Synthesis, Characterization, X-Ray Crystallography Analysis and Kinetic Study of tris(2-(4-trifluoromethylbenzylideneamino)ethyl)amine Copper Derivatives

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ABSTRACT

A two-component synthetic procedure for a tetradentate, tripodal organo-fluorine derivative; along with copper(I) and copper(II) analogues is presented. Solid state studies show that the (4TFM-TREN) ligand crystallizes in a monoclinic system with $P2_1/c$ space group, while the $[\text{Cu}^{\text{I}}(4\text{TFM-TREN})][\text{PF}_6]$ complex crystallizes in a cubic crystal system with $P2_13$ space group. Kinetic studies monitoring the addition of carbon tetrachloride to the copper(I) analogue produced an activation rate constant value of $5 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$. UV-Vis spectroscopy results confirmed the ability of compounds presented here to slow down the activation step of atom transfer radical addition reactions employing fast initiators such as carbon tetrachloride. This work addresses a need to develop novel methods that can be used in activation rate constant value calculations for ideal atom transfer radical addition (ATRA) reactions incorporating active copper catalysts and fast initiators.

KEYWORDS

Schiff-Base Synthesis, Atom Transfer Radical Addition (ATRA), Pseudo First-Order Kinetics, Activation Rate.

1. INTRODUCTION

Atom Transfer Radical Addition (ATRA) and Polymerization (ATRP) of haloalkanes and α -halocarbonyls to α -olefins have emerged as some of the most atom economical methods for simultaneously forming C–C and C–X bonds; leading to the synthesis of more attractive molecules with defined compositions, architectures, and functionalities.^[1–6] First reported by Morris S. Kharasch in the 1940s,^[7] the reaction incorporates halogen group functionalities within products which can be used as starting reagents in further functionalization reactions.^[8,9] Most proceed in the presence of a free-radical precursor, or transition metal complex (catalyst), as the halogen atom transfer agent and have been efficiently catalyzed by complexes incorporating nickel,^[10] ruthenium,^[11] iron,^[12] and copper.^[13–15] The reaction model has since evolved to include processes such as Atom Transfer Radical Polymerization (ATRP),^[16–18] and Atom Transfer Radical Cyclization (ATRC).^[19,20]

The generally accepted mechanism for transition metal catalyzed atom transfer radical addition reactions involves free radicals as shown in Figure 1.^[21] Homolytic cleavage of an alkyl halide bond by the

copper(I) complex generates the corresponding copper(II) complex and an organic radical (k_{act}). The radical may terminate (k_t), or add to an alkene (k_{add}) in an inter- or intra-molecular fashion; or can abstract the halogen from the copper(II) complex and return to the original dormant alkyl halide species. If abstraction of the halogen atom occurs after addition to an alkene, the desired alkyl halide monoadduct will be formed (k_{deact}). This step regenerates the corresponding copper(I) complex completing the catalytic cycle.^[22] In order to obtain increased selectivity towards desired monoadducts, the following reaction conditions need to be achieved utilizing Figure 1 as a reference: (a) radical concentration levels must be low in order to suppress radical termination reactions [activation rate constant (k_{act}) << deactivation rate constant (k_{deact})]; (b) further activation of the preferred monoadducts should be avoided; and (c) formation of oligomers or polymers should be suppressed {rate of transfer [$k_{deact}(\text{Cu}^{\text{II}}\text{L}_m\text{X})$] >> rate of propagation [$k_p(\text{alkene})$]}.^[23]

If a large amount of alkyl halide is used, the reaction ($K_{\text{ATRA}} = k_{act}/k_{deact}$) will shift towards the product and, due to irreversible radical termination reactions, all copper(I) complexes will be converted to analogous copper(II) complexes. To compensate for this side reaction, and ensure that the deactivator species ($\text{Cu}^{\text{II}}\text{L}_m\text{X}_2$) is continuously converted back to activator species ($\text{Cu}^{\text{I}}\text{L}_m\text{X}$), reducing agents such as AIBN and ascorbic acid are now utilized.^[24-26] Radicals generated from slow thermal decomposition of reducing agents constantly convert copper(II) complexes back to copper(I). Efficient regeneration of the activator species (a process commonly referred to as ARGET) now enable ATRA reactions to be conducted using significantly lower amounts of catalyst, approaching ppm levels in some cases.^[27-29] The outlined methodology could have a significant impact on the synthesis of various feed-stocks and complex molecules, which are currently predominantly manufactured utilizing stoichiometric amounts of organotin and organosilane reagents.^[30,31]

Figure 1. Proposed mechanism for copper-catalyzed Atom Transfer Radical Addition (ATRA) reactions.^[22]

1.1.OBJECTIVE

As presented in Figure 1, the overall reaction has a conspicuous kinetic component and is governed by many steps and rates. Efficient reactions depend largely on the presence of a suitable equilibrium between the activation process (k_{act}) which generates the radicals, and deactivation process (k_{deact}) which produces the alkyl halide monoadducts. That equilibrium (K_{ATRA}) controls the overall reaction and is expressed as follows: ($K_{\text{ATRA}} = k_{\text{act}}/k_{\text{deact}}$).^[32,33] Developing methods to evaluate both rate constants (k_{act} , k_{deact}) and the equilibrium constant (K_{ATRA}) is necessary to better understand and optimize the catalytic process; resulting in future improvements to the reaction model. Even more important is the correlation of these kinetic terms with reaction parameters such as ligand design for catalysts and alkyl halide (R-X) initiator structures.

Activation rate constants (k_{act}) for copper catalyzed ATRA reactions incorporating fast initiators (alkyl halides) are difficult to measure accurately using standard techniques such as NMR or UV-Vis spectroscopy; as they occur rather quickly (estimated on the order of approximately $10^6 \text{ M}^{-1} \text{ s}^{-1}$).^[34] Other methods such as stopped-flow spectroscopy have been successfully employed to monitor fast activation rates, but are restricted to an upper limit of approximately $10^4 \text{ M}^{-1} \text{ s}^{-1}$.^[34b] Subsequently, kinetic modeling methods are typically used to estimate fast activation rates for atom transfer radical addition reactions incorporating efficient copper catalysts and highly active alkyl halide initiators.^[34,35] Kinetic studies by Pintauer *et al.*, utilizing highly active complexes $[\text{Cu}^{\text{II}}(\text{TPMA})(\text{Cl})][\text{Cl}]$ and $[\text{Cu}^{\text{II}}(\text{Me}_6\text{TREN})(\text{Cl})][\text{Cl}]$ with fast initiators such as carbon tetrachloride and 2-chloro-2-methylpropanenitrile produced ATRA activation steps that were too fast to monitor.^[35] Modeling results, in the case of $[\text{Cu}^{\text{II}}(\text{TPMA})(\text{Cl})][\text{Cl}]$ with carbon tetrachloride, suggested activation rate constant values on the order of $1.0 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.^[34] Further studies show that the activation step in these cases can be impeded by using less active pseudo-halide initiators such as benzyl thiocyanate (BzSCN). When utilized with $[\text{Cu}^{\text{II}}(\text{TPMA})(\text{Cl})][\text{Cl}]$, the activation step became slow enough to monitor using UV/Vis spectroscopy, producing an activation rate constant value of $(3.4 \pm 0.4) \times 10^{-4} \text{ M}^{-1} \text{ s}^{-1}$.^[35]

These studies provide valuable information on the kinetic parameters governing ATRA reactions incorporating slow initiators and active copper complexes; but do not provide us with measureable (k_{act}) values for ATRA reactions incorporating fast initiators such as carbon tetrachloride (CCl_4). Herein, we set out to design a new class of copper complexes that will allow for determination of activation rate constant values in ATRA reactions employing carbon tetrachloride. To achieve this, a modified ligand structure was designed resulting in activity reduction of corresponding copper complexes. These slow activating complexes can be paired up with slow initiators such as benzyl thiocyanate (BzSCN) in future studies, producing activation steps that can also be monitored utilizing UV-Vis spectroscopy. The activation rate constant values obtained in this study and future studies with benzyl thiocyanate will allow us to calculate an activity difference for copper catalysts presented here. This activity difference can be employed in kinetic studies with robust catalysts and slow initiators to help measure, with better accuracy, (k_{act}) values for ideal ATRA reactions as demonstrated in well-established studies focused on ATRP reactions.^[36] As such, we present the synthesis, characterization, and kinetic study of *tris*(2-(4-trifluoromethylbenzylideneamino)ethyl)amine copper derivatives that can be employed in activation rate determinations for atom transfer radical processes.

2. MATERIALS AND METHODS

2.1.1. General Procedures: Chemicals were purchased from commercial sources and used as received. Air-sensitive 4-(trifluoromethyl)benzaldehyde was stored under nitrogen. All manipulations involving copper(I) complexes were performed under nitrogen in a drybox (<1.0 ppm O₂ and < 0.5 ppm H₂O), or using standard Schlenk line techniques with solvents (pentane, acetonitrile, and methanol) degassed and deoxygenated prior to use. Copper(II) complexes were synthesized under ambient conditions with solvents used as received.

2.1.2. Instrumentation: ¹H, ¹³C, and VT-NMR spectra were obtained using Bruker Avance III HD 400 MHz and Bruker Avance III HD 500 MHz spectrometers with chemical shifts given in parts per million relative to residual solvent peaks (CDCl₃ δ 7.26 ppm, CD₃OD δ 3.35 ppm and δ 4.78 ppm). MestReNova version 8.1.2 was used to generate images of NMR spectra. A Perkin Elmer FT-ATR spectrometer was used to collect IR spectra with scans from 200 nm to 900 nm at a resolution of 1 cm⁻¹. UV-Vis spectra were obtained using a Varian Cary 100 Bio-Spectrometer in 1.0 cm path-length airtight quartz cuvettes. High resolution electrospray ionization spectra were acquired on a Bruker MicroTOF II time of flight mass spectrometer. Spectra were acquired covering the range of 50 to 3000 m/z while accumulating data for two seconds per cycle. Samples were diluted in spectroscopic grade methanol and presented to the instrument through direct injection method.

2.1.3. X-Ray Crystal Structure Determination: Diffraction data were collected on Bruker Apex II CCD and Quest CMOS diffractometers at 100 K using monochromatic Mo Kα radiation with the omega scan technique. Integrations and corrections for absorption were made using Apex2 suite of programs.^[37] Space groups were assigned and structures solved by direct methods using the SHELXTL suite of programs then refined by full matrix least squares against F² with all reflections using Shelxl2014.^[38,39] Hydrogen atoms attached to carbon and nitrogen were positioned geometrically and constrained to ride on their parent atoms, with C–H bond distances of 0.95 Å for alkene and aromatic, 1.00, 0.99 and 0.98 Å for aliphatic C–H, CH₂ and CH₃ and 0.88 Å for N–H moieties, respectively. Methyl H atoms were allowed to rotate but not tip to best fit the experimental electron density. U_{iso}(H) values were set to a multiple of U_{eq}(C/N) with 1.5 for CH₃ and 1.2 for C–H, CH₂ and N–H units. Complete crystallographic data in CIF format have been deposited with the Cambridge Crystallographic Data Centre as CCDC 1414758 and 1414759 and can be obtained free of charge via CCDC.

2.2.1. Activation Rate Constant (k_{act}) Calculation: The activation rate constant was calculated following literature procedures.^[40,41] A 10 mL solution of 0.005 M [Cu^I(4TFM-TREN)Cl] was prepared in a drybox and a 3 mL aliquot (0.015 mmol) transferred to an air-tight quartz cuvette. 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (46.9 mg, 0.3 mmol) was added to the solution. The cuvette was sealed and removed from the dry box; degassed and deoxygenated carbon tetrachloride dried with molecular sieves (29.0 μL, 0.3 mmol) was transferred into the air-tight cuvette using a syringe purged three times with argon gas. Absorbance of the

copper(II) complex was monitored by UV-Vis spectroscopy at λ_{max} value of 668 nm for $[\text{Cu}^{\text{II}}(\text{4TFM-TREN})(\text{Cl}_2)]$ for a 24 hour period. The activation rate constant was then determined utilizing first-order plots.

2.2.2. Synthesis of *tris*(2-(4-trifluoromethylbenzylideneamino)ethyl)amine (4TFM-TREN) Ligand: In a drybox, *tris*(2-(amino)ethyl)amine (2.56 mL, 17.10 mmol) was dissolved in 100 mL methanol in a 250 mL round-bottom flask. Ligand precursor 4-(trifluoromethyl)benzaldehyde (6.90 mL, 51.29 mmol) was added to the flask to give a light yellow colored solution. The reaction was sealed and allowed to mix for 48 hours producing a clear yellow solution. Solvent was removed using a rotary evaporator and dried under vacuum for one hour to yield a yellow solid (10.40 g, 99%). ^1H NMR (CDCl_3 , 500 MHz): δ 2.94 (t, J = 7.5 Hz, 2H), 3.70 (t, J = 7.5 Hz, 2H), 7.56 (br, 2H), 8.08 (s, 1H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 55.62, 60.32, 122.85 (q, J = 271.0 Hz), 125.73 (q, J = 3.6 Hz), 128.35, 132.44 (q, J = 33.0 Hz), 139.62, 160.42. FT-IR (solid) ν (cm^{-1}): 1321 (s), 1169 (s), 1118 (s), 1062 (s), and 834 (s). Melting Point Observed: 71.0 °C. TOF-ESI-MS: (m/z) [M + (H)] $^+$ calculated for $\text{C}_{30}\text{H}_{28}\text{N}_4\text{F}_9$ = 615.2165; found 615.2194 (4.8 ppm). Colorless single crystals suitable for X-Ray crystallography were obtained from slow evaporation of a dilute solution of the ligand in dried methanol.

2.2.3. Synthesis of $[\text{Cu}^{\text{I}}(\text{4TFM-TREN})(\text{Cl})]$: *tris*(2-(4-trifluoromethylbenzylideneamino)ethyl)amine (4TFM-TREN) (1.000 g, 1.63 mmol) was dissolved in 20 mL methanol in a 100 mL Schlenk flask in a drybox. Copper(I) chloride (0.161 g, 1.63 mmol) was added to the flask producing a yellowish-red colored solution. Reaction was allowed to mix for six hours then 15 mL of pentane was slowly added to the solution to generate a bright orange precipitate. Solvent was removed from the Schlenk flask using a vacuum line. Precipitate obtained was washed twice by transferring 10 mL aliquots of pentane into the flask and stirring vigorously for thirty minutes. Solvent was removed and precipitate dried under vacuum for two hours to yield a bright orange solid (1.110 g, 96%). ^1H NMR (CDCl_3 , 500 MHz): δ 3.18 (br, 2H), 3.95 (br, 2H), 7.50 (d, J = 9.6 Hz, 1H), 8.18 (br, 1H), 8.34 (s, 1H). ^1H NMR (CD_3OD , 400 MHz): δ 3.21 (br, 2H), 3.97 (br, 2H), 7.01 (d, J = 4.6 Hz, 1H), 8.03 (d, J = 4.6 Hz, 1H), 8.68 (s, 1H). FT-IR (solid): ν (cm^{-1}) = 1318 (s), 1284 (s), 1165 (s), 1120 (m), 1061 (s), 1008 (s), 829 (s). TOF-ESI-MS: (m/z) [M - (Cl)] $^+$ calculated for $\text{C}_{30}\text{H}_{27}\text{N}_4\text{F}_9\text{Cu}$ = 677.1383; found 677.1369 (2.1 ppm). Orange crystals suitable for single crystal X-Ray diffraction were obtained from a counter-ion exchange reaction between the copper complex and (TBAPF₆) in methanol at room temperature.

2.2.4. Synthesis of $[\text{Cu}^{\text{II}}(\text{4TFM-TREN})(\text{Cl}_2)]$: *tris*(2-(4-trifluoromethylbenzylideneamino)ethyl)amine ligand (4TFM-TREN) (1.000 g, 1.63 mmol) was dissolved in 20 mL of methanol in a 100 mL round bottom flask. Copper(II) chloride (0.219 g, 1.63 mmol) was added to the flask to give a teal colored solution. The reaction was allowed to mix for six hours then 20 mL of pentane was slowly added to the solution producing a teal colored precipitate. The mixture was filtered and precipitate washed twice with 30 mL aliquots of pentane. Residual solvent was removed using a rotary evaporator and final precipitate obtained dried under vacuum for one hour producing a teal colored solid (1.140 g, 93%). FT-IR (solid): ν (cm^{-1}) = 1636 (m), 1506 (s), 1473 (s), 1317 (s), 1163 (s), 1109 (br), 1024 (s), 874 (s), 830 (s). UV-Vis spectroscopy (methanol) λ_{max} = 668 nm. TOF-ESI-MS: (m/z) [M - 2(Cl)] $^{2+}$ calculated for $\text{C}_{30}\text{H}_{27}\text{N}_4\text{F}_9\text{Cu}$ complex = 677.1383; found 677.1381 (0.2

Compounds incorporating tetradentate N-donor ligands such as *tris*(2-(dimethylamino)ethyl)amine (Me₆TREN) and *tris*((2-pyridyl)methyl)amine (TPMA), are currently some of the most active structures utilized in ATRA / ATRP (Figure 2).^[32,33] Structural studies suggest that ligand design plays a significant role in the activity of corresponding copper complexes.^[32] Consistent with literature predictions, replacing the aliphatic amine groups in Me₆TREN with aromatic moieties to form TPMA generated less active copper complexes.^[42] Independent studies by Zuberbühler also showed that increasing the electron-withdrawing ability of *para*-substituents in TPMA diminishes the reducing power of corresponding complexes by 300 mV; a five order decrease in the equilibrium constant for electron transfer.^[43] Analogous studies by Matyjaszewski also reported a decline in the reducing power of *tris*(2-(amino)ethyl)amine (TREN) based copper complexes as a result of altering the electron-withdrawing power of substituents present in the ligand.^[42]

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Figure 3. Reaction scheme for *tris*(2-(4-trifluoromethylbenzylideneamino)ethyl)amine (4TFM-TREN) ligand.

Figure 4. ¹H NMR spectra (500 MHz, CDCl₃) for 4-(trifluoromethyl)benzaldehyde precursor [bottom], *tris*(2-(4-trifluoromethylbenzylideneamino)ethyl)amine precursor [middle], 4TFM-TREN ligand [top]. Chloroform-*d* solvent peak denoted as (S₁).

The ¹³C NMR spectrum obtained for 4TFM-TREN [Figure 5] displays five singlets (C₁–C₅) and three quartets (C₆–C₈). Each splitting has relative intensities of 1:3:3:1, indicative of AX₃ systems with increasing coupling constants as follows: C₆ (³J_{CF} 3.6 Hz), C₇ (²J_{CF} 33 Hz), and C₈ (¹J_{CF} 271 Hz). This pattern is due to coupling between ¹⁹F fluorine and ¹³C carbon atoms, which both have *I* = ½ spins. Coupling constant increases are attributed to each carbon's proximity to the three fluorine atoms with C₈ being closest and C₆ being farthest. Coupling constants obtained in the experiment agree with those reported in the literature.^[44]

Figure 5. ^{13}C NMR spectrum (125 MHz, CDCl_3) for *tris*(2-(4-trifluoromethylbenzylideneamino)ethyl)amine ligand [bottom], and zoomed in region of 4TFM-TREN ligand [top]. Chloroform-*d* peak is denoted as (S_1).

A 2-D COSY experiment performed on 4TFM-TREN [Fig. 6, top] displays the expected 3J coupling between protons (H_E) and (H_D), then (H_A) and (H_B). We observed a long range 4J coupling between protons (H_C) and (H_D). Such long range coupling across π -systems are the most encountered 4J couplings, including meta coupling in aromatic compounds and 4-bond allylic, propargylic and allenic couplings.^[45] A 2-D HSQC experiment [Fig. 6, bottom] displays five carbon-proton coupling cross-peaks and confirms the overlap of two proton signals (H_A & H_B) at 7.56 ppm, as the protons are coupled to separate carbon atoms (C_5 and C_6).

Figure 6. 2-D NMR Spectrum (400 MHz, $CDCl_3$):COSY [top], HSQC [bottom]; obtained for thetrakis(2-(4-trifluoromethylbenzylideneamino)ethyl)amine (4TFM-TREN) ligand. Chloroform- d peak denoted as (S_1).

4. COMPLEX SYNTHESIS AND CHARACTERIZATION

Figure 7 shows the proposed reaction scheme between one equivalent of copper(I) chloride and 4TFM-TREN in methanol. Progressive 1H NMR spectra obtained for the ligand and complex are shown in Figure 8. The complex [Fig. 8, middle] displays the right number of signals in chloroform- d , but unusual symmetry for protons (H_A) and (H_B) indicative of some fluxionality or exchange. This type of fluxionality is common in d^{10} copper(I) complexes incorporating neutral ligands.^[46] The exchange observed could be due to a ligand arm dissociation to accommodate binding between the chlorid ligand and the Cu^I metal center, in order to

Figure 7. Reaction Scheme for Copper(I) *tris*(2-(4-trifluoromethylbenzylideneamino)ethyl)amine chloride.

maintain a four-coordinate species [Fig. 9(A)]. This type of exchange has been well documented for copper(I) complexes incorporating tripodal ligands such as *tris*((2-pyridyl)methyl)amine (TPMA).^[23,28,47] When a ^1H NMR experiment was performed on the same complex in methanol- d_4 , a spectrum displaying resolved peaks with no indication of exchange was obtained [Fig. 8, top]. Assuming ligand arm dissociation still occurs in this solvent, the resolved spectrum could be due to solvent coordination at the metal center generating a four-coordinate species that may circumvent exchange with the chloride ligand [Fig. 9 (B)]. This is not surprising given the nature of solvent used as several studies have been published detailing the ability for methanol to coordinate to metal sites in various complexes.^[48,49] The exchange process observed in chloroform- d can be mitigated by performing a variable-temperature NMR experiment which slows down the exchange, producing a spectrum with resolved peaks for protons (H_A) and (H_B) at 243 K (Figure 10). The structure observed at

Figure 8. ^1H NMR spectra (500 MHz, CDCl_3 and CD_3OD) of 4TFM-TREN ligand [bottom], $[\text{Cu}^{\text{I}}(4\text{TFM-TREN})(\text{Cl})]$ in chloroform- d [middle], and $[\text{Cu}^{\text{I}}(4\text{TFM-TREN})(\text{Cl})]$ in methanol- d_4 [top]. Chloroform- d solvent peak denoted as (S_1) and methanol- d_4 peaks denoted as (S_2).

Figure 9. VT-NMR spectrum (400 MHz, CDCl_3) for $[\text{Cu}^{\text{I}}(4\text{TFM-TREN})(\text{Cl})]$ with (H_A) and (H_B) highlighted.

lower temperatures could either be the four-coordinate species with all four ligand nitrogen donor atoms bound to the metal center with a free chloride counter-ion; or a four-coordinate species with one ligand arm dissociated and three ligand nitrogen donor atoms plus one chloride ligand bound to the metal center. Air-stable copper(II) complexes were synthesized in methanol following analogous reaction scheme presented in Figure 7. Due to the paramagnetic nature of the metal center and large quadrupole moment of both isotopes of copper (^{63}Cu & ^{65}Cu ; $I = 3/2$), proton-NMR experiments are not applicable to obtain information about the coordination sphere around the metal. As a result, synthesis of the complex was confirmed utilizing mass spectrometry results, with characterizations performed utilizing IR spectroscopy, and UV-Vis spectroscopy.

Figure 10. VT-NMR spectrum (400 MHz, CDCl_3) for $[\text{Cu}^{\text{I}}(4\text{TFM-TREN})(\text{Cl})]$ with (H_A) and (H_B) highlighted.

5. X-RAY CRYSTALLOGRAPHY ANALYSIS

Single crystals suitable for X-Ray analysis were obtained for the ligand (4TFM-TREN) and copper(I) complex $[\text{Cu}^{\text{I}}(4\text{TFM-TREN})][\text{PF}_6]$. The molecular structure obtained for the ligand (Figure 11, A) displays a monoclinic system with $P2_1/c$ space group and a molecular non-crystallographic C_3 symmetry axis. Onetrifluoromethyl group in the structure was observed to be rotationally disordered. As a result, C–F distances were restrained to be similar (e.s.d 0.02 Å) and atoms were subjected to a rigid body restraint (RIGU command in Shelxl). Subject to these conditions, the occupancy ratio refined from 0.690(14) to 0.310(14). A counter-ion exchange reaction was used to facilitate the growth of single crystals for the copper(I) complex as $[\text{Cu}^{\text{I}}(4\text{TFM-TREN})(\text{Cl})]$ did not produce crystals suitable for structural analysis. An exchange reaction was carried out with $(\text{TBA})\text{PF}_6$ in methanol at room temperature producing the complex $[\text{Cu}^{\text{I}}(4\text{TFM-TREN})][\text{PF}_6]$. The structure obtained for this complex salt (Figure 11, B) displays a cubic crystal system with the chiral $P2_13$ space group. The cation exhibits three-fold rotational symmetry with the copper ion and the apical nitrogen located on a crystallographic three-fold axis. The copper center adopts a distorted trigonal-pyramidal geometry and the hexafluorophosphate counter-ion is multiply disordered. A major moiety in the structure is triply disordered around a threefold axis with two of the fluorine atoms on the axis, and the remaining four fluorine atoms triply disordered. A minor moiety is located along the three fold axis, slightly inclined with respect to the major moiety. All moieties share the phosphorous atom. F–F distances of *cis*-fluorine atoms were restrained to be approximately equal using distance restraints (e.s.d 0.02 Å). A rigid body restraint was

Figure 11. Molecular structures for 4TFM-TREN (A) and $[\text{Cu}^{\text{I}}(4\text{TFM-TREN})][\text{PF}_6]$ (B) complex collected at 100 K, shown with 50% probability displacement ellipsoids. Hydrogen atoms have been omitted for clarity purposes. Selected distances [Å] and angles [deg] for $[\text{Cu}^{\text{I}}(4\text{TFM-TREN})][\text{PF}_6]$: Cu1–N1 2.187(4), Cu1–N2 1.992(2), N2–Cu–N2ⁱ 119.431(18), N1–Cu–N2 85.65(6). (Symmetry operators: $i+z, +x, +y$; $ii+y, +z, +x$).

applied for the hexafluorophosphate atoms (RIGU in Shelxl). With respect to the fluorine atoms in the minor moiety, they were restrained to be approximately isotropic (e.s.d 0.01 Å²). Subject to these conditions, occupancy rates refined to 0.305(2) for the three major fluorine moieties and 0.085(6) for the minor moiety.

Table 1. X-ray crystallographic experimental details for 4TFM-TREN ligand and [Cu^I(4TFM-TREN)][PF₆].

	4TFM-TREN Ligand	[Cu ^I (4TFM-TREN)][PF ₆]
Formula	C ₃₀ H ₂₇ F ₉ N ₄	C ₃₀ H ₂₇ CuF ₉ N ₄ •PF ₆
<i>M_r</i>	614.55	823.06
<i>V</i> [Å ³]	2885.1(9)	3341.3(3)
<i>Z</i>	4	4
<i>a</i> [Å]	12.126(2)	14.9499(5)
<i>b</i> [Å]	16.820(3)	14.9499(5)
<i>c</i> [Å]	14.784(3)	14.9499(5)
β [deg]	106.907(3) ^o	90 ^o
<i>R</i> ₁	5.29%	3.69%
θ _{min}	1.9 ^o	2.4 ^o
θ _{max}	31.7 ^o	32.0 ^o

6. KINETIC STUDIES

Activation rate constant (*k_{act}*) value for the copper complex was determined by kinetically isolating the activation step process from the deactivation step process following well established procedures (Figure 12).^[40] Radicals generated by halogen transfer from alkyl halide initiator to Cu^I complex [Figure 12, eq. 1] were trapped utilizing excess amount of the radical trapping agent, 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO, T•), generating an alkoxyamine [eq. 3]. Due to this scavenging process, possible deactivation [eq. 2], thermal dissociation [eq. 4], and self-coupling [eq. 5] processes become negligible as a result of: (a) low Cu^{II}X₂/L_n concentrations, (b) smaller thermal decomposition rate constants (*k_{diss}*),^[36,50] and (c) lower radical concentrations.^[51] Given these modified reaction conditions, the rate of activation becomes equivalent to the rate of consumption of alkyl halide (R-X) initiator and rate of formation for alkoxyamine (R-T). Following the expressions and derivations provided below: excess amount of alkyl halide initiator (approximately 20 times with respect to copper) can be utilized to provide pseudo-first-order reaction conditions (eq. ii), making kinetic analysis of the atom transfer radical addition reaction straight-forward. A first-order kinetic plot of ln([Cu^IX/L_n]₀/[Cu^IX/L_n]_t) versus time (eq. vi) should produce a straight line, with the slope corresponding to

the observed rate constant (k_{obs}) value (eq. vii). This term is equal to the product of alkyl halide concentration $[R-X]$ and desired activation rate constant (k_{act}) value; which can be obtained as shown in expression (viii).

$$\text{Rate} = k_{\text{act}} [\text{Cu}^I]^x [\text{R} - \text{X}]^y \quad (i) \quad \text{Rate} = k_{\text{obs}} [\text{Cu}^I]^1 \quad (ii) \quad \text{where } k_{\text{obs}} = k_{\text{act}} [\text{R} - \text{X}]$$

$$\frac{d[\text{Cu}^I]}{[\text{Cu}^I]} = -k_{\text{obs}} dt \quad (iii) \quad \int_{[\text{Cu}]_0}^{[\text{Cu}]_t} \frac{d[\text{Cu}^I]}{[\text{Cu}^I]} = -k_{\text{obs}} \int_0^t dt \quad (iv) \quad \ln \left[\frac{[\text{Cu}^I]_t}{[\text{Cu}^I]_0} \right] = -k_{\text{obs}} t \quad (v)$$

$$\ln \left[\frac{[\text{Cu}^I]_0}{[\text{Cu}^I]_t} \right] = k_{\text{obs}} t + 0 \quad (vi) \quad \text{Slope} = k_{\text{obs}} = k_{\text{act}} [\text{R} - \text{X}] \quad (vii) \quad k_{\text{act}} = \frac{k_{\text{obs}}}{[\text{R} - \text{X}]} \quad (viii)$$

Figure 12. Model reaction scheme for kinetic isolation and measurement of activation rate constant values.

Figure 13 shows the kinetic results obtained from this study. Absorbance vs. wavelength dilution plots were obtained for the independently synthesized $[\text{Cu}^{II}(\text{4TFM-TREN})][\text{Cl}_2]$ complex showing λ_{max} at 668 nm [Fig. 13, A]. The $[\text{Cu}^{II}(\text{4TFM-TREN})][\text{Cl}_2]$ solution concentrations used for this experiment ranged from 0.0015 M to 0.006 M. Absorbance values obtained at different concentrations were used to calculate an extinction coefficient (ϵ) for $[\text{Cu}^{II}(\text{4TFM-TREN})][\text{Cl}_2]$, which was then used to obtain $[\text{Cu}^I]_t$ values [Fig. 13, B]. The activation step for conversion of $[\text{Cu}^I]$ to $[\text{Cu}^{II}]$ was isolated and monitored at 668 nm for 24 hours from a reaction between $[\text{Cu}^I(\text{4TFM-TREN})][\text{Cl}]$ and CCl_4 in the presence of TEMPO [Fig. 13, C]. Absorbance values obtained from this reaction were converted to concentration analogues using the extinction coefficient obtained earlier, allowing us to obtain a pseudo first order kinetic plot of $\ln([\text{Cu}^I\text{X}/\text{L}_n]_0/[\text{Cu}^I\text{X}/\text{L}_n]_t)$ vs. time (with slope = k_{obs}). The (k_{obs}) value obtained from this experiment was $5 \times 10^{-3} \text{ s}^{-1}$. An activation rate constant (k_{act}) value of $5 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ was obtained by dividing the (k_{obs}) value obtained by $[\text{CCl}_4]$ used in the experiment ($1 \times 10^{-1} \text{ M}$). The activation rate constant value obtained is slower by a factor of 1×10^8 compared to the estimated values for active copper complexes (see supporting information for detailed calculations).

Figure 13. (A) absorbance vs. wavelength dilution plots for $[\text{Cu}^{\text{II}}(4\text{TFM-TREN})][\text{Cl}_2]$ showing λ_{max} at 668 nm; (B) extinction coefficient ($\epsilon = \text{slope}$) plot for $[\text{Cu}^{\text{II}}(4\text{TFM-TREN})][\text{Cl}_2]$ complex utilizing values from plot (A); (C) isolating the activation step and monitoring formation of $[\text{Cu}^{\text{II}}(4\text{TFM-TREN})][\text{Cl}_2]$ at 668 nm from reaction between $[\text{Cu}^{\text{I}}(4\text{TFM-TREN})][\text{Cl}]$ and CCl_4 in the presence of TEMPO at $[\text{Cu}^{\text{I}}]:[\text{CCl}_4]:[\text{TEMPO}] = [1]:[20]:[20]$; (D) first order kinetic plot (slope = k_{obs}) of $\ln([\text{Cu}^{\text{I}}\text{X}/\text{L}_n]_0/[\text{Cu}^{\text{I}}\text{X}/\text{L}_n]_t)$ vs. time used to calculate activation rate constant (k_{act}) value. All UV-Vis experiments were conducted utilizing dry methanol as solvent at $23 \pm 2^\circ\text{C}$.

7. CONCLUSION

In summary, synthesis, characterization, and activation rate study of *tris*(2-(4-trifluoromethylbenzylideneamino)ethyl)amine copper derivatives are reported. The Cu^{I} complex displayed coalescence behavior in proton NMR experiments performed using CDCl_3 , which may be due to a slow monomer/dimer equilibrium but could also be the result of reduced fluxionality or hindered exchange. Solid state studies showed the 4TFM-TREN ligand to crystallize in a monoclinic system with $P2_1/c$ space group, while the $[\text{Cu}^{\text{I}}(4\text{TFM-TREN})][\text{PF}_6]$ complex crystallized in a cubic crystal system with $P2_13$ space group. An activation rate constant value of $5 \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$ was obtained from first-order kinetic plots measuring the addition of

carbon tetrachloride to the copper(I) complex. Our results confirmed the ability of compounds presented here to slow down the activation step of ATRA reactions employing fast initiators such as carbon tetrachloride. This was achieved by employing trifluoromethyl electron withdrawing functional groups in the complex design. We are currently pursuing studies to fine-tune, and ultimately control, kinetic properties of the ligand motif presented here by investigating effects of incorporating functional groups with varying electron withdrawing power (Cl, CN, and NO₂) on ATRA activation steps.

ASSOCIATED CONTENT

Supporting Information: Detailed X-Ray crystallography tables and packing diagrams, infrared spectra, mass spectrometry results, and kinetic plots used to determine activation rate constant value are provided.

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APPENDIX A. Supplementary Data

CCDC 1414758 and 1414759 contain the supplementary crystallographic data for 4TFM-TREN and [Cu^I(4TFM-TREN)][PF₆]. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html>, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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REFERENCES

- [1] Pintauer, T., Matyjaszewski, K. *Encyclopedia of Radicals in Chemistry, Biology and Materials*. John Wiley & Sons Ltd., Chichester, UK. **2012**, 1, 1851–1894.
- [2] Tsarevsky, N. V., Matyjaszewski, K. *RCS Polym. Chem. Ser.* **2013**, 4, 287–357.
- [3] Tsarevsky, N. V., Matyjaszewski, K. *Chem. Rev.* **2007**, 107, 2270–2299.
- [4] Matyjaszewski, K. *Macromol.* **2012**, 45, 4015–4039.

- [5] Matyjaszewski, K., Davis, T. P. *Handbook of Radical Polymerization*. Wiley, Hoboken, **2012**.
- [6] Oh, J.K., Drumright, R., Siegwart, D.J., and Matyjaszewski, K. *Prog. Poly. Sci.* **2008**, 33, 448–477.
- [7] Kharasch, M. S., Elwood, V. J., and Urry, W. H. *Science*. **1945**, 102, 128–129.
- [8] Iqbal, J., Bhatia, B., and Nayyar, N. K. *Chem. Rev.* **1994**, 94, 519–564.
- [9] Gossage, R. A., Van de Kuil, L. A., and Van Koten, G. *Acct. Chem. Res.* **1998**, 31, 423–431.
- [10] Kleij, A. W., Gossage, R. A., Jastrzebski, J. T., Boersma, J., and Van Koten, G. *Angew. Chem. Int. Ed.* **2000**, 39, 176–178.
- [11] Severin, K. *Curr. Org. Chem.* **2006**, 10, 217–224.
- [12] Bendetti, M., Forti, L., Ghelfi, F., and Ronzoni, R. *Tetrahedron*, **1997**, 53, 14031–14042.
- [13] Udding, J. H., Tuijip, C. J., Hiemstra, H., and Speckman, W. N. *Tetrahedron*, **1999**, 50, 1907–1918.
- [14] Udding, J. H., Tuijip, C. J., Hiemstra, H., and Speckman, W. N. *J. Org. Chem.* **1994**, 59, 1993–2003.
- [15] Clark, A. J., Battle, G. M., and Bridge, A. *Tet. Lett.* **2001**, 42, 4409–4412.
- [16] Grogne, E.L., Claverie, J., and Poli, R. *J. Am. Chem. Soc.* **2001**, 39, 9513–9524.
- [17] Brandts, J.A., Geijn, P.V., Faassen, E.E., Boersma, J., and Koten, G.V. *J. Organom. Chem.* **1999**, 584, 246–253.
- [18] Maria, S., Stoffelbach, F., Mata, J., Daran, J., Richard, P., and Poli, R. *J. Am. Chem. Soc.* **2005**, 127, 5946–5956.
- [19] Eckenhoff, W.T., and Pintauer, T. *Cat. Rev., Sci. & Eng.* **2010**, 51, 1–59.
- [20] Pintauer, T. *European Journal of Inorg. Chem.* **2010**, 17, 2449–2460.
- [21] Pintauer, T., and Matyjaszewski, K. *Coord. Chem. Rev.* **2005**, 249, 1155–1184.
- [22] Pintauer, T., and Matyjaszewski, K. *Top. Organomet. Chem.* **2009**, 26, 221–251.
- [23] Eckenhoff, W.T., Garrity, S.T., and Pintauer, T. *Eur. J. Inorg. Chem.* **2008**, 16, 563–571.
- [24] Taylor, M.J., Eckenhoff, W., and Pintauer, T. *Dalton Trans.* **2010**, 39, 11475–11482.
- [25] Kaur, A., Ribelli, T. G., Schroder, K., Matyjaszewski, K., and Pintauer, T. *Inorg. Chem.* **2015**, 54, 1474–1486.
- [26] Pintauer, T., Eckenhoff, W.T., Ricardo, C., Balili, M.N., Biernesser, A.B., Noonan, S.T., and Taylor, M. T. *Chem. Eur. Jour.* **2009**, 15, 38–41.
- [27] Quebatte, L., Thommes, K., and Severin, K. *J. Am. Chem. Soc.* **2006**, 23, 7440–7441.
- [28] Eckenhoff, W., and Pintauer, T. *Inorg. Chem.* **2007**, 15, 5844–5846.
- [29] Ricardo, C., and Pintauer, T. *Chem. Comm.* **2009**, 3029–3031.
- [30] Eckenhoff, W., and Pintauer, T. *Cat. Rev.* **2010**, 52, 1–59.
- [31] Pintauer, T., and Matyjaszewski, K. *Chem. Soc. Rev.* **2008**, 37, 1087–1097.
- [32] Matyjaszewski, K., Gobelt, B., Paik, H., and Horwitz, C. *Macromol.* **2001**, 34, 430–440.
- [33] Matyjaszewski, K., Paik, H., Zhou, P., and Diamanti, S. J. *Macromol.* **2001**, 34, 5125–5131.
- [34] (a) Balili, M. N., and Pintauer, T. *Inorg. Chem.* **2010**, 49, 5642–5649; (b) Pintauer, T., Braunecker, W., Collange, E., Poli, R., Matyjaszewski, K. *Macromol.* **2004**, 37, 2679–2682.
- [35] Eckenhoff, W.T., Biernesser, A. B., and Pintauer, T. *Inorg. Chem.* **2012**, 51, 11917–11929.
- [36] Marque, S., Le Mercier, C., Tordo, P., and Fisher, H. *Macromol.* **2000**, 33, 4403–4410.
- [37] Apex2 v2013.4-1 (**2013**) Bruker Advanced X-ray Solutions, Bruker AXS Inc., Madison, Wisconsin, USA.

- [38] (a) SHELXTL (Version 6.14) (**2000-2003**) Bruker Advanced X-ray Solutions, Bruker AXS Inc., Madison, Wisconsin: USA; (b) Sheldrick, G. M. *Acta Cryst.* **2008**, A64, 112–122.
- [39] Sheldrick, G. M. (**2013**). University of Göttingen, Germany.
- [40] Pintauer, T., Zhou, P., Matyjaszewski, K. *J. Am. Chem. Soc.* **2002**, 124, 8196–8197.
- [41] Matyjaszewski, K., Paik, H., Zhou, P., Diamanti, S. J. *Macromol.* **2001**, 34, 5125–5131.
- [42] Tang, W., Kwak, Y., Braunecker, W., Tsarevsky, N.V., Coote, M.L., and Matyjaszewski, K. *J. Am. Chem. Soc.* **2008**, 130, 10702–10713.
- [43] Zhang, C.X., Kaderli, S., Costas, M., Kim, E., Neuhold, Y., Karlin, K.D., and Zuberbuhler, A.D. *Inorg. Chem.* **2003**, 42, 1807–1824.
- [44] Dolbier, W. R. *Guide to Fluorine NMR for Organic Chemists*, First ed.; John Wiley & Sons: USA, Chapter 5, **2009**.
- [45] Hasse, C., Sarko, C. R., DiMare, M. *J. Org. Chem.* **1995**, 60, 1777–1787.
- [46] Mason, J. *Chem. Rev.* **1987**, 87, 1299–1312.
- [47] Hsu, S. C., Chien, S. S., Chen, H. H., Chiang, M. Y. *Chin. Chem. Soc.* **2007**, 54, 685–692.
- [48] Ma, E. S., Patrick, B. O., James, B. R. *Dalton Trans.* **2013**, 42, 4291–4298.
- [49] Buchler, J. W., Hvastijova, M., Kohout, J., Kozisek, J. *Trans. Met. Chem.* **1998**, 23, 215–220.
- [50] Skene, W. G., Belt, S. T., Connolly, T. J., Hahn, P., and Scaiano, J. C. *Macromol.* **1998**, 31, 9103–9105.
- [51] Li, I., Howell, B. A., Matyjaszewski, K., Shigemoto, T., Smith, P. B., and Priddy, D. B. *Macromol.* **1995**, 28, 6692–6693.