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Copper(I)/Ligand–Catalyzed 5–*endo* Radical Cyclization–Aromatization of 2,2,2–Trichloroethyl Vinyl Ethers: Synthesis of 2,3–Difunctionalized 4–Chlorofurans

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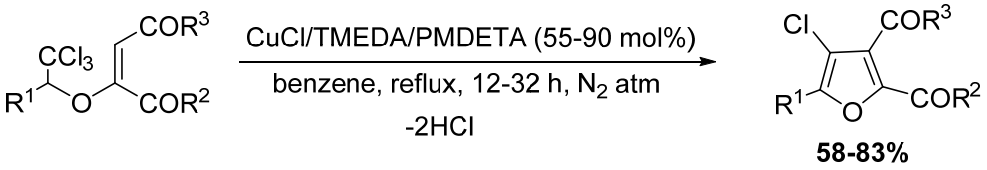


R^1 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$, *n*-Et, *i*-Pr, H; R^2 = Me, OMe, R^3 = OEt, OMe and R^2-R^3 = 1,2-C_6H_4

Abstract: Copper(I)/ligand–catalyzed one pot synthesis of highly substituted 2,3–difunctionalized–4–chlorofurans has been reported. The reaction proceeds via a Cu(I)–catalyzed regioselective 5–*endo–trig* radical cyclization of 2,2,2–trichloroethyl vinyl ethers followed by the base–promoted dehydrochlorination. The success of the kinetically disfavored 5–*endo* cyclization was attributed to the formation of captodatively stabilized radical intermediate in the cyclization step and relatively high reaction temperature. Synthetic application of this protocol was also demonstrated in the preparation of alkyl and aryl substituted 4–chlorofuranonapthoquinones.

INTRODUCTION

5–*Endo–trig* radical cyclization is a kinetically 'disfavored' process according to the Baldwin–Beckwith set of empirical rules but its product is thermodynamically stable due to less ring strain.[1] Therefore, it has been observed in good number of systems involving cyclization of radicals[2] such as carbon–,[2a-c] sulphur–[2d] and silicon–,[2e] nitrogen–centered[2f,2g] onto C=C bond and carbon–centered radicals[3] onto heteroatom–containing double bonds such as azo,[3a-b] imine[3c-d] and carbonyl[3e-g] groups etc. producing a variety of carbo– and heterocyclic compounds. Haloenamides[4] are most extensively investigated systems for *5–endo* radical cyclization reactions and their products have found applications in synthesis of natural products and drugs.[4i] On the contrary, 5–*endo* radical cyclization on β–haloalkyl vinyl ether is scarcely investigated and is a methodological challenge.[5] A tin hydride–promoted 5–*endo* radical cyclization of β–iodovinyl ethers has been reported to yield a few tetrahydrofurans.[5a] However, the reaction suffers from several disadvantages associated with this methodology such as non–regioselectivity, access of toxic tin

reagent, low yields of the products, reductive dehalogenation of the starting material and tedious separation of the products. On the other part, Copper(I)–catalyzed *5–endo–trig* halogen atom transfer radical cyclization (HATRC) is free of such limitations.[4a] A combination of copper(I) salt and *tert*–amine ligands[4a,4e] under different reaction conditions[4f] in the *5–endo* cyclization of structurally different α–haloacetaenamides is proven to be a highly flexible, mild and efficient methodology. Moreover, the *5–endo* cyclic product undergo Cu(II)–mediated radical polar–crossover reaction and *tert*–amine ligand–mediated dehydrohalogenation to generate two olefinic bonds.[4c] Although, our laboratory previously demonstrated a DBU–promoted double dehydrohalogenation of trichlorotetrahydrofuran to yield chlorofurans.[6] The potential of β–trihaloroethylvinyl ethers as viable system to undergo *5–endo* radical cyclization and spontaneous dehydrohalogenations of its *5–endo* product in the presence of Cu(I)/ligand to give an aromatic system (furan ring) in single step, has not been envisaged so far.

A furan core bearing ester, acid and keto functionalities is a key structural unit of many naturally occurring compounds[7] (pentacyclic polyketides,[7b] furanonapthoquinones,[7c] furanosesquiterpenes,[7d] furanosteroids,[7e] pseudopterenes,[7f] furanocembranolides[7g]), drugs molecules[7a,8] (**Fig. 1**), materials[9] and useful synthetic intermediates.[10] A β–chlorine functionality[6,11] in a furan ring enhances its synthetic utility further by influencing the reactivity of its furan ring[6b] and providing a center for specific chemical reactions such as metal–catalyzed coupling and nucleophilic substitution reactions.[11a–c] Such β–chlorofurans have been transformed into bioactive natural products,[12] pharmaceutically important furans and non–furanoid compounds.[13] They are potential substrates for studying 'structure–activity relationships"[14] and 'halogen–effect" in Diels–Alder cycloaddition reaction.[6b] High stability and low cost of chlorofurans among other halofurans make them suitable particularly for industrial applications.[6b,13,15] Despite their useful applications, a few methods are reported for the synthesis of functionalized β–chlorofurans. Furthermore, these methods suffer from the limitations with regard to substrate specificity,[11c,15] low yield of the products,[16] number of steps,[17,14c] accessibility of starting materials,[14c,18] and nature of the substituents.[11c,15,19] Although, the reactions of activated alkenes and alkynes (or their derivatives) and has been extensively explored.[20] Recently, Antonchick and co-worker[21] reported a highly efficient, mild and direct method for the synthesis of polysubstituted furans by an intermolecular radical addition of carbonyl compounds to alkynes. However, there is still a need for a method of general applicability to install the highly useful halogen atom functionality.

With consideration to achieve a Cu(I)–catalyzed regiospecific 5–*endo*–*trig* radical cyclization of β–haloethylvinyl ethers, and develop a direct and efficient route for the synthesis of such chlorofurans, herein, we report one pot cyclization–aromatization of β–haloethylvinyl ethers to access highly functionalized β–chlorofurans.

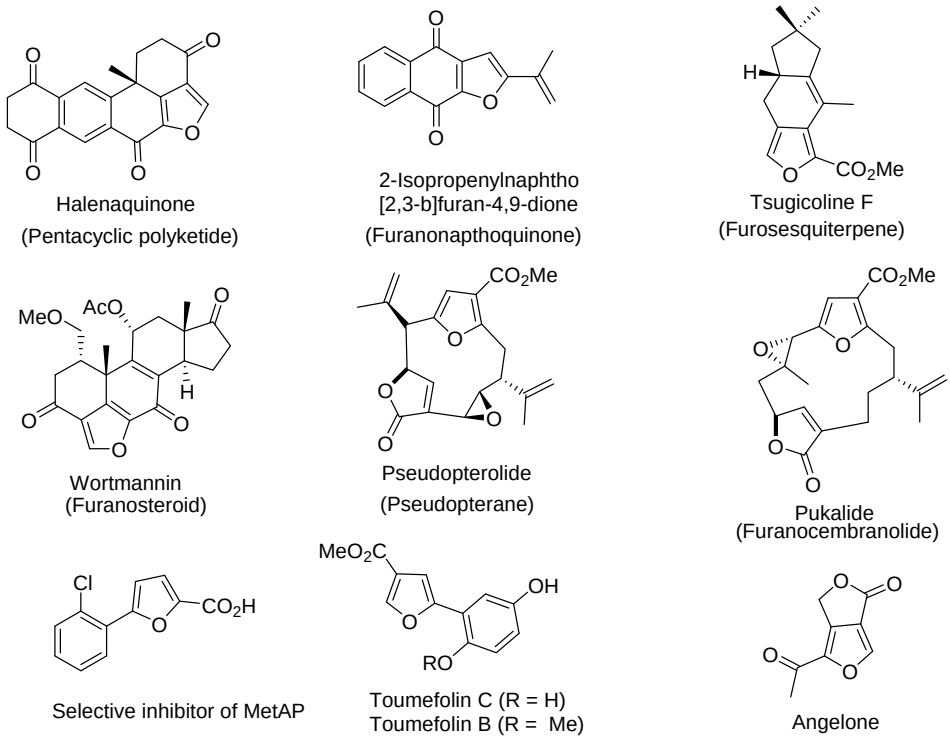


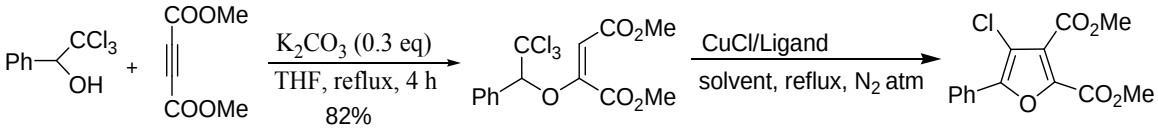
Fig. 1 Some Natural products and Drugs Molecules

RESULT AND DISCUSSION

First, an HATRC precursor (*E*)–dimethyl–2–(2,2,2–trichloro–1–phenylethoxy)maleate **2a** (**Table 1**) was prepared by Michael addition of 1–phenyl–2,2,2–trichloroethanol[22] **1a** to DMAD.[23] The reaction of vinyl ether **2a** with varying amounts of CuCl was performed in the presence of commercially available 2,2′–bipyridine (bpy), tetramethylethylenediamine (TMEDA) and pentamethyldiethylenetriamine (PMDETA) ligands at reflux under a nitrogen atmosphere. The data with minimum required amount of the catalyst to complete the reaction are shown in Table 1. The reaction followed a regioselective 5–*endo*–*trig* radical cyclization pathway. Although, the reaction required more than stoichiometric amount of the CuCl/bpy (120 mol%) for completion (**Entry 1**, **Table 1**). Purification of the crude product by column chromatography using neutral alumina afforded a colorless solid as the major product **3a** and a very small amount of the reduced starting material. The reduced starting material was

formed probably due to hydrogen atom abstraction by the intermediate radical from the solvent DCE.[24] The reaction of the vinyl ether **2a** in a poor hydrogen atom donor solvent benzene[24] at reflux was heterogeneous but the reduction of the starting material could be prevented (**Entry 2**, **Table 1**). TMEDA was found to be more effective. The reaction was completed in 18 h to obtain **3a** in 81% yield with lower catalyst loading (**Entry 3**, **Table 1**). However, PMDETA was not as effective as TMEDA as a higher amount of the catalyst was required for reaction completion with extended reaction time (**Entry 4, Table 1**). A possible explanation of relatively higher reactivity of Cu(I)/TMEDA complex over Cu(I)/PMDETA could be the availability of more nitrogen sites for proton abstraction in earlier case (**Table 1**, see molar concentration of ligands) in the base–promoted dehydrochlorination step. The necessity of higher amount of the complex might be due to its deactivation by the liberated HCl produced during the reaction by protonating the ligand. However, the reaction was incomplete with lower amount of the catalyst, for example 10 mol% of CuCl provided <10% of **3a** in all cases. No cyclization product formed when the reaction of **2a** was conducted at room temperature for 24 h even with the stoichiometric amount of CuCl/TMEDA and CuCl/PMDETA in benzene.

Table 1. CuCl/Ligand catalyzed 5–*endo* chlorine atom transfer radical cyclization–aromatization of **2a**[a]



1a **2a** **3a**

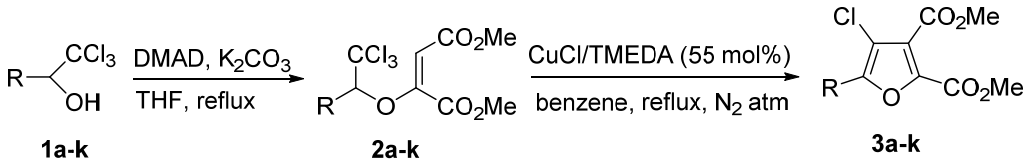
Entry	CuCl (mol %)	Ligand	CuCl/Ligand (molar ratio)	Solvent[b]	Time (h)	3a (%)
1	120	bpy	1:1	DCE	18	69
2	120	bpy	1:1	benzene	24	75
3	55	TMEDA	1:2	benzene	18	81
4	70	PMDETA	1:1	benzene	20	80

[a]All he reactions were performed with 1 mmol of **2a** under a N_2 atmosphere at reflux.

[b]Reaction mixture was heterogeneous in benzene.

This methodology was further applied to 2,2,2–trichloroethyl vinyl ethers **2b–k** under the optimized reaction conditions to synthesize functionalized chlorofurans **3b–k** in 67–82% yields with complete regioselectivity (**Table 2**). The structures of chlorofurans **3** were established by ^{1}H NMR, ^{13}C NMR and IR spectroscopy and mass spectrometry. The formation of the chlorofurans **3** was further supported by single crystal X–ray diffraction data of the *p*–tolyl derivative **3b** (see supporting information). The reaction time required for the formation of chlorofurans **3** was in accordance with the ease of dehydrochlorination of the cyclized product (*p*–$O_2NC_4H_4$ < pyridyl < Ph < alkyl). Several functional groups such as nitro, ester and halogen atoms were survived under such reaction conditions.

Table 2. Synthesis of functionalized 4–chlorofurans **3**[a]

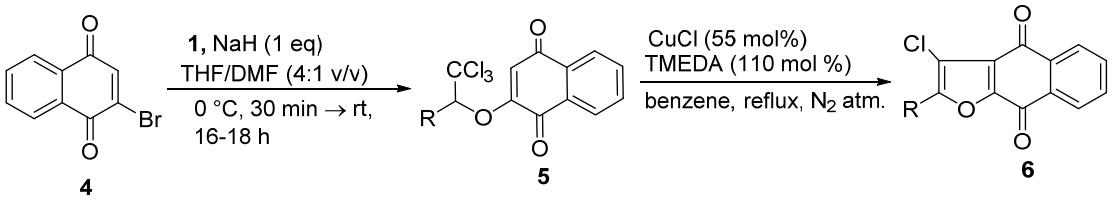


1a-k **2a-k** **3a-k**

Entry	**1**	**R**	Vinyl ether **2**		4–Chlorofuran **3**	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	**a**	Ph	4	82	18	81
2	**b**	4–MeC_6H_4	4	80	18	71
3	**c**	2–ClC_6H_4	5	70	24	67
4	**d**	3–ClC_6H_4	4	78	18	73
5	**e**	4–ClC6H4	4	80	16	75
6	**f**	4–BrC_6H_4	4	82	18	71
7	**g**	4–$MeOC_6H_4$	4	80	16	75
8	**h**	4–$O_2NC_6H_4$	4	79	12	76
9	**i**	2–pyridyl	4	80	16	75
10	**j**	*n*–Et	4	78	24	80
11	**k**	*i*–Pr	4	75	24	82

[a]In first step, all the reactions were performed by taking **1** (10 mmol) and DMAD (10 mmol) and K_2CO_3 (3 mmol) in THF at reflux. In second step, vinyl ether (1 mmol), CuCl (55 mol%) and TMEDA (110 mol%) were reacted in benzene at reflux under a nitrogen atmosphere.

Furanonapthoquinones are biologically important natural products and their cytotoxic activity varies with the type of substituent on parent naphtho[2,3–b]–furan–4,9–dione.[7c] The synthetic application of this approach was demonstrated by the treatment of vinyl ethers **5a** and **5b** (**Scheme 1**) with CuCl/TMEDA under the optimized reaction conditions to obtain 4–chlorofuranonapthoquinones **6a** (R = Ph) and **6b** (R = Me) in 76% and 83% yields, respectively.

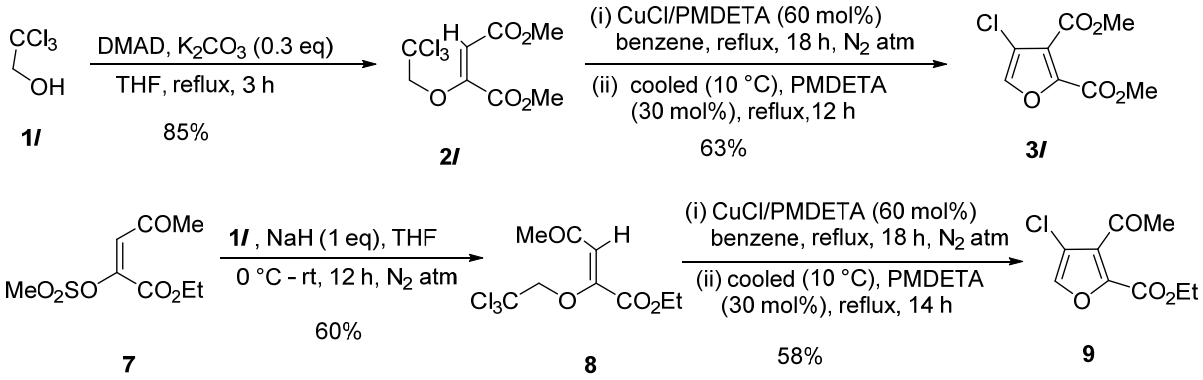


1 R	Time (h)	5	Time (h)	6
a: Ph	18	76	10	76
b: Et	16	78	12	83

Scheme 1

Furthermore, the synthesis of trisubstituted 4–chlorofurans could be realized with slight modifications in the reaction conditions. The α–unsubstituted vinyl ether **2*l*** (**Scheme 2**) did not undergo the expected 5–*endo* cyclization to completion on treatment with CuCl/TMEDA catalyst even after prolonged heating for 24 h with large excess of the catalyst (1 equiv) and only 23% of the product **3*l*** along with 67% of starting material was obtained. In this case, the ligand PMDETA was found to be more effective than TMEDA. Probably, a more effective ligand i.e. PMDETA was required to promote the reaction of less activated vinyl ether **2*l*** during the cyclization step. Thus, **2*l*** was refluxed 60 mol% of CuCl/PMDETA (1:1 mol ratio) in benzene at reflux for 18 h, followed by addition of 30 mol % of PMDETA into the cooled reaction mixture and reflux for another 12 h. Usual work up of the reaction mixture and purification by column chromatography gave **3*l*** in 63% isolated yield. The vinyl ether **8** on a similar two stage treatment with CuCl/PMDETA (60 mol%) for 18 h and with PMDETA (30 mol%) for 14 h furnished **9** in 58%

yield. In these cases, the dehydrochlorination was not as facile as in the case of tetrasubstituted 4–chlorofurans due to the absence of the substituent at C–5 position, thus requiring an additional amount of the basic ligand.

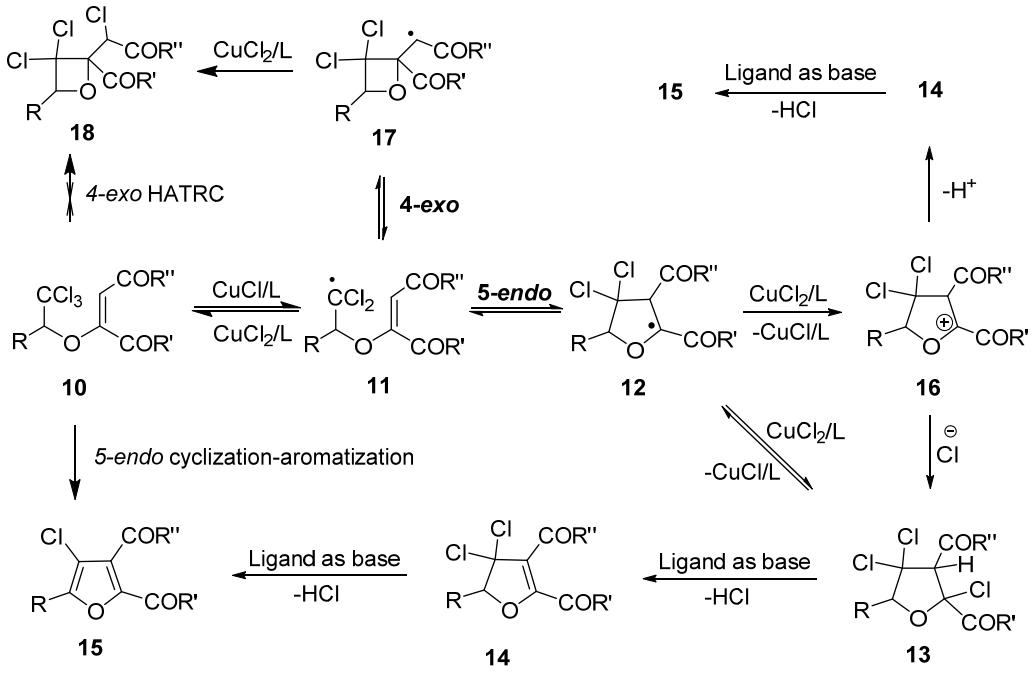


Scheme 2

The functionalized 4–chlorofurans **3**, **6** and **9** were stable at low temperatures unlike earlier reported alkyl and aryl substituted 3–chlorofurans which were stable in hydrocarbon solvents.[6b]

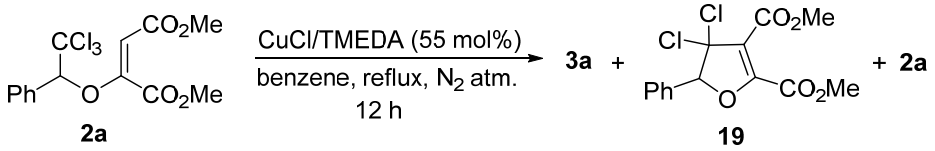
MECHANISTIC STUDY

A plausible mechanism involving 5–*endo*–*trig* chlorine atom transfer radical cyclization of the trichloroethyl vinyl ethers **10 (Scheme 3**) to the α–chlorotetrahydrofuran **13** followed by ligand–promoted dehydrochlorination has been proposed. Captodative radical center bearing electron donating alkoxy and electron withdrawing ester groups are known to abstract halogen atom from halogen atom source easily.[25] α–Chlorotetrahydrofuran **13** might undergo successive dehydrochlorination to furan **15** in the presence of tertiary amine. Another possibility is the formation of a carbocation **16** by losing one electron from the radical intermediate **12** to Cu(II), followed by proton abstraction to give **14** first and then dehydrochlorination to **15**. Such ligand promoted dehydrochlorination reaction in some CuCl/bpy–catalyzed ATRC reactions has been observed earlier where bpy promoted the elimination.[4d,4f] α–Chloroethers are known to undergo dehydrochlorination easily.[26] Further, the dehydrochlorination of the dihydrofuran **14** occurs easily due to the formation of the aromatic product **15**.



Scheme 3. Proposed mechanism for the formation of 4–chlorofurans

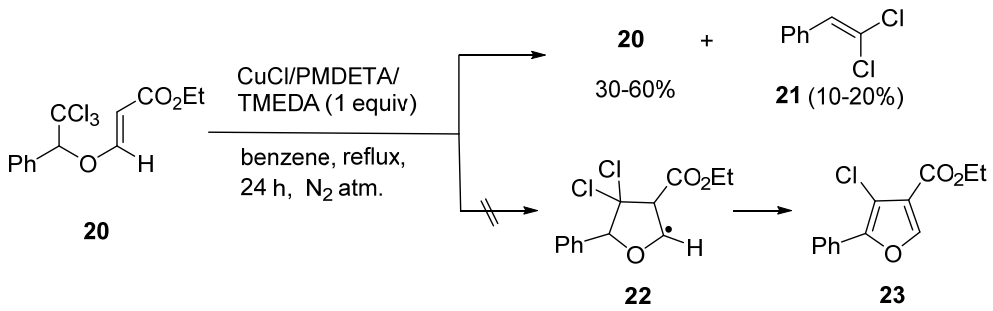
The formation of the dihydrofuran intermediate **14** (**Scheme 3**) was confirmed by quenching the reaction of the vinyl ether **2a (Scheme 4)** under optimized condition after 12 h instead of 18 h. Further purification of the crude product gave the 4–chlorofuran **3a**, a small amount of the dihydrofuran **19** and the starting material **2a**.



Scheme 4

Although, the 4–*exo*–*trig* radical cyclization is kinetically favored according to Beckwith–Baldwin's rule,[1] no 4–*exo* cyclization product **18** could be detected in ^{1}H NMR of crude products. 5–*Endo* radical cyclizations are called 'disfavored' but lead to the formation of thermodynamically more stable products due to relatively less ring strain in the 5–membered ring. Chatgilialoglu et al.[1d] have further elaborated the kinetics of *4-exo* and *5-endo*-trig radical cyclizations by experimental and theoretical studies. 5–*endo* products are predominantly or exclusively formed under equilibrium conditions.[4g] In the present case, the relatively high reaction temperature (refluxing benzene)

might also have promoted reversibility of the 4–*exo* cyclization leading to the formation of the thermodynamically more stable 5–*endo* cyclization product **12**. The preference to the formation of 5–*endo* product at higher temperatures has been observed earlier.[4h] Additionally, a carbonyl group on the radical acceptor alkenic bond at α–position, has been observed earlier to provide assistance in attainment of a less strained transition state for the generally unfavorable 5–*endo* cyclization.[5a] 5–*Endo* cyclization was expected to be further facilitated due to greater stabilization of the radical intermediate **12** by captodative effect.[1,25] These features might have contributed to the formation of the 5–*endo* cyclization product exclusively in the present case. The effect of captodative stablization was supported by the fact that the trichloroethyl vinyl ether mono–ester **20** (**Scheme 5**) did not undergo 5–*endo* cyclization in the absence of an ester or a keto group at α–position to stabilize the radical intermediate **22** initially formed by 5–*endo* cyclization by the captodative effect. No 5–*endo* cyclization product **23** was isolated or detected. Using PMDETA in the place of TMEDA under the same reaction conditions produced higher amount of the elimination product **21** (20%), nearly 30% of the starting material **20** and an unidentifiable complex mixture. The elimination product **21** could have arisen by fragmentation of **20** by C–O bond cleavge.[5b-c]



Scheme 5

CuCl/bpy–catalyzed cyclization reaction of O–homoallylic α–chloroglycolic esters occur preferentially via a similar but acyclic captodative radical mechanism,[27] the oxidation of captodative radical intermediate to carbocation by $CuCl_2$/bpy complex also occurred to some extent (<10%). Under the similar reaction conditions employed in the present case, the captodative radical **12** might be expected to oxidize to the carbocation **16** (**Scheme 3**) by $CuCl_2$–complex formed during progress of the reaction. This carbocation may reversibly combine with the chloride ion to produce the α–chlorotetrahydrfuran intermediate **13** and undergo dehydrochlorination or undergo fast deprotonation[4d,4f] to give the dihydrofuran intermediate **14** directly. Attempts to trap the captodative radical **12**

intermolecularly[4b,4c] in the reaction of **2a** by IBN radical (AIBN) and alkenes styrene and methyl acrylate under the optimized reaction conditions met with failure and only chlorofuran **3a** was isolated by column chromatography. An attempt to trap the carbocation **16** or α-chlorotetrahydrofuran **13** with ethanol in the reaction of **2a** in benzene/ethanol (4:1 ratio) in the presence of 1 equivalent of CuCl and TMEDA failed. The vinyl ether **2a** decomposed under such reaction conditions. Therefore, the exact nature of these intermediates could not be confirmed. Acyclic captodative radical center bearing an alkoxy and an ester groups is not known to be much sensitive to oxidation (<10%) to carbocation in the presence of Cu(II) species.[27] The retention of radical character of cyclic captodative radical **12** under similar radical conditions is expected in the present case as well. Thus, a radical mechanism appears to be more favorable. However, the oxidation of the captodative radical intermediate to a carbocation by Cu(II) species followed by aromatization could not be ruled out.

CONCLUSIONS

In conclusion, a novel copper(I)/ligand–catalyzed tandem 5–*endo* radical cyclization–aromatization of 2,2,2–trichloroethyl vinyl ethers has been reported for the synthesis of polysubstituted 4–chlorofurans in good yields. The success of the kinetically disfavored 5–*endo* cyclization was attributed to the formation of the captodatively stabilized radical intermediate in the cyclization step and relatively high reaction temperature. A plausible mechanism has been proposed. Application of this methodology for the synthesis of biologically important furanonapthoquinones has also been demonstrated. These furans could be potential synthetic intermediates for various biologically important molecules and as substrates for studying 'structure–activity relationships and halogen–effect'.

EXPERIMENTAL SECTION

General Information

IR spectra were recorded on an FT–IR spectrometer by taking solid samples as KBr pellets and liquids as thin films on KBr disks. NMR spectra were recorded on a 300 MHz FT NMR spectrometer in $CDCl_3$ with TMS as internal standard. Multiplicities are indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublet). ^{13}C DEPT spectra were routinely recorded to identify different types of carbons. Mass spectra were recorded on a high–resolution mass spectrometer (ESI–TOF) in positive–ion mode.

Melting points were determined on an electrically heated apparatus by taking the samples in a glass capillary sealed at one end and are uncorrected. The progress of the reaction was monitored by TLC using a glass plate coated with a TLC grade silica gel. Iodine was used for visualizing the spots. For column chromatography, silica gel and neutral alumina were used as the stationary phase, and *n*–hexane–ethyl acetate mixtures were used as the mobile phase. Solvents were evaporated on a rotary evaporator under reduced pressure using an aspirator. Methyl acrylate, styrene, AIBN, DBU and sodium trichloroacetate, sodium hydride, 2,2,2–trichloroethanol, DMAD, bpy, TMEDA, PMDETA, ethyl propiolate, aliphatic and aromatic aldehydes, methanesulphonyl chloride, K_2CO_3, liquid ammonia and DMF (dried) were commercially available and used as received. THF was dried over KOH pellets overnight, distilled and stored over sodium wires. Benzene was distilled, and stored over sodium wires. DCE was dried by distilling over anhydrous P_2O_5. The commercial nitrogen gas was used after passing successively through traps containing solutions of alkaline anthraquinone–sodium dithionite, alkaline pyrogallol, conc. H_2SO_4 and KOH pellets. Nitrogen atmosphere was created by Schlenk technique in all the experiments carried out under a nitrogen atmosphere.

All the trichloromethy carbinols **1a–k** were prepared by the reaction of aldehydes with chloroform in the presence of catalytic amounts of DBU[22b] or by reaction of aldehydes with trichloroacetic acid in DMSO as reported in the literature.[22a] 2–Bromo–1,4–napthoquinone[28] **4** and ethyl 2–hydroxy–4–oxopent–2–enoate[29] were prepared by known procedures.

Preparation of 2,2,2–trichloroethyl vinyl ethers 2a–*l*: Acyclic precursors **2a–*l*** prepared by Michael addition of 2,2,2–trichloroethanol[22] **1a–*l*** to DMAD relying on the well known addition of alcohol to DMAD[23] with slight modifications. The (*E*)–stereochemistry was assigned to them by comparing the values of the ^{1}H NMR chemical shifts (δ) of the olefinic protons with the ones reported in the literature[23a] for the olefinic protons of structurally analogous dimethyl 2–alkoxymaleates.

General procedure: A suspension of the 2,2,2–trichloroethalnol **1a–*l*** (10 mmol), DMAD (1.420 g, 10 mmol) and K_2CO_3 (0.424 g, 3 mmol) in dry THF (40 mL) was heated at reflux. The progress of the reaction was monitored by TLC, which indicated completion of the reaction by disappearance of the starting organic material after 3–5 h. After completion of the reaction, the reaction mixture was cooled and evaporated under reduced pressure. The residual mass was treated with diethyl ether or ethyl acetate (150 mL) and filtered. The filtrate was washed with water (2×20

mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure to obtain the crude adduct which on purification by column chromatography on a small pad of neutral alumina using a *n*–hexane/ethylacetate mixture (95:5–90:10, v:v) as solvent for elution afforded the trichloroethyl vinyl ethers **2a–*l*** in (75–85%) high yields.

Dimethyl 2–(2,2,2–trichloro–1–phenylethoxy)maleate ***2a:*** White crystals, mp 120 ˚C (DCM–*n*–hexane), 3.013g, 82% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.63 (s, 3H), 3.91 (s, 3H), 5.07 (s, 1H), 5.42 (s, 1H), 7.43–7.47 (m, 3H), 7.57–7.60 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.6 , 53.0 , 89.0, 97.6, 98.0, 128.4, 129.3, 130.3, 130.8, 158.4, 162.8, 165.2 ppm; IR (KBr): ν_{max} 2950(w), 1729(s), 1633(s), 1443(m), 1383(m), 1223(s), 1183(s), 1150(s), 1041(m), 832(m), 782(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{13}Cl_3O_5Na$ 388.9721, found 388.9721.

Dimethyl 2–(2,2,2–trichloro–1–p–tolylethoxy)maleate ***2b:*** White crystals, mp 114 ˚C (DCM–*n*–hexane), 3.052g, 80% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.37 (s, 3H), 3.61 (s, 3H), 3.90 (s, 3H), 5.07 (s, 1H), 5.39 (s, 1H), 7.23 (d, 2H, *J* = 8.1 Hz), 7.46 (d, 2H, *J* = 8.1 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.3, 51.6, 53.1, 89.1, 97.5, 98.3, 127.9, 129.1, 129.2, 140.5, 158.5, 162.9, 165.4 ppm; IR (KBr): ν_{max} 2948(w), 1729(s), 1636(s), 1438(w), 1213(s), 1155(s), 1026(m), 830(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{15}Cl_3O_5Na$ 402.9865, found 402.9877.

Dimethyl 2–(2,2,2–trichloro–1–(2–chlorophenyl)ethoxy) maleate ***2c:*** Colorless crystals, mp 94 ˚C (DCM–*n*–hexane), 2.815g, 70% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.63 (s, 3H), 3.90 (s, 3H), 5.11 (s, 1H), 6.03 (s, 1H), 7.34–7.48 (m, 3H), 7.79 (dd, 1H, *J* = 7.2, 2.1 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.8, 53.2, 83.9, 97.3, 97.7, 127.4, 129.2, 129.7, 129.8, 131.7, 135.5, 158.1, 162.8, 165.3 ppm; IR (KBr): ν_{max} 2956(w), 1750(s), 1721(s), 1633(s), 1438(m), 1376(m), 1327(m), 1211(s), 1150(s), 1034(m), 825(m), 784(m), 754(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}Cl_4O_5Na$ 422.9331, found 422.9341.

Dimethyl2–(2,2,2–trichloro–1–(3–chlorophenyl)ethoxy) maleate ***2d:*** Colorless crystals, mp 107 ˚C (DCM–*n*–hexane), 3.135g, 78% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.64 (s, 3H), 3.90 (s, 3H), 5.09 (s, 1H), 5.39 (s, 1H), 7.34–7.49 (m, 3H), 7.58 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.7, 53.1, 88.2, 97.6, 98.0, 127.5, 129.3, 129.7, 130.6, 132.9, 134.4, 158.1, 162.6, 165.1 ppm; IR (KBr): ν_{max} 3103(w), 1727(s), 1632(s), 1574(m), 1476(m), 1437(s), 1380(s), 1220(s), 1145(s), 1034(m), 820(m), 763(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}Cl_4O_5Na$ 422.9331, found 422.9345.

Dimethyl 2–(2,2,2–trichloro–1–(4–chlorophenyl)ethoxy) maleate ***2e:*** Colorless crystals, mp 116 ˚C (DCM–*n*–hexane), 3.216g, 80% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.63 (s, 3H), 3.90 (s, 3H), 5.07 (s, 1H), 5.41 (s, 1H), 7.41 (d, 2H, *J* = 8.4 Hz), 7.52 (d, 2H, *J* = 8.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.8, 53.1, 88.3, 97.8, 98.0, 128.8, 129.5, 130.7, 136.6, 158.2, 162.7, 165.1 ppm; IR (KBr): ν_{max} 2998(w), 1745(s), 1632(s), 1494(m), 1442(m), 1375(m), 1216(s), 1154(s), 1023(m), 830(s), 775(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}Cl_4O_5$ Na 422.9331, found 422.9346.

Dimethyl 2–(1–(4–bromophenyl)–2,2,2–trichloroethoxy) maleate ***2f:*** Colorless crystals, mp 117 ˚C (DCM–*n*–hexane), 3.660g, 82% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.64 (s, 3H), 3.90 (s, 3H), 5.06 (s, 1H), 5.39 (s, 1H), 7.46 (d, 2H, *J* = 8.4 Hz), 7.59 (d, 2H, *J* = 8.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.8, 53.2, 88.4, 97.7, 98.0, 125.0, 130.0, 130.9, 131.8, 158.2, 162.7, 165.1 ppm; IR (KBr): ν_{max} 3088(w), 1745(s), 1721(s), 1631(s), 1492(w), 1440(m), 1375(m), 1340(m), 1215(s), 1154(s), 1020(m), 865(w), 772(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}BrCl_3O_5Na$ 466.8810, found 466.8826.

Dimethyl 2–(2,2,2–trichloro–1–(4–methoxyphenyl)ethoxy) maleate ***2g:*** Colorless crystals, mp 104 ˚C (DCM–*n*–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz), 3.183g, 80% yield; δ 3.62 (s, 3H), 3.82 (s, 3H), 3.90 (s, 3H), 5.07 (s, 1H), 5.38 (s, 1H), 6.94 (d, 2H, *J* = 8.4 Hz), 7.50 (d, 2H, *J* = 8.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.7, 53.1, 55.2, 88.9, 97.5, 98.6, 113.8, 122.7, 130.7, 158.5, 161.0, 162.9, 165.4 ppm; IR (KBr): ν_{max} 3025(w), 1752(s), 1709(s), 1633(s), 1515(m), 1442(m), 1374(m), 1309(m), 1256(m), 1212(s), 1150 (s), 1027(m), 831(m), 752(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{15}Cl_3O_6Na$ 418.9809, found 418.9826.

Dimethyl 2–(2,2,2–trichloro–1–(4–nitrophenyl)ethoxy) maleate ***2h:*** Light yellow crystals, mp 144 ˚C (DCM–*n*–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz), 3.260g, 79% yield; δ 3.64 (s, 3H), 3.92 (s, 3H), 5.09 (s, 1H), 5.56 (s, 1H), 7.83 (d, 2H, *J* = 8.7 Hz), 8.31 (d, 2H, *J* = 8.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.9, 53.3, 87.8, 97.1, 98.7, 123.5, 130.6, 137.8, 149.1, 157.8, 162.5, 164.9 ppm; IR (KBr): ν_{max} 2921(w), 1747(s), 1721(s), 1635(s), 1525(m), 1438(m), 1349(m), 1144(s), 1030(m), 957(m), 826(m), 779(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}Cl_3NO_7$ Na 433.9565, found 433.9572.

Dimethyl 2–(2,2,2–trichloro–1–(pyridin–2–yl)ethoxy)maleate ***2i:*** Low melting solid, 2.950g, 80% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.62 (s, 3H), 3.92 (s, 3H), 5.16 (s, 1H), 5.63 (s, 1H), 7.37 (dd, 1H, *J* = 7.2, 5.1 Hz),

7.72–7.84 (m, 2H), 8.68 (d, 1H, J = 4.5 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.8, 53.2, 89.9, 96.9, 98.0, 123.4, 124.9, 137.1, 149.2, 151.7, 158.3, 162.8, 164.4 ppm; IR (KBr): ν_{max} 3106(w), 1721(s), 1644(w), 1593(m), 1517(s), 1438(m), 1345(s), 1303(s), 1129(s), 1073(m), 859(m), 801(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{13}H_{12}Cl_3NO_5Na$ 389.9672, found 389.9673.

Dimethyl 2–(1,1,1–trichlorobutan–2–yloxy)maleate ***2j:*** Colorless liquid, 2.495g, 78% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.11 (t, 3H, J = 7.5 Hz), 1.89–2.04 (m, 1H), 2.25–2.31 (m, 1H), 3.70 (s, 3H), 3.90 (s, 3H), 4.49 (dd, 1H, J = 9.6, 2.1 Hz), 5.48 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.1, 24.6, 51.8, 53.0, 89.2, 96.5, 99.2, 161.1, 163.1, 165.9 ppm; IR (KBr): ν_{max} 2983(m), 1753(s), 1716(s), 1632(s), 1440(m), 1368(m), 1273(m), 1152(s), 1036(m), 785(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{13}Cl_3O_5Na$ 340.9709, found 340.9721

Dimethyl 2–(1,1,1–trichloro–3–methylbutan–2–yloxy) maleate ***2k:*** Colorless liquid, 2.503g, 75% yield;; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.00 (d, 3H, J = 6.9 Hz), 1.08 (d, 3H, J = 6.9 Hz), 2.43–2.48 (m, 1H), 3.57 (s, 3H), 3.77 (s, 3H), 4.38 (d, 1H, J = 3.3 Hz), 5.37 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.7, 22.2, 30.9, 51.3, 52.6, 90.4, 95.9, 98.9, 161.0, 162.7, 165.4 ppm; IR (KBr): ν_{max} 2959(m), 1752(s), 1722(s), 1633(s), 1440(w), 1366(s), 1205(m), 1146(s), 1039(m), 823(w), 764(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{11}H_{15}Cl_3O_5Na$ 354.9885, found 354.9877.

Dimethyl 2–(2,2,2–trichloroethoxy)maleate ***2l:*** Colorless solid, mp 82–84 ˚C (DCM–*n*–hexane), 2.480g, 85% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.73 (s, 3H), 3.93 (s, 3H), 4.43 (s, 2H), 5.33 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.9, 53.2, 79.4, 93.3, 96.4, 159.2, 162.7, 165.3 ppm; IR (KBr): ν_{max} 3096(w), 2955(w), 1756(s), 1712(s), 1630(s), 1438(m), 1373(s), 1209(s), 1164(s), 1082(w), 1041(m), 852(m), 734(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_8H_9Cl_3O_5Na$ 312.9409, found 312.9408.

Preparation of 2,2,2–trichloroethyl vinyl ethers 5a and 5b: Acyclic precursors **5a–b** prepared by nucleophilic substitution reaction of 2–bromo–1,4–napthoquinone **4** with sodium salt of 1–substituted 2,2,2–trichloroethanols **1a** and **1j** using a method reported in the literature[30] with slight modification.

General procedure: To a suspension of NaH (0.48 g, 0.01 mol, 60% dispersion in mineral oil) in dry THF/DMF (25 mL, 4:1 v/v) was added a solution of the trichloroethanol **1a** (2.254 g, 0.01 mol) or **1j** (1.775 g, 0.01 mol) in dry THF (10 mL) drop wise at 0˚C over 15 min duration. The mixture was stirred at 0 ˚C for another 30 min and then

2–bromo–1,4–naphthoquinone **4** (2.370 g, 0.01 mol) was added into the suspension. The ice bath was then removed and the mixture was stirred at room temperature (25–30 ˚C). The progress of the reaction was monitored by TLC, which indicated the completion of the reaction by disappearance of the starting material after 18 h (16 h in the case of **1j**). The volatiles were removed under reduced pressure and water (20 mL) was added to the residual mass. The resulting suspension was extracted with ethylacetate (2×50 mL) and the combined solvent extract was washed with brine (2×20 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification of the residual mass by column chromatography on a small pad of neutral alumina using *n*–hexane/ethyl acetate mixture (98:1%, v/v) afforded the pure trichloroethyl vinylic ethers **5a** and **5b** as yellow solids in high yields.

2–(2,2,2–Trichloro–1–phenylethoxy)naphthalene–1,4–dione ***5a:*** Yellow solid, mp 101 ˚C (DCM–*n*–hexane), 2.60 g, 78% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.60 (s, 1H), 6.02 (s, 1H), 7.42–7.44 (m, 3H), 7.65 (d, 2H, *J* = 6 .0 Hz), 7.71–7.74 (m, 2H), 7.99–8.03 (m, 1H), 8.13–8.16 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 88.3, 98.3, 113.1, 126.0, 126.5, 128.3, 129.3, 130.3, 130.8, 131.0, 131.4, 133.4, 134.1 , 157.0, 178.7, 184.2 ppm; IR (KBr): ν_{max} 3061(w), 1689(m), 1656(s), 1609(s), 1330(w), 1243(m), 1210(m), 1064(w), 1036(m), 1006(m), 820(s), 775(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{18}H_{11}Cl_3O_3Na$ 402.9668, found 402.9666.

2–(1,1,1–Trichlorobutan–2–yloxy)naphthalene–1,4–dione ***5b.*** Yellow crystals, mp 110 ˚C (DCM–*n*–hexane), 2.905g, 76% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.20 (t, 3H, *J* = 7.5 Hz), 2.11–2.22 (m, 1H), 2.33–2.39 (m, 1H), 4.82 (dd, 1H, *J* = 8.4, 2.1 Hz), 6.42 (s, 1H), 7.75–7.77 (m, 2H), 8.07–8.10 (m, 1H), 8.14–8.17 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.4, 24.5, 88.7, 99.5, 112.6, 126.1, 126.8, 131.1, 131.6, 133.6, 134.3, 159.3, 179.1, 184.9 ppm: IR (KBr): ν_{max} 3067(w), 1690(s), 1653(s), 1612(s), 1587(m), 1238(m), 1206(s), 1052(m), 1022(w), 819(m), 745(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{11}Cl_3O_3$ Na 354.9656, found 354.9666.

Preparation of (Z)–ethyl 2–(2,2,2–trichloroethoxy)–4–oxopent–2–enoate 8: The required starting material ethyl 2–(methylsulfonyloxy)–4–oxo–2–enoate **7** was obtained in 1.227 g, 52% yield as colorless liquid by reaction of ethyl 2–hydroxy–4–oxopent–2–enoate[29] (10 mmol) with methansulfonyl chloride following a procedure reported in the literature[31]; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, 3H, *J* = 7.1 Hz), 2.40 (s, 3H), 3.37 (s, 3H), 4.26 (q, 2H, *J* = 7.1 Hz), 6.75 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.8, 31.2, 40.2, 63.0, 126.3, 141.0, 161.7, 195.9 ppm. IR

(KBr): ν_{max} 2924(w), 1731(s), 1667(s), 1603(m), 1236(s), 1136(m), 1131(s), 1044 (m), 972(m), 823(m), 724(m)cm^{-1}, m/z [M+Na]$^+$ calcd for $C_8H_{12}O_6SNa$ 259.0252, found 259.0263.

To a suspension of NaH (0.48 g, 0.01 mol, 60% dispersion in mineral oil) was added a solution of the 2,2,2–trichloroethanol **2*l*** (1mL, 1.494 g, 0.01 mol) in dry THF (10 mL) drop wise at 0˚C over 15 min duration. The mixture was stirred at 0 °C for another 30 min and then ethyl 2–(methylsulfonyloxy)–4–oxo–2–enoate **7** (2.360 g, 0.01 mol) was added in one lot and the reaction mixture was stirred at room temperature for 12 h. The crude product obtained after work up (as described for vinyl ethers **5a–b**) was further purified by column chromatography on a small pad of neutral alumina using *n*–hexane/ethyl acetate mixture (95:5, v:v) as the solvent for elution to get the vinyl ether **8** in (1.70 g, 60 % yield) as a colorless liquid; The *Z*–configuration was assigned to **8** on the basis of the chemical shift of δ 6.33 of the vinylic CH proton which was in the range of the chemical shifts assigned in the literature[23a,32] to the vinylic protons of 2–alkoxyfumarates. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (t, 3H, *J* = 7.1 Hz), 2.53 (s, 3H), 4.33 (q, 2H, *J* = 7.1 Hz), 4.77 (s, 2H), 6.33 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0, 32.0, 62.7, 82.3, 95.4, 118.2, 150.4, 162.6, 197.7 ppm. IR (KBr): ν_{max} 2924(w), 1732(s), 1668(s), 1603(m), 1236(s), 1136(s), 1045m), 824(m), 724(m) cm^{-1}; HRMS (ESI+): m/z [M+Na]$^+$ calcd for $C_9H_{11}Cl_3O_4Na$ 310.9615, found 310.9615.

Preparation of (*E*)–ethyl 3–(2,2,2–trichloro–1–phenylethoxy)acrylate 20: It was prepared according to a procedure (as described for vinyl ethers **2a–*l***) by taking 2,2,2–trichloro–1–phenylethanol **1a** (2.255 g, 10 mmol), ethyl propiolate (0.910 g, 1.01 mL, 10 mmol) and K_2CO_3 (0.424 g, 3 mmol) in THF (40 mL) and heating at reflux for 3 h. The crude product obtained after work up was purified by column chromatography on a small pad of neutral alumina using a *n*–hexane/ethyl acetate mixture (95:5, v:v) as the solvent for elution to get the vinyl ether **20** (2.750 g, 85%) as a white crystalline, mp 89 ˚C (DCM–*n*–hexane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.23 (t, 3H, *J* = 7.2 Hz), 4.11 (q, 2H, *J* = 7.2 Hz), 5.32 (s, 1H), 5.35 (d, 1H, *J* = 12.9 Hz), 7.42–7.44 (m, 3H), 7.52–7.58 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.2, 60.0, 91.4, 98.7, 100.5, 128.2, 129.5, 130.1, 132.1, 159.7, 166.9 ppm; IR (KBr): ν_{max} 2993(w), 1694(s), 1637(s), 1383(m), 1317(m), 1215(m), 1123(s), 1037(m), 974(m), 780(m), 744(m) cm^{-1}; HRMS (ESI+): m/z [M+Na]$^+$ calcd for $C_{13}H_{13}Cl_3O_3Na$ 344.9823, found 344.9822.

Preparation of the functionalized 4–chlorofurans 3a–k and 6a–b: **CuCl/TMEDA–catalyzed chlorine atom transfer 5–*endo* radical cyclization–aromatization of 2,2,2–trichloroethyl vinyl ethers 2a–k and 5a–b**: A flame–dried two–neck round–bottom flask was charged with CuCl (0.055g, 0.55 mmol), TMEDA (0.2 mL, 0.128 g, 1.10 mmol) and degassed dry benzene (40 mL). An atmosphere of nitrogen was created inside the flask using Schlenk technique. The suspension was stirred for 10 minutes at room temperature (25–30 ˚C) and trichloroethyl vinyl ether **2a–k** or **5a–b** (1 mmol) was added to it. The reaction mixture was degassed again by applying vacuum and refilled with the N_2 gas. The mixture was heated at reflux with stirring and the progress of the reaction was monitored by TLC. After completion of the reaction as indicated by disappearance of the starting vinyl ether (10–24 h), the reaction mixture was cooled and diluted with ethyl acetate (100 mL). The resulting mixture was washed with brine (2x50 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. In case the organic extract was dark in color, the organic extract was also washed with aqueous ammonia solution (20 mL) prior to drying and evaporating. The solid thus obtained was recrystallized from DCM–*n*–hexane or diethyl ether–*n*–hexane at room temperature (low temperature in case needed). In the cases where the crude product was a liquid or could not be crystallized by the above process, it was purified by column chromatography on a small pad of neutral alumina using *n*–hexane/ethyl acetate mixture (90:10 to 80:20%, v/v) as the solvent for elution. Thus, the tetrasusbtituted 4–chlorofurans were obtained as crystalline solids or liquids in good to high yields (67–83%).

*Dimethyl 4–chloro–5–phenylfuran–2,3–dicarboxylate **3a**:* Colorless crystals, mp 58 ˚C (DCM–*n*–hexane), 0.238g, 81% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (s, 3H), 3.99 (s, 3H), 7.43–7.52 (m, 3H), 7.99-8.03 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.6, 53.0, 111.8, 126.0, 126.3, 127.4, 129.1, 135.9, 140.0, 149.6, 157.4, 161.6 ppm; IR (KBr): ν_{max} 2954(w), 1737(s), 1640(w), 1599(w), 1538(w), 1484(w), 1444(m), 1315(s), 1272(m), 1233(s), 1170(s), 1069(m), 797(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{11}ClO_5Na$ 317.0187, found 317.0178.

*Dimethyl 4–chloro–5–p–tolylfuran–2,3–dicarboxylate **3b**:* Colorless crystals, mp 46 ˚C (DCM–*n*–hexane), 0.220g, 71% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.31 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 7.18 (d, 2H, J = 7.8 Hz), 7.80 (d, 2H, J = 7.8 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.4, 52.5, 52.9, 110.7, 124.8, 126.1, 126.4, 129.4, 139.4, 140.2, 151.0, 157.5, 161.8 ppm; IR (KBr): ν_{max} 2955(w), 1740(s), 1598(w), 1548(w), 1492(m), 1446(m), 1380(w), 1309(s), 1231(m), 1199(s), 1167(m), 1068(m), 989(m), 824(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{13}ClO_5Na$ 331.0339, found 331.0344.

*X–ray crystallography data of **3b**:* Formula: $C_{15}H_{13}ClO_5$, Formula weight: 308.7 g/mol; Crystal system: triclinic; Space group: P –1 (2); Unit cell dimensions: a = 7.170(3) Å b = 9.128(4) Å c = 11.218(5) Å α = 98.826(7)° β = 90.908(7)° γ = 92.801(7)°; Cell volume = 724.43(50) Å^3, Z = 2; Density calculated = 1.41512 g/cm^3; R_{All} = 0.0688. Detailed X–ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 989265).

Dimethyl 4–chloro–5–(2–chlorophenyl)furan–2,3–dicarboxylate ***3c**:* Colorless crystals, mp 66 ˚C (DCM–*n*–hexane) , 0.221g, 67% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (s, 3H), 4.0 (s, 3H), 7.35–7.47 (m, 2H), 7.50–7.55 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.7, 53.0, 114.6, 125.0, 126.0, 126.7, 130.3, 131.7, 131.9, 134.2, 141.2, 149.8, 157.4, 161.7 ppm; IR (KBr): ν_{max} 2951(w), 1731(s), 1596(w), 1555(w), 1437(m), 1310(s), 1228(m), 1205(m), 1164(m), 1051(m), 763(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{10}Cl_2O_5$ Na 350.9797, found 350.9797.

Dimethyl 4–chloro–5–(3–chlorophenyl)furan–2,3–dicarboxylate ***3d**:* Colorless crystals, mp 51 ˚C (DCM–*n*–hexane), 0.240g, 73% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.95 (s, 3H), 3.99 (s, 3H), 7.41 (d, 2H, *J* = 5.1 Hz), 7.91 (t, 1H, *J* = 3.8 Hz), 7.99 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.6, 53.0, 111.8, 124.2, 126.3, 126.4, 127.5, 130.1, 131.6, 132.0, 140.0, 149.6, 157.4, 161.5 ppm; IR (KBr): ν_{max} 2956(w), 1746(s), 1643(m), 1595(w), 1440(m), 1313(s), 1209(m), 1072(m), 993(m), 780(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{10}Cl_2O_5Na$ found 350.9797, found 350.9787.

Dimethyl 4–chloro–5–(4–chlorophenyl)furan–2,3–dicarboxylate ***3e**:* Colorless crystals, mp 58 ˚C (DCM–*n*–hexane) , 0.247g, 75% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.94 (s, 3H), 3.98 (s, 3H), 7.42 (d, 2H, *J* = 8.4 Hz), 7.92 (d, 2H, *J* = 8.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.6, 53.0, 111.8, 126.0, 126.3, 127.4, 129.1, 135.9, 140.0, 149.6, 157.4, 161.6 ppm; IR (KBr): ν_{max} 3011(w), 1738(s), 1659(w), 1591(m), 1478(m), 1440(m), 1312(s), 1238(m), 1206(m), 1176(m), 1070(m), 830(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{10}Cl_2O_5$ Na found 350.9797, found 350.9807.

Dimethyl 5–(4–bromophenyl)–4–chlorofuran–2,3–dicarboxylate ***3f**:* Colorless crystals, mp 57 ˚C (DCM–*n*–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz), 0.265g, 71% yield; δ 3.91 (s, 3H), 3.95 (s, 3H), 7.57 (d, 2H, *J* = 8.7 Hz), 7.85 (d, 2H, *J* = 8.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.6, 53.0, 111.8, 124.1, 126.25, 126.33,

127.4, 132.0, 140.0, 149.5, 157.3, 161.5 ppm; IR (KBr): ν_{max} 2957(w), 1728(s), 1643(w), 1590(w), 1478(m), 1437(m), 1300(s), 1232(m), 1197(m), 1068(m), 1006(m), 821(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{10}BrClO_5Na$ 394.9292, found 394.9298.

Dimethyl 4–chloro–5–(4–methoxyphenyl)furan–2,3–dicarboxylate ***3g:*** White solid, mp 56 ˚C (DCM–*n*–hexane), 0.244g, 75% yield; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.86 (s, 3H), 3.92 (s, 3H), 3.97 (s, 3H), 6.98 (d, 2H, *J* = 8.7 Hz), 7.95 (d, 2H, *J* = 8.7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.5, 52.9, 55.4, 109.8, 114.2, 120.3, 126.5, 127.9, 139.1, 151.0, 157.6, 160.8, 161.9 ppm; IR (KBr): ν_{max} 3001(w), 1731(s), 1603(m), 1546(w), 1493(m), 1446(m), 1300(s), 1266(s), 1235(s), 1169(m), 1075(m), 1009(m), 829(m), 795(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{15}H_{13}ClO_6Na$ 347.0303, found 347.0293.

Dimethyl 4–chloro–5–(4–nitrophenyl)furan–2,3–dicarboxylate ***3h:*** Yellow crystals, mp 105 ˚C (DCM–*n*–hexane), 0.258g, 76% yield; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.89 (s, 3H), 3.92 (s, 3H), 8.14 (d, 2H, *J* = 8.4 Hz), 8.26 (d, 2H, *J* = 8.4 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.8, 53.1, 114.3, 124.0, 126.2, 126.5, 133.0, 141.2, 147.7, 147.8, 157.0, 161.0 ppm; IR (KBr): ν_{max} 3111(w), 1727(s), 1595(w), 1518(m), 1445(w), 1347(m), 1316(s), 1242(w), 1205(w), 1074(m), 859(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{10}ClNO_7Na$ 362.0056, found 362.0038.

Dimethyl 4–chloro–5–(pyridin–2–yl)furan–2,3–dicarboxylate ***3i:*** Colorless crystals, mp 81 ˚C (DCM–*n*–hexane), 0.222g, 75% yield; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.88 (s, 3H), 3.92 (s, 3H), 7.26 (t, 1H, *J* = 6.0 Hz), 7.75 (t, 1H, *J* = 6.0 Hz), 7.94 (d, 1H, *J* = 7.8 Hz), 8.70 (d, 1H, *J* = 3.6 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.7, 53.1, 114.2, 121.8, 123.9, 126.4, 136.8, 140.8, 146.8, 149.1, 150.1, 157.4, 161.5 ppm; IR (KBr): ν_{max} 3110 (w), 1727(s), 1643(w), 1598(w), 1520(m), 1349(m), 1316(m), 1205(m), 1174(m), 1073(m), 1024(w), 859(w) cm^{-1}; HRMS (ESI+): m/z $[M+H]^+$ calcd for $C_{13}H_{10}ClNO_5H$ 296.0324, found 296.0320.

Dimethyl 4–chloro–5–ethylfuran–2,3–dicarboxylate ***3j:*** Colorless liquid, 0.197g, 80% yield; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.26 (t, 3H, *J* = 7.5 Hz), 2.74 (q, 2H, *J* = 7.5 Hz), 3.89 (s, 3H), 3.93 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.4, 19.1, 52.3, 52.8, 111.2, 124.6, 139.7, 156.6, 157.4, 161.9 ppm; IR (KBr): ν_{max} 2953(m), 1734(s), 1648(w), 1603(w), 1551(m), 1442(m), 1314(s), 1252(m), 1206(m), 1167(m), 1086(m), 1023(m), 796(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{10}H_{11}ClO_5Na$ 269.0195, found 269.0187.

Dimethyl 4–chloro–5–isopropylfuran–2,3–dicarboxylate ***3k:*** Colorless liquid, 0.213g, 82% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (d, 6H, *J* = 6.9 Hz), 3.20 (sept, 1H, *J* = 6.9 Hz), 3.89 (s, 3H), 3.95 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.9, 26.3, 52.4, 52.8, 110.1, 124.8, 139.4, 157.5, 159.6, 162.1 ppm; IR (KBr): ν_{max} 2970(m), 1733(s), 1603(w), 1547(m), 1414(m), 1377(w), 1314(s), 1227(m), 1201(m), 1166(m), 1075(m), 1022(m), 796(w) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{11}H_{13}ClO_5Na$ 283.0346, found 283.0344

3–Chloro–2–phenylnaphtho[2,3–b]furan–4,9–dione ***6a:***. Yellow crystals, mp 127 ˚C (DCM–*n*–hexane), 0.235g, 76% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48–7.55 (m, 3H), 7.71–7.75 (m, 2H), 8.10–8.16 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 110.6, 126.6, 126.8, 127.0, 127.2, 127.7, 128.9, 130.5, 132.2, 133.1, 133.9, 134.0, 149.8, 153.9, 172.6, 179.4 ppm; IR (KBr): ν_{max} 3067(w), 1679(s), 1587(m), 1531(w), 1480(m), 1360(m), 1216(m), 1038(w), 941(m), 766(w), cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{18}H_9ClO_3Na$ 331.0121, found 331.0132.

3–Chloro–2–ethylnaphtho[2,3–b]furan–4,9–dione ***6b:*** Yellow crystals, mp 112 ˚C (DCM–*n*–hexane), 0.216g, 82% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.36 (t, 3H, *J* = 7.5 Hz), 2.87 (q, 2H, *J* = 7.5 Hz), 7.68–6.70 (m, 2H, *J* = 3.0 Hz), 8.09 (d, 2H, *J* = 3.0 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.4, 19.3, 110.4, 126.6, 126.7, 126.8, 131.9, 132.8, 133.78, 133.83, 150.0, 160.7, 172.4, 179.3 ppm; IR (KBr): ν_{max} 2930(m), 1679(s), 1587(m), 1536(m), 1458(w), 1199(m), 1063(w), 995(m), 718(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_9ClO_3Na$ 283.0122, found 283.0132.

Synthesis of trisubstituted 4–chlorofurans 3*l* and 9: A flame–dried two–necked round–bottom flask was charged with CuCl (0.06 g, 0.6 mmol), PMDETA (0.12 mL, 0.103 g, 0.6 mmol) and degassed dry benzene (40 mL). An atmosphere of nitrogen was created using Schlenk technique. The suspension was stirred for 10 minutes at room temperature (25–30 ˚C) and trichloroethyl vinyl ether **2*l*** (0.292 g, 1 mmol) or **8** (0.290 g, 1 mmol) was added to it. The reaction mixture was degassed again by applying vacuum and refilled with the N_2 gas. The mixture was heated at reflux with stirring for 18 h. The heating was stopped and the reaction mixture was cooled to 5–10 ˚C. An additional amount of PMDETA (0.06 mL, 0.052 g, 0.3 mmol) was added and the reaction mixture was stirred for 10 min at the same temperature. The heating at reflux temperature was then resumed for an additional 12 h (in the case of **2*l***) or 14 h (in the case of **8**). The reaction mixture was worked up (as described for 4–chlorofurans **3a–k** and

6a–b). The crude products were purified by column chromatography on a small pad of neutral alumina using *n*–hexane/EtOAc mixture (90:10 to 80:20, v/v) as the solvent for elution to obtain **3*l*** and **9**.

*Dimethyl 4–chlorofuran–2,3–dicarboxylate **3l:*** Colorless crystals, mp 45 ˚C (DCM–*n*–hexane), 0.138 g, 63% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.93 (s, 3H), 3.96 (s, 3H), 7.57 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.7, 53.0, 116.7, 123.9, 141.7, 142.6, 157.3, 161.5 ppm; IR (KBr): ν_{max} 3147(w), 1737(s), 1594(w), 1508(m), 1442(s), 1312(m), 1279(m), 1218(m), 1170(w), 1066(m), 794(w) cm^{-1}. HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_8H_7ClO_5Na$ 240.9871, found 240.9874.

*Ethyl 3–acetyl–4–chlorofuran–2–carboxylate **9:*** Colorless liquid, 0.126 g, 58% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.35 (t, 3H, *J* = 7.1 Hz), 2.57 (s, 3H), 4.36 (q, 2H, *J* = 7.1 Hz), 7.52 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0, 31.7, 62.0, 115.7, 131.6, 141.0, 141.7, 157.2, 195.0 ppm; IR (KBr): ν_{max} 3146(w), 1722(s), 1586(m), 1503(m), 1389(m), 1293(s), 1182(s), 1118(m), 1018(m), 782(s) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_9H_9ClO_5$ Na 239.0081, found 239.0082.

*Dimethyl 4,4-dichloro-5-phenyl-4,5-dihydrofuran-2,3-dicarboxylate **19:*** It was obtained in trace amount by quenching the reaction of **2a** after 12 h (before completion of the reaction, which required 18 h) followed by usual work up and purification (as described for 4–chlorofurans **3a–k** and **6a–b**). Colorless solid, mp 40 ˚C (DCM–*n*–hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.82 (s, 3H), 3.84 (s, 3H), 5.80 (s, 1H), 7.39–7.41 (m, 3H), 7.56 (d, 2H, *J* = 6.3 Hz) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.5, 52.8, 90.7, 95.7, 125.8, 128.4, 128.6, 129.5, 136.1, 142.8, 161.9, 168.7 ppm; IR (KBr): ν_{max} 2940(m), 1728(s), 1638(m), 1582(s), 1538(s), 1486(m), 1363(m), 1266(m), 1097(m), 968(m), 817(m), 761(m) cm^{-1}; HRMS (ESI+): m/z $[M+Na]^+$ calcd for $C_{14}H_{12}Cl_2O_5Na$ 352.9954, found 352.9954.

Attempted CuCl/PMDETA–catalyzed chlorine atom transfer radical cyclization of the 2,2,2–trichloro–1–phenylethyl vinyl ether 20: The experiment was performed by the same procedure (as described for 4–chlorofurans **3a–k** and **6a–b**) for the synthesis of the tetrasubstituted 4–chlorofurans using 1 equiv of CuCl/PMDETA (1:1 mol ratio). Purification of the crude product by column chromatography on neutral alumina column using *n*–hexane/ethyl acetate mixture (99:01–80:20, v:v) as the solvent for elution gave a small amount of

the known (2,2–dichlorovinyl)benzene **21**[22b] (0.035 g, 20%) and the starting material **20** (0.100 g, 30%). Other products could not be separated and purified.

Experiments towards attempted trapping of intermediates in the CuCl/TMEDA–catalyzed cyclization of 2a:

(a) Attempted trapping of captodative radical intermediate 12 with alkenes and AIBN: This experiment was performed by the same procedure (as mentioned for 4–chlorofurans **3a–k** and **6a–b**) for the synthesis of the tetrasubstituted 4–chlorofurans. Excess amount of CuCl/TMEDA (1:2 mol ratio) (60 mol%) was used to ensure complete disappearance of the starting material **2a**. Large excess of alkenes were deliberately taken to promote the trapping of the possible radical intermediate **12**. Similarly, an excess of AIBN (1 equiv) was chosen due to possible involvement of IBN radical in the reduction of Cu(II) to Cu(I)–complex.

General Procedure: A flame–dried two–neck round–bottom flask was charged with CuCl (0.060 g, 0.6 mmol) and degassed benzene (40 mL) under a N_2 atmosphere using Schlenk technique. TMEDA (0.18 mL, 0.139 g, 1.2 mmol) was injected to this suspension and the suspension stirred for 10 minutes. Next, the vinyl ether **2a** (0.367 g, 1 mmol) and AIBN (0.137 g, 1 mmol) or styrene (0.58 mL, 0.52 g, 5 mmol) or methyl acrylate (0.45 mL, 0.43 g, 5 mmol) were added and the mixture was heated at reflux. In the case of alkenes, the formation of the polymeric material along the wall of the round bottom flask was observed. After the disappearance of the starting material (20–24 h) as indicated by TLC, the reaction mixture was cooled and ethyl acetate (100 mL) was added. The resulting solution was washed with brine (3x25 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure. The purification of the residual mass by column chromatography on a small pad of neutral alumina column using *n*–hexane/ethyl acetate mixture (90:10 to 80:20, v:v) as the solvent for elution gave the chlorofuran **3a** 0.240 g (76%) in the case of AIBN), 0.215 g (68%) in the case of methyl acrylate and 0.221 g (70%) in the case of styrene.

(b) Attempted trapping of the carbocationic intermediate 16 with ethanol: This experiment was performed by the same procedure as mentioned for 4–chlorofurans **3a–k** and **6a–b** using benzene/ethanol (40 mL, 4:1, v:v) as solvent system. Excess catalyst (1 equiv. CuCl/TMEDA in 1:2 mol ratio) was taken to ensure complete disappearance of the starting material **2a**. However, most of the vinyl ether **2a** decomposed into unidentifiable complex mixture in 6 h as indicated by TLC and ^{1}H NMR of the crude product.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of **2**, **3**, **5-9**, **19** and **20**, and X-ray data of **3b**. CIF file of **3b**. This material is available free of charge via the internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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REFERENCES

1. (a) Review: Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695–713. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *Chem. Soc. Chem. Commun.* **1976**, 736–738. (c) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736. (d) Chatgilialoglu, C.; Ferreri, C.; Guerra. M.; Timokhin. V. *J. Am. Chem. Soc*. **2002**, *124*, 10765–10772 and the references therein.

2. C–radical in all carbon system, cyclopentane: (a) Bogen, S.; Gulea, M.; Fensterbank, L.; Malacria, M. *J. Org. Chem.* **1999**, *64*, 4920–4925. (b) Nonami, Y.; Baran, J.; Sosnicki, J.; Mayr, H.; Masuyama,A.; Nojima, M. *J. Org. Chem.* **1999**, *64*, 4060–4063. C–radical, dihydropyrrolidine: (c) Gimisis, T.; Chatgilialoglu. *J. Org. Chem.*, **1996**, *61,* 1908–1909. S–radical, dihydrothiophene: (d) Journet, M.; Rouillard, A.; Cai, D.; Larsen, R.D. *J. Org. Chem.*, **1997**, *62*, 8630–8631. Si–radical, silolane: (e) Barton, T. J.; Revis, A. *J. Am. Chem. Soc*. **1984**, *106*, 3802–3805. N–radical: (f) Tang, Y.; Li, C. *Org. Lett.*, **2004**, *6,* 3229–323. (g) Du, W.; Zhao, M.–N.; Ren, Z.–H.; Wang, Y.–Y.; Guan, Z.–H. *Chem. Commun.,* **2014**, *50*, 7437–7439.

3. (a) Kunka, C. P. A.; Warkentin, J. *Can. J. Chem*. **1990**, *68,* 575−580. (b) Engel, P. S.; He, S. L.; Smith, W. B. *J. Am. Chem. Soc.* **1997**, *119*, 6059–6065. (c) Tanner, D. D.; Rahimi, P. M. *J. Org. Chem.* **1979**, *44*, 1674−1677. (d) Orito, K.; Uchiito, S.; Satoh, Y.; Tatsuzawa, T.; Harada, R.; Tokuda, M. *Org. Lett.* **2000**, *2*, 307−310. (e) Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **1985**, 50, 10−18. (f) Yamamoto, Y.; Ohno, M.; Eguchi, S. *J. Org. Chem.* **1996**, 61, 9264−9271 and the references therein. (g) Cui, X.; Xu,X.; Wojtas, L.; Kim, M. M.; Zhang, X. P. *J. Am. Chem. Soc*. **2012**, *134*, 19981−19984.

4. (a) Review on Cu(I)–catalyzed radical cyclizations: Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1–11. (b) Baker, S. R.; Burton, K. I.; Parsons, A. F.; Pons, J.–F.; Wilson, M. *J. Chem. Soc*., *Perkin Trans. 1* **1999**, 427–436. (c) Parsons, A.F.; Kapur, N.; Daviies, D.T. *Tetrahedron Lett*. **1999**, *40*, 8615−8618. (d) Parsons, A. F.; Davies, D. T. *Tetrahedron* **2000**, *56*, 3941−3949. (e) Bryans, J. S.; Chessum, N. E. A.; Parsons, A. F.; Ghelfi, F. *Tetrahedron Lett.* **2001**, *42*, 2901−2905 and references therein. (f) Ishibashi, H.; Kodama, K.; Higuchi, M.; Muraoka, O.; Tanabe, G.; Takeda, Y. *Tetrahedron* **2001**, *57*, 7629−7637. (g) Bryans, J. S.; Chessum, N. E. A.; Huther, N.; Parsons, A. F.; Ghelfi, F. *Tetrahedron* **2003**, *59*, 6221−6231. (h) Clark, A. J.; Curran, D. P.; Geden, J. V.; James, N.; Wilson, P. *J. Org. Chem.*, **2011**, *76.* 4546–4551.

5. (a) Ponaras. A. A.; Zaim, A. N. *Tetrahedron Lett.* **1993**, *34*, 2879−2882. (b) Crich, D.; Yao, Q. *J. Chem. Soc. Chem. Commun.* **1993**, 1265−1267. (c) Crich, D.; Yao, Q. *Tetrahedron* **1994**, *50*, 12305−12312.

6. (a) Ram, R. N.; Charles, I. *Chem. Commun*. **1999**, 2267−2268. (b) Ram, R. N.; Kumar, N. *Tetrahedron Lett.* **2008**, *49*, 799−802 and the references therein.

7. (a) Boto, A.; Alvarez, L. Furan and Its Derivatives. In Heterocycles in Natural Product Synthesis; Wiley−VCH Verlag GmbH & Co. KGaA: 2011; pp 97−152. (b) Harada, N.; Sugioka, T.; Uda, H.; Kuriki, T.; Kobayashi,

M.; Kitagawa, I. *J. Org. Chem.* **1994**, *59*, 6606–6613. (c) Gormann, R.; Kaloga, M.; Li, X.–C.; Ferreira, D.; Bergenthal, D.; Kolodziej, H. *Phytochem*. **2003**, *64*, 583–587. (d) Anderson, E. A.; Alexanian, E. J. Sorensen, E. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 1998–2001. (e) Doe, M.; Shibue, T.; Haraguchi, H.; Morimoto, Y. *Org. Lett*. **2005**, *7*, 1765–1768. (f) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298–317. (g) Donohoe, T. J.; Ironmonger, A.; Kershaw, N. M. *Angew. Chem. Int. Ed*. **2008**, *47*, 7314–7316.

8. (a) Kratochvil, J. F.; Burris, R. H.; Seikel, M. K.; Harkin, J. M. *Phytochemistry* **1971**, *10*, 2529−2531. (b) Krause, T.; Gerbershagen, M. U.; Fiege, M.; Weisshorn, R.; Wappler, F. *Anaesthesia* **2004**, *59*, 364−373. (c) Lin, Y. L.; Tsai, Y. L.; Kuo, Y. H.; Liu, Y. H.; Shiao, M. S. *J. Nat. Prod.* **1999**, *62*, 1500−1503. (d) Ye, O. Z.; Xie, S. X.; Huang, M.; Huang, W. J.; Lu, J. P.; Ma, Z. Q. *J. Am. Chem. Soc.* **2004**, *126*, 13940−13941. (e) Sperry, J. B.; Wright, D. L. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723−740. (f) Kharb, R.; Birla, S.; Sharma, A. K. *Int. J. Pharm. Phytopharm. res.* **2014**, *3*, 451–459.

9. Gandini, A.; Coelho, D.; Gomes, M.; Reis, B.; Silvestre. *A. J. Mater. Chem*. **2009**, *19*, 8656–8664.

10. (a) Kubota, T. *Tetrahedron* **1958**, *4*, 68–86 (+/–)–*trans*–ipomeamarone using furanoester. (b) Monna, J.; Holland, J. H. *Tetrahedron* **1987**, *43*, 2533–2542 (Selective functional group transformations in furan–dicarboxylates). (c) Agapiou, K.; Krische, J. M. *Org. Lett.* **2003**, *5*, 1737–1740 (total synthesis of potent molluscicide (+/–)–riccicarpin using ketofuran). (d) Ding, H.; Zhang, Y.; Bian, M.; Yao, W.; Ma, C. *J. Org. Chem.* **2008**, *73*, 578–584 (Formation of 7–oxanorbornadienes useful in synthesis of natural product and analogs). (e) Miller–Moslin, K.; Peukert, S.; Jain, R. K.; McEwan, M. A.; Karki, R.; Llamas, L.; Yusuff, N.; He, F.; Li, Y.; Sun, Y.; Dai, M.; Perez, L.; Michael, W.; Sheng, T.; Lei, H.; Zhang, R.; Williams, J.; Bourret, A.; Ramamurthy, A.; Yuan, J.; Guo, R.; Matsumoto, M.; Vattay, A.; Maniara, W.; Amaral, A.; Dorsch, M.; Kelleher, J. F. *J. Med. Chem.* **2009**, *52*, 3954–3968 (synthesis of pyridazine ring–fused antagonist from furan–2,3–diester). (f) Li, Y.; Pattenden, G. *Tetrahedron Lett*., **2011**, *52*, 2088–2092 (Furan ring opening to ketoesters system found in plumarellide). (g) Pérez–Vázquez, I. J.; Veiga, A. X.; Prado, G.; Sardina, F. J.; Palez, M. R. *Eur. J. Org. Chem.* **2012**, 975–987 (Stereoselective dearomatization–annulation of furan 2,3–dicarboxylate).

11. (a) Geissler, H.; Haber, S.; Scherer, S.; Meudt, A.; Vollmuller, F, A.; Clariant, G. Patent WO, 1083163, 2001. . (b) Strekowski, L.; Ismail, M. A.; Zoorob, H. H. *Heterocycl. Commun.* **1999**, *5*, 107–110. (c) Cheng, G.; Hu, *Y. J. Org. Chem.* **2008**, *73*, 4732–4735.

12. Klein, L. L.; Shanklin, M. S. *J. Org. Chem.* **1988**, *53*, 5202–5209.

13. (a) Cai, S. X.; Zhang, H.–Z.; Drewe, J. A.; Reddy, P. S.; Kasibhatla, S.; Kuemmerle, J.; Ollis, K. P. Patent WO 2002100826, 2002. (b) Mazurov, A.; Miao, L.; Xiao, Y.–D.; Hammond, P. S.; Miller, C. H.; Akireddy, S. R.; Murthy, V. S.; Whitaker, R. C.; Breining, S. R.; Melvin, M. S. Patent WO 2008057938, 2008. (c) Combs, A. P.; Yue, E. W.; Sparks, R. B.; Zhu, W.; Zhou, J.; Lin, Q.; Weng, L.; Yue, T.–Y.; Liu, P. I. Patent WO 2010005958, 2010.

14. (a) Michaels, J. G.; Gever, G.; Wei, P. H. L. *J. Med. Pharma. Chem.* **1962**, *5*, 1042–1048. (b) Zhang, H.–Z.; Kasibhatla, S.; Kuemmerle, J.; Kemnitzer, W.; Ollis–Mason, K.; Qiu, L.; Crogan–Grundy, C.; Tseng, B.; Drewe, J.; Cai, S. X. *J. Med. Chem.* **2005**, *48*, 5215–5223. (c) Basarab, G. S.; Hill. P. J.; Rastagar, A. J.; Webborn, P. J. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4716–4722. (d) Dang, Q.; Brown, B. S.; Liu, Y.; Rydzewski, R. M.; Robinson, E. D.; van Poelje, P. D.; Reddy, M. R.; Erion, M. D. *J. Med. Chem*. **2009**, *52*, 2880–2898. (e) Mazurov, A. A.; Miao, L.; Bhatti, B. S.; Strachan, J.–P.; Akireddy, S.; Murthy, S.; Kombo, D.; Xiao, Y.; Hammond, P.; Zhang, J.; Hauser, T. A.; Jordan, K. G.; Miller, C. H.; Speake, J. D.; Gatto, G. J.; Yohannes, D. *J. Med. Chem*. **2012**, *55*, 9181–9194.

15. Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 4440–4444 and the references therein.

16. Larock, R. C.; Liu, C.–L. *J. Org. Chem*. **1983**, *48*, 2151–2158.

17. Piller, F.M.; Knochel, P. *Synthesis* **2011**, 1751–1758.

18. (a) Schnute, M. E.; Brideau, R. J.; Collier, S. A.; Cudahy, M. M.; Hopkins, T. A.; Knechtel, M. L.; Oien, N. L.; Sackett, R. S.; Scott, A.; Stephan, M. L.; Wathen, M. W.; Wieber, J. L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3856–3859. (b) Singh, A. P.; Lee, K. M.; Kim, K.; Jun, T.; Churchill, D. G. *Eur. J. Org. Chem.* **2012**, 931–939. .

19. Nazarova, Z. N.; Goryaev, S. S. *Zh. Org. Khim.* **1975**, *11*, 1955–1958.

20. For selected examples, see: Reviews: (a) Patil, N. T.; Yamamaro, Y. *Arkivoc* **2007**, 121–141. (b) Brown, R. C. D. *Angew. Chem. Int. Ed*. **2005**, *44*, 850–852.; Other references: (c) Shibata, Y.; Noguchi, K.; Hirano, M.;

Tanaka, K. *Org. Lett.* **2008**, *10*, 2825–2828. (d) Cao, H.; Jiang, H.; Yao, W.; Liu, X. *Org. Lett.* **2009**, *11*, 1931–1934. (e) Liu, W.; Jiang, H.; Zhang, M.; Qi, C. *J. Org. Chem*. **2010**, *75*, 966–968. (f) Cao, H.; Zhan, H.; Wu, J.; Zhong, H.; Lin, Y.; Zhang, H. *Eur. J. Org. Chem.* **2012**, 2318–2322. (g) Tang, S.; Liu, K.; Long, Y.; Qi, X.; Lan, Y.; Lei, A. *Chem. Commun.* **2015**, *51*, 8769–8772. (h) Clark, J. S.; Romiti, F.; Hogg, K. F.; Hamid, M. H. S.; Richter, S. C.; Boyer, A.; Redman, J. C.; Farrugia, L. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 5744–5747.

21. Manna, S.; Antonchick, A. P. *Org. Lett.* **2015**, *17*, 4300–4303.
22. (a) Atkins, P. J.; Gold, V.; Wassef, W. N. *Chem. Commun.* **1983**, 283–284. (b) Aggarwal, V. K.; Mereu, A. *J. Org. Chem.* **2000**, *65*, 7211–7212.
23. (a) Fan, M.–J.; Li, G.–Q.; Liang, Y.–M. *Tetrahedron* **2006**, *62*, 6782–6791. (b) Sarrafi, Y.; Sadatshahabi, M.; Alimohammadi, K.; Tajbakhsh, M. *Green Chem.* **2011**, *13*, 2851–2858.
24. Ram, R. N.; Kumar, N.; Singh. N. *J. Org. Chem*. **2010**, *75*, 7408–7411.
25. Reviews: (a) Viehe, H. G.; Merenyi, R.; Stella, R.; Janousek. Z. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 917–932. (b) Beckwith, A. L. J. *Chem. Soc Rev.* **1993**, 143–151. Other references: (c) Singh, H.; Tedder, J. M. *J. Chem. Soc. Chem. Comm*. **1980**, 1095–1096. (d) Viehe, H. G.; Janousek. Z.; Merenyi, R. *Acc. Chem. Res.* **1985**, *18*, 148–154.
26. (a) Kim, C. U.; Misco, P. F. *Tetrahedron Lett.* **1992**, *33*, 5733–5736. (b) Zachova, H.; Man, S.; Necas, M.; Potacek, M. *Eur. J. Org. Chem.* **2005,** 2548–2557.
27. Udding, J. H.; Heimstra, H.; Speckamp, W. N. *J. Chem. Soc. Perkin Trans. 2* **1992**, 1529–1530.
28. Tandon, V. K.; Yadav, D. B.; Singh, R. V.; Chaturvedic, A. K.; Shukla, P. K. *Bioorg. & Med. Chem. Lett.* **2005**, *15*, 5324–5328.
29. Marvel, C. S.; Dreger, E. E. *Org. Synth*. **1941**, *1*, 238–240.
30. Bolognesi, M. L.; Lizzi, F.; Perozzo, R.; Brunc, R.; Cavallia, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2272–2276.
31. da Silva, E. N.; de Melo, I. M. M.; Diogo, E. B. T.; Costa, V. A.; Filho, J. D. S.; Valença, W. O.; Camara, C. A.; de Oliveira, R. N.; de Araujo, A. S.; Emery, F. S.; dos Santos, M. R.; de Simon, C. A.; Menna–Barreto, R. F. S.; Castro, S. L. E. *J. Med. Chem.* **2012,** *52*, 304–312.

32. Kobayashi, Y.; William, A. D.; Mizojiri, R. *J. Organomet. Chem.* **2002**, *653*, 91–97.