Copper(I) complexes as catalysts for the synthesis of N-sulfonyl-1,2,3-triazoles from N-sulfonylazides and alkynes†

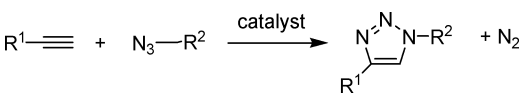
Israel Cano, M. Carmen Nicasio* and Pedro J. Pérez*

FINAL VERSION ACCEPTED

The well-defined complex [Tpm*,BrCu(NCMe)]BF_4 efficiently catalyses the [3+2] cycloaddition between alkynes and N-sulfonylazides under mild conditions, with conversions comparable to others obtained with *in situ* generated catalytic systems previously described for this transformation.

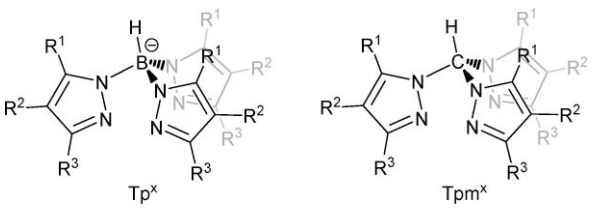
Introduction

The synthesis of 1,2,3-triazoles from the direct, metal-catalysed reaction of alkynes and organic azides is marked by two milestones: the seminal work by Huisgen[1] for the thermal reaction and the independent discovery, at the beginning of this decade, by Meldal and Tornøe[2] and by Sharpless[3] of the capabilities of copper(I) complexes to catalyse such transformation. Since then, a large number of catalytic systems have been reported,[4] in which an alkyne and an azide undergo a 1,3-dipolar addition reaction to provide the triazole ring (eqn (1)).



(1)

Recently, an excellent review[5] by Meldal and Tornøe has provided a comprehensive knowledge of this procedure. Most of the already described catalytic systems are based on the use of a copper salt and a ligand added to the reaction mixture,[6–29] the use of well-defined complexes being limited to a few examples.[30–36] The role of the ligand is mainly explained in terms of protecting the Cu(I) center from oxidation. Because of this, a number of systems are based on the use of a Cu(II) salt and a reducing agent, or in a Cu(0) source with an oxidizing agent.[4] We became interested in the study of well-defined, stable Cu(I) complexes as catalysts for this transformation, in order to design a simple catalytic system exclusively formed by the copper complex, the azide, the alkyne and the solvent. It is also worth mentioning that when using N-sulfonylazides,[4,37–43] the formation of the triazole is usually precluded. In this case, the cuprate intermediate commonly proposed in the reaction mechanism is not stable enough and N–N bond cleavage takes place avoiding the isolation of the desired triazole. We are aware of only two examples in which the triazole is formed with these reagents (N-sulfonylazides).[44,45] On the basis of this, we decided to explore the catalytic capabilities of isolated, well-defined Cu(I) complexes with tridentate ligands (Scheme 1) of type trispyrazolylborate (Tp^x) and trispyrazolylmethane (Tpm^x) in the reaction of sulfonylazides and alkynes.



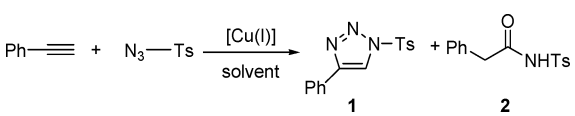
Tp^x	R^1	R^2	R^3
Tp*	Me	H	Me
Tp^{Br3}	Br	Br	Br
Tp^{Ph}	H	H	Ph

Tpm^x	R^1	R^2	R^3
Tpm*	Me	H	Me
$Tpm^{*,Br}$	Me	Br	Me
Tpm^{Ms}	H	H	Ms

Scheme 1 Ligands employed in this work.

Results and discussion

In a screening set of experiments, several complexes of general formulae $Tp^xCu(NCMe)$[46] or [Tpm^xCu(NCMe)]BF_4[47] were employed in catalytic amounts in the reaction of phenylacetylene and tosylazide (eqn (2)). As shown in Table 1, the trispyrazolylmethane-containing catalysts, cationic in nature, were more active than the neutral, Tp^x-containing complexes toward the formation of the 1,2,3-triazole (**1**). It is worth mentioning that these compounds are easily synthesised by direct reaction of CuI and the Tpm^x ligand. In addition, the complexes are air-stable and can be handled without any special caution.



(2)

At room temperature, the complex [$Tpm^{*,Br}$Cu(NCMe)]BF_4 provided the best selectivity in chloroform as the solvent, the addition of 2.5 equiv. of water (relative to the azide) leading to the enhancement of the conversions but also to the formation of amide **2** (eqn (2)). The latter was the major product when a 2 : 1 mixture of *t*-BuOH : H_2O was employed as the reaction solvent. A slight increase in the reaction temperature up to 40 °C, for 24 h, gave a 95 : 5 mixture of **1** and **2**, respectively, after the total

Laboratorio de Catálisis Homogénea, Departamento de Química y Ciencia de los Materiales, Unidad Asociada al CSIC, Campus de El Carmen s/n, Universidad de Huelva, 21007-, Huelva, Spain. E-mail: perez@dqcm.uhu.es, mcnica@dqcm.uhu.es; Fax: +34 959219942; Tel: +34 959219956

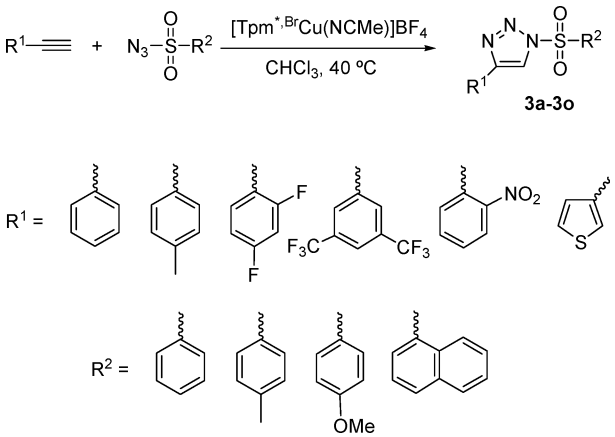
Table 1 Catalysts and conditions screening for the reaction of phenylacetylene and tosylazide[a]

Tp^x or Tpm^X	Solvent	T/° C	Time/h	Yields [b](**1 : 2**)
Tp^{Br3}	$CHCl_3$	r.t.	24	0 : 0
Tp^{Br3}	$ClCH_2CH_2Cl$	60	24	<1%
Tp*	$CHCl_3$	r.t.	24	< 1%
Tp^{Ph}	$CHCl_3$	r.t.	24	<5%
Tpm*	$CHCl_3$	r.t.	24	<1%
Tpm^{Ms}	$CHCl_3$	r.t	12	<1%
$Tpm^{*,Br}$	$CHCl_3$	r.t	24	48 : 1
$Tpm^{*,Br}$	$CHCl_3$–H_2O[c]	r.t.	24	67 : 5
$Tpm^{*,Br}$	*t*-BuOH/H_2O (2 : 1)	r.t.	24	44 : 66
Tpm*	$CHCl_3$	40	24	21 : 1
Tpm^{Ms}	$CHCl_3$	40	24	<1%
$Tpm^{*,Br}$	$CHCl_3$	40	24	95 : 5
$Tpm^{*,Br}$	$CHCl_3$–H_2O[c]	40	24	87 : 13

[a] Reaction conditions: alkyne (0.6 mmol), N-sulfonyl azide (0.5 mmol), catalyst (0.025 mmol), solvent (1 mL). [b] Conversions determined by ^1H NMR using an internal standard, unreacted starting materials accounting for mass balance. [c] Reaction performed with 2.5 equiv. of H_2O with respect to the azide.

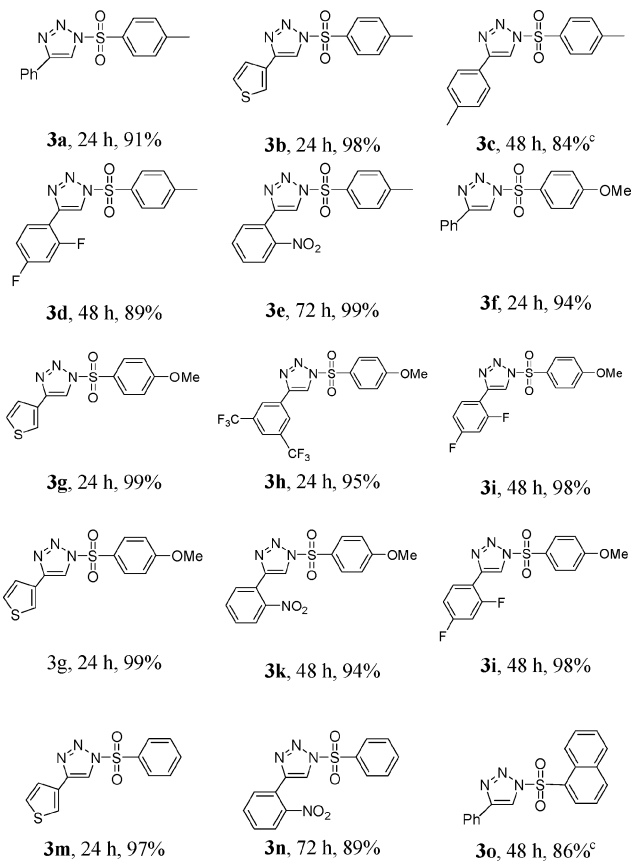
consumption of the azide. The sterically demanding Tpm^{Ms} ligand seemed to be of no use for this transformation, since no reaction was observed at room temperature or at 40 °C. On the other hand, the complex with the 3,5-dimethylpyrazolyl afforded significantly lower conversions, in spite of the similar steric pressure induced by both Tpm^* and $Tpm^{*,Br}$. The more electron-withdrawing character of the latter should be invoked to explain that different behavior.

After these preliminary results, and under the optimal conditions based on the use of $[Tpm^{*,Br}Cu(NCMe)]BF_4$ as the catalyst, chloroform as the solvent and 40 °C as the reaction temperature, a series of sulfonyl azides and different terminal alkynes were tested (Scheme 2) with the results shown in Scheme 3. High to very high yields of the N-sulfonyl-1,2,3-triazoles were obtained, under mild conditions (40–50 °C), with an azide : alkyne ratio of 1.2 : 1 and a 5% catalyst loading.



Scheme 2 Synthesis of N-sulfonyl-1,2,3-triazoles.

As mentioned above, and to the best of our knowledge, only two systems have been reported to promote the cycloaddition reactions using N-sulfonylazides. Fokin, Chang and co-workers reported[44] the use of CuI (10 mol%) and 2-6-lutidine in $CHCl_3$ at 0 °C to promote this transformation in high yield. Later, work by Fu and co-workers demonstrated[45] that CuBr/PhSMe could serve as the catalyst in water as the solvent and at room temperature (10% catalyst loading). A comparison between the results reported therein and those shown in Scheme 3 indicates that our well-defined catalyst behaves in a similar manner. For instance, the reaction of phenylacetylene with tosylazide led to a 91% (isolated yield) of the corresponding triazole in 24 h at 40 °C (Scheme 3) whereas the CuI/lutidine systems gave 78% in 12 h at 0° C and the CuBr/PhSMe afforded 90% in 16 h at room temperature. The use of a well-defined catalyst avoids problems derived of the existence of well-known coordination-dissociation equilibria between several CuL_n species that could affect the concentration of the real catalytic species in solution. In addition, there is no leakage of excess ligand from the catalyst and the metal complex is easily removed by filtration through a plug of silica.



Scheme 3 [a] Reaction conditions: alkyne (0.6 mmol), N-sulfonyl azide (0.5 mmol), catalyst (0.025 mmol), chloroform (1 mL), temperature 40 °C. [b] Isolated yields (average of two runs). [c] Reaction performed at 50 °C.

Conclusions

In conclusion, a new copper-based catalytic system, developed with the complex $[Tpm^{*,Br}Cu(NCMe)]BF_4$, has been found to efficiently promote the formation of N-sulfonyl-1,2,3-triazoles from sulfonylazides and alkynes under mild conditions. The conversions are at least, comparable to those already reported in the scarce examples known to work with sulfonylazides.

Experimental

General

All manipulations were carried out under a nitrogen atmosphere using standard Schlenk techniques. The chemicals were purchased and used without purification. The complexes $[Tpm^{X}Cu(NCMe)]BF_4$[47] and sulfonyl azides[48] were prepared according to literature procedure. ^1H and ^{13}C NMR spectra were recorded on a 400 (^1H)/100 (^{13}C) MHz spectrometer. Chemical shifts (δ) are reported relatively to tetramethylsilane as internal standard in ppm. Assignments of some ^1H and ^{13}C signals rely on g-COSY and/or g-HSQC experiments. Elemental Analysis were performed at Unidad de Análisis Elemental of the Universidad de Huelva.

General catalytic procedure for [3 + 2] cycloaddition of alkynes and sulfonyl azides catalyzed by $[Tpm^{*,Br}Cu(NCMe)]BF_4$

The catalyst (18.2 mg, 0.025 mmol, 5 mol%) and sulfonyl azide (0.5 mmol) were dissolved in anhydrous chloroform (1 mL) in an ampoule. The alkyne (0.6 mmol) was added to the solution under a nitrogen atmosphere. The reaction mixture was stirred at a given temperature (40 or 50 °C) for a given time (24–72 h) (see Scheme 3). The reaction crude was diluted with dichloromethane and filtered through a plug of silica to remove the copper catalyst. The solvent was evaporated under reduce pressure and the residue was purified by flash chromatography on silica gel with ethyl acetate to afford the desired product.

Acknowledgements

We thank the MEC (Proyecto CTQ2008-00042/BQU) and the Junta de Andalucía (Proyecto P07-FQM-02745) for financial support. IC thanks MEC for a research fellowship.

Notes and references

1 R. Huisgen, *Pure Appl. Chem.*, 1989, **61**, 613.
2 C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057.
3 V. V. Rostovtsev, L. G. Grenn, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596.
4 (*a*) P. M. E. Gramlich, C. T. Wirges, A. Manetto and T. Carrell, *Angew. Chem., Int. Ed.*, 2008, **47**, 8350; (*b*) J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, 2007, **36**, 1249; (*c*) M. Meldal, *Macromol. Rapid Commun.*, 2008, **29**, 1016; (*d*) J.-F. Lutz, *Angew. Chem., Int. Ed.*, 2007, **46**, 1018; (*e*) V. D. Bock, H. Hiemstra and J. H. Maarseven, *Eur. J. Org. Chem.*, 2006, 51; (*f*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004.
5 M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952.
6 B. Baeza, L. Casarrubios, P. Ramírez-López, M. Gómez-Gallego and M. A. Sierra, *Organometallics*, 2009, **28**, 956.
7 J. Kalisiak, K. B. Sharpless and V. V. Fokin, *Org. Lett.*, 2008, **10**, 3171.
8 P. Kele, G. Nezö, D. Achatz and O. S. Wolfbeis, *Angew. Chem., Int. Ed.*, 2009, **48**, 344.
9 L. Ackermann, H. K. Potukuchi, D. Landsberg and R. Vicente, *Org. Lett.*, 2008, **10**, 3081.
10 J. S. Yadav, B. V. S. Reddy, G. M. Reddy and D. N. Chary, *Tetrahedron Lett.*, 2007, **48**, 8773.
11 T. L. Mindt and R. Schibli, *J. Org. Chem.*, 2007, **72**, 10247.
12 V. O. Rodionov, S. I. Presolsky, S. Gardinier, Y.-H. Lim and M. G. Finn, *J. Am. Chem. Soc.*, 2007, **129**, 12696.
13 V. O. Rodionov, S. I. Presolsky, D. Diaz Diaz, V. V. Fokin and M. G. Finn, *J. Am. Chem. Soc.*, 2007, **129**, 12705.
14 Y. Angell and K. Burgess, *Angew. Chem., Int. Ed.*, 2007, **46**, 3649.
15 K. Odlo, E. A. Hoydahl and T. V. Hansen, *Tetrahedron Lett.*, 2007, **48**, 2097.
16 H. S. G. Beckmann and V. Wittmann, *Org. Lett.*, 2007, **9**, 1.
17 X. Zhang, H. Li, L. You, Y. Tang and R. P. Hsung, *Adv. Synth. Catal.*, 2006, **348**, 2437.
18 V. Aucagne and D. A. Leigh, *Org. Lett.*, 2006, **8**, 4505.
19 Z.-Y. Yan, Y.-B. Zhao, M.-J. Fan, W.-M. Liu and Y.-M. Liang, *Tetrahedron*, 2005, **61**, 9331.
20 J.-F. Lutz, H. G. Börner and K. Weichenhan, *Macromol. Rapid Commun.*, 2005, **26**, 514.
21 F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210.
22 P. Appukkuttan, W. Dehaen, V. V. Fokin and E. V. Eycken, *Org. Lett.*, 2004, **6**, 4223.
23 A. K. Feldman, B. Colasson and V. V. Fokin, *Org. Lett.*, 2004, **6**, 3897.
24 M. Ahlquist and V. V. Fokin, *Organometallics*, 2007, **26**, 4389.
25 C. Nolte, P. Mayer and B. F. Straub, *Angew. Chem., Int. Ed.*, 2007, **46**, 2101.
26 M. Séverac, L. L. Pleux, A. Scarpaci, E. Blart and F. Odobel, *Tetrahedron Lett.*, 2007, **48**, 6518.
27 B. Gerard, J. Ryan, A. B. Beeler and J. A. Porco, *Tetrahedron*, 2006, **62**, 6405.
28 W. G. Lewis, F. G. Magallon, V. V. Fokin and M. G. Finn, *J. Am. Chem. Soc.*, 2004, **126**, 9152.
29 (*a*) F. Pérez-Balderas, M. Ortega-Muñoz, J. Morales-Sanfrutos, F. Hernández-Mateo, F. G. Calvo-Flores, J. A. Calvo-Asín, J. Isac-García and F. Santoyo-González, *Org. Lett.*, 2003, **5**, 1951; (*b*) K. Kamata, Y. Nakagawa, Y. Zazuya and N. Mizuno, *J. Am. Chem. Soc.*, 2008, **130**, 15304.
30 S.-Q. Bai, L. L. Koh and T. S. A. Hor, *Inorg. Chem.*, 2009, **48**, 1207.
31 S. Díez-González and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2008, **47**, 8881.
32 P. S. Donnelly, S. D. Zanatta, S. C. Zammit, J. M. White and S. J. Williams, *Chem. Commun.*, 2008, 2459.
33 N. Candelon, D. Lastécourés, A. K. Diallo, J. R. Aranzaes, D. Astruc and J.-M. Vincent, *Chem. Commun.*, 2008, 741.
34 S. Díez-González, A. Correa, L. Cavallo and S. P. Nolan, *Chem.–Eur. J.*, 2006, **12**, 7558.
35 T. R. Chan, R. Hilgraf, K. B. Sharpless and V. V. Fokin, *Org. Lett.*, 2004, **6**, 2853.
36 V. Aucagne, K. D. Hänni, D. A. Leigh, P. J. Lusby and D. B. Walker, *J. Am. Chem. Soc.*, 2006, **128**, 2186.
37 J. Raushel, S. M. Pitram and V. V. Fokin, *Org. Lett.*, 2008, **10**, 3385.
38 M. Whiting and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2006, **45**, 3157.
39 M. P. Cassidy, J. Raushel and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2006, **45**, 3154.
40 S. Chang, M. Lee, D. Y. Jung, E. J. Yoo, S. H. Cho and S. K. Han, *J. Am. Chem. Soc.*, 2006, **128**, 12366.
41 E. J. Yoo, I. Bae, S. H. Cho, H. Han and S. Chang, *Org. Lett.*, 2006, **8**, 1347.
42 S. H. Cho, E. J. Yoo, I. Bae and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 16046.
43 I. Bae, H. Han and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 2038.
44 (*a*) E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless and S. Chang, *Angew. Chem., Int. Ed.*, 2007, **46**, 1730; (*b*) E. J. Yoo, M. Ahlquist, I. Bae, K. B. Sharpless, V. V. Fokin and S. Chang, *J. Org. Chem.*, 2008, **73**, 5520.
45 F. Wang, H. Fu, Y. Jiang and Y. Zhao, *Adv. Synth. Catal.*, 2008, **350**, 1830.
46 M. M. Díaz-Requejo and P. J. Pérez, *J. Organomet. Chem.*, 2005, **690**, 5441.
47 (*a*) P. Rodríguez, A. Caballero, M. M. Díaz-Requejo, M. C. Nicasio and P. J. Pérez, *Org. Lett.*, 2006, **8**, 557; (*b*) P. Rodríguez, E. Álvarez, M. C. Nicasio and P. J. Pérez, *Organometallics*, 2007, **26**, 6661; (*c*) D. L. Reger, J. E. Collins, A. L. Rheingold and L. M. Liable-Sands, *Organometallics*, 1996, **15**, 2029.
48 4-Methylbenzenesulfonyl azide, 4-methoxybenzene sulfonyl azide and benzenesulfonyl azide were prepared as described in: J. V. Ruppel, J. E. Jones, C. A. Huff, R. M. Kamble, Y. Chen and X. P. Zhang, *Org. Lett.*, 2008, **10**, 1995. 2-Nitrobenzenesulfonyl azide and naphthalene-1-sulfonyl azide were prepared as published in: J. Waser, B. Gaspar, H. Nambu and E. M. Carreira, *J. Am. Chem. Soc.*, 2006, **128**, 11693.