Re-Mediated C−C Coupling of Pyridines and Imidazoles

Maialen Espinal Viguri,[‡] Miguel A. Huertos,[‡,†] Julio Pérez,*[‡] Lucía Riera,*[§] and Irene Ara[§]

[‡]Departamento de Química Orgánica e Inorgánica-IUQOEM, Universidad de Oviedo-CSIC, C/Julián Clavería, 8, 33006 Oviedo-Spain

[§]Instituto de Síntesis Química y Catálisis Homogénea, Departamento de Química Inorgánica, CSIC-Universidad de Zaragoza, C/Pedro Cerbuna, 12, 50009 Zaragoza, Spain

S *Supporting Information*

ABSTRACT: Rhenium tricarbonyl complexes with three *N*-heterocyclic ligands (*N*-alkylimidazoles or pyridines) undergo deprotonation with $KN(SiMe_3)_2$ and then oxidation with AgOTf to afford complexes with pyridylimidazole or bipyridine bidentate ligands resulting from deprotonation, C−C coupling and rearomatization.

Heteroaromatic biaryls are important structural motifs found in many natural products, pharmaceuticals, agrochemicals, and functional materials.[1] Classical palladium-catalyzed cross-coupling methods require previously activated substrates, a heteroaryl halide and an organometallic species.[2] In the last years, catalytic direct arylations have emerged which avoid the introduction of functional groups by C−H activation prior to cross-coupling of at least one of the two coupling partners.[3] This strategy is especially useful for heteroaromatic substrates as their prefunctionalizations are often difficult (organometallic derivatives are often troublesome to prepare and unstable).[4] Recently, this concept has been developed one step further designing dehydrogenative cross-coupling of two heteroarenes.[5] However, to date, efficient C−H/C−H cross-coupling between very similar partners remains a challenge because of their tendency to undergo homocoupling.[6]

Herein, we report the metal-templated synthesis of (a) pyridylimidazole complexes by selective cross-coupling of pyridines and imidazoles, and (b) 2,2′-bipyridine complexes by C−C coupling of two pyridyl ligands. In both cases, coordination to the same organometallic fragment is the only previous functionalization.

Metal coordination of *N*-heterocycles can increase the acidity of their α-CH groups,[7] and make them more electrophilic.[8] We decided to explore if the combination of both features could be used to effect C−C coupling between two *N*-heterocyclic ligands coordinated to the same metal fragment.

The reaction of $[Re(OTf)(CO)_3(N\text{-MeIm})_2]$ (*N*-MeIm = *N*-methylimidazole) with the equimolar amount of $NaBAr'_4$ (Ar′ = 3, 5-bis(trifluoromethyl)phenyl)[9] and either pyridine (py) or γ-picoline (pic) afforded the new compounds $[Re(CO)_3(N\text{-MeIm})_2(pyR)]BAr'_4$ (R = H, **1a**; Me, **1b**; see Scheme 1), which were characterized by IR, and NMR.[10] The IR spectra showed the typical two intense ν_{CO} bands pattern for *fac*-$\{Re(CO)_3\}$ complexes (e.g., at 2028 and 1914 cm^{-1} for **1a**). ^{1}H and ^{13}C NMR spectra indicate the incorporation of one pyridinic ligand per rhenium fragment.

Scheme 1. Synthesis of $[Re(CO)_3(N\text{-MeIm})_2(pyR)]BAr'_4$ Compounds
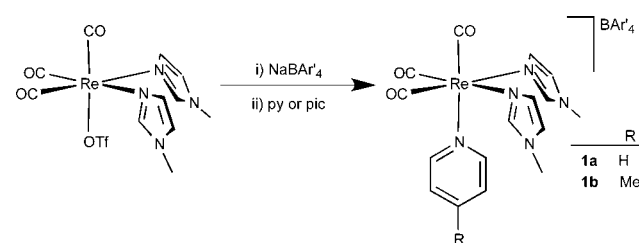
When compound **1a** was treated with $KN(SiMe_3)_2$ in THF at −78 °C, a neutral product was formed, as shown by a large shift to lower wavenumbers of the ν_{CO} IR (to 2004, 1890, and 1877 cm^{-1}), which was too unstable for isolation. Addition of silver trifluoromethanesulfonate afforded compound **2a** along with metallic silver (Scheme 2).

Scheme 2. Reactivity of $[Re(CO)_3(N\text{-MeIm})_2(pyR)]BAr'_4$ Compounds
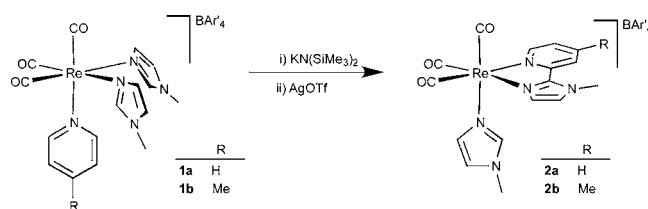
The solid-state structure of **2a**, determined by X-ray diffraction (see Figure 1a),[11] despite its low quality, shows that the cationic complex consists of a *fac*-$\{Re^I(CO)_3\}$ fragment bonded to *N*-MeIm, and 2-pyridylimidazole ligands. The latter results from the C−C coupling of the imidazole C2, once deprotonated, and one pyridine C_{ortho} followed by oxidative rearomatization. Pyridylimidazoles, usually synthesized via de novo construction of the imidazole ring,[12] are used as ligands in the preparation of luminiscent complexes, including two rhenium tricarbonyl examples.[13] The γ-picoline derivative **1b** afforded, under the same reaction conditions, complex **2b**, which was fully characterized, including an X-ray structure determination (Figure 1b),[14] that confirms the formation of the bidentate ligand. No side reactions affecting the methyl group
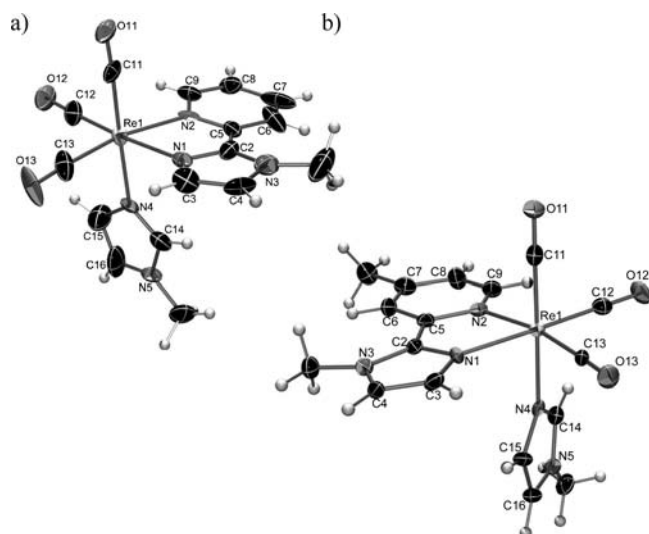
Figure 1. (a) Molecular structure of the cationic complex of **2a**; (b) molecular structure of the cation in **2b**.

of the γ-picoline unit were detected. The pyridine and imidazole rings are planar, as expected, and nearly coplanar, with a dihedral angle of 4.1(0.4)°. The Re−N(1) [2.180(6) Å] is longer than the Re−N(2) bond distance [2.132(5) Å], reflecting the stronger basicity of the imidazole and both distances are virtually identical to those found for the only pyridylimidazole rhenium(I) compound structurally characterized.[13a]

A growing number of pyridylimidazole complexes are known; however, their chemistry remains somewhat underdeveloped as a result of synthetic difficulties.[15] No precedent of their metal-templated synthesis has been reported, and the synthesis of bidentate ligands via C−C coupling of monodentate ligands remains rare.[16] The highly reactive Sc(III) complex [(NN^{fc})Sc(η^2-N,C-1-methylimidazolyl)(N-MeIm)] (NN^{fc} = fc-(NSi^{t}BuMe$_2$)$_2$, fc = 1,1′-ferrocenylene) does not react with pyridines, but does react with 2,2′-bipyridine to yield the coupled product which does not undergo further transformation (rearomatization or ring-opening) even upon prolonged heating.[16c]

To test the generality of the reaction, we extended our study to the bis(pyridyl) complex [Re(CO)$_3$(dmap)$_2$(N-MeIm)]-BAr′$_4$ (dmap = 4-dimethylaminopyridine, **3**).[10] Treatment of **3** with the stoichiometric amount of KN(SiMe$_3$)$_2$ in THF at −78 °C followed by reaction with AgOTf yielded the cationic pyridylimidazole complex **4**, analogously to the formation of **2a** and **2b**. This shows that the employment of the more electron-rich dmap ligand did not prevent the proposed (see below) nucleophilic attack of the imidazol-2-yl, and the formation of pyridylimidazole ligand.

Note that, regardless of the particular composition of the cationic complex (two imidazoles and one pyridine, as in **1a,b** or one imidazole and two pyridines, as in **3**), no homocoupling products (containing biimidazole or bipyridine chelates) have been detected, suggesting a clear-cut difference between the two type of ligands in that N-methylimidazole is significantly more acidic, and pyridines are more electrophilic.

In the absence of mechanistic studies, we speculate that the formation of the pyridylimidazole complexes occurs via deprotonation of the imidazole C2−H, nucleophilic attack of the deprotonated carbon onto a pyridine *ortho* carbon to afford

a dearomatized intermediate,[17] which then would be oxidized by Ag$^+$,[18,19] the latter step encouraged by the restoration of the aromaticity and the conjugation between the two adjacent aromatic cycles.[20] We have encountered that 2 equiv of AgOTf are needed for the reactions to reach completion. This could be an indication of two 1e$^−$ oxidations: the neutral C−C coupled product would undergo one electron oxidation to a radical cation, followed by deprotonation to a radical, and oxidation to the observed product. The base for the second deprotonation (only 1 equiv of KN(SiMe$_3$)$_2$ was used) would be HN(SiMe$_3$)$_2$ formed in the first deprotonation step.[21] An alternative mechanism involving initial 2e$^−$ oxidation of Re(I) to Re(III) by Ag(I), and subsequent deprotonation of the 2-pyridyl group, which would rearomatize the ligand and return the metal oxidation state to (I) could not be ruled out.

Finally, we wondered if this reactivity could be extended to tris(pyridyl) derivatives to get, after the dehydrogenative C−C coupling reaction, bipyridine (bipy) ligands. There are obvious difficulties: (1) as for the site of the deprotonation, pyridines are less acidic than N-alkylimidazoles;[22] and (2) monodentate pyridines could be more problematic electrophiles because of their lability that could promote attack to the metal instead. 2,2′-bipyridines are one of the most versatile bidentate ligands in organometallic and inorganic chemistry.[23] Heterogeneous catalytic pyridine homocoupling is not applicable to 4-substituted pyridines,[24] and the other major method to prepare bipys, transition-metal catalyzed cross-coupling reactions require prefunctionalization of the substrates.[23,25]

Compound [Re(CO)$_3$(dmap)$_3$]OTf (**5**), prepared straightforwardly by thermal substitution from [Re(OTf)(CO)$_5$] and dmap, reacted with the strong base KN(SiMe$_3$)$_2$ and AgOTf to afford the coupling product [Re(CO)$_3$(bipy′)(dmap)]OTf (bipy′ = 4,4′-bis(dimethylamino)-2,2′-bipyridine, **6**; see Scheme 3).

Scheme 3. Formation of the Bipyridine Derivative 6
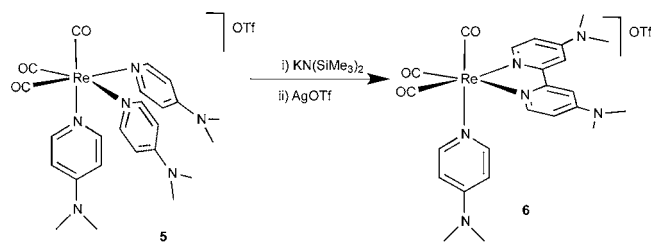
The new compound **6** (Figure 2) displays a 2,2′-bipyridine ligand showing that the deprotonation of an *ortho* C−H group of a pyridyl ligand has been achieved, a reaction that, as far as we know, lacks precedents. In fact, there are just a few examples of metal-mediated coupling of pyridines, restricted to alkali or very reactive early transition metals.[16a,26] Coordination of metals fragments in the rare κ^2 and κ^6 coordination modes have been employed for enhancing the reactivity of pyridines.[27] In the majority of its metal complexes, pyridines are κ^1(N) coordinated. Nucleophilic attack to nonfunctionalized pyridine in such complexes has been the subject of a long-standing controversy,[28] and clear-cut evidence remains scarce.

In summary, unprecedented intramolecular C−C coupling via deprotonation/oxidation sequences allowed the synthesis of complexes of pyridylimidazole chelates from complexes containing monodentate, nonfunctionalized pyridine and imidazole ligands. Extension of this methodology to tris-
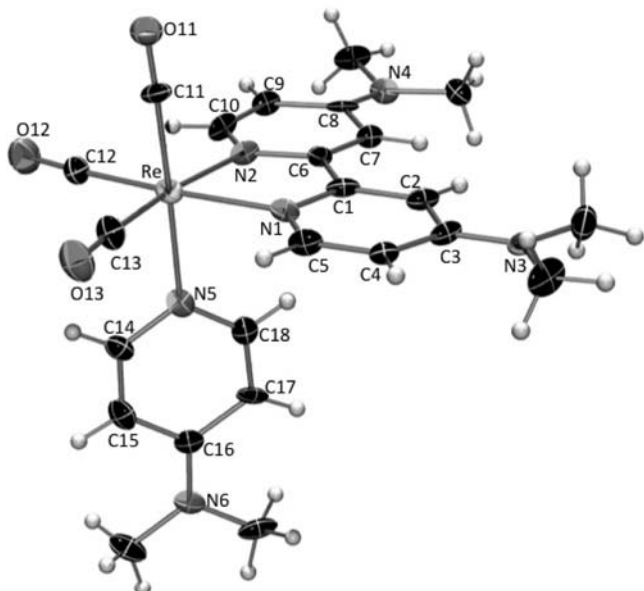
Figure 2. Molecular structure of the cationic complex of **6**.[29]

(pyridyl) species afforded a 4,4′-disubstituted 2,2′-bipyridine, which synthesis is not well established nowadays.

ASSOCIATED CONTENT

Supporting Information

Crystallographic information of compounds **2a**, **2b**, **I** and **6**, and experimental details for the synthesis of **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
riera@unizar.es; japm@uniovi.es

Present Address
†Department of Chemistry, Inorganic Chemistry Laboratories, South Parks Road, University of Oxford, Oxford, U.K. OX1 3QR.

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

REFERENCES

(1) See, for example: (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (c) For a recent review focused on the coupling of two heteroarenes: Zhao, D.; You, J.; Hu, C. *Chem.—Eur. J.* **2011**, *17*, 5466.

(2) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461 and references therein.

(3) Recent reviews on this topic: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677.

(4) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073 and references therein.

(5) (a) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (b) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (c) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (d) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (e) Cho, S. J.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (f) Han, W.; Mayer, P.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 2178. (g) Bugaut, X.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7479.

(6) (a) Li, Y.; Jin, J.; Qian, W.; Bao, W. *Org. Biomol. Chem.* **2010**, *8*, 326. (b) Truong, T.; Alvarado, J.; Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 1200. (c) Monguchi, D.; Yamamura, A.; Fujiwara, T.; Omete, T.; Mori, A. *Tetrahedron Lett.* **2010**, *51*, 850.

(7) (a) Buncel, E.; Clement, O.; Onyido, I. *J. Am. Chem. Soc.* **1994**, *116*, 2679. We have noted this effect for transition metal complexes of *N*-alkylimidazoles: (b) Pérez, J.; Riera, L.; Ion, L.; Riera, V.; Anderson, K. M.; Steed, J. W.; Miguel, D. *Dalton Trans.* **2008**, 878. (c) Huertos, M. A.; Pérez, J.; Riera, L. *J. Am. Chem. Soc.* **2008**, *130*, 5662. (d) Huertos, M. A.; Pérez, J.; Riera, L.; Menéndez-Velázquez, A. *J. Am. Chem. Soc.* **2008**, *130*, 13530. (e) Huertos, M. A.; Pérez, J.; Riera, L.; Díaz, J.; López, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 6409.

(8) (a) There are a few examples in which metal coordination of α-diimines activate them towards nucleophilic attacks, see ref 7c and Tzalis, D.; Tor, Y. *Angew. Chem., Int. Ed.* **1997**, *36*, 2666. (b) For nucleophilic attack onto *N*-alkylimidazole ligands, see ref 7d.

(9) Brookhart, M.; Grant, B.; Volpe, A. F., Jr. *Organometallics* **1992**, *11*, 3920.

(10) See Supporting Information for complete experimental details.

(11) Selected crystallographic data for **2a**: $C_{48}H_{27}BF_{24}N_5O_3Re$, $M = 1374.76$, orthorhombic, $Pna2(1)$, $a = 17.071(2)$ Å, $b = 15.982(2)$ Å, $c = 18.311(1)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, 100(2) K, $V = 4995.8(11)$ Å^3, $Z = 8$. 11278 reflections measured, 7715 independent (Rint = 0.0543). $R_1 = 0.00531$, w$R_2 = 0.1211$ (all data).

(12) (a) Reeder, K. A.; Dose, E. V.; Wilson, L. J. *Inorg. Chem.* **1978**, *17*, 1071. (b) Gerber, T. I. A.; Hosten, E.; Mayer, P.; Tshentu, Z. R. *J. Coord. Chem.* **2006**, *59*, 243.

(13) (a) Wang, K.; Huang, L.; Gao, L.; Jin, L.; Huang, C. *Inorg. Chem.* **2002**, *41*, 3353. (b) Ko, C.-C.; Siu, J. W.-K.; Cheung, A. W.-Y.; Yiu, S.-M. *Organometallics* **2011**, *30*, 2701.

(14) Selected crystallographic data for **2b**: $C_{49}H_{29}BF_{24}N_5O_3Re$, $M = 1388.78$, monoclinic, $P21/c$, $a = 13.369(10)$ Å, $b = 9.4769(7)$ Å, $c = 39.453(2)$ Å, $\alpha = 90°$, $\beta = 93.559(1)°$, $\gamma = 90°$, 100(2) K, $V = 4988.8(6)$ Å^3, $Z = 4$. 41214 reflections measured, 11394 independent (Rint = 0.1108). $R_1 = 0.0511$, w$R_2 = 0.1063$ (all data).

(15) Carranza, J.; Sletten, J.; Lloret, F.; Julve, M. *Polyhedron* **2009**, *28*, 2249.

(16) (a) Soo, H. S.; Diaconescu, P. L.; Cummins, C. C. *Organometallics* **2004**, *23*, 498. (b) Lorcy, D.; Guerro, M.; Pellon, P.; Carlier, R. *Chem. Commun.* **2004**, 212. (c) Carver, C. T.; Williams, B. N.; Ogilby, K. R.; Diaconescu, P. L. *Organometallics* **2010**, *29*, 835.

(17) This reaction pattern is reminiscent of that found for the deprotonation of $[Re(CO)_3(N\text{-}N)(N\text{-}RIm)]OTf$ (N-N = bipy, phen) compounds that afforded the C−C coupling and dearomatized products, see ref 7c.

(18) Oxidatively metal-induced C-C coupling is known to occur in the presence of $1e^-$ chemical oxidants such as Ag$^+$ salts, see for example: (a) Seligson, A. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 7805. (b) Lanci, M. P.; Remy, M. S.; Kaminsky, W.; Mayer, J. M.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 15618.

(19) Ag$^+$ salts are also common additives in organic transformations, for recent examples, see refs 5c, 5e, and. (a) Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10930. (b) Chen, X.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 12364.

(20) Parenty, A. D. C.; Smith, L. V.; Pickering, A. L.; Long, D.-L.; Cronin, L. *J. Org. Chem.* **2004**, *69*, 5934.

(21) Matsuo, T.; Mayer, J. M. *Inorg.Chem.* **2005**, *44*, 2150.

(22) Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568.

20328

dx.doi.org/10.1021/ja310981m | *J. Am. Chem. Soc.* 2012, 134, 20326−20329

(23) Hapke, M.; Brandt, L.; Lützen, A. *Chem. Soc. Rev.* **2008**, *37*, 2782.

(24) Hagelin, H.; Hedman, B.; Orabona, I.; Åkermark, T.; Åkermark, B.; Klug, C. A. *J. Mol. Catal. A: Chem.* **2000**, *164*, 137 and references therein.

(25) Dehydrogenative coupling of 4-substituted pyridines yielding symmetrical bipyridines can be found in: Kawashima, T.; Takao, T.; Suzuki, H. *J. Am. Chem. Soc.* **2007**, *129*, 11006.

(26) (a) Clarke, A. J.; McNamara, S.; Meth-Cohn, O. *Tetrahedron Lett.* **1974**, *15*, 2373. (b) Deelman, B.-J.; Stevels, W. M.; Teuben, J. H.; Lakin, M. T.; Spek, A. L. *Organometallics* **1994**, *13*, 3881. (c) Carver, C. T.; Benitez, D.; Miller, K. L.; Williams, B. N.; Tkatchouk, E.; Goddard, W. A., III; Diaconescu, P. L. *J. Am. Chem. Soc.* **2009**, *131*, 10269.

(27) (a) Davies, S. G.; Edwards, A. J.; Shipton, M. R. *J. Chem. Soc., Perkin Trans.* **1991**, 1009. (b) Harrison, D. P.; Sabat, M.; Myers, W. H.; Harman, W. D. *J. Am. Chem. Soc.* **2010**, *132*, 17282.

(28) (a) Gillard, R. D. *Comments Inorg. Chem.* **1986**, *5*, 175. (b) Constable, E. C. *Inorg. Chim. Acta* **1984**, *82*, 53.

(29) Selected crystallographic data for **6**: $C_{25}H_{28}F_3N_6O_6ReS$, $M = 783.79$, triclinic, $P\overline{1}$, $a = 13.6164(8)$ Å, $b = 15.5341(9)$ Å, $c = 16.0883(11)$ Å, $\alpha = 89.142(4)°$, $\beta = 77.599(4)°$, $\gamma = 77.534(3)°$, 150.0(1) K, $V = 3243.5(3)$ Å^3, $Z = 4$. 1993 reflections used. $R_1 = 0.0976$, w$R_2 = 0.2418$ (all data).