1}C6** with a relative energy of 3.4 kcal mol^{-1} (Figure 5). Formation of the C–N bond proceeds through transition state **^{1}TS6–7** (Figure 4). From **^{1}C7**, a rotation of the acyl group allows its coordination to the copper center, leading to the formation of a six-membered ring intermediate in **^{1}C8**. Subsequent C–O ring closure can take place with virtually no barrier, resulting in species **^{1}C9**, in which the oxazole product is weakly coordinated to the catalyst. The highest energy barrier in path B1 is 5.2 kcal mol^{-1}, which is significantly lower than the 22.4 kcal mol^{-1} reported above for the formation of the Cu–nitrene intermediate (Figure 3, pathway B).

Pathway B2 initiates with formation of the acetylide from the terminal alkyne. The problem with the proton abstraction step is the same as discussed above for path A, and we have taken the same approach described above and in the Supporting Information to obtain a low-limit estimate of the free energy cost of this abstraction. When doing so, the copper–acetylide–nitrene intermediate **^{1}C10** is located at 12.5 kcal mol^{-1} (see Figure 5). We estimated an energy of 12.7 kcal mol^{-1} for the subsequent transition state **^{1}TS10–11**, corresponding to C–N bond formation (the PES is very flat in this region and the TS could not be located with the M06 functional, the energy presented corresponds to a species with the Cu–N and C–N distances frozen at the B3LYP TS geometry, see Figure 4). The next formed intermediate **^{1}C11** is very stable and, from there, the oxazole is formed by rearrangement and protonation steps. The highest energy in in path B2 is 12.7 kcal mol^{-1}. Because of this, this pathway can be discarded when compared with path B1 (5.2 kcal mol^{-1}). This is also in agreement with the experimental results obtained with deuterated phenylacetylene, which are not compatible with path B2.

The real system

To check the validity of the conclusions extracted from the model system, we carried out calculations on key species by using the real ligand Tpm*^{,Br} and the substrates PhC(=O)N_3 and PhC≡CH. These relative energies are summarized in Table 3.

Table 3. Relative free energies of the most relevant species (kcal mol^{-1}) of the model and the real system.

Path	Species	Model	Real
	$[LCu]^+ + RN_3 + HC{\equiv}CR + B$	0.0	0.0
A	$[LCu(C{\equiv}CR)] + RN_3 + BH^+$	8.8	9.2
A	$^1TS([LCu(C{\equiv}CR)] + RN_3 \rightarrow [LCu(triazole)]) + BH^+$	30.7	34.5
B	$^1TS([LCu]^+ + RN_3 \rightarrow [LCu(NR)] + N_2) + B + HC{\equiv}CR$	22.4	24.1
B	$^1[LCu(NR)]^+ + N_2 + B + HC{\equiv}C\text{-}R$	−5.4	−5.5
B	$^3[LCu(NR)]^+ + N_2 + B + HC{\equiv}C\text{-}R$	−6.7	−7.2
B1	$^1TS([LCu(NR)]^+ + HC{\equiv}CR \rightarrow [LCu(RC{\equiv}C(H){-}NR)]^+) + B + N_2$	5.2	2.7[a]
B2	$^1[LCu(NR)(C{\equiv}CR)] + BH^+ + N_2$	12.5	16.3[a]
B2	$^1TS([LCu(NR)(C{\equiv}CR)] \rightarrow [LCu(RC{\equiv}C{-}NR)]^+) + BH^+ + N_2$	12.7[b]	14.0[c]

[a] Corresponding to an optimized geometry with the C–N distance frozen to that of the model system. [b] Frozen structure at the Cu–C, Cu–N and C–N distances of the B3LYP geometry. [c] Frozen structure at the Cu–N and C–N distances of the B3LYP geometry.

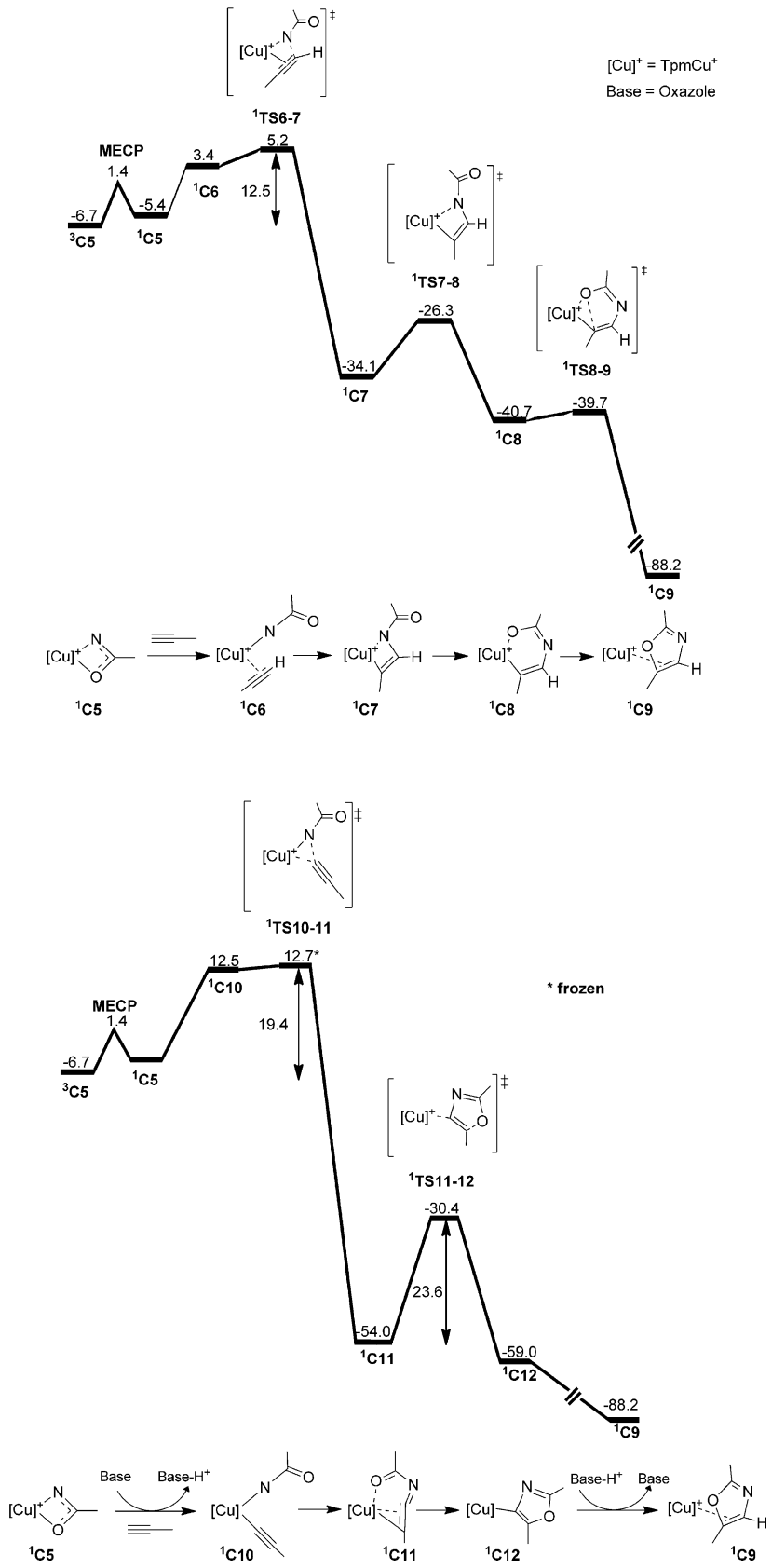


Figure 5. Calculated reaction pathways B1 (top) and B2 (bottom) leading to the formation of the final oxazol from the copper–nitrene intermediate ^{1}**C5**. Free energy values in kcal mol^{-1}.

The reaction profiles do not change significantly from the model to the real system. From data shown in Table 3, pathway B is also preferred over pathway A in the real system (highest free energy points of 24.1 vs. 34.5 kcal mol^{-1}). Furthermore, path B1 is also preferred over path B2 (highest energies of 2.7 and 16.3 kcal mol^{-1}, respectively). Therefore, formation of the oxazole is expected to take place through the copper–acyl nitrene intermediate, followed by coordination of the alkyne, and formation of the C–N bond. The overall rate-limiting step of the reaction is N_2 extrusion, which leads to the formation of the copper–acyl nitrene intermediate.

We also examined the overall regioselectivity of the process in our calculations. The exclusive formation of the 2,5-disubstituted oxazoles is experimentally observed, and it was reproduced by our calculations. The regioselectivity-determining transition state is ^{1}**TS6–7**, when the N–C bond is made (shown in Figure 4). The transition state leading to the favored regioisomer has lower energy than the transition state ^{1}**TS6–7′** leading to the (unobserved) 2,4-disubstituted oxazole. The energy difference between the two transition states is related to the nonsymmetric coordination of the alkyne to copper. The unsubstituted carbon binds more strongly, and is thus more activated towards attack by the nitrogen, as can be observed in Figure 4. The difference is 1.6 kcal mol^{-1} (5.2 vs. 6.8 kcal mol^{-1}) for the model system and 3.6 kcal mol^{-1} (2.7 vs. 6.3 kcal mol^{-1}) for the real system, which is sufficiently large to explain the observation of a single regioisomer.

Conclusion

Cationic [Tpm*,^{Br}Cu(NCMe)]BF_4 and [Tpa*Cu]PF_6 complexes catalyze the regioselective formation of 2,5-disubstituted oxazoles from carbonyl azides and terminal alkynes. The Tpa*-based system is found to be more selective and active than the Tpm*,^{Br}–Cu derivative. Experimental and computational evidence indicates that the reaction proceeds by coordination of the carbonyl azide to the copper center and subsequent extrusion of a dinitrogen molecule to produce $[LCu(NC(O)R)]^+$ intermediate. Formation of this copper–nitrene intermediate is the rate-limiting step of the whole process. Subsequently, the alkyne binds to the metal, forming a π-complex rather than the copper–acetylide intermediate, and the system evolves through low barriers to the observed 2,5-disubstituted oxazole product. This mechanism differs from that proposed for the related alkyne–azide cycloadditions (CuAAC), and opens the way for new developments in this field.

Experimental Section

General methods

All reactions and manipulations were carried out under an oxygen-free nitrogen atmosphere by using standard Schlenk techniques. All substrates were purchased from Aldrich. Solvents were dried and degassed before use. Tris(3,5-dimethyl-pyrazolylmethyl)amine[28b] and complexes [Tpa*Cu]PF_6[28c] and [Tpm*,^{Br}Cu(NCMe)]BF_4[39] were prepared according to published procedures. The synthesis and full structural characterization of unknown Tpa ligands and [Tpa*Cu]PF_6 complexes will be reported elsewhere. NMR spectra were recorded with a Varian Mercury 400 MHz spectrometer. ^{1}H NMR shifts were measured relative to deuterated solvents peaks but are reported relative to tetramethylsilane. Elemental analyses were performed with a PerkinElmer 2400 Series II instrument. Identification and characterization of oxazole derivatives are given in the Supporting Information.

General catalytic procedure for the reaction of terminal alkynes and carbonyl azides catalyzed by [Tpa*Cu]PF_6

The catalyst (28.35 mg, 0.05 mmol) and the carbonyl azide (1 mmol) were dissolved in the alkyne (1.2 mmol) under a nitrogen atmosphere and the reaction mixture was stirred at 40 °C for 24 h. Volatiles were then removed under vacuum and the residue was dissolved in $CDCl_3$. An precisely weighted amount of trimethylvinylsilane was added as internal standard and the mass balance was then determined by ^{1}H NMR spectroscopic analysis. The sample was recovered and the crude reaction material was then purified by flash chromatography on silica gel (diethyl ether/petroleum ether, 1:30) to afford the desired products.

Reaction of deuterated phenyl acetylene and 4-methoxybenzoyl azide catalyzed by copper(I) complexes

The catalyst (0.05 mmol) and 4-methoxybenzoyl azide (177 mg, 1 mmol) were dissolved in deuterated phenylacetylene (132 μL, 1.2 mmol), and the reaction mixture was stirred at 40 °C for 24 h, then the residue was dissolved in $CDCl_3$. A precisely weighted amount of trimethylvinylsilane was added as internal standard and the mass balance was determined by ^{1}H NMR spectroscopic analysis. The sample was recovered and the crude reaction material was purified by flash chromatography on silica gel (diethyl ether/petroleum ether, 1:30) to afford the desired product as a white solid. Yield: 85% for [Tpa*,^{Br}Cu(NCMe)]BF_4 and 62% for [Tpa*Cu]PF_6; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.98$ (d, $J = 8.8$ Hz, 2H), 7.64 (d, $J = 7.5$ Hz, 2H), 7.37 (t, $J = 7.7$ Hz, 2H), 7.26 (t, $J = 7.4$ Hz, 1H), 6.93 (d, $J = 8.8$ Hz, 2H), 3.81 ppm (s, 3H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): $\delta = 161.3$, 150.4, 128.8, 128.1, 128.1, 127.9, 124.0, 120.2, 114.2, 55.4 ppm; elemental analysis calcd (%) for $C_{16}H_{12}DNO_2$: C, 76.17; H, 4.80; N, 5.55; found: C, 76.03; H, 5.10; N, 5.55.

Computational details

Calculations were performed by using the Gaussian 09 package[40] within the B3LYP[41] and M06[42] formalisms. The standard 6–31+G(d)[43] basis set was used to describe the H, C, N, O and Br atoms, with the exception of the C and H atoms of the Tpm*,^{Br} ligand in the real system for which the 6–31G basis set was used instead. The large core scalar relativistic pseudopotentials developed by Dolg et al.[44] were used for the copper coupled to a double-zeta quality basis set. Full geometry optimizations were performed in solution with the Polarizable Continuum Model (PCM) method,[45] with Gaussian 09 defaults for chloroform. Unless otherwise stated, all energies presented correspond to M06 free energies computed in solution (temperature 298 K, pressure 1 atm). The B3LYP method produced qualitatively similar results, which can be found in the Supporting Information. The nature of the stationary points encountered were characterized by a vibrational analysis performed within the harmonic approximation. Transition states were identified by the presence of one imaginary frequency and minima by a full set of real frequencies. Minimum Energy Crossing Points (MECPs) were located by using the code developed by Harvey's group;[46] free energies at the MECP were approximated to the averaged projected frequencies at the two potential energy surfaces. The triplet electronic state has a minor contribution to the overall chemistry of the system; because of this, we did not compute the open-shell singlet electronic state, which should have a similar energy. For more details see the Supporting Information.

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Keywords: alkynes · click chemistry · copper · nitrenes · oxazoles · reactive intermediates

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