Bis(μ-iodo)bis[(−)-sparteine]-dicopper: A Versatile Catalyst for Direct *O*-Arylation and *O*-Alkylation of Phenols and Aliphatic Alcohols with Haloarenes

Ponnam Satyanarayana,[1]
Hariharasarma Maheswaran,*[1]
Mannepalli Lakshmi Kantam,[1]
and Suresh Bhargava[2]

[1]Inorganic and Physical Chemistry Division, Indian Institute of Chemical Technology, Hyderabad-500007, India

[2]School of Applied Sciences, RMIT University, Melbourne, Australia

Received January 5, 2011
E-mail: maheswaran_dr@yahoo.com

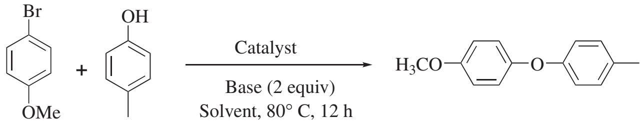
The easy to prepare dimeric bis(μ-iodo)bis[(−)-sparteine]-dicopper ([CuI{(−)-spa}]$_2$ complex) is shown to be versatile catalyst for *O*-arylation and *O*-alkylation with various aryl halides with phenols and aliphatic alcohols respectively, including less reactive aryl chlorides, such as chlorobenzene under mild conditions.

Many synthetically challenging and biologically important compounds, for example isodityrosin family and derivatives such as vancomycin and antitumoral bouvardin contain diaryl ether and aryl alkyl ether groups in their skeletal framework.[1] Both diaryl ether and aryl alkyl ether moieties have been shown to be prevalent in agrochemicals, pesticides, fragrances, cosmetics, solvents, and materials.[2,3]

Traditionally, copper-catalyzed Ullmann coupling reaction has been used for the synthesis of diaryl ethers by using aryl alcohols and aryl halides. Unfortunately, these Ullmann coupling reactions require stoichiometric amounts of copper, high temperatures, and harsh reaction conditions.[4] In addition, these Ullmann reactions are very sensitive to the substituent groups on the aryl halides and often give poor yields for the desired products.[4] Other protocols involves palladium-catalyzed synthesis of diaryl ethers from corresponding aryl halides and aryl alcohols or their sodium salts.[5] However, this methodology suffers from disadvantages such as moisture sensitivity, high oxophilicity associated with phosphine ligands, the use of expensive palladium metal catalyst, and environmental toxicity. These disadvantages have rendered palladium-based protocols unpopular, in particular, for large-scale reactions.[6]

During last few years, significant improvements have been made for the synthesis of diaryl ethers using more attractive copper-catalyzed Ullmann type *O*-arylation/*O*-alkylation methods using external supporting ligand additives. These external additives are thought to act as ligands to copper, and increase the efficiency of the Ullmann reaction by increasing the solubility of the copper salts by preventing their aggregation. In this direction, many researchers showed copper-catalyzed *O*-arylation reactions in the presence of organic additives such as ethylene glycol diacetate,[7a] 8-hydroxyquinoline,[7b] 1-naphthoic acid,[7c] triphenylphosphine,[7d] 2,9-dimethyl-1,10-phenanthroline,[7e] 2,2,6,6-tetramethylheptane-3,5-dione,[7f] (2*S*,4*R*)-4-hydroxyproline,[7g] the tripod ligand such as 1,1,1-tris(hydroxymethyl)ethane,[7h] chelating ligands like Chxn-Py-Al, salicylaldoxime, dimethyldioxime,[7i] silica-supported Cu(II),[7j] 1,10-phenanthroline,[7k] β-ketoester,[7l] phosphazene P$_4$-*t*-Bu base,[7m] bipyridyl complex,[7n] 1,1′-binaphthyl-2,2′-diol,[7o] 1,1′-binaphthyl-2,2′-diamine (BINAM),[7p] and *N*,*N*-dimethylglycine,[7q,7r] and tetraethyl orthosilicate as solvent.[8]

Table 1. Screening of Reaction Parameters for Copper(I)-Catalyzed *O*-Arylation of *p*-Bromoanisole and *p*-Cresol



Entry	Catalyst	Solvent	Base	Yield/%[d)]
1	CuI[a)]	DMSO	K_2CO_3	85
2	Cu_2O[a)]	DMSO	K_2CO_3	58
3	CuBr[a)]	DMSO	K_2CO_3	55
4	CuCl[a)]	DMSO	K_2CO_3	50
5	[CuI{(−)-spa}]$_2$[b)]	DMSO	K_2CO_3	93
6	[CuI{(−)-spa}]$_2$[b)]	DMSO	Cs_2CO_3	85
7	[CuI{(−)-spa}]$_2$[b)]	DMSO	K_3PO_4	75
8	[CuI{(−)-spa}]$_2$[b)]	DMF	K_2CO_3	42
9	[CuI{(−)-spa}]$_2$[b)]	NMP	K_2CO_3	ND[e)]
10	[CuI{(−)-spa}]$_2$[b)]	1,4-Dioxane	K_2CO_3	ND[e)]
11	[CuI{(−)-spa}]$_2$[b)]	Toluene	K_2CO_3	ND[e)]
12	CuI[c)]	DMSO	K_2CO_3	ND[e)]

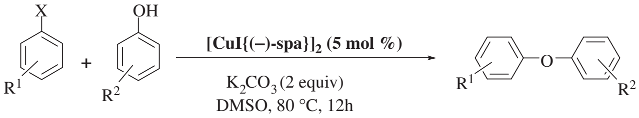
a) Reactions (Entries 1–4) were performed on a 1.0 mmol scale with catalyst (0.1 mmol), (−)-sparteine (0.1 mmol), *p*-bromoanisole (1.0 mmol), *p*-cresol (1.0 mmol), base (2.0 mmol) in 3 mL solvent at 80 °C for 12 h. b) Reactions (Entries 5–11) were performed on a 1.0 mmol scale with preformed bis(μ-iodo)bis[(−)-sparteine]-dicopper(I) complex (5.0 mol %), *p*-bromoanisole (1.0 mmol), *p*-cresol (1.0 mmol), base (2.0 mmol) in 3 mL solvent at 80 °C for 12 h. c) Reaction (Entry 12) was carried out with cuprous iodide (0.1 mmol) without (−)-sparteine. d) Isolated yields after silica gel column chromatography. e) Product not detected.

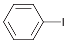
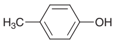
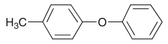
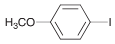
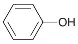
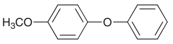
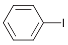
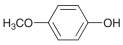
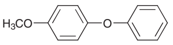
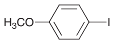
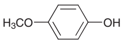
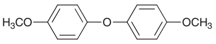
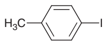
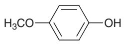
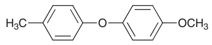
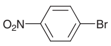
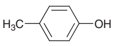
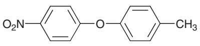
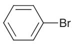
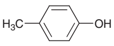
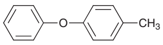
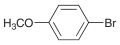
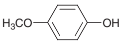
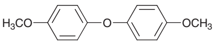
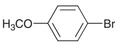
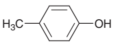
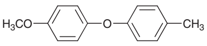
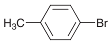
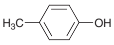
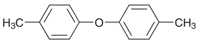
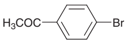
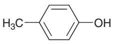
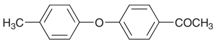
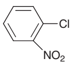
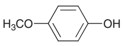
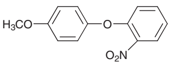
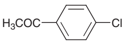
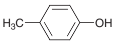
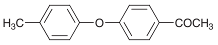
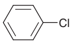
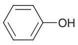
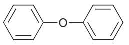
The above advances in the field of Ullmann coupling are not sufficient as most of the reactions still require long reaction times, high reaction temperatures (>120 °C), and in some cases, very high catalytic loading. In particular, the coupling of aryl bromides with aliphatic alcohols does not provide the alkyl aryl ether at all or only provides poor yields or the relative catalyst amount or the temperature has to be increased to improve the yields.[7k,7r] Thus, there are greater needs to develop new and improved catalytic processes for *O*-arylation and *O*-alkylation reactions with aryl halide and phenol or alcohols as coupling partners to further improve the efficiency and generality of the copper-catalyzed coupling of phenols and alcohols with aryl halides.

We have recently identified (−)-sparteine as new efficient supporting ligand for copper-catalyzed direct *N*-arylation reactions of various NH-heterocycles and aryl halides.[9] It is to be noted that (−)-sparteine contains tertiary nitrogen atoms, which makes N-donor site poor σ-donors; which is well-known to result in larger thermodynamic stabilization of catalytically active lower-valent Cu(I) species.[10] It is very likely that such poor σ-donor characteristics of the (−)-sparteine ligand additive play an important role in

Published on the web July 2, 2011; doi:10.1246/bcsj.20110001

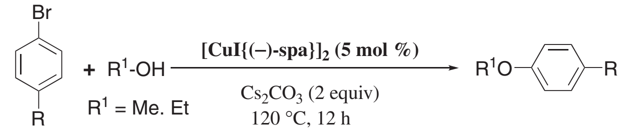
Table 2. Direct *O*-Arylation Reactions of Phenols with Various Aryl Halides Catalyzed by Bis(μ-iodo)bis[(−)-sparteine]-dicopper(I)

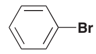
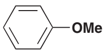
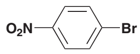
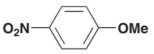
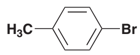
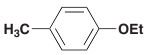
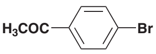
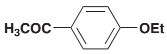
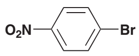
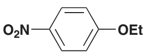
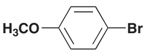
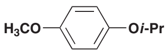
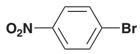
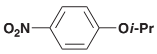
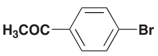
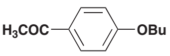
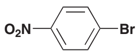
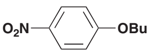
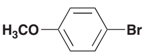
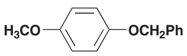


Entry[a)]	Aryl halide	Aryl alcohol	Product	Yield /%[b)]
1				91
2				88
3				89
4				85
5				85
6				92[c)]
7				89
8				83
9				93
10				84
11				92
12				68
13				71
14				62[d)]

a) Reactions were performed on a 1.0 mmol scale with preformed bis(μ-iodo)bis[(−)-sparteine]dicopper complex (5.0 mol %), phenol (1.0 mmol), aryl halide (1.0 mmol), K_2CO_3 (2.0 mmol) in 3.0 mL DMSO at 80 °C for 12 h. b) Isolated yields after silica gel column chromatography reaction was carried out at 110 °C for 16 h. c) Reaction (Entries 1–6) was carried out for 8 h. d) Reaction was carried out at 110 °C for 16 h.

Table 3. Direct *O*-Alkylation Reactions of Aliphatic Alcohols with Various Aryl Halides Catalyzed by Bis(μ-iodo)bis[(−)-sparteine]dicopper(I)



Entry[a)]	Aryl halide	Alcohol	Product	Yield /%[b)]
1		MeOH		65
2		MeOH		87
3		EtOH		62
4		EtOH		81
5		EtOH		86
6		*i*-PrOH		61[c)]
7		*i*-PrOH		85[c)]
8		*n*-BuOH		78[c)]
9		*n*-BuOH		79[c)]
10		$PhCH_2OH$		75

a) Reactions were performed on a 1.0 mmol scale with preformed bis(μ-iodo)bis[(−)-sparteine]dicopper complex (5.0 mol %), aliphatic alcohols (1.5 mL), aryl halide (1.0 mmol), Cs_2CO_3 (2.0 mmol) at 120 °C for 12 h. b) Isolated yields after silica gel column chromatography. c) Reaction performed using 15 mol % of catalyst.

promoting the reaction of the copper-catalyzed *N*-arylation reaction for a range of aryl halide and N-heterocycle substrate combinations. Notably, superior performance was observed when a preformed dimeric $[CuI\{(-)\text{-spa}\}]_2$ complex (bis(μ-iodo)bis[(−)-sparteine)]-dicopper) with a discrete Cu_2X_2 core were employed as catalysts.[11] As a natural extension of our studies, herein, we present our findings that such discrete and dimeric $[CuI\{(-)\text{-spa}\}]_2$ complexes efficiently catalyze direct *O*-arylation reaction (C–O coupling reactions) between various aryl halides including less reactive chlorobenzene and phenol or aliphatic alcohol as coupling partners at much lower temperature, and with larger substrate scope. The results from these studies form the focus of this paper.

Initially, *p*-bromoanisole and *p*-cresol were chosen as model substrates for optimization studies for the *O*-arylation reactions, and these substrates were subjected to various reaction conditions using copper(I) salts in combination with (−)-sparteine under in situ conditions. The results of these studies are summarized in Table 1. As seen in Table 1, a variety of cuprous salts such as CuI, CuBr, CuCl, and Cu_2O promote coupling reaction with K_2CO_3 as base in DMSO at 80 °C. These results showed that the choice of copper salts has profound effect on the yield of the desired product. The yield was only moderate when the reaction was carried out with different cuprous salts such as Cu_2O, CuBr, and CuCl (Table 1, Entries 2–4). However, there was a remarkable improvement in the yield when the reaction was performed using CuI as the copper source (Table 1, Entry 1). Further, when preformed dimeric $[CuI\{(-)\text{-spa}\}]_2$ complex was evaluated as catalyst for the reaction, an excellent yield for the desired coupled product (Table 1, Entry 5) was obtained. Thereafter, further screening studies were carried out using preformed $[CuI\{(-)\text{-spa}\}]_2$ catalyst for finding the appropriate base for the reaction (Table 1, Entries 5–7). Among various bases that were screened, for the reaction, a comparatively high yield of the coupled product was obtained when K_2CO_3 was used as base. Similarly, the choice of the solvent also has a profound effect on the yield of the reaction. For example, the reaction failed to proceed in solvents like NMP, 1,4-dioxane, and toluene, whereas only moderate yield was obtained in DMF (Table 1, Entries 8–11). Notably, yields as high as 93% were obtained when the reaction was carried out in DMSO (Table 1, Entry 5).

Given these optimized reaction conditions in hand, the direct *O*-arylation reactions of phenols with structurally divergent haloarenes were studied. As depicted in Table 2, this protocol is rather general in nature for the reactions of electron-rich and electron-deficient haloarenes with phenols. The reactions of aryl iodides with phenols were rather fast, and their coupling reactions gave excellent yields (Table 2, Entries 1–5). The reaction of electron-deficient aryl halides such as *p*-bromonitrobenzene proceeds faster and furnished excellent yield of the product (Table 2, Entry 6). In contrast, the reaction of electron-rich aryl halides like *p*-bromoanisole and *p*-bromotoluene gave excellent yields (Table 2, Entries 9 and 10). It is interesting to note that this catalytic system works fairly for the *O*-arylation reaction of activated chloroarene substrates such as *o*-chloronitrobenzene and 1-(4-chlorophenyl)ethanone (4-chloroacetophenone) gave good yields (Table 2, Entries 12 and 13), and difficult unactivated substrates like chlorobenzene and phenol (Table 2, Entry 14) albeit at slightly higher temperature (110 °C).

In the hope of broadening the scope of this protocol, we have checked the efficiency of our catalyst system $[\mathrm{CuI}\{(-)\text{-spa}\}]_2$ with more challenging substrates that are rather difficult to couple using aliphatic alcohols instead of phenol as coupling partner. As illustrated in Table 3, the reactions of aryl bromides with aliphatic alcohols proceed smoothly, albeit at slightly higher temperature (120 °C). As can be seen from Table 3, in general, the reaction of activated aryl bromides with aliphatic alcohols afforded better yields compared to those of electron-rich aryl bromides. For example, bromobenzene and *p*-bromonitrobenzene reacted readily with methanol and give corresponding cross-coupled products in good yields (Table 3, Entries 1 and 2). Similarly, *p*-bromotoluene, *p*-bromoacetophenone, and *p*-bromonitrobenzene reacted with ethanol under optimized reaction conditions and give good yields for the cross-coupled products (Table 3, Entries 3–5). As was the case with methanol and ethanol as coupling partners, the reactions of aryl halides with aliphatic alcohols such as 2-propanol, and 1-butanol also gave the corresponding cross-coupled products in excellent yields (Table 3, Entries 6–9). Finally, this method was successfully applied for the reaction of benzyl alcohol with *p*-bromoanisole which gave 1-(benzoyloxy)-4-methoxybenzene in good yield (Table 3, Entry 10).

In summary, the easy to prepare, dimeric bis(μ-iodo)bis[(−)-sparteine]dicopper $[\mathrm{CuI}\{(-)\text{-spa}\}]_2$ complex, is shown to be versatile catalyst for C–O coupling reactions of phenols and aliphatic alcohols with various aryl halides. An important finding is that the reaction of aryl halides including activated aryl chloride substrates with various phenols proceeds smoothly and provides good to excellent yields for the coupled products at temperatures as low as 80 °C with K_2CO_3 as base in DMSO. Another important finding is that the present protocol is extendable to less reactive deactivated aryl chloride substrates such as chlorobenzene for coupling with phenolic substrates albeit at slightly higher temperature (110 °C).

P.S.N. thanks DST New Delhi for financial assistance.

Supporting Information

General synthesis procedure for *O*-arylation, *O*-alkylation reactions and NMR spectral data for all products are provided. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

References

1 a) J. Zhu, *Synlett* **1997**, 133. b) D. L. Boger, M. A. Patane, J. Zhou, *J. Am. Chem. Soc.* **1994**, *116*, 8544.

2 a) *The Pesticide Manual: Incorporating the Agrochemicals Handbook*, 10th ed., ed. by C. Tomlin, Crop Protection Publications, Farham, U.K., **1994**. For selected examples of medicinally important diaryl ethers, see: b) M. E. Jung, J. C. Rohloff, *J. Org. Chem.* **1985**, *50*, 4909. c) S. B. Singh, G. R. Pettit, *J. Org. Chem.* **1990**, *55*, 2797. d) V. H. Deshpande, N. J. Gokhale, *Tetrahedron Lett.* **1992**, *33*, 4213. e) D. E. Evans, K. M. DeVries, in *Glycopeptide Antibiotics*, ed. by R. Nagarajan, Marcel Decker, New York, **1994**, pp. 63–104. f) S. Zenitani, S. Tashiro, K. Shindo, K. Nagai, K. Suzuki, M. Imoto, *J. Antibiot.* **2003**, *56*, 617. g) P. Cristau, J.-P. Vors, J. Zhu, *Tetrahedron* **2003**, *59*, 7859.

3 a) N. Yamazaki, I. Washio, Y. Shibasaki, M. Ueda, *Org. Lett.* **2006**, *8*, 2321. b) M. Asano, M. Inoue, T. Katoh, *Synlett* **2005**, 2599. c) H. Jiang, J.-M. Léger, I. Huc, *J. Am. Chem. Soc.* **2003**, *125*, 3448. d) C. Bolm, J. P. Hildebrand, K. Muñiz, N. Hermanns, *Angew. Chem., Int. Ed.* **2001**, *40*, 3284. e) B. Cao, H. Park, M. M. Joullié, *J. Am. Chem. Soc.* **2002**, *124*, 520. f) T. Temal-Laïb, J. Chastanet, J. Zhu, *J. Am. Chem. Soc.* **2002**, *124*, 583. g) S. Kawata, M. Harima, *Tetrahedron Lett.* **1998**, *39*, 8707.

4 a) F. Ullmann, *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853. b) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359. c) S. V. Ley, A. W. Thomas, *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

5 a) J. S. Sawyer, *Tetrahedron* **2000**, *56*, 5045. b) J. F. Hartwig, *Angew. Chem., Int. Ed.* **1998**, *37*, 2046; J. F. Hartwig, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 1, **2002**. c) J. F. Hartwig, *Pure Appl. Chem.* **1999**, *71*, 1417. d) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 852. e) J. F. Hartwig, *Synlett* **1997**, 329. f) D. Barañano, G. Mann, J. F. Hartwig, *Curr. Org. Chem.* **1997**, *1*, 287. Recent reports on Palladium-catalyzed aryl ether synthesis, see: g) A. V. Vorogushin, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 8146. h) D. Prim, J.-M. Campagne, D. Joseph, B. Andrioletti, *Tetrahedron* **2002**, *58*, 2041.

6 Q. Shelby, N. Kataoka, G. Mann, J. Hartwig, *J. Am. Chem. Soc.* **2000**, *122*, 10718.

7 a) H. Weingarten, *J. Org. Chem.* **1964**, *29*, 3624. b) R. Oi, C. Shimakawa, S. Takenaka, *Chem. Lett.* **1988**, 899; P. J. Fagan, E. Hauptman, R. Shapiro, A. Casalnuovo, *J. Am. Chem. Soc.* **2000**, *122*, 5043. c) J.-F. Marcoux, S. Doye, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 10539. d) R. K. Gujadhur, D. Venkataraman, *Synth. Commun.* **2001**, *31*, 2865. e) R. K. Gujadhur, C. G. Bates, D. Venkataraman, *Org. Lett.* **2001**, *3*, 4315. f) E. Buck, Z. J. Song, D. Tschaen, P. G. Dormer, R. P. Volante, P. J. Reider, *Org. Lett.* **2002**, *4*, 1623. g) F. Monnier, M. Taillefer, *Angew. Chem., Int. Ed.* **2008**, *47*, 3096. h) Y.-J. Chen, H.-H. Chen, *Org. Lett.* **2006**, *8*, 5609. i) H.-J. Cristau, P. P. Cellier, S. Hamada, J.-F. Spindler, M. Taillefer, *Org. Lett.* **2004**, *6*, 913. j) T. Miao, L. Wang, *Tetrahedron Lett.* **2007**, *48*, 95. k) M. Wolter, G. Nordmann, G. E. Job, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 973. l) X. Lv, W. Bao, *J. Org. Chem.* **2007**, *72*, 3863. m) C. Palomo, M. Oiarbide, R. López, E. Gómez-Bengoa, *Chem. Commun.* **1998**, 2091. n) J. Niu, H. Zhou, Z. Li, J. Xu, S. Hu, *J. Org. Chem.* **2008**, *73*, 7814. o) A. B. Naidu, E. A. Jaseer, G. Sekar, *J. Org. Chem.* **2009**, *74*, 3675. p) A. B. Naidu, O. R. Raghunath, D. J. C. Prasad, G. Sekar, *Tetrahedron Lett.* **2008**, *49*, 1057; A. B. Naidu, G. Sekar, *Tetrahedron Lett.* **2008**, *49*, 3147. q) D. Ma, Q. Cai, *Org. Lett.* **2003**, *5*, 3799. r) H. Zhang, D. Ma, W. Cao, *Synlett* **2007**, 243.

8 Y. Zhao, Y. Wang, H. Sun, L. Li, H. Zhang, *Chem. Commun.* **2007**, 3186.

9 a) H. Maheswaran, G. G. Krishna, K. L. Prasanth, V. Srinivas, G. K. Chaitanya, K. Bhanuprakash, *Tetrahedron* **2008**, *64*, 2471. b) H. Maheswaran, K. L. Prasanth, G. G. Krishna, K. Ravikumar, B. Sridhar, M. L. Kantam, *Chem. Commun.* **2006**, 4066. c) H. Maheswaran, G. G. Krishna, V. Srinivas, K. L. Prasanth, C. V. Rajasekhar, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 515.

10 a) E. R. Strieter, B. Bhayana, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 78. b) G. O. Jones, P. Liu, K. N. Houk, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132* 6205. c) G. Golub, H. Cohen, P. Paoletti, A. Bencini, L. Messori, I. Bertini, D. Meyerstein, *J. Am. Chem. Soc.* **1995**, *117*, 8353. d) D. Meyerstein, *Coord. Chem. Rev.* **1999**, *185–186*, 141. e) P. V. Bernhardt, *J. Am. Chem. Soc.* **1997**, *119*, 771. f) P. V. Bernhardt, *Inorg. Chem.* **2001**, *40*, 1086.

11 Copper(I) ion shows diversity in coordination geometries, and is capable of attaining linear, triangular planar, or tetrahedral structures. For a comprehensive review on haloamine–copper(I) complexes, see: a) K. G. Caulton, G. Davies, E. M. Holt, *Polyhedron* **1990**, *9*, 2319. b) A. Johansson, M. Vestergren, M. Håkansson, B. Gustafsson, S. Jagner, *New J. Chem.* **2004**, *28*, 1000.