

Versatile synthesis of chiral 6-oxoverdazyl radical ligands – new building blocks for multifunctional molecule-based magnets†

Atena B. Solea,^a Tobie Wohlhauser,^a Parisa Abbasi,^b Yvan Mongbanziama,^a
Aurelien Crochet,^c Katharina M. Fromm,^c Ghenadie Novitchi,^d Cyrille Train,^d
Melanie Pilkington^{*b} and Olimpia Mamula^{id *a}

A versatile synthetic methodology to access the first family of chiral verdazyl N,N'-chelate ligands is described and exemplified by N,N'-dimethyl-, N,N'-di-isopropyl- and N,N'-diphenyl oxoverdazyls bearing two isomers of the pinene-pyridine functional group. Their physical properties were probed by X-band EPR spectroscopy, cyclic voltammetry and DFT calculations. Preliminary reactivity studies show they can act as N,N'-chelate ligands affording a chiral 1:1 complex (3b) with CuCl₂, which was characterized by single-crystal X-ray diffraction. Variable temperature EPR studies on (3b) confirm the presence of antiferromagnetic interactions between the spins of the Cu(II) ion and the verdazyl radical.

The unique properties associated with chiral molecules and their interaction with light *inter alia* has a rich history that today plays a central role in many areas of chemistry that include organometallic, coordination compounds, metal nanoparticles and molecule-based materials.¹ The marriage of chirality with free radical chemistry has also found applications in diverse fields ranging from enantioselective catalysis² to the development of chiral radicals as building blocks for chiral organic, or hybrid organic/inorganic magnets.³ In the latter case, crystallization of chiral molecules into non-centrosymmetric space groups can confer unique physical phenomena that include ferroelectric, piezoelectric, second harmonic generation (SHG) and/or non-linear optical (NLO) properties.⁴

Furthermore, in select examples, when magnetic chirality coexists with nuclear chirality, the spatial and temporal symmetry is simultaneously broken affording a range of magneto-optical properties that includes magneto-chiral dichroism (MChD).⁵ In the field of single molecule magnets (SMMs), a promising strategy to increase the blocking temperatures is to employ radical bridging ligands to couple the large magnetic anisotropy of 4f ions.⁶ The introduction of chirality into such linkers could therefore not only facilitate strong magnetic exchange, but also afford novel multifunctional compounds where interplay between two or more physical properties may be achieved.⁷ The development of versatile synthetic routes to chiral radicals is therefore an important milestone towards multifunctional SMMs. Although a range of different stable organic radicals are known,⁸ the majority of progress in this field has focussed on synthetic routes to chiral nitronyl nitroxides.⁹ Over the past decade, verdazyl (vd) radicals have been prepared and exploited as attractive ligands for the development of molecular magnets, coordinating to a range of both d- and f-block ions.¹⁰ However, in contrast to the nitronyl nitroxides, methodologies to incorporate chirality into the vd unit have not been explored, with only one example reported in the literature to-date.¹¹ In the current paper we describe the versatile synthesis and characterization of two isomeric series of enantiopure N,N'-chelate vd radical ligands bearing (–)-pinene-pyridyl functionality, *i.e.* the (–)-5,6 series, **1a–1c** and the (–)-4,5 series, **2a–2c**, bearing different substituents at the 1,5 positions of the oxoverdazyl radical in order to modify the stereo-electronics, (Fig. 1). We also show proof-of-principle studies for future coordination chemistry through the

^aDepartment of Chemistry, University of Applied Sciences Western Switzerland (HES-SO), HEIA-FR, Péroilles 80, CH-1700 Fribourg, Switzerland.

E-mail: olimpia.mamulasteiner@hefr.ch

^bDepartment of Chemistry, Brock University, 1812 Sir Isaac Brock Way, St Catharines, Ontario L2S3A1, Canada. E-mail: mpilkington@brocku.ca

^cDepartment of Chemistry, University of Fribourg, Ch. du Musée 9, CH-1700 Fribourg, Switzerland

^dLaboratoire National des Champs Magnétiques Intenses, UPR CNRS 3228, 25, rue des Martyrs, B.P. 166 38042 Grenoble, France

†Electronic supplementary information (ESI) available: Syntheses, crystallographic data, analytical/spectroscopic data, DFT studies. CCDC 1532176–1532178 and 1811236. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8dt00840j

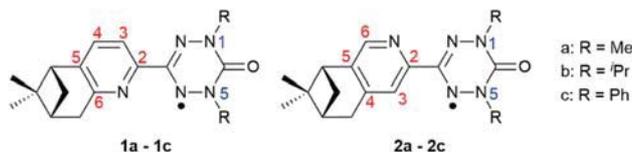


Fig. 1 Molecular structures of two families of chiral verdazyl radicals.

synthesis and structural characterization of the 1 : 1 complex **3b** prepared from the isopropyl radical ligand **2b** and CuCl₂.

An important approach to the design of chiral radicals is to utilize a range of readily accessible precursors drawn from a chiral library. In this context we targeted the preparation of chiral aldehydes, which prove to be useful precursors for a range of stable radicals including both nitronyl nitroxides¹² and verdazyls.^{8,13} The chiral (–)-5,6- and (–)-4,5-aldehyde intermediates **P1** and **P2** respectively (Scheme 1) were synthesized in three steps from (–)-myrtenal or (–)-alpha-pinene according to the procedure proposed by Bernhard *et al.*,¹⁴ and their structures confirmed by X-ray diffraction (see S2 of the ESI†). Subsequent condensation of these aldehydes with the appropriate dialkyl- or diphenyl-carbonylhydrazide in methanol afforded the corresponding tetrazinanone intermediates **T1** and **T2** in 45–85% recovered yields (Scheme 1). Although synthetic approaches to diisopropyl- and diphenyl-carbonylhydrazines have been reported previously,¹⁵ we found that Boc protection of their hydrazine precursors followed by reaction with phosgene and subsequent deprotection afforded the best yields. The solid state structure of 1,5-diisopropyl-3-(4,5-pinene)pyridine tetrazinanone, **T2b** was determined by X-ray diffraction as a representative member of this series (Fig. 2).

The compound **T2b** crystallizes in the chiral space group *P*2₁2₁2₁, with one independent molecule in the asymmetric unit. The four N atoms and the carbonyl C atom of the tetrazinanone heterocycle are close to co-planarity with the carbonyl atom C14 showing the largest displacement from the ring plane (0.174 Å), while the sp³ hybrid C atom (C1) adopts a tetrahedral geometry and is displaced out of the ring plane by 0.571 Å. The displacement of the two C atoms from the ring plane generates a “screw boat” conformation with a puckering parameter ($\theta = 68.7(7)^\circ$)¹⁶ similar to achiral pyridine and pyrazole substituted tetrazinanones.^{17,18} Previous studies on tetrazinanone derivatives place the C-substituent either equatorial¹⁷ or axial,^{17,18} with equatorial positions favoured for systems capable of undergoing intramolecular hydrogen bonding. In the case of **T2b**, the pyridine substituent at C1 adopts an equatorial position with respect to the tetrazinanone and is rotated almost perpendicular to the tetrazinanone ring (angle between the two planes: 82.55°), permitting the pyridyl N atom (N1) to form a bifurcated set of intramolecular N⋯H–N hydrogen bonds to N2 and N5 (N1⋯N2 at 2.820(8) Å and N1⋯H–N2 angle of 104(4)°; N1⋯N5 at 2.916(8) Å and N1⋯H–N5 angle of 109(4)°). Oxidation of these tetrazinanones with benzoquinone in toluene afforded the two series of 5,6- and 4,5-substituted vd radicals **1a–1c** and **2a–2c** respectively, with final yields after

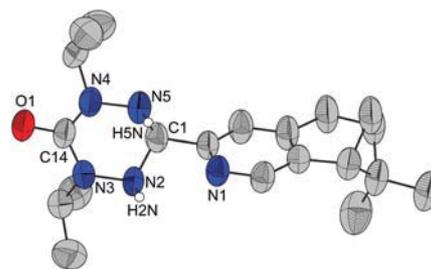
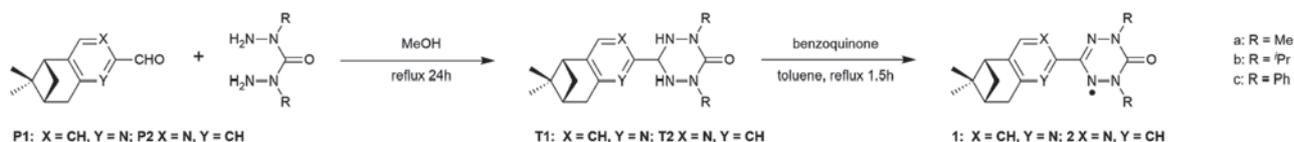


Fig. 2 Crystal structure of intermediate tetrazinanone **T2b** with thermal ellipsoids at 50% probability. The H atoms bound to C atoms have been removed for clarity.

column chromatography in the range of 10–40%. In the case of **1c**, the radical could not be separated from benzoquinone and has been attributed to formation of a stable charge-transfer salt with hydroquinone reflected in a broad charge transfer band¹⁹ centred around 430 nm in the UV-Vis spectrum which is conspicuously absent from the other derivatives in the series (see S3.3 ESI†). Although these radicals failed to provide X-ray diffraction quality crystals under a range of solvent combinations, their molecular structures were confirmed by CHN, HRMS, UV-Vis and X-band EPR spectroscopy and their chirality was confirmed by optical rotation studies. The EPR spectra of **2a–2c** (Fig. 3) illustrate the differing coupling patterns due to the R substituents along this series. Notably, the isomeric form of the pinene-pyridyl substituent does not affect the hyperfine coupling patterns.

The corresponding spectra for the 5,6-series **1a–1c** are provided in the S-3 of the ESI.† Although previous studies have established that the redox properties of vd radicals are sensitive to the nature of the bridging carbon (*e.g.*, C=O vs. CH₂) as well as the R substituents on the two N atoms,²⁰ we were interested to investigate if the substitution pattern of the chiral pinene heterocycle had any direct effect on the redox chemistry of the radicals. For this we chose to carry out electrochemical studies on the dimethyl radicals **1a** and **2b**, as representative examples from each series. As demonstrated previously, vd radicals can be reduced to the 8- π electron-containing anion and oxidized to the 6- π electron-containing cation.²⁰ From our studies, radical **1a** displays a quasi-reversible oxidation potential at +0.26 V and a quasi-reversible reduction potential at –1.5 V (*vs.* Fc/Fc⁺) (Fig. 4, left), and radical **2b** displays the same quasi reversible oxidation at +0.26 V (*vs.* Fc/Fc⁺), but the reduction at –1.5 V is irreversible (Fig. 4, right).

In this context, both radicals are fairly good electron donors; their oxidation potentials fall at the lower end of the



Scheme 1 Synthetic route to verdazyl radicals **1** and **2**.

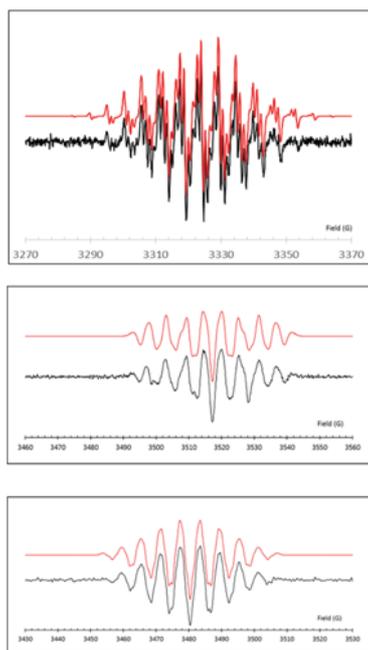


Fig. 3 Room temperature solution EPR spectra of the (–)-4,5-series (top) **2a**, R = CH₃; (middle) **2b**, R = ⁱPr and (bottom) **2c**, R = Ph in CH₂Cl₂. Experimental spectra in black and simulations in red. Simulation parameters are provided in S3.5 of the ESI.†

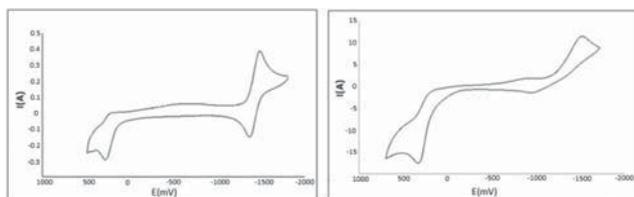


Fig. 4 Cyclic voltammery measurements of a 1 mM solution of **1a** (left) and **2a** (right) in CH₃CN. The redox event centered at 0 mV corresponds to the ferrocene/ferrocenium redox couple (ferrocene added as an internal reference). Both CVs were performed in MeCN solution at a scan rate of 100 mV s⁻¹ with 0.1 M Bu₄NBF₄ electrolyte.

range for previously reported pyridyl oxoverdazyls which suggests that they are easier to oxidize, most likely since the electron withdrawing ability of their pyridine rings are compromised by the electron donating nature of their fused pinene heterocycles. The quasi reversibility in their oxidation potentials is also not unusual and has been observed for other dimethyl substituted vd radicals measured at low scan rates. The reduction potentials of both radicals occur at negative potentials and are on the lower end of the range (–1.14 to –1.33 V) reported previously for other oxoverdazyl radicals.²⁰ The irreversibility observed in the reduction process of **2a** is also not unusual and was reported previously for a related dimethyl pyridyl oxoverdazyl radical.¹⁹

DFT and TD-DFT calculations based on geometry optimized UB3LYP-6311G structures of **2a** and **2b** reveal that in both compounds the unpaired electron density is primarily located on

the vd moiety (S-4, ESI†). The presence of the pyridyl ring clearly leads to a breaking of the symmetry and a slight asymmetry in the spin distribution within both molecules. Nevertheless, each radical can be considered as having two pairs of near-equivalent N atoms with each pair bearing *ca.* 39% and 19.5% spin density. This is consistent with the experimental EPR spectra which reveal coupling to two sets of two chemically distinct ¹⁴N nuclei (*I* = 1), with additional hyperfine coupling to the methyl-H atoms arising through hyper-conjugation effects (S-3, ESI†).^{13b}

Previous studies have shown that the chirality of pyridine ligands bearing pinene substituents can be successfully transferred to their d/f coordination complexes.²¹ In order to probe the coordination chemistry of this series of radicals the reactivity of **2b** with CuCl₂ in EtOH was examined, leading to the 1 : 1 complex (**3b**). This complex crystallizes in the non-centrosymmetric space group *P2*₁ with two crystallographically independent molecules in the asymmetric unit. This structure is very similar to the previously reported vd-CuCl₂ complex described by Hicks and co-workers.²² However, in that example a long Cu...N intermolecular contact (3.889 Å) linked two units together affording a centrosymmetric dimer. In the current case, aggregation appears inhibited by the steric bulk of the pinene-pyridyl moiety. In both molecules of **3b**, the copper ion adopts an intermediate geometry ($\tau_4 = 0.67$ and 0.59 for Cu1 and Cu2 respectively), between square planar ($\tau_4 = 0$) and tetrahedral ($\tau_4 = 1$),²³ consistent with a Jahn–Teller distortion away from idealized tetrahedral coordination (Fig. 5).

For an idealized square planar geometry, the π -magnetic orbital of the vd radical is mutually orthogonal to the Cu²⁺ d_{x²-y²} magnetic orbital and thus is expected to lead to a ferromagnetic interaction. Conversely, under tetrahedral symmetry an antiferromagnetic interaction is expected due to the non-zero overlap of the two magnetic orbitals. The intermediate coordination geometry is therefore challenging to predict, but the emergence of non-zero overlap integrals typically leads to a rapid dominance of antiferromagnetic interaction. In the structurally related [CuCl₂(vd)]₂ system the coordination geometry is pseudo-5-coordinate with CuCl₂ and CuN₂ ring planes twisted by 47.8° and a strong antiferromagnetic exchange

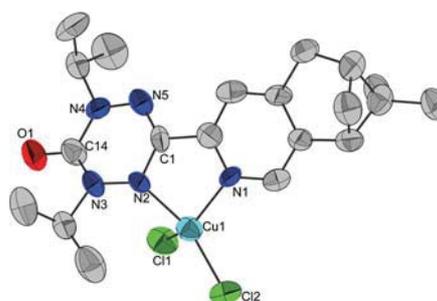


Fig. 5 Crystal structure of one of the crystallographically independent molecules of **3b** with the thermal ellipsoids at 50% probability. The H atoms have been removed for clarity.

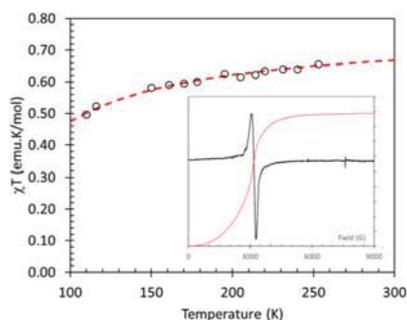


Fig. 6 Temperature dependence of χT for **2b** (circles) determined from EPR spectroscopy (scaled to that expected for exchange coupling between two $S = 1/2$ ions) with fit to the Bleaney–Bowers model (dashed line); (inset) Solid state EPR spectra of **2b** at 150 K with double integral of the EPR spectrum.

coupling ($J = -204 \text{ cm}^{-1}$) was observed, but with a strong exchange term to account for exchange between $\text{CuCl}_2(\text{vd})$ sub-units ($zJ' = -260 \text{ cm}^{-1}$).²²

Variable temperature EPR studies on **3b** were undertaken and the EPR signal intensity examined (Fig. 6) in the range 100–300 K as a function of temperature (the double integral of the first derivative EPR spectrum is proportional to the magnetic susceptibility).²⁴ A fit to the Bleaney–Bowers equation²⁵ afforded $J/k = -60 \text{ K}$ for this system.

In summary we have described the versatile synthesis of two chiral aldehydes from which we have prepared novel enantiopure verdazyl ligands bearing pinene-pyridyl substituents in which the stereo-electronic effects at the 1,5-positions of the verdazyl radical can be controlled. Preliminary studies reveal that these ligands can coordinate d-block metals, which offers the potential for magnetic exchange coupling. This augurs well for the future development of high spin chiral molecules and further studies are underway to explore their coordination chemistry with magnetically interesting 3d and/or 4f metal ions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

OM, AS, TW, YM acknowledge the undergraduate students who participated in this project during their second year laboratory courses or Bachelor work (S. Agrebi, M. Poretti, A. Spörri, F. Miserez, N. Beretta) and ChemTech for financial support. MP would like to thank NSERC DG and PA acknowledges the Ontario Trillium Scholarship program for financial support. AC and KMF thank the Fribourg Center for Nanomaterials FRIMAT for support. CT and GN acknowledge the ANR (ANR-13-BS08-0016-01 project).

Notes and references

- (a) M. Dutartre, J. Bayardon and S. Juge, *Chem. Soc. Rev.*, 2016, **45**, 5771; (b) Y. Wang, J. Xu, Y. Wang and H. Chen, *Chem. Soc. Rev.*, 2013, **42**, 2930; (c) E. C. Constable, *Chem. Soc. Rev.*, 2013, **42**, 1637.
- (a) T. Hashimoto, Y. Kawamata and K. Maruoka, *Nat. Chem.*, 2014, **6**, 702; (b) J. G. Stack, D. P. Curran, S. V. Geib, J. Rebeck Jr. and P. Ballester, *J. Am. Chem. Soc.*, 1992, **114**, 7007.
- (a) J. R. Gallan-Mascaros, E. Coronado, P. A. Goddard, J. Singleton, A. I. Coldea, J. D. Wallis, S. J. Coles and A. Alberola, *J. Am. Chem. Soc.*, 2010, **132**, 9271; (b) M. Minguet, D. B. Amabilino, I. Mata, E. Molins and J. Veciana, *Synth. Met.*, 1999, **103**, 2253.
- (a) C. Train, M. Gruselle and M. Verdaguer, *Chem. Soc. Rev.*, 2011, **40**, 3297; (b) M. Minguet, D. Luneau, C. Paulsen, E. Lhotel, A. Gorski, J. Waluk, D. B. Amabilino and J. Veciana, *Polyhedron*, 2003, **22**, 2349; (c) P. Sarbadhikary, S. Shil, A. Panda and A. Misra, *J. Org. Chem.*, 2016, **81**, 5623.
- (a) G. L. J. A. Rikken and E. Raupach, *Nature*, 1997, **390**, 493; (b) J. R. Galan-Mascaros, *Nat. Phys.*, 2014, **11**, 7; (c) R. Sessoli, M.-E. Boulon, A. Caneschi, M. Mannini, L. Poggini, F. Wilhelm and A. Rogalev, *Nat. Phys.*, 2015, **11**, 69; (d) C. Train, R. Gheorghie, V. Krstic, L.-M. Chamoreau, N. S. Ovanesyan, G. L. J. A. Rikken, M. Gruselle and M. Verdaguer, *Nat. Mater.*, 2008, **7**, 729.
- (a) C. A. Gould, L. E. Darago, M. I. Gonzalez, S. Demir and J. R. Long, *Angew. Chem., Int. Ed.*, 2017, **56**, 10103; (b) S. Demir, J. M. Zadrozny, M. Nippe and J. R. Long, *J. Am. Chem. Soc.*, 2012, **134**, 18546; (c) J. D. Rinehart, M. Fang, W. J. Evans and J. R. Long, *Nat. Chem.*, 2011, **3**, 538.
- H. Kumagai and K. Inoue, *Angew. Chem., Int. Ed.*, 1999, **38**, 1601.
- See for example. *Stable Radicals: Fundamentals and Applied Aspects of Odd-Electron Compounds*, ed. R. G. Hicks, J Wiley & Sons, 2010.
- (a) S. Shimono, R. Tamura, N. Ikuma, T. Takimoto, N. Kawame, O. Tamada, N. Sakai, H. Matsuura and J. Yamauchi, *J. Org. Chem.*, 2004, **69**, 475; (b) M. Minguet, D. B. Amabilino, K. Wurst and J. Veciana, *J. Solid State Chem.*, 2001, **159**, 440.
- (a) B. D. Koivisto and R. G. Hicks, *Coord. Chem. Rev.*, 2005, **249**, 2612; (b) R. G. Hicks, B. D. Koivisto and M. T. Lemaire, *Org. Lett.*, 2004, **6**, 1887; (c) M. Chahma, X. S. Wang, A. van der Est and M. Pilkington, *J. Org. Chem.*, 2006, **71**, 2750; (d) G. Novitchi, S. Shova, Y. Lan, W. Wernsdorfer and C. Train, *Inorg. Chem.*, 2016, **55**, 12122; (e) L. Norel, F. Pointillart, C. Train, L.-M. Chamoreau, K. Boubekeur, Y. Journaux, A. Brieger and D. J. R. Brook, *Inorg. Chem.*, 2008, **47**, 2396.
- T.-N. Le, H. Grewal, V. Changoco, V. Truong and D. J. R. Brook, *Tetrahedron*, 2016, **72**, 6368.
- (a) E. F. Ullman, J. H. Osiecki, D. G. B. Boocock and R. Darcy, *J. Am. Chem. Soc.*, 1972, **94**, 7049; (b) C. Stroh, M. Mayor and C. von Hanisch, *Tetrahedron Lett.*, 2004, **45**, 9623.
- (a) F. A. Neugebauer, H. Fischer and R. Siegel, *Chem. Ber.*, 1988, **121**, 515; (b) E. C. Pare, D. J. R. Brook, A. Brieger, M. Badik and M. Shinke, *Org. Biomol. Chem.*, 2005, **3**, 4258.

- 14 A. L. Sauers, D. M. Ho and S. Bernhard, *J. Org. Chem.*, 2004, **69**, 8910.
- 15 (a) Y. Masuda, M. Kuratsu, S. Suzuki, M. Kozaki, D. Shiomi, K. Sato, T. Takui and K. Okada, *Polyhedron*, 2009, **28**, 1950; (b) D. Matuschek, S. Eusterwiemann, L. Stegemann, C. Doerenkamp, B. Wibbeling, C. G. Daniliuc, N. L. Doltsinis, C. A. Strassert, H. Eckert and A. Studer, *Chem. Sci.*, 2015, **6**, 4712.
- 16 J. C. A. Boeyens, *J. Cryst. Mol. Struct.*, 1978, **8**, 317.
- 17 O. Oms, L. Norel, L.-M. Chamoreau, H. Rousselière and C. Train, *New J. Chem.*, 2009, **33**, 1663.
- 18 M. J. Plater, J. P. Sinclair, S. Kemp, T. Gelbrich, M. B. Hursthouse and C. J. Gómez-García, *J. Chem. Res.*, 2006, **8**, 515.
- 19 C. L. Barr, P. A. Chase, R. G. Hicks and M. T. Lemaire, *J. Org. Chem.*, 1999, **64**, 8893.
- 20 J. B. Gilroy, S. D. J. McKinnon, B. D. Kovisto and R. G. Hicks, *Org. Lett.*, 2007, **9**, 4837.
- 21 (a) M. Lama, O. Mamula, G. S. Kottas, F. Rizzo, L. De Cola, A. Nakamura, R. Kuroda and H. Stoeckli-Evans, *Chem. – Eur. J.*, 2007, **13**, 7358; (b) O. Mamula and A. von Zelewsky, *Coord. Chem. Rev.*, 2003, **242**, 87.
- 22 J. B. Gilroy, B. D. Koivisto, R. McDonald, M. J. Ferguson and R. G. Hicks, *J. Mater. Chem.*, 2006, **16**, 2618.
- 23 L. Yang, D.R. Powell and R.P. Houser, *Dalton Trans.*, 2007, 955.
- 24 P. E. Richardson and R. W. Kreilick, *J. Magn. Reson.*, 1978, **29**, 285.
- 25 B. Bleany and K.D. Bowers, *Proc. R. Soc. London, Ser. A*, 1952, **214**, 451.