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Title: β,β,β-Trichloroethyl-NH-Enamine As Viable System For 5-Endo-trig Radical Cyclization Via Multifaceted CuI-CuII Redox Catalysis: Single Step Synthesis of Multi-Functionalized NH-pyrroles

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β,β,β-Trichloroethyl-*N*H-Enamine as Viable System for 5-*Endo-trig* Radical Cyclization *via* Multifaceted Cu^{I}-Cu^{II} Redox Catalysis: Single Step Synthesis of Multi-Functionalized *N*H-Pyrroles

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Abstract. Here we report a mild and regioselective copper-catalyzed direct synthesis of multi-substituted and functionalized *N*H-pyrroles in high yields from diverse β,β,β-trichloroethyl-*N*H-enamines *via* a novel 5-*endo-trig* radical cyclization mode, previously known to be unviable in the enamine system. An approach to transform a geometrically 'disfavored to favored' 5-*endo-trig* radical cyclization mode in *N*H-enamine systems *via* multifaceted Cu^{I}-Cu^{II} redox catalysis generating radicals, preventing dehalogenative reduction of radical precursors and dehydrohalogenating the 5-*endo-trig* cyclized products have been demonstrated experimentally. With wider substrate scope, this method incorporates halo-, *N*H- and carbonyl functionalities besides alkyl, aryl and heteroaryl substituents in the pyrrole unit easily. These difficult to prepare 3-halo-*N*H-pyrroles are potential sources for natural products, agrochemicals, pharmaceuticals and organometallic chemistry.

Keywords: 5-*Endo-trig* radical cyclization; *N*H-Pyrrole; *N*H-enamine; Cu(I)-catalyst; captodative-stabilization

Introduction

The structure-activity relationship (SAR) studies of a large number of bioactive pyrrole derivatives reveal the pharmacophoric properties of various substiuents, functionalities and halogen(s) present at specific position on the pyrrole ring.[1] *N*H-, halogen-, carbonyl and related functionalities of a pyrrole ring[2] are reaction centers to construct natural and artificial bioactive pyrrole derivatives,[2a-c] agrochemicals and pharmaceuticals,[2d-f] advance materials[2g] and catalysts.[2h] In recent times, the development of direct, regioselective, cost-effective and industry-oriented methods capable of incorporating diverse functionalities and substituents on the *N*H-pyrrole ring while using a cheap catalyst and easily accessible raw materials are in great demands.[3] In this regard, the *N*H-enamine system is such a synthetically simple, easily diversifiable and an economical building block for *N*-heterocycles.[4] However, the synthetic potential of such *N*H-enamine systems in the formation of diversely substituted- and functionalized 3-halo-*N*H-pyrroles using a regioselective intramolecular cyclization reaction in a single operation has been scarcely exploited so far.[3h]

Among various types of cyclization protocols,[3] free radical cyclization reaction is a powerful tool to construct cyclic frameworks from acyclic unsaturated radical precursors *via* carbon-carbon bond formation in the fewest and concise steps.[5] Over the years, Copper(I)-catalyzed halogen atom transfer radical cyclization (HATRC) of unsaturated polyhalomethyl substrates has emerged as a mild, catalytic, cost-effective and high yielding strategy to synthesize various heterocycles with wider substrate scope, 100 % atom efficiency and functional group tolerance including halogens.[6] AIBN and ascorbic acid (ARGET), and platinum electrode surface (eATRC) regenerate an active Cu(I)-catalyst by reducing a Cu(II)-complex to decrease the catalyst loading drastically even below 1 mol %.[6a-b] However, there is a scarcity of radical cyclization approaches to access an aromatic ring in single step.[6] Quayle and co-workers reported an efficient benzannulation reaction to access chloronaphthalenes using trichloroacetates.[6e] However, to the best of our knowledge, synthesis of a *N*H-pyrrole unit *via* the cyclization of a *N*H-enamine system under a radical condition is undiscovered so far.[5-6]

The pioneers Ikeda, Ishibashi and co-workers[7] found that an internal C=O group in the cyclizing 5-membered transition state **2** (Scheme 1) assists in the realization of 5-*endo-trig* radical cyclization in an enamide **1** to furnish a γ-lactam **3**. Whereas the *N*-substituted enamine **4** with an external C=O group fails to give the pyrrolidine **7** *via* 5-*endo* radical cyclization **6**[7] due to high geometrical constraints in the 5-*endo*-trig transition state,[5] as reported by Baldwin et al.[8] in other systems. Unlike geometrically favored vinyl ether[8a-b] and *N*-protected enamide **1**,[8a,c] and disfavored *N*-substituted enamine **4**,[7] 5-*endo-trig* radical cyclization of a geometrically disfavored *N*H-enamine of type **8** is further a bigger challenge for a radical chemist due to three reasons.[9-10] First, a *N*H-enamine is sensitive to both acidic and basic conditions,[9a] needs a neutral reaction condition.

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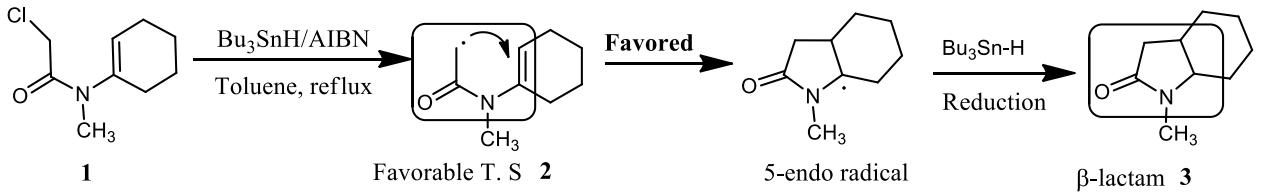
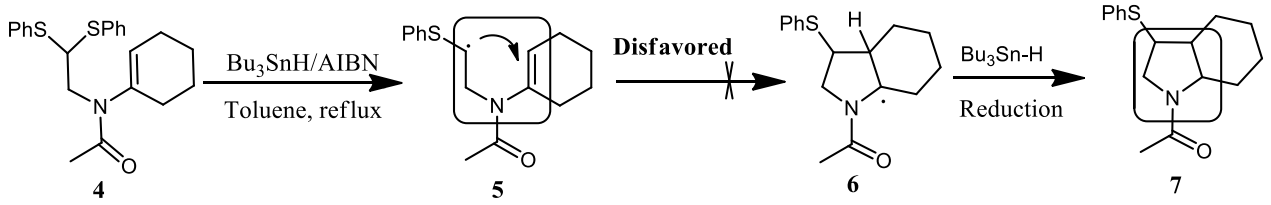
a. Previous report on 5-*endo-trig* radical cyclization: **Favored** in **enamide 1**



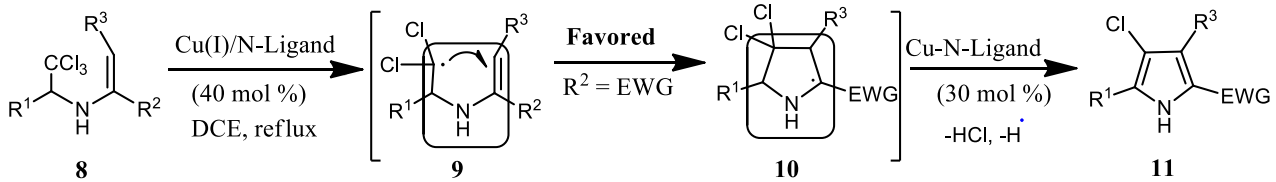
1 Favorable T. S **2** 5-endo radical β-lactam **3**

b. Previous report on 5-*endo-trig* radical cyclization: **Disfavored** in **enamine 4**



4 **5** Highly strained T.S **6** not possible **7** pyrrolidine not formed

c. This work: Novel Cu-catalyzed favored 5-*endo-trig* radical cyclization in **NH-enamines 8**



8 **9** Less strained T.S **10** pyrrolidine radical formation **11** NH-pyrrole

Investigations:
i) Roles of NH-enamine-structures, ii) Roles of radical catalysts & additives, iii) Roles of solvents & reaction conditions

Scheme 1. a) Viable 5-*endo-trig* radical cyclizations in *N*-substituted enamide, b) unviable 5-*endo-trig* radical cyclizations in *N*-substituted enamine and c) transformation of unviable to viable mode in present work

Secondly, there is a greater geometric constraint in the transition state of the *N*H-enamine **8** than *N*-substituted enamine **4** as the nitrogen atom in **8** is not pre-substituted with any group or functionality acting as a cyclization auxillary.[9b] Thirdly, a free *N*H-group in an enamine can bind to a Cu(I)-catalyst to form an inactive Cu(I)-*N*H complex[9d] causing the loss of catalyst-redox activity essential to perform the radical reactions.[10b] Despite all these challenges, a single step synthesis of a *N*H-pyrrole from a *N*H-enamine is advantageous over multisteps *N*-preprotection post deprotection dependent protocols usually suffering with the loss of the yields.[9c]

Our previous experiences with substrate-[10a] and catalyst-controlled[10b] radical cyclization reactions prompted us to investigate roles of enamine-structures, radical initiators, additives and reaction conditions in a "disfavored" 5-*endo*-mode of radical cyclization in an enamine system. This led to a discovery of an efficient approach to convert a "disfavored mode **5** to a favored mode **9**" of a 5-*endo-trig* radical cyclization to form pyrrolidine radical **10** which spontaneously converts to *N*H-pyrrole **11** having a 4-halo-and the carbonyl functionalities at 2- and 3-positions (Scheme 1). This functionalized 3-chloro-*N*H-pyrrole unit of type **11** is frequently encountered in several bioactive natural products **12-13**,[11,2e] (**figure 1**) pharmaceuticals **13-16**,[12] functionalized materials,[13] and agrochemicals **12**.[14] Carbonyl and *N*H-functionalities in a 3-chloropyrrole unit are well-established centers for its intra- and intermolecular chemical transformations to obtain complex pyrroles and natural products,[2a-b,e-f,11b,15] agrochemicals,[14] medicines **17**,[16] and aromatic compounds.[3g] The β-chlorine atom modulates the physical and biological properties of the pyrrole moiety, thus they find frequent applications in SAR studies[17,1-2,11b,16] for drug development.[18,12] This chlorine atom on a pyrrole ring is a center for substitution[2g] and transition metal-catalyzed cross-coupling[19] reactions, and acts as a reductively removable blocking group for a regioselective substitution on its adjacent position[20] to furnish natural products, drugs and materials.

A few methods to synthesize functionalized 3-chloro-pyrroles are known.[21] They are not typically general and suffer from the problems of non regio-selectivity, over-halogenation, multi-steps synthesis, low to moderate yield, high cost, inaccessibility of starting materials and are mostly limited to the synthesis of simple *N*-protected pyrroles.[21] Here we report a first, single step, general and an efficient cyclization protocol to access tri- and tetrasubstituted multi-functionalized 3-chloro-*N*H-pyrroles in good to high yields from cheaper and diversely accessible β-haloalkyl-*N*H-enamines using environmentally

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benign and cost-effective Cu(I)-catalyst *via* a novel 5−*endo*−*trig* radical cyclization in *N*H-enamine systems.

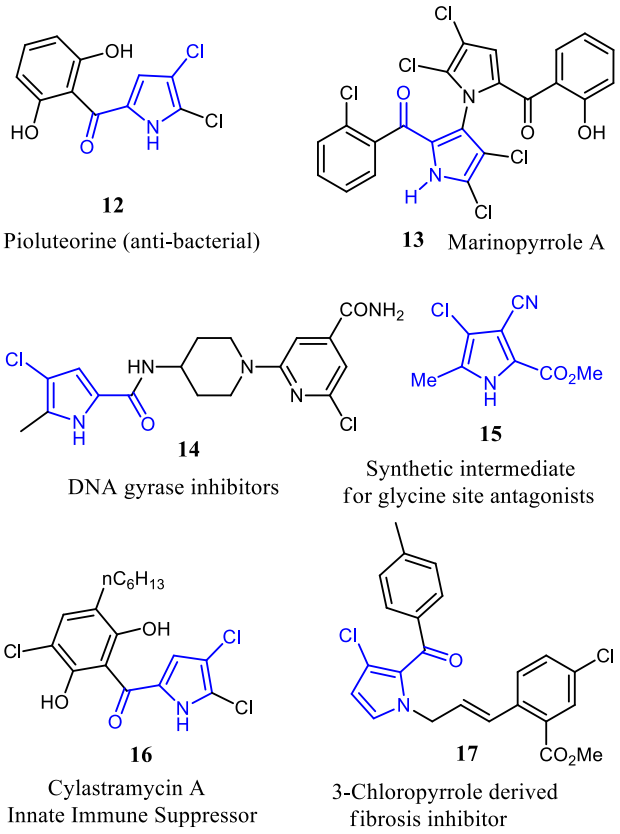

Fig. 1 Some selective examples of functionalized 3-chloro-*N*H-pyrrole unit occuring in natural products, drug molecules, agrochemicals and their synthetic intermediates

Results and Discussion

More reactive 2,2,2-trichloroethyl amines **19** (**Scheme 2**) than 2-monochloro- or 2,2,-dichloroethyl amines were chosen to produce *N*H-enamine precursors **20**. Aza-Michael addition of 1−phenyl−2,2,2−trichloroethyl amine **19a** to dimethyl acetylenedicarboxylate(DMAD) afforded dimethyl 2-(2,2,2-trichloro-1-phenyl-ethylamino)fumerate **20a** as the representative precursor. The reactions of enamine **20a** were performed with redox active CuCl- and $CuCl_2$-[complexes with 2,2′−bipyridine (bpy), tetramethylethylenediamine (TMEDA), pentamethyldiethylenetriamine (PMDETA) and tris(2-pyridylmethyl)amine (TPMA) ligands[6a-b]], $Ni(OAc)_3$, Mn/AcOH, and reductive nBu_3SnH/AIBN[7] radical initiators using various solvents and additives under a nitrogen atmosphere (**Table 1**) to explore the suitable catalytic system.

The reaction of enamine **20a** with varying amounts of CuCl (30-140 mol %) in 1,2-dichloroethane (DCE) was first performed in the presence of bpy, TMEDA, PMDETA and TPMA ligands at reflux under a nitrogen atmosphere. PMDETA was the most effective ligand in terms of the product yield (74 %) (**Table 1**, **entry1-4**). Only the Cu(I)/PMDETA complex could effectively retain its redox activity, unaffected by deactivating *N*H-groups of the enamine **20a** and/or pyrroles **21a** formed during progress of the radical reaction.[10b]

In order to reduce the catalyst loading, easily accessible and cheap reducing agents AIBN and ascorbic acid were chosen to regenerate the active Cu(I)-catalyst from the inactive Cu(II)-complex accumulated over the long reaction time[22] (**Table 1**, **entry3-4**). However, a catalytic amount of AIBN (10 mol % to begin with) did not give satisfactory result. Finally, by using one equivalent of AIBN from the beginning of the reaction, the amount of the catalyst CuCl/PMDETA was almost halved from 130 mol % to 70 mol % and the time of the reaction was dramatically reduced from 24 h to 6 h (**Table 1**, **entry-5**). The slow rate of reaction in **entry-3** as compared to **entry-5** was due to low solubility of $CuCl_2$/PMDETA in the reaction medium. The high concentration of soluble and reactive IBN radicals (produced on decomposition of AIBN) efficiently reduced the $CuCl_2$/PMDETA to CuCl/PMDETA leading to higher solubility of the reaction mass. The IBN radicals acted as soluble halogen carriers to promote the HATRC reaction further.[22b] An attempt to lower the catalyst loading using ascorbic acid-Na_2CO_3 combination in ethanol by employing a method reported in literature[22e-f] was ineffective due to the heterogeneous nature of the reaction mass (**Table 1**, **entry-6**). Reaction of enamine **20a** (**Table 1**, **entry-5**) with CuCl/PMDETA (0.7 eq) and AIBN (1 eq) in the presence of two equivalents of insoluble NaCl salt prolonged the reaction time from 6 h to 8h, suggests towards low solubility of the reaction mass retarding the rate of reaction in **entry 3-4**,**6 Table 1**.

Easy to handle AIBN whose by-products were volatile was selected for further study. Dropwise addition of a solution of one equivalent of AIBN in DCE took a longer time (8 h) for the completion of the reaction. Further an attempt to lower the catalyst loading gave inferior results even with higher amount of AIBN (**Table 1**, **entry-7**). Although AIBN is a well-known radical initiator, it has been reported to be ineffective in the absence of Cu(I)-catalyst in the HATRC of bromoacetamides,[22d] so was in this case also (**Table 1**, **entry-8**).

The necessity of higher amount of the copper-complex (**Table 1**, **entry 3-4**) might be due to catalyst-deactivation *via* protonation of nitrogenous-ligands by liberated HCl produced during the dehydrohalogenations of pyrrolidine ring.[23] This possibility was supported by the fact that the reaction proceeded to completion even with a lower (40 mol %) catalyst loading in the presence of additional bases pyridine and PMDETA to give the product **21a** (**Table 1**, **entry 9-10**). However, the use of only base was rather detrimental to the enamine substrate **20a** (**Table 1**, **entry-11**) as several spots were obtained on TLC plate. No cyclization product was formed on TLC plate when the reaction of **20a** was performed at room temperature for 24 h (**Table 1**, **entry-12**).

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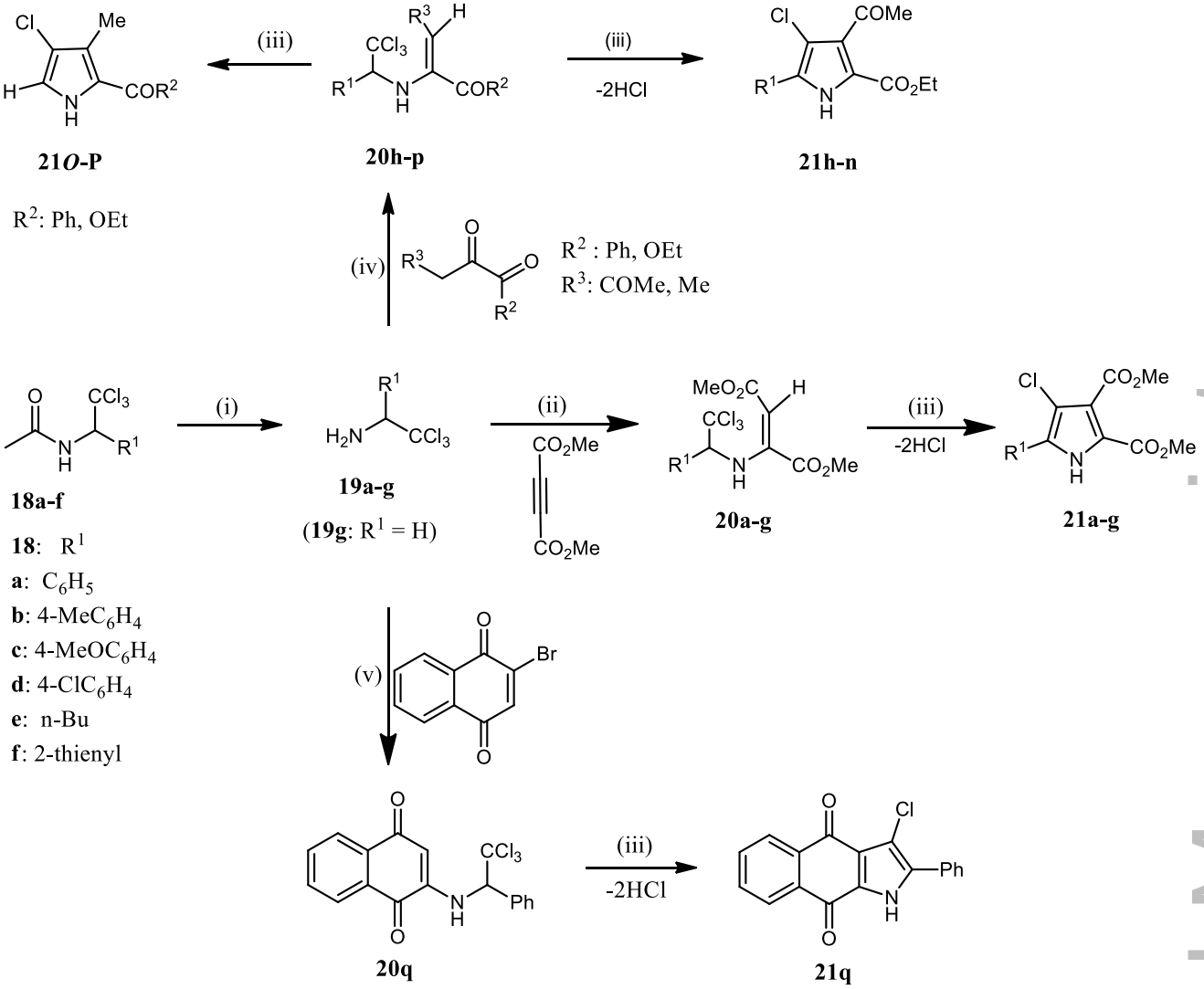
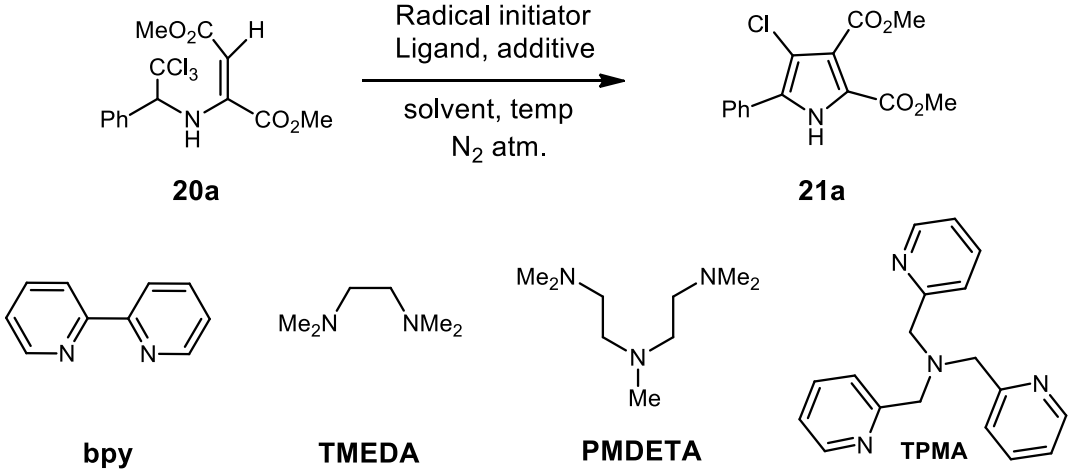


Reactions Conditions: i) a: H+/$H_2$0, b: Aq. NaOH (2N), 66-81 %. ii) THF, rt. iii) CuCl/PMDETA (70 mol %), AIBN (1equiv), DCE, reflux, **20**[a-c (6 h), d-f,h-l (8 h), m,q (9 h), g,n-p (12 h)], N_2 atm., 50-84 %. iv) PTSA, benzene, reflux, 4-8 h. 35-78 %. v) Na_2CO_3, ethanol, 40 °C, 14 h, 65 %.

Scheme 2. Synthesis of 3-chloro-*N*H-pyrroles **21** by Cu(I)/PMDETA-catalyzed 5-*endo-trig* radical cyclization-aromatization of *N*H-enamines **20**

Table 1. Optimization of reaction conditions for cyclization of **20a**[a]



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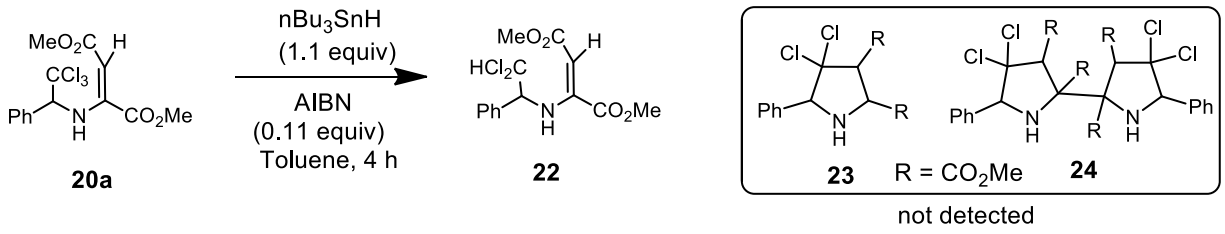
Entry	Radical initiator (mol eq)/Ligand (mol eq)/Additive (mol eq)	Solvent	Time (hrs)	**20a** (%) Recovered	**21a** (%) Isolated yield
1	CuCl(1.3)/bpy (1.3)	DCE	24	90	-
2	CuCl(1.3)/TMEDA (2.6)	DCE	24	75	15
3	CuCl(1.3)/PMDETA (1.3)	DCE	24	-	74[b]
4	CuCl(1.4)/TPMA(1.4)	DCE	24	-	72[b]
5	CuCl(0.7)/PMDETA(0.7)/AIBN(1.0)	DCE	6	-	84[c]
6	CuCl(0.7)/PMDETA(0.7)/Ascorbic acid (1.0)/Na_2CO_3(1.5)	EtOH	12	15[d]	10[b]
7	CuCl(0.4)/PMDETA(0.4)/AIBN(2.0)	DCE	12	25	52
8	AIBN (1.0)	DCE	6	92	-
9	CuCl(0.4)/PMDETA(0.4)/Pyridine(1.0)	DCE	24	-	65
10	CuCl(0.4)/PMDETA(0.4+0.5)/AIBN (0.5)	DCE	20	-	74
11	PMDETA (1.0)	DCE	6[d]	-	--
12	CuCl(0.7)/PMDETA(0.7)/AIBN (1.0)	DCE	24	90[e]	--
13	$CuCl_2$(0.8)/PMDETA(0.8)/AIBN (1.2)	DCE	9	--	70
14	*n*Bu_3SnH(1.1)/AIBN (0.2)	benzene	6	10	--
15	CuCl(0.4)/PMDETA(0.4)/AIBN (1.0) + CuCl(0.3)/PMDETA(0.3)	DCE	7	-	80
16	Ni(30.0)/acetic acid(20.0)/NaOAc(3.0)	*i*-PrOH	6	--	--[d]
17	$Mn(OAc)_3.2H_2O$(4.0)	MeOH	8	--	--[d]

[a] All the reactions were performed with 1 mmol of **20a** at reflux temperature (except entry 6 at 60 ˚C & entry 12 at RT) under N_2 atmosphere. [b] Formation of insoluble reaction mass was observed. [c] Better soluble than the reaction masses in entry 3-4. [d] Formation of inseparable decomposed side products. [e] No product formation at room temperature, as observed on TLC plate.



Scheme 3. Fate of 5-*endo*-*trig* cyclization of **20a** with reductive radical agent

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CuCl-PMDETA-AIBN combination was found to be more efficient catalyst system than $CuCl_2$-PMDETA-AIBN complex in terms of yield, catalyst loading and reaction time (**Table 1**, **entry 5** & **13**).

Like Ikeda, Ishibashi and co-workers,[7a] we also obtained a mixture containing major reduced starting material **22** (**Table 1, entry-14** and **Scheme 3**) when **20a** was treated with *n*Bu_3SnH/AIBN by their general reaction procedure reported in the literature[7a] for the attempted 5-*endo* cyclization of enamine **4** (**Scheme 1**). No isolation of expected *5-endo trig* cyclization product **23** or its dimer **24** by column chromatography of the crude product suggests a less possibility for 5-*endo* radical cyclization for *N*H-enamines **20** under reductive radical conditions.

The cyclization of enamine **20a** was under taken with two lots of the catalyst to understand its roles in 5-*endo*-cyclization and aromatization processes. Reaction of **20a** was performed first with catalytic 40 mol % CuCl/PMDETA at reflux for 2 hours, followed by addition of a pre-prepared solution of 30 mol % CuCl/PMDETA in DCE into the reaction mass at 50 °C (**Table 1, entry-15**) and then heating at reflux for 5 hours. This afforded a better yield of the product **21a** than with 40 mol% catalyst along with pyridine and PMDETA bases (**Table 1, entry 9-10**). This comparison suggests 40 mol % catalyst performs the 5-*endo-trig* HATRC reaction and remaining 30 mol % catalyst (using its internal *tert*-amine centers in PMDETA ligands) performs the *in situ* dehydrohalogenation reactions of the *N*H-pyrrolidine intermediate to produce *N*H-pyrrole. Further, PMDETA in coordination with CuCl, constitutes a milder basic catalyst system suitable for sensitive substrates like **20a** (**Table 1**, **entry 9-10**, **15**) where free bases like PMDETA/pyridine decompose them. Thus, use of additional 30 mol % CuCl/PMDETA over 1 equivalent pyridine or 50 mol % PMDETA for *in-situ* dehydrochlorinations of HATRC intermediate to pyrrole ring was prefered.

30-40 mol % is a generally used catalytic amount of Cu(I)-complex in the HATRC reactions in the synthesis of halogenated *O*- and *N*-heterocycles.[10b,e-f] The double dehydrohalogenations-isomerization of these heterocycles to corresponding aromatic compounds require an excess amount of strong base (DBU 2.5 eq.) and longer reaction time (24 hrs)[10b] in the next step of the synthesis protocols.[10b,e-f,,21c,g] Advantageously, this Cu(I)/PMDETA-catalyst uses overall lesser amount of PMDETA and lesser reaction time (**Table 1, entry-5**) than required for the aromatization of an isolated halogenated pyrrolidine in the next aromatization reaction. Thus, it shortens the synthetic operations and reaction time for, otherwise a multi-step synthetic protocol.[10b,3g,,21c,g]

An increase in the amount of Cu(I)/*tert*-amine catalyst over the catalytic 40 mol %, due to HCl-mediated catalyst-deactivation, even with stronger tetradentate TMPA ligand in the 5-*endo* cyclization of α-halo-enamide systems to unsaturated γ-lactam, is well-known.[24] Similarly, a high consumption of the AIBN (50 mol %) in Cu(I)/TPMA-catalyzed 6-*exo-trig* radical cyclization of trichloroacetamides, a kinetically 'favored' system, to 2-azabicyclo[3.3.1]nonane rings, was reported by Bonjoch, Belderrain and co-workers[24c]. Thus, an increase in quantity of AIBN and CuCl/PMDETA (**entry-5 table-1**) in the cyclization of **20a** is reasonable due to two reasons. First, a very high geometrical constraint in the occurrence of *5-endo* radical cyclization step of enamine **20a** necessitates a continuous regeneration of active Cu(I)-catalyst by continuous supply of IBN radicals. Second, the Cu(I)-catalyst performs the radical generation in enamine **20a** and the double dehydrohalogenation reactions in the 5-*endo-trig* product (pyrrolidine intermediate) to give an aromatic product (**Scheme 5**) while undergoing HCl-catalyst-deactivation.[6a-b,23,24]

Cu(I)-catalyst is a cheap, recyclable, easily available, easy to use and remove from the reaction mass. In addition, it has unique *in situ* dehydrohalogenation ability. Thus, this is preferable over other transition metals,[25] 30 equivalents of Ni/acetic acid/NaOAc[25a] or 4 equivalents of $Mn(OAc)_3.2H_2O$/methanol[25b] where the decomposition of enamine **20a** was observed (**Table 1, entry 16-17**) under the reported procedure therein. The use of very costly $RuCl_2(PPh_3)_3$ more than 0.5 equivalent of radical precursor is least preferable in view of bulk scale synthesis and industrial applications.[25c-d]

After selecting CuCl as radical initiator, PMDETA as ligand, AIBN as reducing agent and reflux as reaction temperature, screening of solvents for the cyclization of **20a** was done at reflux to select the most suitable solvent (**Table 2**). The reaction mixture blackened in complexing solvent acetonitrile (**Table 2**, **entry-2**) against the gradual colour change in chlorinated solvent DCE from green to orange to red (**Table 2**, **entry-1**). Though the reaction was observed to be complete in a slightly shorter time (5 h) due to better solubility of the copper-catalyst,[10b-c] the very same solubility characteristic made the removal of the copper complex difficult during work up. This led to greater loss of the product (75 %). Replacing DCE with non polar benzene lead to incompletion of reaction due to insolubility of the copper complex (**Table 2**, **entry-3**). Raising of reaction temperature using a high boiling toluene went in vain (**Table 2**, **entry-4**). The use of high solublizing protic bio-solvent ethanol and DCE-ethanol mixture lead to the decomposition of enamine (**Table 2**, **entry-5-6**).

After having the optimized radical conditions (**Table 1**, **entry-5**), the conformational role of substituents and functionalities of a *N*H-enamine system in the 5-*endo-trig* radical cyclization was investigated by comparing the radical reactions of α-substituted **20a** and α-unsubstituted **20n** having an α′-ester group attached to the radical acceptor C=C with that of trichloroethyl enamine **28** and **33** having a α′-methyl and α′-phenyl group, respectively under the usual optimized reaction conditions for 12 h (**Scheme 4**).

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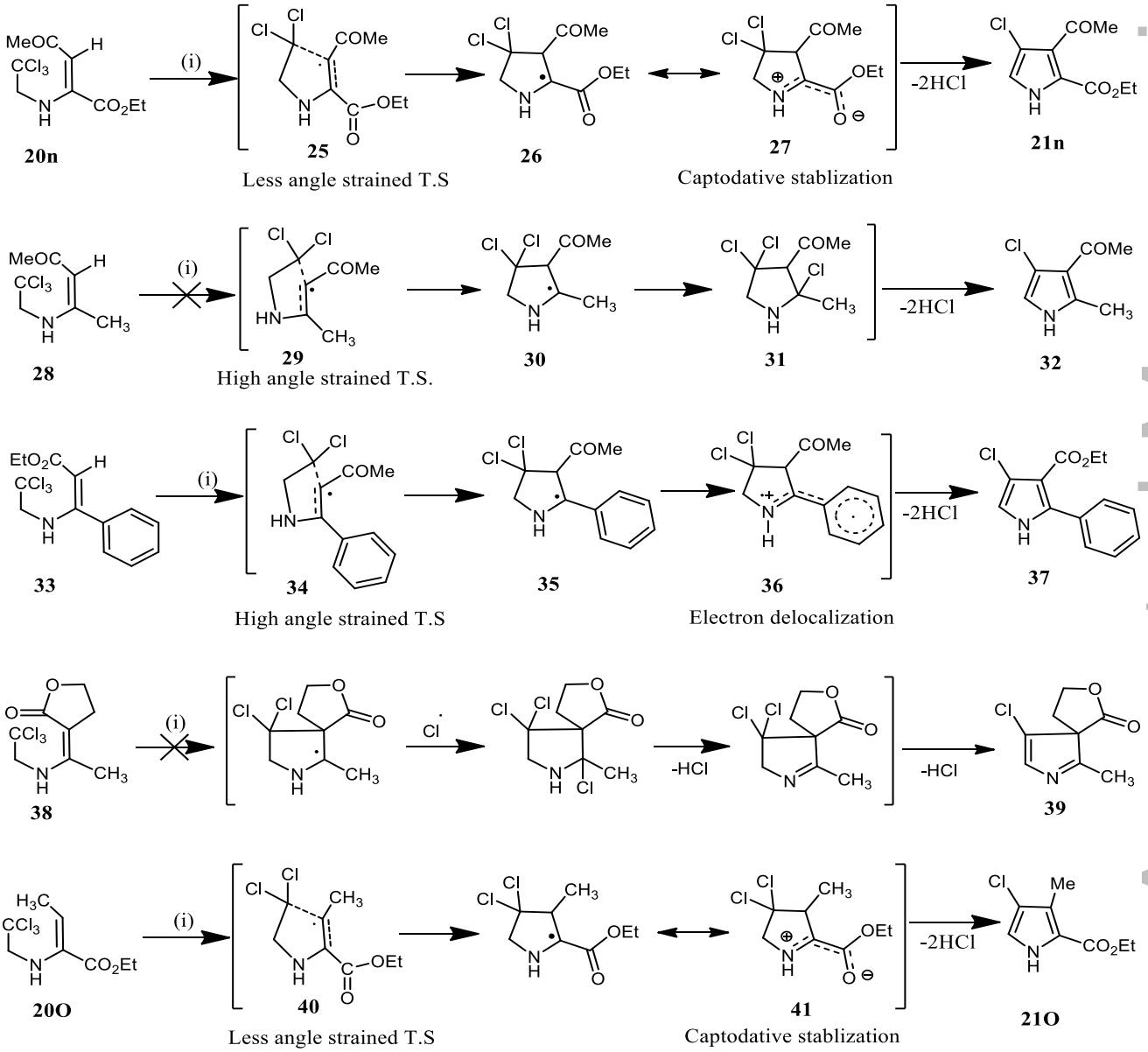
Table 2.Screening of solvents in the cyclization of **20a**[a]

Entry	Solvents	Reaction Time (h)	20a (%) Recovered	21a (%) Isolated yield	Nature of reaction mass
1	DCE	6	-	84	Initially soluble
2	MeCN	5	-	75	Highly soluble
3	Benzene[b]	24	16	58	Highly insoluble
4	Toluene[b]	24	10	60	Insoluble
5	Ethanol[b]	5	-	10	Highly soluble
6	DCE/Ethanol[b](4:1 v/v)	12	-	12	Soluble

[a]All the reactions were performed with 1 mmol of **20a** and with CuCl(0.7)/PMDETA(0.7)/AIBN (1.0) at reflux temperature under N_2 atmosphere. [b] Formation of decomposition side products was observed on TLC plate.



Reaction conditions: i) CuCl/PMDETA (70 mol %), AIBN (1 eq), DCE, reflux, N_2 atm.,12 h

Scheme 4. Study of the conformational role of substituents and functionalities of *N*H-enamines in the 5-*endo*-*trig* radical cyclization process

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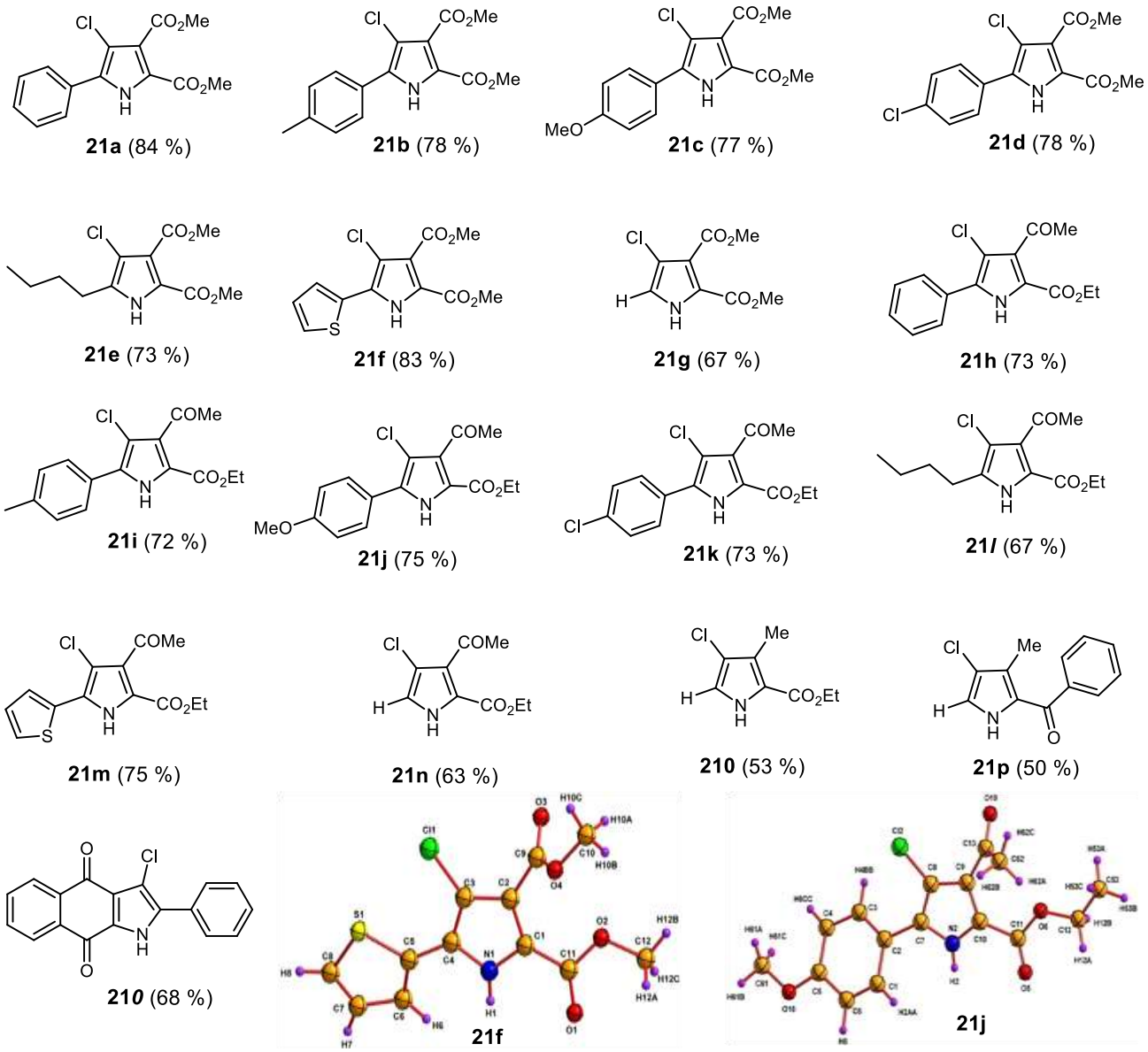

Figure 2. Chemical structures and yields of 5-*Endo-Trig* radical cyclization products **21** of enamines **20** and ORTEP diagrams of 3-chloro-*N*H-pyrrole **21f** and **21j**

No pyrrole moiety of type **32** could be isolated by column chromatography of the crude product, formed expectedly through dehydrochlorinations[26,10b] of HATRC product **31**. A trace of pyrrole **37** was obtained on the purification of the crude product by column chromatography whereas enamines **20a**,**n** underwent the cyclization smoothly.

A radical approaches an α-unfunctionalized double bond above and directly behind the p-orbitals generating great angle strain in the *5-endo-trig* transition state. An attached carbonyl group to this double bond modifies this trajectory in accordance with Baldwin's approach vector analysis whereby the radical approaches the double bond above and behind the p-orbitals, but also away from the carbonyl group resulting into the formation of a less strained 5-*endo* transition state.[27] Thus, clearly in the absence of this α′-ester group, generation of comparatively greater angle strain in the 5-*endo* conformation **29** and **34** than **25** can be expected in these cases also. Further, 5-*Endo* radical cyclization is not only thermodynamically but also kinetically favored when the transition state is stabilized by the delocalization of the unpaired electrons, was theoretically anticipated by Chatgilialoglu, Gimisis and co-workers [8c] in enamides. Thus, easier formation of 5-*endo* cyclic radical **26** than **30** and **35** might have been further facilitated in the enamine **20n** due to an effective stabilization of the transition state **25** than **29** and **34** by relatively a stronger stabilizing captodative effect (of type **27**).[28] An attempt to perform the 5-*endo* radical cyclization of cyclic *N*H-enamine **38** under the optimized conditions failed to deliver **39**, although its structural analog aceto-enamide is known to give 5-*endo* radical cyclization product easily under same Cu(I)-catalyzed radical conditions.[25c] This indicates towards no involvement of a β-carbonyl group at C=C bond in the 5-*endo* radical cyclization. This was further vindicated by the smooth 5-*endo-trig* cyclization-aromatization of **20*O***

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to mono-functionalized *N*H-pyrrole **21*O*** under the same reaction condition *via* less strained transition state **40** and captodative stabilization **41**due to the presence of a carbonyl group at α-carbon (not at β-carbon to the olefinic bond as in **28** and **38**).

After successful cyclization of enamine **20a** under the optimized condition (**Table 1**, **entry-5**), diversely substituted and functionalized enamines **20b−q** were synthesized, their structures were established using NMR, IR, HRMS and their stereochemistry was confirmed by single crystal X-ray diffraction spectroscopy of **20f** (**Fig**. **S1**, refer SI). This methodology was successfully extended to 2,2,2−trichloroethyl-*N*H-enamines **20b−q** (**Scheme 2**) to obtain functionalized 3-chloro-*N*H-pyrroles **21b−q** (**Figure 2**) in high yields with complete regioselectivity. This method successfully cyclized *N*H-enamine **20*O*-p** containing an α′-ketone and α′-ester group to **21*O*-p** in good isolated yields in single step. They are potential bioactive molecules like **12-17** (**fig 1**).[11-18] The method is suitable for synthesis of synthetic intermediate **15** for glycine site antagonists,[12e] obtained simply by condensing methyl amine (**19**, R^1: Me) with ethyl 3-cyano-2-oxopropanoate to give β-cyano-*N*H-enamine (**20** R^3: CN) precursor and its subsequent 5-*endo* radical cyclization (Scheme 2). The structures of 3-chloro-*N*H-pyrroles **21a−q** were established by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and mass spectrometry. The formation of the 3-chloro-*N*H-pyrroles **21a-q** was further supported by single crystal X-ray diffraction spectroscopy of the 2-thienyl derivative **21f** and 2-(4-methoxyphenyl) derivative **21j**. The ORTEP diagrams of **21f** and **21j** are shown in **Figure 2**.

Mechanistic Study

A plausible mechanism involving the 5-*endo-trig* cyclization of 2,2-dichloroethyl-*N*H-enamine radical **43** (**Scheme 5**) to α-pyrrolidine radical intermediate **45** and subsequent chlorine atom abstraction from Cu(II)Cl_2/PMDETA to form mainly the α-chloropyrrolidine intermediate **46** followed by copper/ligand-promoted successive dehydrochlorinations to **47-48** and isomerization by concerted [1,5]-sigmatropic H-shift to aromatic 3-chloro-*N*H-pyrroles **21** has been proposed.

No 4-*exo* cyclization product **42** except the 5-*endo* cyclization product **21** was detected in the ^{1}H NMR of the crude products and isolated by the column chromatography in the cyclization of the enamines **20a-q**. It might be due to high ring strain and more steric congestion in the 4-*exo* transition state.[8a,c] The relatively high reaction temperature in the present cyclization reactions (refluxing DCE) might have enforced the equilibrating reaction conditions arguably towards the formation of the thermodynamically controlled 5-*endo* cyclization product **45** exclusively. The preference for the formation of the 5-*endo* products at higher temperatures has been observed earlier.[29]

Further, participation of the α′-carbonyl group attached to the C=C bond in the easing of the angle strain in the 5-*endo* transition state **44** and its further transformation to the cyclic radical **45** by kinetic stabilization of the transition state through a stronger stabilizing captodative effect[28] might be reason for successful cyclization of all enamines **20a-q** as observed in **Scheme 4**.

No isolation of a 5-*endo* cyclization product **23** except reduced enamine **22** (**Scheme 3**) arising due to *n*Bu_3SnH-mediated reduction of dichloroethyl-*N*H-enamine radicals of type **43** before their 5-*endo-trig* cyclization to **23** could occur, suggests very slow occurrence of 5-*endo-trig* cyclization step (**43** to **44**). Advantageously in Cu(I)-catalyzed HATRC, the radical **43** abstracts readily and reversibly the chlorine atom from $CuCl_2$/PMDETA to regenerate the active CuCl/PMDETA and enamine **20** which, with longer life time, could attempt repeatedly in 5-*endo-trig* cyclization step to eventually give **45**. Thus, $CuCl_2$-complex prevents wasteful reduction of enamines **20**, was equally important in the cyclization of such geometrically constraints systems. It was therefore concluded that the presence of an α′-carbonyl group on the radical acceptor alkenic bond, high reaction temperature and the reversible Cu^I-Cu^{II} catalyst system might have contributed in realizing the 5-*endo* cyclization in these geometrically constraint enamines **20a-q** to form the 5-*endo* cyclization radical **45** exclusively.

The captodative stabilization in the radical intermediate **45** (**Scheme 5**) might also promote the reaction by reducing the reversibility of the 5-*endo*-cyclization product. At the same time, it may also reduce the reactivity of the radical in abstracting a chlorine atom from $CuCl_2$/PMDETA complex in the next step leading to the formation of α-chloropyrrolidine intermediate **46**. This would result in accumulation of the $CuCl_2$/PMDETA complex and disruption of the catalytic cycle. Thus, the role of AIBN appears to restore the catalytic cycle by continuously reducing $CuCl_2$/PMDETA to the active $CuCl_2$/PMDETAcatalyst and promote the formation of HATRC product **46**.[22b]

This α-chloropyrrolidine **46** was expected to spontaneously eliminate a molecule of HCl to form the pyrroline intermediate **47** due to basic Cu(I/II)/PMDETA complex as reported by Stevens et al.[26] However, when the reaction of **20a** under the optimized reaction condition was intercepted after 4 h, 2 h before the completion of the reaction, no pyrroline derivative (of type **47** or isopyrazole **48**) except the pyrrole **21a** and the unreacted starting material **20a** were obtained by column chromatography of the crude product. Probably the pyrroline **47** had high propensity to spontaneously dehydrohalogenate and isomerize to pyrrole ring in the presence of basic Cu(I/II)/PMDETA complex and high reaction temperature condition.

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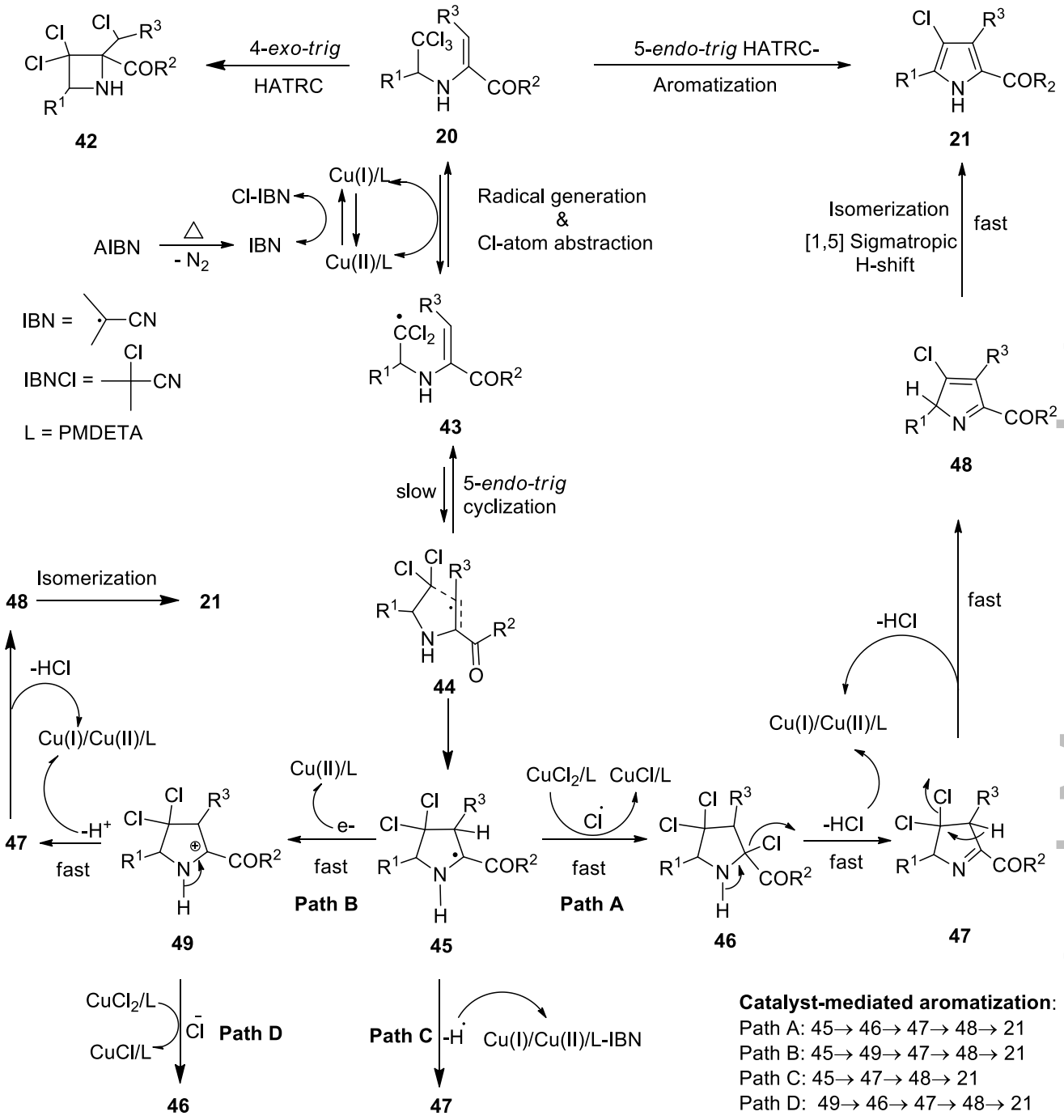

Scheme 5. Plausible mechanism for 5-*endo*-*trig* radical cyclization-aromatization of *N*H-enamines **20**

The precise mechanism for the transformation of cyclic captodative radical **45** (**Scheme 5**) to pyrroline **47** occuring *via* either α-chloropyrrolidine intermediate (**path A**) or carbocation-deprotonation (**Path B**) or hydrogen atom abstraction (**Path C**) or carbocation-addition (**Path D**) routes, might be debatable. Cu(II)-mediated oxidation of an acyclic captodative radical center bearing an *N*H and an ester group, and subsequent addition of the anion of the Cu(II) salt to the corresponding carbocation giving an adduct is known.[30] In the present case also, $Cu(II)Cl_2$/PMDETA-complex produced in the first step may oxidize radical **45** to carbocation **49** which might reversibly combine with chloride ion of the $Cu(II)Cl_2$/PMDETA to give α-chloropyrrolidine **46**(**Path D**) or might eliminate a proton to give pyrroline **47**(**Path B**) directly without involving α-chloropyrrolidine intermediate **46**(**Path A**), cannot be ruled out entirely. However, in both of these processes, the chlorine atom transfer from $CuCl_2$/PMDETA to the radical **45** and oxidation of **45** to carbocation **49** by single electron transfer to $CuCl_2$/PMDETA, appear to be slow probably due to low solubility of the $CuCl_2$/PMDETA complex in the reaction medium. This was indicated by the reaction of **20a** with CuCl/PMDETA in the absence of AIBN (**Table 1**, **entry-3**), where the reaction required long time (24 h) and large amount of the catalyst (1.3 eq)

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to complete the reaction. However, In the presence of a reasonably good amount of AIBN used in the present reactions (**Table 1**, **entry-5**), the chlorine atom transfer mechanism (**path A**) appear to be preferentially promoted. The high concentration of soluble and more reactive IBN radicals would more efficiently reduce the $CuCl_2$/PMDETA to regenerate the active soluble catalyst CuCl/PMDETA. Presumably, an IBN radical might also serve as a soluble halogen carrier in the chlorine atom transfer step[22b] leading to the formation of the α-chloropyrrolidine intermediate **46**. Further due to continuous consumption of the $CuCl_2$/PMDETA by the IBN radicals, the concentration of the former would considerably decrease in the solution, thus disfavoring the oxidation of the captodatively stabilized radical **45** to the carbocationic intermediate **49**. An attempt to cyclize enamine **20a** with oxidizing $CuCl_2$/PMDETA (1.5 eq) failed to give **21a**. However, this cyclization reaction occured completely when enamine **20a** was heated at reflux with 0.8 equivalent of $CuCl_2$/PMDETA in the presence of 1.2 equivalent of AIBN in the reaction mass (**Table 1**, **entry-13**). This indicates that the Cu(I)/PMDETA complex is an active catalyst for the present 5-*endo*-*trig* radical cyclization and the extent of oxidation of the radical **45** to cation **49** due to Cu(II)/PMDETA complex (**Path B**) appears to be insignificant.

Further, the possibility of IBN radical-mediated oxidation of captodatively stabilized radical **45** to the carbocationic intermediate **49** followed by deprotonation to **47** seems to be arguably less. In *n*Bu_3SnH/AIBN-mediated 5-*endo* cyclization of acetamides, Miranda and co-workers [31] reported that, unlike peroxide radicals, an IBN-radical hardly involves in the oxidation of a carbon radical and subsequent deprotonation of the carbocation to form an olefinic bond. Experimentally, upon treatment of a deuterated *N*H-enamine (*N*D instead of *N*H in **20a**) under the optimized reaction conditions, HRMS of the reaction mixture showed no m/z value corresponding to Me_2CDCN. Moreover, Cu(I)-diamine/tri-amine ligand complex-mediated hydrogen abstraction (oxidation) from the cyclic mono- and dienes to give diene and benzene ring, respectively has been noticed by parsons,[23] Clark[6b] and co-workers also. It is further evident from experiments (**Table 1**, **entry-7**,**9-10** and **15**), despite excess of AIBN, enamine **20a** did not undergo complete 5-*endo* cyclization reaction and the reaction completed on addition of pyridine and PMDETA bases or CuCl/PMDETA catalyst to the same amount of catalyst (0.4 equivalent) in each case. Furthermore, in the absence of AIBN also, Cu(I)-complexes alone were able to cyclize enamine **20a** and aromatize the pyrrolidine intermediate to pyrrole (**Table 1**, **entry 3-4**). These experimental and literature evidences suggest higher possiblity of Cu-PMDETA than IBN radical mediated dehydrohalogenation (Path A) and hydrogen atom abstraction (path C) reactions to **47**, although the involvement of IBN radicals in path C cannot be completely ignored.

The captodative radical of type **45** might be expected to disproportionate to a pyrroline of type **47** and a pyrrolidine of type **23**, and dimerize to 2,2'-bipyrrolidine (of type **24**).[23,28c-d] However, in none of the cyclization reactions of enamines **20** in the present study, the conceivable products derived from it was isolated or detected, thus ruling out this possibility in the formation of **47** and **21** through disproportionation route.

Attempts to intramolecularly [32-33] (**Scheme S1**) and inter-molecularly (**Scheme S2**) trap the possible captodative radical **45** and carbocation **49** with internal alkene,[32-33] external alkenes and an alcohol[34] failed. No IBN-captodative radical coupled product[34] (**Scheme S2**) was isolated or detected in any of the cyclization reactions of **20a-q** carried out under the optimized conditions even though all these experiments were performed in the presence of relatively excess amount of AIBN. Failure to trap captodative radical **45** and carbocation **49** may be understood in terms of faster rate of the chlorine atom transfer (path A) and hydrogen atom abstraction (path C) or it could be also due to faster rate of its oxidation-deprotonation (path B) in the (*N*H)amino ester radicals due to basic nature of copper catalyst (**Table 1, entry-15**) as compared to radical addition to alkenes, coupling to IBN radicals and alcohol addition to carbocation in the present case.

From the foregoing account, the conversion of captodative radical **45** (**Scheme 5**) to the cationic intermediate **49** appears less likely to occur in these reactions. Even in the case of the reported Cu(I) catalyzed 5-*endo* cyclizations of haloenamides, only the electron rich tertiary carbon-radicals, which are prone to oxidation, have been reported to be oxidized by Cu(II) species.[6a-b] For example, Hiemstra, Speckamp and co-workers[36] reported that a carbon radical center bonded to an amino group and an ester group hardly oxidizes to carbocation in CuCl/bpy-catalyzed radical reaction due to its captodative stabilization, gives the pyrrolidine only *via* 5-*exo* radical cyclization. Whereas, in the absence of an ester group, the α-amino carbon radical undergoes Cu(II)-mediated oxidation to a carbocation to give a piperidine *via* 6-*endo* cationic cyclization. Due to similarities in the structure of α-aminoester captodative radicals **45** and Cu(I)-catalyzed reaction conditions in the present study and this literature,[36] the retention of radical character at the captodative radical **45** is expected in the present case as well. Thus, a mechanism involving a persistent 5-*endo*-captodative radical and subsequent dehydrochlorinations of HATRC product (path A) appears to be more favorable. However, the intermediacy of carbocation due to oxidation of the captodative radical by Cu(II) species (Path B) followed by deprotonation to pyrroline could not be ruled out completely.

CONCLUSION

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CuCl/PMDTA-complex acts as both a radical initiator and a mild base, catalyzes *5-endo-trig* radical cyclization of *N*H-enamine precursors and doubly dehydrohalogenates the *5-endo*-pyrrolidine product in single step to give polysubstituted and multi-functionalized 3-chloro-*N*H-pyrroles with high degree of functional groups tolerance and regioselectivity. The success of the kinetically 'disfavored' 5−*endo* cyclization was attributed to the availability of a radical acceptor α′-carbonyl group bonded to olefinic bond (causing the formation a less strained transition state and its further stabilization by captodative effect), high reaction temperature, copper (I)-catalyst homolysing the C-X bond and $CuCl_2$-complex prolonging the life time of radical precursor suitable for slow 5-*endo* cyclization step. This reaction experimentally proves that the 5-*Endo* radical cyclization is not only thermodynamically but also kinetically favored due to stabilization of the 5-*endo* transition state by delocalization/captodative stabilization of the unpaired electrons. A mechanism through a preferentially cyclic captodative radical over the carbocation has been anticipated. Transition metals Ni and Mn, reductive and Irreversible *n*Bu_3SnH or similar radical initiators, are ineffective in the 5-*endo* cyclization of these geometrically constraint systems due to a very slow cyclization step leading to reductive dehalogenation of amine precursor. Besides keto and ester groups, this method can introduceother electron withdrawing groups particularly at α-positions in *N*H-pyrrole ring by virtue of their participation in captodative radical stabilizationof a carbon radicalalong with a *N*H group[28] (Scheme 4). CF_2Br or $CFBr_2$ unit in starting material trihaloamines is a potential source for the preparation of 3-fluoropyrroles. This shows method has wider substrate scope. This method further provides a synergistic approach to attain a cyclisable 5-*endo* transition state in other geometrically constraint or partially successful vinylic systems in the literature,[8a] by their structural modifications while employing reversible redox active transition metal catalysts under suitable reaction conditions. With halogens, *N*H and carbonyl functionalities, such pyrroles are valuable source for halogen effect[10e] and SAR studies, halogen based organometallic reactions besides functional group elaborations towards bioactive and pharmaceutically important molecules.

EXPERIMENTAL SECTION

1.1. General Remarks. 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 DMSO (D_6) and $CDCl_3$ with TMS as internal standard. Multiplicities are indicated by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), sext (sextet), m (multiplet), dd (doublet doublet), ddd (doublet of a doublet of adoublet). DEPT spectra were routinely recorded to identify different types of carbons. Massspectra 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 sample 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, basic and neutral alumina was 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. N-(2,2,2-trichloro-1-hydroxy)ethyl acetamide was obtained by condensation of chloral hydrate and acetamide by a method reported in the literature.[37] Ethyl acetopyruvate was prepared by condensation of acetone and diethyl oxalate.[38]Dimethyl acetylenedicarboxylate (DMAD), para-toluene sulphonic acid monohydrate (PTSA) and AIBN was commercially available and used as received. THF was dried over KOH pellets overnight, distilled over 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.

1.2 Preparation of starting materials

1.2.1. *N*-(1-substituted-2,2,2-trichloroethyl) acetamides 18a-f

N-(1-substituted-2,2,2-trichloroethyl)acetamides**18a-f** (Table S1) were synthesized using an one pot strategy. Simple chlorination of *N*-(2,2,2-trichloro-1-hydroxy)ethyl acetamide,[39] subsequent dehydrochlorination of *N*-(1,2,2,2-tetrachloroethyl)acetamide to *N*-acetylchloralimine[40] and addition of Grignard reagents[41] furnished acetamides **18a-f**.

General procedure: To a stirred suspension of *N*-(2,2,2 trichloro-1-hydroxy)ethyl acetamide (4.13 g, 20 mmol) in dry chloroform (100 mL), a suspension of phosphorus pentachloride (4.165 g, 20 mmol) in dry chloroform (60 mL) was slowly added with stirring over a period of 10 min. The temperature of the reaction was carefully controlled and was not allowed to rise above 20 ˚C. The stirring was continued for another 30 min. During this time the evolution of HCl and a progressive loss of turbidness of the reaction mixture were perceptible and the mixture became totally transparent. Then chloroform was removed under reduced pressure at the optimum temperature to get *N*-(1,2,2,2-tetrachloroethyl) acetamide as a white solid. To this solid, dry THF (60 mL) was added, the reaction mass was stirred to dissolve and cooled to 0 °C. To this solution of the *N*-(1,2,2,2-tetrachloroethyl)acetamide in THF, NaH (0.800 g, 60 % as dispersion in mineral oil, 20 mmol) was added with stirring at 0 ˚C. The stirring was continued for 0.5 h at the same temperature to obtain *N*-acetylchloral imine. This solution was cooled to -15 ˚C under a nitrogen atmosphere and was added with a solution of Grignard reagent (20 mmol, 1 equiv) [prepared by a reaction of alkyl or aryl or heteroaryl bromides (20 mmol) with magnesium (0. 486 g, 20 mmol) activated by iodine (cat.) in THF by usual procedure]. The reaction mixture was stirred for 2 h at the same temperature and then the temperature was allowed to slowly rise to 0 ˚C. The stirring was continued for further 30 min duration. The reaction mixture was then quenched at 10 ˚C by addition of a saturated aq. solution of NH_4Cl (20 mL) slowly and extracted with ethyl acetate (3x50 mL). The combined organic layer was dried (anhydrous Na_2SO_4) and filtered. The solvent from the filtrate was removed under reduced pressure and the residue was purified by column chromatography on a basic alumina column using a mixture *n*-hexane/ethyl acetate (9:1, v/v) as the solvent for elution to obtain *N*-(1-substituted-2,2,2-trichloroethyl)acetamides **18a-f** in high yields (80-83 %).

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1.2.2. 1-Substituted 2,2,2-trichloroethyl amines 19a-f: Hydrolysis of 18a-f

2,2,2-Trichloroethyl amines **19a-f** (Table S2) were prepared by acid hydrolysis of *N*-(1-substituted-2,2,2-trichloroethyl)acetamides **18a-f** by using methods reported in the literature[42] for acid-catalyzed hydrolysis of *N*-substituted acetamide derivatives.

General procedure: A mixture of *N*-(1-substituted-2,2,2-trichloroethyl)acetamide **18** (10 mmol), 5N H_2SO_4 (or 4N HCl in the case of **18c**) (50 mL) and methanol (50 mL) was heated at reflux. After completion of the reaction as indicated by disappearance of the starting acetamide on TLC monitoring (8-16 h), the reaction mixture was allowed to cool to room temperature (25-30 ˚C). It was washed with benzene (2x20 mL) to remove any organic residue. The aqueous phase was cooled at 0 ˚C and NaOH (aq. 2N) was added to it with stirring. The solution became gradually turbid in this process. The addition of NaOH solution was stopped when the pH of the turbid suspension rose to 9-10. The suspension was further stirred for 15 min and extracted with ethyl acetate (3x30 mL). The combined extract was dried (anhydrous Na_2SO_4), filtered and evaporated under reduced pressure to obtain 1-substituted 2,2,2-trichloroethylamines **19a-f** in good yield (66-81 %). The amines were directly used in the next step without further purification.

This previously known 2,2,2-trichloroethylamine **19g** was prepared by reduction of trichloroacetonitrile with $LiAlH_4$ according to a method reported as reported in our previous article.[10b]

1.2.3. Preparation of *N*-2,2,2-trichloroethylenamines 20a-g

The previously unknown enamines **20a-g** (Table S3)were prepared by Michael addition of trichloroethyl amines **19** to DMAD following a procedure reported in the literature with slight modification.[4e]

General procedure: A solution of the 2,2,2-trichloroethylamine **19** (10 mmol) and dimethyl acetylenedicarboxylate (DMAD) (1.23 mL, 1.421 g, 10 mmol) in THF was stirred at room temperature (25-30 ˚C) for 6-8 h. After the completion of the reactions as indicated by TLC, the THF was evaporated under reduced pressure and the residual mass was purified by column chromatography using basic alumina column. The column was run through initially by *n*-hexane then by a solution of ethyl acetate in *n*-hexane (1%, v:v). The enamines **20a-g** were obtained in 72-80 % yields as mentioned in **Table S3**.

1.2.4. Preparation of *N*-(2,2,2-trichloroethyl)enamines 20h-n derived from ethyl acetopyruvate

The previously unknown enamines **20h-n** (Table S4)were prepared by using a method reported in the literature,[4d] in which similar enamines were prepared by acid-catalyzed azeotopic condensation reaction of various 2,4-dioxoester derivatives with non-chlorinated primary amines.

General procedure: A solution of the 2,2,2-trichloroethylamine **19** (10 mmol), ethyl acetopyruvate(1.582 g, 10 mmol) and a catalytic amount of PTSA (0.344 g, 2 mmol) in benzene was heated at reflux in a Dean Stark apparatus. The progress of the reaction was monitored by TLC as well as by ^{1}H NMR of aliquots taken from the reaction mixture from time to time. After completion of the reaction (4-5 h), the reaction mixture was cooled to room temperature (25-30 ˚C). The benzene was evaporated under reduced pressure. The purification of the residual mass on basic alumina column by running through with *n*-hexane followed by a solution of ethyl acetate in *n*-hexane (1%, v/v) as the solvent for elution furnished the enamine **20h-n** in 63-78 % yield.

(*Z*)-ethyl 2-((2,2,2-trichloroethyl)amino)but-2-enoate 20*O*: It was prepared by acid-catalyzed condensation reaction between 2,2,2-trichloroethyl amine 19**g** (1.485 g, 10 mmol)of ethyl 2-oxobutanoate (1.30 g, 10 mmol) for 7 h in same manner as other enamines **20h-n**.

(*Z*)-1-phenyl-2-(2,2,2-trichloroethylamino)but-2-en-1-one 20p: It was prepared by acid-catalyzed condensation reaction between 2,2,2-trichloroethyl amine **19g** (1.485 g, 10 mmol)of 1-phenylbutane-1,2-dione (1.62 g, 10 mmol) for 8 h in same manner as other enamines **20h-n**.

2-(2,2,2-Trichloro-1-phenylethoxy)naphthalene-1,4-dione 20q:This was prepared by a procedure reported in the literature with a slight modification.[42, 4c] A mixture of 2-bromo-1,4-naphthoquinone (10 mmol), 2,2,2-trichloro-1-phenylamine **19a**, (12 mmol) and Na_2CO_3 (15 mmol) in abs. EtOH (40 mL) was stirred at 40-45 °C for 14 h. The resulting mixture was filtered and the filtrate was removed under reduced pressure and water (100 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 (90:10 %, v/v) afforded the pure enamine **20q**.

(*Z*)-4-(2,2,2-Trichloroethylamino)pent-3-en-2-one 28: It was prepared by acid-catalyzed condensation reaction between 2,2,2-trichloroethyl amine **19g** (1.485 g, 10 mmol)of acetyl acetone (1.002 g, 1.02 mL, 10 mmol) for 8 h in same manner as other enamines **20h-n**.

(*Z*)-Ethyl 3-phenyl-3-((2,2,2-trichloroethyl)amino) acrylate33: It was prepared by acid-catalyzed condensation reaction between trichloroethyl amine **2g** (1.485 g, 10 mmol)and ethyl 3-oxo-3-phenylpropanoate (1.92 g, 10 mmol) for 8 h in same manner as other enamines **20h-n**.

(*Z*)-4-(2,2,2-Trichloroethylamino)pent-3-en-2-one 38: It was prepared by acid-catalyzed condensation reaction between 2,2,2-trichloroethyl amine **19g** (1.485 g, 10 mmol)of 3-acetyl-dihydrofuran-2(3*H*)-one (1.28 g, 10 mmol) for 8 h in same manner as other enamines **20h-n**.

(*Z*)-Allyl 4-oxo-2-(2,2,2-trichloro-1-(4-chlorophenyl) ethylamino)pent-2-enoate50: It was also prepared by acid-catalyzed condensation reaction between amine **19d** (2.590 g, 10 mmol) and allyl acetopyruvate (1.72 g, 10 mmol) for 8 h in same manner as other enaminoketoesters**20h-n** under reflux condition in benzene using Dean-Stork apparatus.

Cu(I)/PMDETA-catalyzed 5-*endo* HATRC-Aromatization of *N*H-enamines 20. General procedure: A flame-dried two-neck round-bottom flask was charged with CuCl (70 mg, 0.7 mmol) and degassed DCE (30 mL) under a N_2 atmosphere using Schlenk technique. PMDETA (0.146 mL, 0.121g, 0.7 mmol) was injected to the suspension and the suspension was stirred magnetically for 10 min. Next, the 2,2,2-trichloroethyl enamine **20a-*q***(1 mmol) and solid AIBN (0.137g, 1 mmol) were added. The reaction mixture was degassed again by applying vacuum and refilled with the N_2 gas. The solution was then heated at reflux with stirring. After completion of reaction (6-12 h) as indicated by TLC monitoring, the reaction mixture was cooled and the solvent was evaporated. Ethyl acetate (150 mL) was added to the residual mass and the resulting solution was washed with brine (3x25 mL) till the color of the solution became reddish or yellowish. The combined aqueous layer was treated with ammonium chloride

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solution and extracted with ethyl acetate to ascertain that there is no loss of the product into the aqueous layer along with copper complexes. All the organic extract was combined and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and the residual mass was purified by column chromatography using neutral alumina column using a mixtures *n*-hexane/ ethyl acetate (9:1-8:2, v/v) as the solvents for elution. The product thus obtained was further purified by recrystallization from *n*-hexane-chloroform or *n*-hexane-DCM to obtain the 2,3-difunctionalized 5-substituted 3-chloropyrroles **21a-*q***in (50-84 %) good to high yields.

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FULL PAPER

β,β,β,-Trichloroethyl-*N*H-Enamine As Viable System For 5-*Endo-trig* Radical Cyclization *Via* Multifaceted Cu^{I}-Cu^{II} Redox Catalysis: Single Step Synthesis of Multi-Functionalized *N*H-pyrroles

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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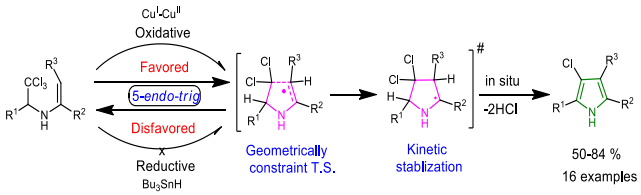

R^1 = Aryls, heteroaryl, alkyls, H; R^2 = Aryl, COR (R : OMe, OEt, Ph), R^3 = CO_2Me, COMe, Me: R^2-R^3 = 1,2$(CO)_2C_6H_4$ Reaction condition: CuCl/PMDETA(0.4-0.7eq)/AIBN, DCE, reflux, N_2 atm, 6-12 h

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