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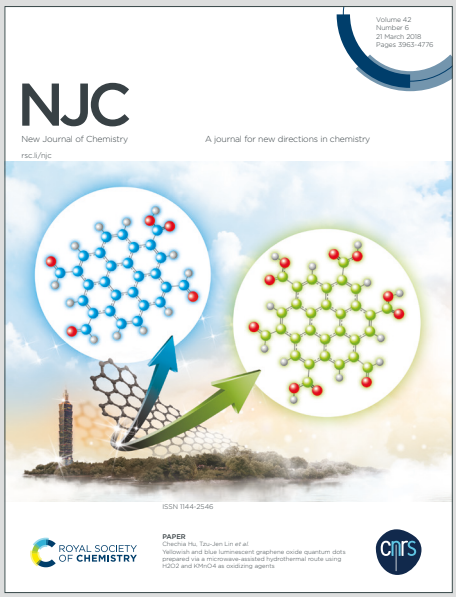

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ARTICLE

Changing Stereo- And Regioselectivity In Copper(I)-Catalyzed 5-*Exo* Cyclization By Chelation And Rigidity In Aminoalkyl Radicals: Synthesis Towards Diverse Bioactive N-heterocycles

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The work reveals that chelate-type interaction in the transition state of a β-aminoalkyl radicals in copper(I)-catalyzed 5-*exo*-*trig* radical cyclization step changes the usual stereochemistry of the *N*H-pyrrolidine ring predicted by Beckwith-Houk transition state model. Whereas, the rigidity in the fused β-aminoalkyl radical changes the Baldwin's predicted 5-*exo* to 6-*endo* cyclization mode preferentially forming piperidine ring over pyrrolidine ring *via* geometrically constraint transition state. The resultant diverse *N*H-pyrrolidines, pyrrolines and piperidines are sources for bioactive natural product Roseophilin and a drug Ritalin among others.

Introduction

Steric and stereoelectronic factors in a cyclizing alkenyl radical govern the Baldwin's rules for 5-*exo* and 6-*endo* cyclization modes to produce five- and/ or six-membered cyclic products including pyrrolidines and piperidines, respectively.[1] The conformational and steric factors in the cyclizing radical further control the stereochemical outcomes in the cyclized product(s) including *N*-heterocycles *via* Beckwith-Houk transition state model.[1] However, a suitably positioned substituent or a functionality in the cyclizing aminyl *N*-radical can change the 5-*exo* mode to 6-*endo* mode to give piperidine preferentially over pyrrolidine against Baldwin's rules.[1i-j] Similarly, an intramolecular hydrogen bonding[2] and lewis-acid (BF_3 and $AlMe_3$) coordinated quartenary-nitrogen[3] in the cyclizing aminoalkyl C-radical can change the usual conformation in the Beckwith-Houk transition state model to change the usual stereochemistry of the pyrrolidine ring. However, these radical cyclzation methods are reductive in nature and require excess of radical initiator nBu$_3$SnH and Lewis acids for *N*-coordination.[3] The ability of a catalytic copper complex to generate a radical and form a chelate ring in the transition state of the cyclising aminoalkyl radical[4] to change the usual stereoselectivity in *N*H-pyrrolidine ring[5-6] is not explored so far. Also, the ability of a fused aminoalkyl C-radical to change the regioselectivity from 5-*exo*- to 6-*endo* mode through a persistent radical rather than the usual carbocation (oxidized C-radical), is scarcely explored.[4-5,6i]

Copper(I)-catalyzed atom transfer radical cyclization (ATRC)[6-7] method is a catalytic, atom-economic, easy to operate, cost-effective, high yielding and environmentally benign protocol which retains the valuable halogen atom(s) of a radical precursor in the cyclized product for further chemical transformations and biological applications. Our previous experiences in Cu(I)-catalyzed ATRC reactions with halo-alkenyl substrates led us to investigate the changes in usual regio- and stereoselectivity during 5-*exo* ATRC reactions of bidentate aminoalkyl radical precursors(capable of forming chelate ring with Cu-catalyst) and the fused-α/β-aminoalkyl radical precursors having different degrees of rigidities. A suitable Cu (I)-catalytic system capable of radical generation and complexation with aminoalkyl radical precursors, particularly at catalytic level, viable at industrial level, was explored. Short-methods to transform resultant N-heterocycles towards bioactive natural products and medicines were also devised.

Results and Discussions

First, a pyridine-substituted β-chloroethyl allyl amine **2a** (**Scheme1**), an aminoalkyl radical precursor with two coordinating centers capable of forming a chelate ring with Cu(I)-catalyst in the transition state, was synthesized by simple addition of CCl_3CO_2H-DMSO solution to a solution of *N*-allyl aldimine **1a** in DMSO at ambient temperature.[5a] Next, the ATRC reactions of *N*H-amine **2a** (**Table 1**) were performed with varying amount of CuCl (5 %, to begin with) and commercially available ligands [2,2'-bipyridine (bpy), tetramethylethylenediamine (TMEDA), and pentamethyldiethylenetriamine (PMDETA) usually employed in Cu(I)-catalyzed ATRC protocols[6b,d]] in different solvents at different temperatures under a nitrogen atmosphere, to explore a suitable catalyst. The progress of the reaction was monitored by thin layer chromatography (TLC) and was further confirmed by ^{1}H NMR of the aliquots taken directly from the reaction mass.

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Scheme 1. Synthesis and Copper(I)-catalyzed ATRC reactions of **2a** [a]

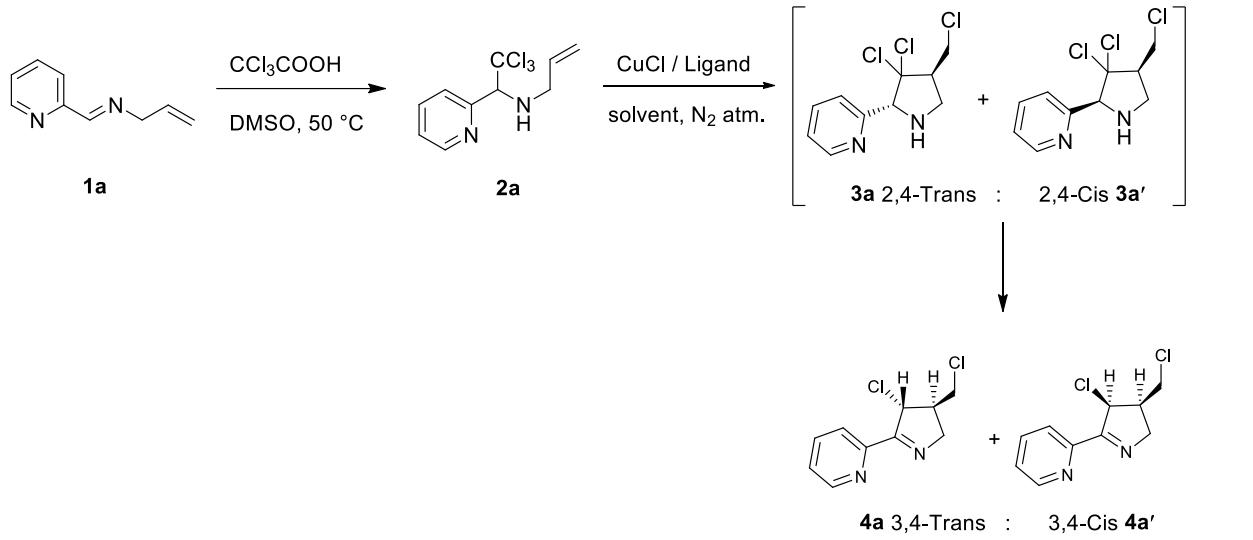

Table 1. Optimization of the reaction conditions in Cu(I)-catalyzed ATRC of **2a**

Entry	Mol % CuCl / Ligand (mol ratio) / additive (eq)	Solvent	Temp.	Time	4a-a′ Yield c	4a-a′ Trans : Cis [b]
1	100 % CuCl / bpy (1:1)	DCE	reflux	8 h	58 %	--
2	80 % CuCl / TMEDA (1:2)	DCE	reflux	6 h	72 %	--
3	40 % CuCl / PMDETA (1:1)	DCE	reflux	4 h	74 %	--
4	40 % CuCl / PMDETA (1:1)	MeCN	reflux	3 h	78 %	50:50
5	40 % CuCl / PMDETA (1:1)	MeCN	RT	5 h	80 %	55:45
6	40 % CuCl / PMDETA (1:1)	MeCN	0 ˚C	6 h	82 %	60:40
7	5 % CuCl / PMDETA (1:1) / AIBN (0.250)	MeCN	reflux	3 h	52 % d	50:50

[a] All the reactions were performed with 1 mmol of **2a** under a nitrogen atmosphere. [b] Mixture of diastereomers in ^{1}H NMR of the crude product.
[c] Isolated yield after purification by column chromatography on basic alumina. [d] Not a clean reaction due to decompositions oftheradical precursor

PMDETA was the most effective ligand in terms of product yield and catalyst loading (**Table 1, entry 1-3**). The reaction in a coordinating solvent acetonitrile (MeCN) was slightly better than chlorinated solvent 1,2-dichloroethane (DCE) in terms of product yield and reaction time due to higher solubility of the Cu-catalyst in acetonitrile (**Table 1, entry 3-4**).[5a,8] Due to the tendency of a β-haloalkyl-*N*H-amine to decompose at high reaction temperature (**SI Fig. S25-S28**),[9] the ATRC reactions of **2a** were performed at lower temperatures. The ^{1}H NMR of the crude product obtained at 0° C was cleaner and had higher percentage of 3,4-*trans*-diastereomer **4a** (**SI Fig. S27-28**) than at 25 °C and reflux though a longer reaction time was required to complete this reaction (**Table 1, entry 5-6**). An attempt was made to lower the catalyst loading to minimum (**Table 1**, **entry 7**, **SI Fig 29**) by using AIBN[7] as a reducing agent for catalyst-regeneration, a method successfully employed in our previous work.[7b] However, this method was found ineffective in this case due to the presence of pyridine substituent (internal base) in **2a** causing the decomposition of **2a**.[7b]

The cyclization of 1-pyridyl *N*H-amine **2a** furnished the pyrrolines **4a-a'** directly as a 3:2 (**4a** *Trans* : *Cis* **4a**', **SI Fig**. **S27-28**) diastereomeric mixture under the optimized reaction conditions (**Table1 entry-6**). The intermediate 2-pyridyl-*N*H-pyrrolidine **3a-a'** (**Scheme 1**) could not be detected or isolated. A considerable amount of the product **4a-a'** was also recovered from the aqueous phase during the work up by treating it with aqueous ammonia solution and extracting with ethyl acetate. This was due to the pyrrolines **4a-a'** being bidentate ligands like *N*-alkyl pyridinemethanimines (*N*-RPMI)[6b,d] which could form a 5-membered C-N-Cu-N-C chelate ring[10] and went into the aqueous solution. The 3,4-*trans* and 3,4-*cis* stereochemistry was assigned unambiguously to the major **4a** and minor **4a'** diastereomers, respectively on the basis of dihedral angle between protons at C-3 and C-4 in the ^{1}H NMR of **4a-a'** mixture.

The preferential formation of major 3,4-*trans* diastereomer **4a** over 3,4-*cis* **4a'** might occur *via 5-exo* ATRC of **2a** (2,4-*trans*-***3a***> 2,4-*cis*-***3a'***) followed by their dehydrochlorination and tautomerization. This assumption was experimentally studied by undertaking a DBU-mediated dehydrochlorination and tautomerization of *N*H-pyrrolidines **3c-d**[5a] (**Scheme 2**) having known 2,4-*trans* geometry which were previously synthesized by us under the same reaction condition (Table 1, entry-6). The reaction of crude 2,4-*trans* pyrrolidines **3c-d** with DBU at 25-30 °C and subsequent purification of crude products by column chromatography afforded 3,4-*trans*-pyrrolines **4c-d** (**SI Fig.**

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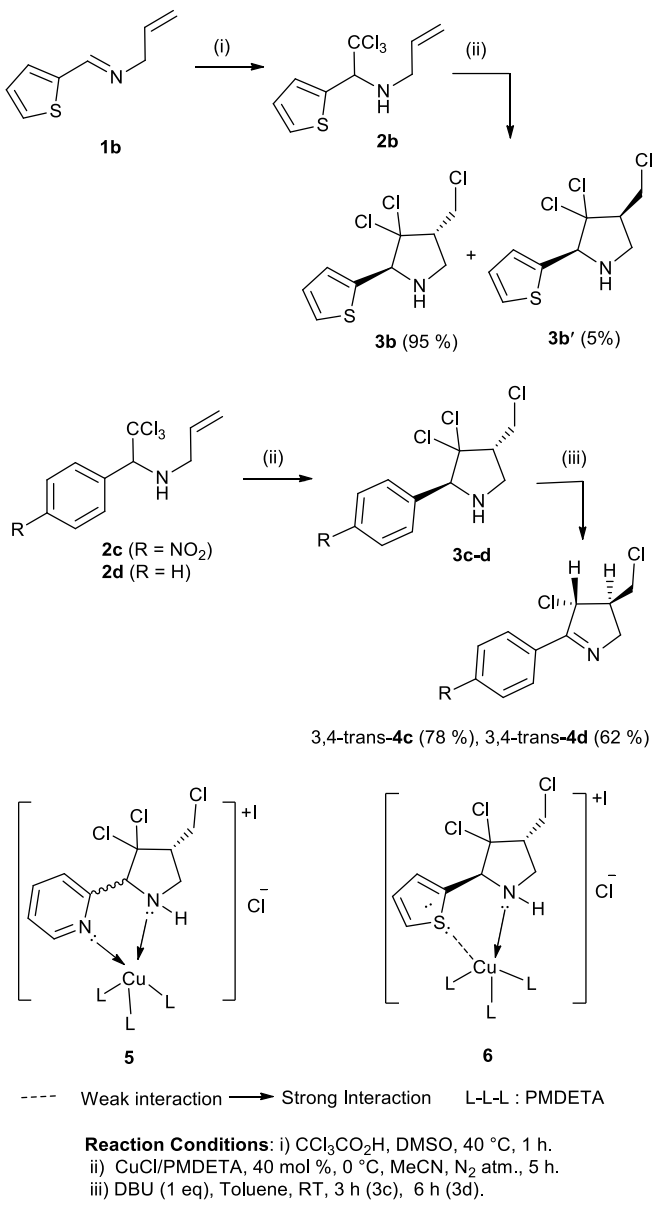
S32-35). The corresponding minor 3,4-*cis*-diastereomers were perhaps too little, to be isolated by column chromatography. The higher acidity of the hydrogen at C-2 in 4-NO_2-phenyl derivative **3c** than **3d** probably facilitated a quick elimination of HCl. Slight basic reaction condition possibly tautomerized the 2,3-dihydro-1*H*-pyrrole intermediates to stable 3,4-dihydro-2*H*-pyrrole (or pyrrolines **4c-d**), also reported by kempe et al.[11] Disappearance of CCl_2 peak, appearance of an olefinic carbon in ^{13}C NMR and no disappearance of any peak belonging to *N*H-proton in the ^1H NMR of the compound in $CDCl_3$ on shaking with D_2O confirmed the formation of pyrrolines **4a-a'**,**c-d**.



Scheme 2: Comparision of impacts of co-coordinative interaction between (pyridine)N—Cu--NH and (Thiophene)S—Cu--NH on 2,4-*trans*stereochemistry of *N*H-pyrrolidine rings

3-chloro-pyrrolines of type (**4a-a',c-d)** aromatize easily to β-chloro-*N*H-pyrroles under basic condition to give variants of Pyrrolnitrin, an antifungal and antibiotic extracted from Pseudomonas Pyrrocinia and other Pseudomonas species.[11] These pyrrolines also give useful chiral 3-chloro-*N*H-pyrrolidines on simple reduction with sodium borohydride, as thoroughly demonstrated by Kimpe et al.[11]

A weak coordinative interaction of sulphur(thiophene) with copper has been reported by Li and co-workers,[5b] and was also observed by us in Cu(I)-promoted radical cyclization of β-haloethyl allyl thioethers to tetrahydrothiophenes.[9b] Thus an insignificant change in the usual 2,4-*trans* stereochemistry in the thiophene-(α) substituted *N*H-pyrrolidine was expected. The Cu(I)-catalyzed radical cyclization of **2b** led to the formation of usual major 2,4-*trans*-*N*H-pyrrolidine **3b** and negligible amount of minor 2,4-*cis*-*N*H-pyrrolidine **3b' (SI Fig. S30-31)** under the optimized reaction condition of **2a** (Table 1, entry-6). Considerably high change in the 2,4-*trans* geometry to 2,4-*cis* geometry in the cyclization of **2a** (**Scheme 1**) than **2b (Scheme 2**) might be due to stronger chelate type interaction in the transition state of pyridine substitutedpyrrolidine (of type **5**)[5c-e] than a weaker one (of type **6**)[5b] in thiophene substituted pyrrolidine as shown in Scheme **2**. The recovery of more pyridine substituted pyrrolidine **3a-a'** (or **4a-a'**≈40%) than thiophene pyrrolidine **3b-b'** (≈5%) from aqueous phases during work up by addition of aqueous ammonia and extraction with ethyl acetate (experimental section), proved the presence of greater chelate type interactions in the transition state of cyclizing aminoalkyl radical of **2a** than **2b**.

Stereocontrol Studies

The effect of chelate type interaction of type 5 (**scheme 2**) in changing the usual 2,4-*trans*-stereochemistry of the *N*H-pyrrolidine was further extended by performing Cu(I)-catalyzed ATRC reaction on bidentate 2,2,2-trichloroethyl allyl *N*H-amines **8** having coordinating keto, amide and nitro group in a side chain at C-2 (**Table 2**). The functionalized precursors **8a-e** were prepared by Aza-Michael addition of allyl amines to Michael acceptors **7a-d** with slight modifications of our previous method on Thio-Michael addition reactions.[9b]

Treatment of *N*H-amines **8a-e** with CuCl/PMDETA (60 mol %) at 0 ˚C for 6-8 h followed by purification by column chromatography (basic alumina) furnished the side chain functionalized 3,3-dichloro-*N*H-pyrrolidines **9a-e** in high isolated yields (**Table 2**, 79-85 %). Ratio of diastereomers was determined from the ^1H NMR of the aliquots taken from the reaction mass after completion of the reactions as indicated by TLC. The structures of unknown *N*H-pyrrolidines were supported by ^1H NMR, ^{13}C NMR, IR spectroscopy and mass spectrometry. With expected carbonyl group-dependent minor differences in the structures, the gross NMR spectral features of **9a-b**,**d** (**SI Fig. S36-43**) were largely similar to those of the phenyl ketone-substituted 2,4-*trans*-*N*H-pyrrolidine **9c**[5a] which was previously synthesized by us using the same reaction conditions (**Table 2**).

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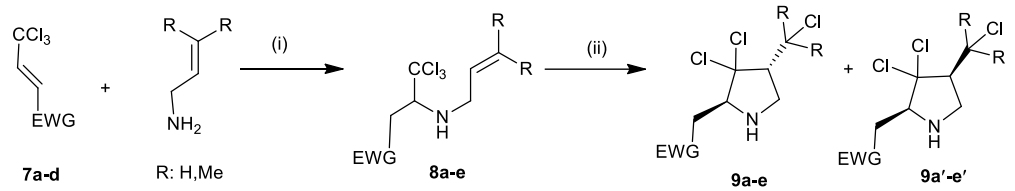
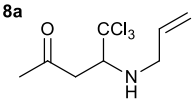
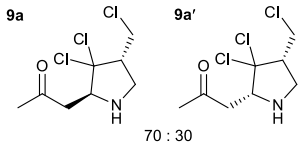
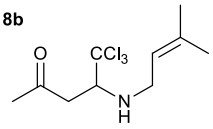
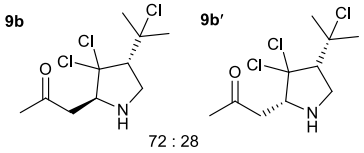
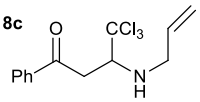
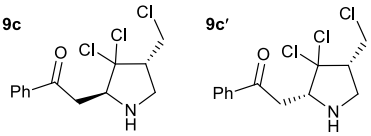
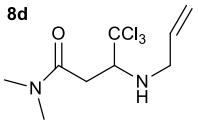
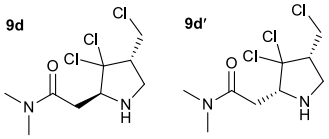
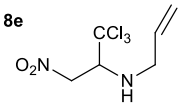
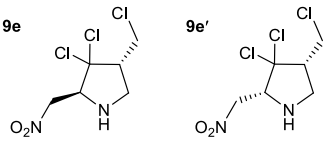
Table 2. Copper(I)-catalyzed radical cyclization of side chain functionalized radical precursors for stereocontrol studies



7 (EWG a: COMe, b: COPh, c: $CONMe_2$, d: NO_2), R : H, Me

Reaction Conditions: i) THF or *tert*-But/ cat base, RT, 4-24 h. ii) CuCl/PMDETA (1:1, 60 mol %), MeCN, 0 °C, 6-8 h.

Entry	2,2,2-trichloroethyl allylamines [a]		Halogenated *N*H-Pyrrolidines [b]	
	Structure	Yield % (time)	Stereochemistry [c]	Yield [d] % (Time)
1		80 % (6 h)	 70 : 30	83 % (6 h)
2		80 % (6 h)	 72 : 28	80 % (7 h)
3		82 % (5 h)	 100 : 0 at 0 °C and 95 : 05 at RT	85 % (6 h)
4		76 % (24 h)	 74 : 26	81 % (8 h)
5		83 % (4 h)	 22 : 78	79 % (8 h)

[a]The reactions were performed with 10 mmol of the Michael acceptor **7a-d** with allyl amines for **8a-e** and were purified by column chromatography using neutral alumina.

[b]The reactions were performed with CuCl/PMDETA (60 mol %) at 0˚C in MeCN using 1 mmol of radical precursorsunder a N_2 atm.

[c] ^{1}H NMR spectrum of crude mass was used for the determination of diastereomeric ratio in *N*H-pyrrolidines.

[d]The products **9a-e**were purified by column chromatography using basic alumina.

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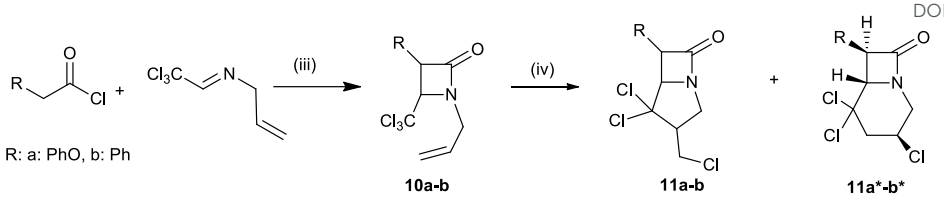
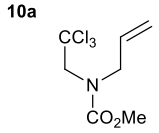
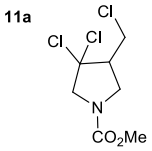
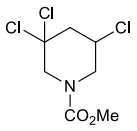
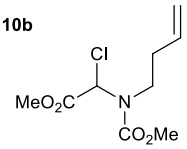
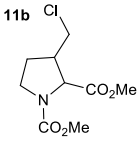
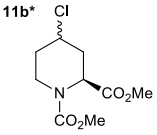
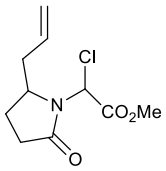
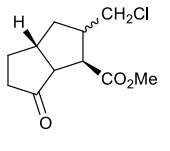
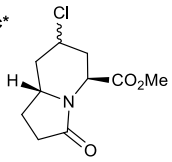
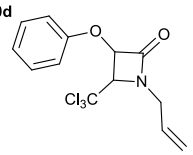
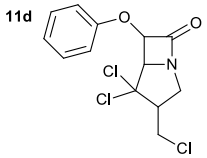
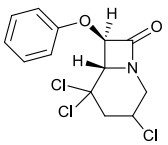
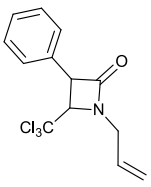
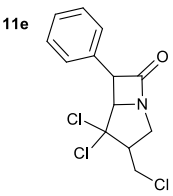
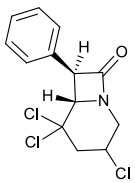
Table 3. Copper (I)-catalyzed radical cyclization of radical precursors for regiocontrol studies

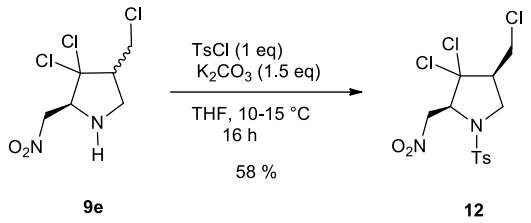


Reaction Conditions: i) Triethyl amine, DCM, 0 °C-RT, 2-3 h. ii) CuCl, TMEDA/PMDETA, DCE/MeCN, reflux, 6 h.

Entry	2,2,2-trichloroethyl allylamines [a]		Halogenated *N*-protected pyrrolidines/piperidines [b]	
	Structure	Yield % (time)	Stereochemistry/Regioselectivity [c,e]	Yield [d] % (time)
1	**10a** 	80 % (5 h)	**11a**  **11a***  100 : 00	88 % (12 h)
2	**10b** 	45 % (7 h)	**11b**  **11b***  70:30	70 % (12 h)
3	**10c** 	75 % (3 h)	**11c**  **11c***  20 : 80	68 % (12 h)
4	**10d** 	58 % (3 h)	**11d**  **11d***  06 : 94	80 % (6 h)
5	**10e** 	46 % (4 h)	**11e**  **11e***  08 : 92	75 % (6 h)

[a] The reactions were performed with 10 mmol of the starting materials and products were purified by column chromatography using neutral alumina. **10a** was prepared by reaction of 2,2,2-trichloroethyl allyl NH-amine[5a] with methyl chloroformate (1 eq) in DCM in the presence of triethyl amine. [b] The reactions were performed with CuCl/TMEDA/PMDETA (25-60 mol %) at RT/reflux in DCE/MeCN using 1 mmol of **10a-e** under a N_2 atm. [c] ^{1}H NMR spectrum of crude mass was used for the determination of stereochemistry and pyrrolidine-piperidine ratio in cyclization products. [d] The products **11a-e** were purified by column chromatography using neutral alumina. [e] Previously known structurally different α-carbon radical precursors **10b**[6h] and **10c**[6h] were reacted with 25 mol % CuCl/PMDETA at RT in DCE. under N_2 atmosphere to compare their regioselectivity with that of β-carbon radical precursors **10a** and **10d-e**, respectively.

The formation of minor 2,4-*cis* diastereomers in pyrrolidines **9a-b** than **9c** (**Table 1**) suggests some effective 6-membered C=O--Cu(I/II)-NH chelate type interaction with MeC=O than the bulky PhC=O group possibly due to high steric hindrance posed by the bulky phenyl group in the transition state. Methyl substituents at the terminal double bond in **8b** seemed not to affect this NH-Cu-O=C interaction. The amide group in the side chain of **8d** interacted with Cu-catalyst to produce the minor diastereomer. The minor isomers detected in ^{1}H NMR of the crude products had almost similar Rf with major products, thus could not be isolated by simple column chromatography. The impact of this interaction was most prominent in the precursor **8e** due to the presence of nitro group in the side chain arguably due to its anionic nature (O^--N^+-O^-) resulting into relatively stronger O=N-O^--Cu—NH interaction in the transition state (**SI Fig. S44-45**).



9e **12**

Scheme 3. Tosylation product **12** of *N*H-pyrrolidines **9e**

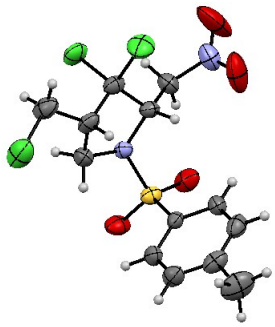


Figure 1. ORTEP diagram of *N*-tosyl-NO_2-pyrrolidine **12**

Determination of the stereochemistry of the major products **9a-d** by 2D NOE or NOESY-spectroscopy was not unambiguous because the relevant proton signals were not well separated (**SI**). A method to determine the stereochemistry of *N*H-pyrrolidines through corresponding *N*-tosyl-pyrrolidines has been employed in many halogenated and functionalized *N*H-pyrrolidines without affecting their chiral centers.[5a] Thus, the stereochemistry in **9e** was confirmed from X-ray single crystal structure of its *N*-tosyl-pyrrolidine **12** (**SI Fig. S54-55**) prepared under milder reaction conditions (**Scheme 3**). The ORTEP diagram of tosylation product **12** (**Fig. 1**) of nitro-functionalized *N*H-pyrrolidine **9e** showed it has 2,4-*cis* geometry of nitro-methylene substituent at C-2 position and chloromethyl substituent at C-4. On the basis of single crystal data of **12** and NMR measurements, the stereochemistry of minor isomers in the inseparable (or undetected in ^{1}H NMR of crude products) diastereomeric mixtures of **9a-a'**,**b-b'**,**d-d'** were assigned 2,4-*cis* geometry. The major isomers were assigned 2,4-*trans* geometry on the basis of 2,4-*trans* geometry of **9c**[5a] due t o structural similarity and use of same radical reaction conditions (**Table 2**).

Regiocontrol Studies

No 6-*endo* radical cyclization products (piperidine ring) could be detected in ^{1}H NMR of the crude products **3a-d** or **9a-e** and could not be isolated by column chromatography also. This indicated an occurrence of a regioselective cyclization of precursors **2a-d** and **8a-e** by 5-*exo* mode which is widely accepted in the cyclization of 3-aza-5-hexenyl (β-carbon) radicals in the allyl *N*H-amines.[1,5a] In order to study the changes in the known regioselectivity from 5-*exo* to 6-*endo* modes in *N*-heterocycles synthesis, different carbon radical centered α/β-haloalkyl alkenyl amines, and the fused-α/β-haloalkyl alkenyl amines having different degrees of rigidities in the rings, were synthesized (**Table 3**).

First, a comparison in the regioselectivity was done by performing Cu(I)-catalyzed ATRC reactions on 3-aza-5-hexenyl (β-carbon) radical precursor **10a** and 2-aza-5-hexenyl (α-carbon) radical precursor **10b**under the same reaction conditions using relatively stronger catalyst CuCl/PMDETA (25 mol %) and milder reaction condition (at room temperature) in a coordinating solvent MeCN. The ATRC reaction of precursor **10a** led to the formation of pyrrolidine **11a** (**SI Fig. S46-47**) exclusively whereas precursor **10b** afforded a mixture of pyrrolidine **11b** and piperidine **11b*** in 70:30 ratio. A less regioselectivity in the 5-*exo* cyclization of acyclic 2-aza-5-hexenyl (α-carbon) radical of precursor **10b** giving a mixture of pyrrolidine **11b** and piperidine **11b*** in similar ratiois documented in the Cu(I)/bpy-catalyzed ATRC reaction in DCE at reflux.[6h] This insignificant impact on regioselectivity is possibly due to the independent nature of cyclizing 2-aza-5-hexenyl (α-carbon) radical of **10b** and its MeOCO-protected nitrogen atom could not interact with the Cu-catalyst to alter this 5-*exo* mode.

An increase in ratio of 6-*endo* cyclization mode **11c*** over 5-*exo* mode **11c** was observed when 2-aza-5-alken-l-y1 radical precursor **10c** was fused with pyrrolidinone ring.[6h] Thus, cyclization reaction of **10c** was performed with CuCl/PMDETA (25 mol %) at room temperature in acetonitrile and compared the changes in regio- and stereoselectivity of **11c-c*** obtained with Cu(I)/bpy catalyst at reflux in DCE.[6h] The reaction led to the formation of a mixture of fused-pyrrolidine **11c** and fused-piperidine **11c*** in almost similar ratio (20:80).

An Ineffective role of the Cu-catalyst and the protected-nitrogen atom of the radical precursors **10a-c** in deciding the regioselectivity indicated towards the dominant role of cyclic template in changing the regioselectivity. Thus, an exclusive 6-*endo* mode of cyclization to piperidine ring in the small ring fused-3-aza-5-alkenyl radical using a highly strained β-lactam template **10d-e** (**Table 3**) was envisaged.

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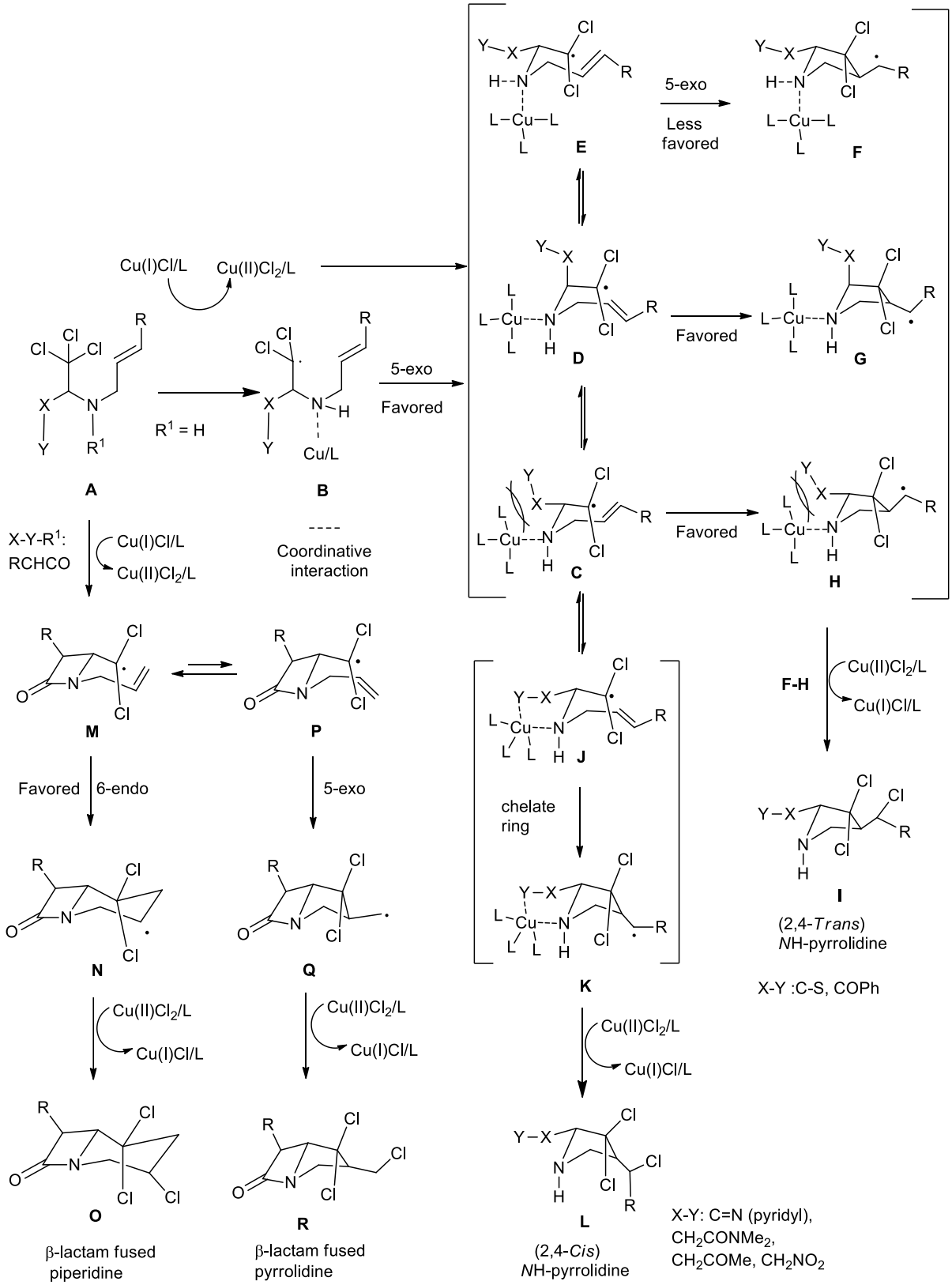

Scheme 4. Probable mechanism for pyrrolidine and piperidine synthesis

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Radical cyclization of precursor **10d** occurred completely with 80 mol % CuCl/bpy, 40 mol % of CuCl/TMEDA and 25 mol % CuCl/PMDETA in DCE solvent in 6, 6 and 5 h, respectively at reflux. However, a trace of reduced starting material of **10d** in ^{1}H NMR of the crude product of **11d-d*** was observed in MeCN solvent with 25 mol % CuCl/PMDETA at reflux. The TMEDA and PMDETA showed similar results and thus, the use of cheaper and easily accessible TMEDA over PMDETA and DCE over MeCN were preferred.

^{1}H NMR of the crude product **11d-d*** showed an occurrence of almost exclusive 6-*endo* radical cyclization (≈ 96 %, **SI Fig. S48-49**) in precursor **10d** with TMEDA ligand in DCE at reflux to afford major β-lactam fused piperidines **11d*** along with minor pyrrolidine product **11d**. Piperidine moieties **11d*-e*** were obtained in high yield (75-80 %, **SI Fig. S50-53**) after purification of the crude product by column chromatography. Both the Cu(I)Cl/TMEDA and Cu(I)Cl/PMDETA catalysts showed similar regioselectivity indicates towards no participation of Cu-catalyst in determining the regioselectivity due to the absence of an effective Cu-O=C-N interaction in **10d-e** (like **10a-c**). Thus, the change in the regioselectivity was mainly due to the inclusion of a rigid β-lactam template in precursors **10d-e.**

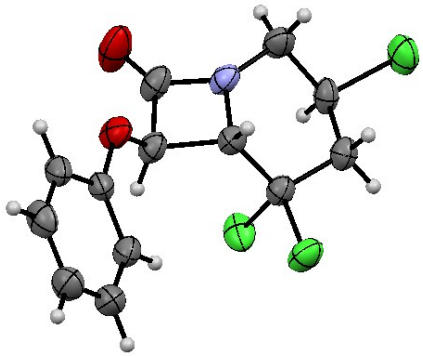


Figure 2. ORTEP diagram of β-lactam fused piperidine**11d***

The structures of **11d*-e*** were supported by ^{1}H NMR, ^{13}C NMR, IR and HRMS, and the stereochemistry of the major piperidines **11d*-e*** was determined from X-ray single crystal structure of **11d***. The ORTEP diagram of piperidine **11d*** is shown in **figure 2**.

Mechanistic Pathways to Stereo- and Regiocontrol

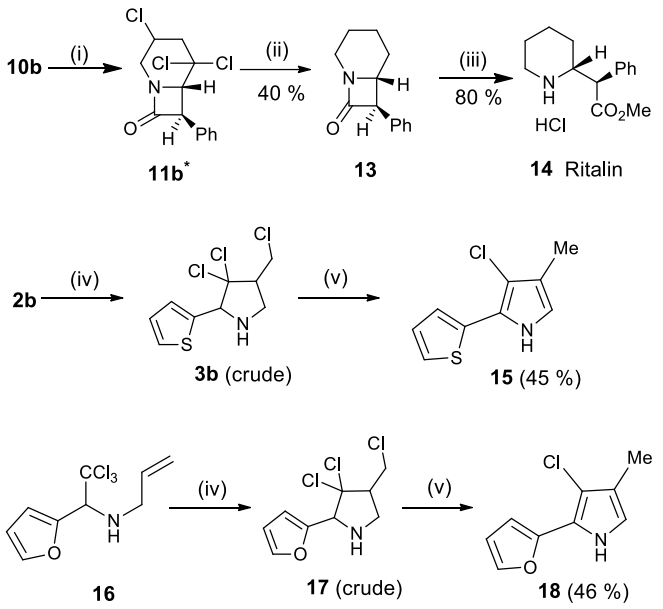
Mechanistically, first the Cu(I)Cl-catalyst reversibly abstracts a chlorine atom from a 2,2,2-trichloroethyl allylamine precursor **A** (**Scheme 4**) to generate 2,2-dichloroethyl allylamine radical **B** along with Cu(II)Cl_2 complex *via* a concerted inner-sphere electron transfer (ET) process.[7a,6b,d] The radical **B** undergoes 5-*exo-trig* and/or 6-*endo-trig* radical cyclization to form 5-*exo* pyrrolidine radical (**F-H**, **K**, **Q**) and 6-*endo* piperidine radical (**N**), respectively. These cyclized radicals then abstract chlorine atom from Cu(II)Cl_2-complex to produce the final ATRC products (**I**, **L**,**O**, **R**) along with active Cu(I)Cl-catalyst which participate again in the next ATRC reaction with another radical precursor.[12]

Stereoselective formation of 2,4-*trans*-diastereomers in 1-substituted-*N*H-pyrrolidines were speculated on the basis of Beckwith–Houk transition state model.[1] The bulky copper-complex bonded to nitrogen atom is expected to occupy preferably sterically less demanding position in chair like transition state[4b] thus the formation of a chair-equatorial conformation(**C**) in the transition state was anticipated. However, a high $A^{1,2}$-strain arising due to steric-repulsion between bulky copper-complex and α-substituent in conformation (**C**) may cause its conformational change to a energetically more favorable boat-axial conformation (**D**). This conformational change may occur as the boat-axial conformation is nearly ca.1 kcal/ mol higher in energy than its corresponding chair-equatorial conformation (**C**).[1b] The change in this conformation (**C**) to chair-equatorial conformation (**E**) is another possiblity, however, it is energetically unfavourable due to the stronger 1,3-axial interaction ($A^{1,3}$ strain) between bulky axial copper-complex and a halogen atom. Thus it is hard to predict whether the chair-equatorial (**C**) or boat-axial conformation (**D**) contributes the most to the preferential formation of the 2,4-*trans*-*N*H-pyrrolidines (**I**) at present. Pyridyl(*N*), NO_2, $CONMe_2$ or CH_3CO groups in the side chain at C-2 position, together with *N*H-group of the cyclizing radical, may act as a bidentate ligand and interact with Cu-catalyst to form a chelate (**J**) in transition state. This interaction may bring these groups in an equatorial orientation in a boat-like conformation (**C→J→K**) leading to a development of 2,4-*cis*-stereochemistry in the corresponding *N*H-pyrrolidine (**L**). Coordinative interaction of a copper complex with a *N*H- and other functionality of a molecule forming a chelate ring in the cyclizing radical is well known.[5d] Complexing agents-mediated conversion of one conformation to another leading to a stereoselective synthesis of pyrrolidines and other heterocycles, is not uncommon.[13]

A rigid β-lactam ring in the radical precursor arguably restrains double bond and dichloromethyl radical group to attain a energetically favorable chair like conformation (**P**) in the transition state. This angle strain results into the formation of a more favoured chair like (piperidine type) conformation (**M**)[14] resulting into preferential formation of β-lactam fused piperidine (**O**) than corresponding pyrrolidine (**R**) after chlorine atom transfer from $CuCl_2$-complex to 6-*endo-trig* (**N**) and 5-*exo-trig* (**Q**) cyclized radicals, respectively. Such preferential regioselectivity of 6-*endo* over the 5-*exo* mode of cyclization has also been observed by Alabugin et al.[14a-b] They found that the 6-*endo* cyclization is kinetically favored in smaller (and strained) cycles and thus, a smaller cycle changes the regioselectivity of closure and such effects are known for a number of cyclizations.

Synthetic Applications

A very low catalyst loading is always preferred in any synthetic chemical reactions particularly for Industrial applications to incur lesser-cost and lesser-operational issues. Thus, an attempt was made to reduce the Cu(I)-catalyst by using AIBN as a reducing agent.[7] Use of 0.2 equivalent of AIBN in ATRC reaction of **10e**, reduced the amount of Cu (I)Cl/TMEDA catalyst to 5 mol % at reflux to afford **11e***. The treatment of 6-*endo* ATRC product **11e*** with *n*Bu_3SnH using a frequently used method for dehalogenative reduction of halogenated N-heterocycles[15] afforded a known 1-aza-bicyclo[4.2.0]octan-8-one **13** (**Scheme 5**) in good yield. Further reaction of **13** with methanolic hydrochloric acid at room temperature using a reported method generally employed for the hydrolysis of the same **13**[16] afforded a D-*threo*-methylphenidate hydrochloride **14**[17], marketed under the name Ritalin.



Reaction Conditions:

i) CuCl/TMEDA (1:2, 5 mol %), AIBN (0.2 eq), DCE, reflux, 4 h, N_2 atm.
ii) *n*Bu_3SnH (4.5 eq), AIBN (0.5 eq), Toluene, reflux, 5 h.
iii) MeOH.HCl, rt, 6 h.
iv) CuCl/PMDETA (1:1, 10 mol%), AIBN (0.3 eq), DCE, reflux, 4 h, N_2 atm.
v) DBU (2.5 eq), Toluene, reflux, 24 h, N_2 atm.

Scheme 5. Synthetic applications of halogenated and functionalized pyrrolidines and piperidine

Synthetic application of halogenated *N*H-pyrrolidines was demonstrated by converting 3,3-dichloro-*N*H-pyrrolidines **3b** and **17** into a corresponding β-chloro-*N*H-pyrrole **15** and **18**, respectively. This unit of type **18** is present in some bioactive pyrroles such as antileukemic Roseophilin **29**[18] (**Figure 3**). Again, an attempt was made to reduce the catalyst loading (to begin with 1 mol %) and use the ATRC product as such in the next step (after simple work up) to produce highly useful β-chloro-*N*H-pyrrole unit **15** and **18** in single operation. Use of 0.3 equivalent of AIBN, reduced the amount of Cu (I)Cl/PMDETA catalyst to 10 mol % at reflux to afford **3b** and **17**. On treatment with DBU, the chlorinated *NH*-pyrrolidine **3b** and **17** underwent double dehydrochlorinations-isomerization in single operation to give *N*H-pyrrole **15** and **18**, respectively.

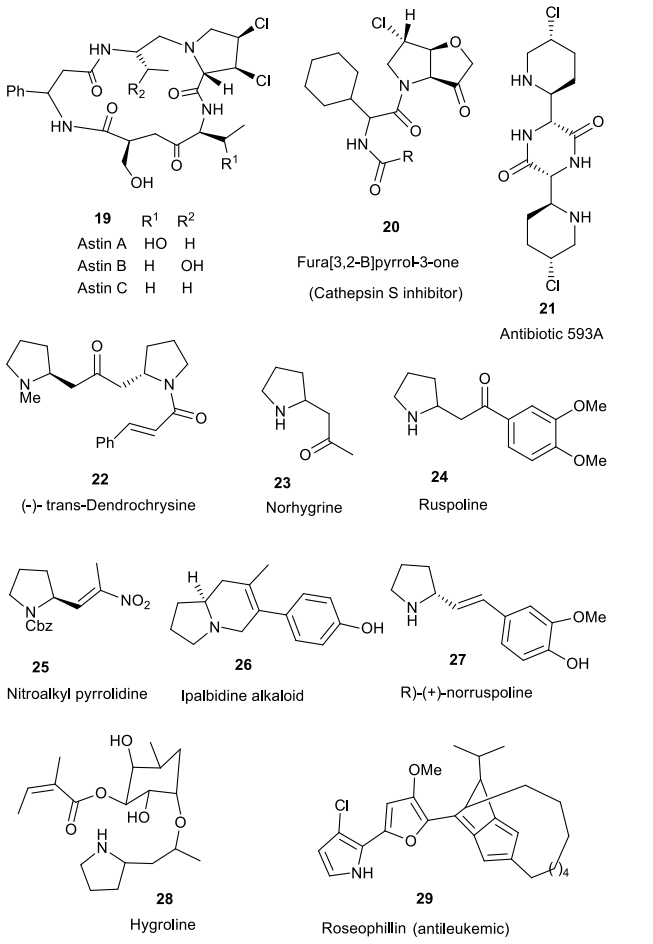


Figure 3. Examples of bioactive halogen- and heteroaryl-substituted and functionalized *N*-heterocycles and their derivatives

Close similarity in structures of functionalized *N*H-pyrrolidines **3** and **9 (Table 2-3)** with molecules shown in **figure 3** make them direct variants of existing natural products[19] such as cyclochlorotine,[19a] islanditoxin,[19b] and Astin A-C **19**,[19c] pharmaceuticals[20] **20** and materials.[21] Further, such 3-chloro-pyrrolidines are constant sources for structure activity relaionship (SAR) studies,[22] inter- and intra-molecular substitution reactions,[23] selective dehalogenation[24] and functional group transformations[25] to give pyrrolidine-based drug Derifenacin,[23a] natural product Ioline alkaloid[23d] and (-)-Trechelanthamidine.[25] Gatto, Göttlich and co-workers reported the antibiotic activity β-chloropiperidine based 593A drug substance **21**.[26] Side chain functionalized pyrrolidines with their *N*H and/or side chain functionalities undergo inter- and intra-molecular reactions to give natural products (**22-24** in **Fig. 3**)[27] and pharmaceuticals.[28] Tilve and co-workers exploited pyrrolidine **25** in the synthesis of (-)-hygrine, (-)-nor-hygrine, (-)-pseutohygroline and (-)-hygroline *via* Nef reaction

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of nitro-group in the side chain.[29] An intramolecular cyclization of methyl ketone in norhygrine **23** gives alkaloid ipalbidine **26**.[30] Ruspoline **24** converts to alkaloid **27** with simple reduction of ketone group and subsequent dehydration forming olefinic bond.[31] Reduction of ketone group of **23** to alcohol followed by its coupling with sugar moiety gives hygroline **28**.[30]

Conclusions

In conclusion, present work describes a mild and general method for the synthesis of 1-hetero-aryl substituted and functionalized *N*H-pyrrolidines. With the introduction of a heteroaryls or side chain functionality at C-2, bidentate *N*H-precursors may interact with copper-catalyst to change the usual 2,4-*trans*-conformation in the Beckwith-Houk transition state leading to the formation of a 2,4-*cis* diastereomer. This conformational shift was not noticeable with the introduction of S-heterocycles and became considerable with *N*-heteroaryl (pyridyl) due to strong (*py*)N--Cu--NH chelate type interaction. Side chain methyl-ketone, amide and nitro groups at C-2 in the *N*H-radical precursor changed the usual 2,4-*trans* geometry to 2,4-*cis via* =O--Cu--NH chelate type interaction in the transition state than the hindered ketone-functionality. β-lactam template in the precursors alters the 5-*exo* cyclization mode to 6-*endo* cyclization mode to form pharmaceutically important piperidine ring against Baldwin's rule. Difficult to prepare in single operation, hetero-aryl substituted, halogenated and functionalized *N*H-pyrrolidines and piperidine rings are potential building blocks for carbapenam, pyrroline and β-chloropyrrole units useful in natural products synthesis and SAR studies for drug development. Decrease in cheap and recyclable Cu (I)-catalyst loading even to 5-10 mol % was easily achievable in the synthesis of drug (Ritalin) and a sub-unit of natural product (Roseophilin), establishes potential industrial applications of this methodology.

Experimental

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). 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, 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. Aliphatic, aromatic and heteroaromatic aldehydes, chloral hydrates,K_2CO_3, trichloroacetic acid, DMSO and $MgSO_4$ were commercially available and were used as received. THF was dried over KOH pellets overnight and distilled over stored over sodium wires. DCM was dried by distilling over anhydrous P_2O_5.

Preparation of α-substituted 2,2,2-trichloroethyl allyl *N*H-amines 2a-b:

General procedure: Schiff's bases **1a-b** were prepared by stirring mole equivalents of aldehydes and amine in DCM in the presence of anhydrous $MgSO_4$ at room temperature for 6-8 h, which on filtration and subsequent concentration on rotary evaporator,[32] was used as such in the next step. To a solution of freshly prepared aldimine **1a-b** (10 mmol) in DMSO (10 mL) was added portion wise a solution of trichloroacetic acid (3.268 g, 20 mmol) in DMSO (20 mL) at 40 ˚C (4.902 g, 30 mmol at 50˚C for **1a**) with stirring during 1 h. After the disappearance of the imine as indicated by TLC (1 h), the solution was poured into ice-cold water and extracted with ethyl acetate/*n*-hexane mixture (50:50 v:v). The combined organic extract was washed with brine (3x50 mL), dried (Na_2SO_4) and filtered. The solvent of the filtrate was evaporated under reduced pressure. The crude product thus obtained was purified by column chromatography on small pad of neutral alumina using *n*-hexane (or mixture of ethyl acetate in *n*-hexane 0-3 %, v/v in case of **2a**) as the solvent for elution to obtain 2,2,2-trichloroethyl allyl *N*H-amines **2a-b** in good to high yields.

N-(2,2,2-trichloro-1-(pyridin-2-yl)ethyl)prop-2-en-1-amine 2a: Light red liquid, 52 % yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.13 (s, br, 1H, NH, D_2O-exchangeable merged with dd at δ 3.16), 3.16 (dd, 1H, *J* = 13.8, 6.3 Hz, allylic CH_2), 3.35 (dd, 1H, *J* = 13.8, 5.7 Hz, allylic CH_2), 4.41 (s, 1H, NCH), 5.07-5.15 (m, 2H, allylic =CH_2), 5.77-5.87 (m, 1H, allylic =CH), 7.27 (t, 1H, *J* = 6.3 Hz, pyridyl CH), 7.48 (d, 1H, *J* = 7.8 Hz, pyridyl CH), 7.68 (t, 1H, *J* = 7.6 Hz, pyridyl CH), 8.62 (d, 1H, *J* = 4.2 Hz, pyridyl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz); δ 50.9 (CH_2), 75.9 (CH), 102.3 (C), 117.0 (CH_2), 123.5 (CH), 126.1 (CH), 135.8 (CH), 135.9 (CH), 149.0 (CH), 155.2 (C) ppm; IR (KBr): ν_{max} 3323(m, br), 3076(m), 2924(m), 1644(w), 1583(s), 1468(s), 1432(s), 1299(w), 1148(m), 1119(m), 995(s), 921(s), 799(s), 752(s) cm^{-1}; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{10}H_{11}Cl_3N_2Na$ 286.9880, found 286.9875.

N-(2,2,2-trichloro-1-(thiophen-2-yl)ethyl)prop-2-en-1-amine 2b: Colorless liquid, 82 % yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.24 (s, br, 1H, *N*H, D_2O-exchangeable), 3.08 (dd, 1H, *J* = 14.1, 6.9 Hz, allylic CH_2), 3.29 (dd, 1H, *J* = 14.1, 4.5 Hz, allylic CH_2), 4.54 (s, 1H, NCH), 5.09-5.15 (m, 2H, allylic =CH_2), 5.75-5.87 (m, 1H, allylic =CH), 6.95 (dd, 1H, *J* = 5.1, 1.8 Hz, thienyl CH), 7.19 (s, br, 1H, thienyl CH), 7.26 (d, 1H, *J* = 1.8 Hz, thienyl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.9 (CH_2), 75.9 (CH), 102.3 (C), 117.0 (CH_2), 126.07 (CH), 126.09 (CH), 128.5 (CH), 132.9 (CH), 138.2 (C) ppm; IR (KBr): ν_{max} 3345(m, br), 3080(m), 2923(m), 1685(m), 1642(w), 1610(m), 1505(w), 1462(s), 1325(m), 1292(m), 1230(s), 112(s), 1014(s), 925(s), 806(s), 709(s) cm^{-1}; HRMS

(ESI+): m/z $[M + H]^+$ calcd for $C_9H_{11}Cl_3NS$ 269.9672, found 269.9675.

Preparation of the functionalized trichloroethyl allyl *N*H-amines 8a-e: First the required Michael acceptors **7a-d** were synthesized using methods reported in our previous works with slight modifications.[5a,9b] 5 mol% CuCl/PMDETA-catalyzed atom transfer radical addition of CCl_4 to 1-phenylprop-2-en-1-one in the presence of AIBN (20 mol %) followed by DBU-mediated dehydrochlorination furnished previously known Michael acceptor **7b**.[33] Use of NEt_3 as a base to dehydrochlorinate similar ATRA adducts at reflux in toluene has been reported earlier also.[34] Previously known (*E*)-4,4,4-trichlorobut-2-enoic acid[33] gives (*E*)-4,4,4-trichlorobut-2-enoyl chloride on treatment with oxalyl chloride in DCM at 0 °C which on subsequent treatment with one equivalent of dimethyl amine (anhydrous) in DCM in the presence of triethyl amine furnished previously known (*E*)-4,4,4-trichloro-*N*,*N*-dimethylbut-2-enamide **7c**[35] in 45 % yield. The Michael addition of allyl amines with different Michael acceptors occurred under slightly different reaction conditions due to their differential reactivity.[9b] The Michael acceptor **7a-b**[9b] and **7d**[9b] containing the keto and nitro groups, respectively were found to react smoothly with allyl amine in THF solvent whereas the Michael acceptor **7c** containing the amide group required a protic solvent methanol and a mild base to react.

General method: A solution of allyl amine (or 3-methylbut-2-en-1-amine, 10 mmol) and the Michael acceptor **7a-b**,**d**[9b](10 mmol) in dry THF (30 mL) was stirred at room temperature (25-30 ˚C). After completion of the reaction (4-6 h) as indicated by TLC, the solvent was removed on a rotary evaporator to obtain almost pure products in quantitative yields. The crude products were further purified by column chromatography on a small pad of neutral alumina using a mixture of ethyl acetate in *n*-hexane (0-3%, v:v) as the solvent for elution to obtain the functionalized acyclic precursor **8a-c**,**e**. The amide precursor **8d** was prepared as above by taking *t*-butanol (30 mL) as the solvent and triethyl amine (0.42 mL, 0.336 g, 3 mmol) as the catalyst and stirring the solution at room temperature (25-30 ˚C) for 24 h. Purification of the crude product by column chromatography on a small pad of neutral alumina gave **8d**. These precursors were obtained in high yields 80-83 % as mentioned in **Table 2**.

2,4,4,4-Tetrachloro-1-phenylbutan-1-one: Yellow liquid, 81% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.33 (d, 1H, *J* = 15.3, 2.7 Hz, CH_2), 4.17 (dd, 1H, *J* = 15.3, 6.9 Hz, CH_2), 5.50 (t, 1H, *J* = 6.9, 2.7 Hz, CH), 7.52 (t, 2H, *J* = 6.9 Hz, aryl CH), 7.63 (t, 1H, *J* = 7.1 Hz, aryl CH), 8.06 (d, 2H, *J* = 7.8 Hz, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.7 (CH_2), 56.7 (CH), 96.1 (C), 128.9 (CH), 129.1 (CH), 133.7 (C), 134.2 (CH), 190.9 (C) ppm; IR (KBr): ν_{max} 3063(w), 2938(m), 1695(s), 1591(m), 1449(m), 1419(w), 1367(w), 1312(m), 1245(m), 1179(m), 1046(m), 957(s), 850(s), 750(s), 692(s) cm^{-1}; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{10}H_8Cl_4ONa$ 306.9221, found 306.9213.

(E)-4,4,4-trichloro-N,N-dimethylbut-2-enamide 7c: Yellow liquid, 80 % yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.91 (s, 3H, CH_3), 2.96 (s, 3H, CH_3), 6.30 (d, 1H, *J* = 14.4 Hz, CH), 7.25 (d, 1H, *J* = 14.4 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 37.0 (CH_3), 37.3 (CH_3), 90.1 (C), 120.1 (CH), 136.2 (CH), 164.4 (C) ppm; IR (KBr): ν_{max} 3063(w), 2938(m), 1695(s), 1591(m), 957(s), 850(s), 750(s), 692(s) cm^{-1}; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_6H_8Cl_3NONa$ 237.9564, found 237.9570.

4-(Allylamino)-5,5,5-trichloropentan-2-one8a: Colorless liquid, 80 % yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.76 (s, br, 1H, *N*H, D_2O-exchangeable), 2.23 (s, 3H, CH_3), 3.03 (dd, 1H, *J* = 17.4, 9.6 Hz, CH_2CO), 3.26 (dd, 1H, *J* = 17.4, 2.4 Hz, CH_2CO), 3.45 (dd, 1H, *J* = 12.9, 6.9 Hz, allylic CH_2), 3.56 (dd, 1H, *J* = 12.9, 7.8 Hz, allylic CH_2), 4.01 (dd, 1H, *J* = 9.6, 2.4 Hz, CHN), 5.12-5.25 (m, 2H, =CH_2), 5.76-5.90 (m, 1H, =CH-) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.8 (CH_3), 38.5 (CH_2), 47.6 (CH_2), 59.3 (CH), 104.3 (C), 118.8 (CH_2), 132.9 (CH), 203.4 (C) ppm; IR (KBr): ν_{max} 3377(m, br), 3080(w), 2952(m), 1741(s), 1644(w), 1439(m), 1358(m), 1175(s), 923(m), 795(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_8H_{13}Cl_3NO$ 244.0057, found 244.0050.

5,5,5-trichloro-4-((3-methylbut-2-en-1-yl)amino)pentan-2-one *8b*: Colorless liquid, 80 % yield; ^{1}H NMR ($CDCl_3$, 300 MHz); δ 1.70 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 2.25 (s, 3H, CH_3CO), 2.30 (s, br, 1H, *N*H, D_2O-exchangeable), 3.04 (dd, 1H, *J* = 16.8, 9.9 Hz, CH_2CO), 3.25 (1H, *J* = 17.1, 2.4 Hz, CH_2CO), 3.48-3.63 (m, 2H, allylic CH_2), 3.96 (dd, 1H, *J* = 9.9, 2.7 Hz, NCH), 5.22-5.25 (m, 1H, =CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.8 (CH_3), 26.7 (CH_3), 31.8 (CH_3), 39.6 (CH_2), 48.6 (CH_2), 60.2 (CH), 102.9 (C), 116.8 (CH), 138.2 (C), 201.2 (CO) ppm; IR (KBr): ν_{max}3365 (m, br), 2971(m), 2924(s), 1720(s), 1668(w), 1418(m), 1362(s), 1243(m), 1149(m), 845(m), 768(s) cm^{-1}; HRMS (ESI+): m/z $[M+H]^+$ calcd for $C_{10}H_{17}Cl_3NO$ 272.0370, found 272.0262.

3-(Allylamino)-4,4,4-trichloro-1-phenylbutan-1-one 8c[5a] **:** Colorless liquid, 82% yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.93 (s, br, 1H, NH, D_2O-exchangeable), 3.26 (dd, 1H, *J* = 18.0, 9.0 Hz, allylic CH_2), 3.49-3.63 {m, 2H, (1H, CH_2CO and 1H, allylic CH_2)}, 3.76 (dd, 1H, *J* = 18.0, 3.0 Hz, CH_2CO), 4.13 (dd, 1H, *J* = 18.0, 3.0 Hz, CHN), 4.99-5.15 (m, 2H, =CH_2), 5.74-5.87 (m, 1H, =CH-), 7.51 (t, 2H, *J* = 7.5 Hz, aromatic CH), 7.62 (t, 1H, *J* = 7.5 Hz, aromatic CH), 7.99 (d, 2H, *J* = 6.0 Hz, aromatic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 42.4 (CH_2), 52.0 (CH_2), 69.6 (CH), 105.4 (C), 116.3 (CH_2), 128.2 (CH), 128.7 (CH), 133.5 (CH), 136.2 (CH), 136.4 (C), 196.4 (C) ppm; IR (KBr): ν_{max} 3375(m, br), 2921(m), 1686(s), 1590(w), 1449(w), 1352(w), 1272(m), 993(m), 795(m), 755(m) cm^{-1}; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_{13}H_{14}C_{l3}NONa$ 328.0020, found 328.0033.

3-(Allylamino)-4,4,4-trichloro-N,N-dimethylbutanamide8d: Colorless liquid, 76 % yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.89 (s, br, 1H, *N*H, D_2O-exchangeable), 2.65 (dd, 1H, *J* = 15.0, 9.9 Hz, CH_2CO), 3.20 (dd, 1H, *J* = 15.6, 9.3 Hz, CH_2CO), 3.21 (s, 6H, CH_3), 3.58-3.72 (m, 2H, allylic CH_2), 3.88-3.95 (m, 1H, CHN). 5.13-5.33 (m, 2H, =CH_2), 5.87-5.96 (m, 1H, =CH-) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 39.3 (CH_3), 39.4 (CH_3), 42.4 (CH_2), 52.0 (CH_2), 69.5 (CH), 105.5 (C), 116.3 (CH_2), 136.2 (CH) 166.4 (CO) ppm; IR (KBr): ν_{max} 3377(m, br), 3080(w), 2952(m), 1705(s), 1604(w), 1439(m), 1358(m), 1274(s), 1175(s), 1024(m), 923(m), 795(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{10}H_{16}Cl_3N_2O$ 273.0323, found 273.0328.

N-(1,1,1-trichloro-3-nitropropan-2-yl)prop-2-en-1-amine 8e: Light yellow liquid, 83 % yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ

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1.82 (s, br, 1H, NH, D_2O-exchangeable), 3.53 (dd, 1H, *J* = 14.1, 6.0 Hz, allylic CH), 3.70 (dd, 1H, *J* = 14.1, 5.7 Hz, CH), 4.26 (dd, 1H, *J* = 9.6, 3.3 Hz, CHN), 4.51 (dd, 1H, *J* = 13.2, 9.6 Hz, CH_2NO_2), 5.06 (dd. 1H, *J* = 13.2, 3.3 Hz, $CHNO_2$ partially overlapped multiplet at δ 5.11-5.24), 5.11-5.24 (m, 2H, olefinic CH_2), 5.72-5.85 (m, 1H, olefinic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.2 (CH_2), 71.0 (CH_2), 77.4 (CH), 101.7 (C), 117.1 (CH_2), 135.5 (CH) ppm; IR (KBr): ν_{max} 3382(m, br), 3081(w), 2926(m), 1643(w), 1561(s), 1472(w), 1425(m), 1379(s), 1162(m), 996(m), 926(m), 802(m), 636(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_6H_{10}Cl_3N_2O_2$ 246.9808, found 246.9802.

Preparation of Methyl allyl(2,2,2-trichloroethyl)carbamate10a: This precursor was prepared by acylation reaction of 2,2,2-trichloroethyl allyl NH-amine with methyl chloroformate (1 eq) in DCM solvent in the presence of triethyl amine base (1 eq).[5a]

Colorless liquid, 80 % yield; ^1H NMR ($CDCl_3$, 300 MHz): δ 3.78 (s, 3H, CH_3), 4.32-4.48 (m, 4H, CH_2), 5.07-5.20 (m, 2H, allylic =CH_2), 5.76-5.90 (m, 1H, allylic =CH-) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): d 52.7 (CH_2), 53.8 (CH_2), 57.7 (CH_3), 100.3 (C), 117.5 (CH_2), 137.1 (CH), 155.5 (C) ppm; IR (KBr): ν_{max} 3079 (w), 2924(m), 1645(w), 1462(m), 1294(m), 1232(s), 1150(m), 1112(s), 1012(s), 924(s), 802(s), 745(s) cm^{-1}; HRMS (ESI+): m/z $[M + Na]^+$ calcd for $C_7H_{10}Cl_3NO_2Na$ 267.9669, found 267.9665.

Preparation of β-lactam fused 2,2,2-trichloroethyl allylamines 9a-b. These precursors were prepared by reaction of aldimine and *in situ* generated ketene by a reported procedure with slight modification.[36]

A mixture of N-(2,2,2-trichloroethylidene)prop-2-en-1-amine[36](Schiff's base, 10 mmol) with triethylamine (20 mmol) in DCM at 0°C (at 10°C in case of **10b**), is added drop wise a solution of phenoxyacetyl chloride (2-phenylacetyl chloride in case of **10b**) (20 mmol) in DCM and stirred at room temperature for 2-3 h. Solvent was removed under vacuum and ethylacetate (200 mL) was taken into the residue. Washed organic layer with water (2x50 mL), concentrated the organic layer under vacuum and the purified the crude product on column chromatography using alumina (neutral) and*n*-hexane: ethylacetate (3 %, v:v) as eluent to obtain the precursor **10a-b** in good isolated yields.

1-Allyl-3-phenoxy-4-(trichloromethy)azetidin-2-one 11d: pinkish crystals, mp 93 °C (*n*-hexane/DCM), 58 % yield;^1H NMR ($CDCl_3$, 300 MHz) δ 3.90 (dd, 1H, *J* = 15.6, 7.5 Hz, CH_2), 4.41 (dd, 1H, *J* = 15.6, 7.5 Hz, CH_2), 4.73 (d, 1H, *J* = 4.8, CH), 5.30-5.34 (m, 3H, olefinic CH_2), 5.39 (d, 1H, *J* = 4.8 Hz, OCH), 5.77-5.88 (m, 1H, olefinic CH), 7.02-7.10 (m, 3H, aryl CH), 7.26-7.31(m, 2H, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.9 (CH_2), 71.8 (CH), 84.7 (OCH), 96.8 (C), 116.7 (CH), 119.8 (CH_2), 123.1 (CH), 129.6 (CH), 130.2 (CH), 157.01 (C), 164.5 (C) ppm. IR(KBr) ν_{max} 3033(s), 2959(s), 2921(s), 1720(s), 1413(m), 1360(s), 1175(m), 816(s), 772(s) ppm. HRMS (ESI+):m/z $[M + H]^+$calcd for $C_{13}H_{13}Cl_3NO_2$ 320.0006, found 320.001

1-allyl-3-phenyl-4-(trichloromethy)azetidin-2-one 11e: pinkish crystals, mp 48 °C, (*n*-hexane/DCM), 46 % yield;^1H NMR ($CDCl_3$, 300 MHz):δ 3.82 (dd, 1H, *J* = 15.6, 7.8 Hz, CH_2), 4.31 (dd, 1H, *J* = 15.36, 4.2 Hz, CH_2), 4.32 (d, 1H, *J* = 3.6 Hz, CH), 4.66 (d, 1H, *J* = 3.9 Hz, CH), 5.23-5.32 (m, 3H, =CH_2), 5.70-5.83 (m, 1H, =CH-), 7.30-7.35 (m, 3H, aryl CH), 7.45-7.56 (m, 2H, aryl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 42.9 (CH_2), 58.9 (CH), 70.7 (CH), 97.8 (C), 119.7 (CH_2), 127.6 (CH), 128.2 (CH), 128.6 (CH), 132.2 (CH), 137.2 (C), 163.5 (C) ppm; IR(KBr):ν_{max} 3033(s), 2959(s), 2921(s), 1720(s), 1413(m), 1360(s), 1175(m), 816(s), 772(s) ppm. HRMS (ESI+):m/z $[M + Na]^+$calcd for $C_{13}H_{12}Cl_3NONa(M+Na)^+$ 325.9877, found 325.9890.

Halogen atom transfer radical cyclization of 2,2,2-trichloroethyl allyl amines 2a-b: General method: A flame-dried two-neck round-bottom flask was charged with CuCl (40 mg, 0.40 mmol) and degassed acetonitrile (20 mL) under a N_2 atmosphere using Schlenk technique. The suspension was cooled to 0 ˚C and PMDETA (0.070 g, 0.8 mL, 0.4 mmol) was injected into it. The mixture was stirred for 10 minutes at the same temperature. *N*-(2,2,2-trichloroethyl)prop-2-en-1-amine **2a-b** (1 mmol) was added to this mixture and stirring was continued further at the same temperature. After the disappearance of the starting material as indicated by TLC monitoring and confirmed by ^1H NMR (4-6 h) of the aliquots taken directly from the reaction mass. The solvent was removed under reduced pressure. Ethyl acetate (100 mL) was added to the residual mass. The organic phase was washed with brine (3x25 mL). [In case of low yield, the combined aqueous layer was treated with dilute aqueous ammonia (20 mL) and extracted with ethyl acetate (2x20 mL) to recover the product from the aqueous layer went with copper complex]. The combined organic layer was dried (Anhydrous Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on a small basic alumina column using different mixture of ethyl acetate in *n*-hexane (10-40 %, v:v) as eluent. The 1-substituted *N*H-pyrrolidines **3b** andpyrroline**4a-a'** were obtained in high yields.

2-(3-Chloro-4-(chloromethyl)-4,5-dihydro-3H-pyrrol-2-yl)pyridine 4a-a': obtained as a light red liquid in 78 % yield as diastereomeric mixture (*Trans*: *Cis* = 3:2). ^1H NMR ($CDCl_3$, 300 MHz): δ [2.92-2.97 (m) (minor isomer) + 3.05-3.11 (m) (major isomer), 1H, C<u>H</u>CH_2], [3.41 (dd, *J* = 11.1, 7.5 Hz) (minor isomer) + 3.53 (dd, *J* = 11.1, 6.6 Hz)(major isomer), 1H, NCH_2], [3.69-3.80 (m) (major isomer + minor isomer), 1H, NCH_2], [3.87 (dd, *J* = 10.8, 8.4 Hz) (minor isomer) + 4.05 (d, *J* = 17.7 Hz)(major isomer), 1H, CH_2Cl], 4.27-4.42 [(m)(minor isomer)(major isomer), 1H, CH_2Cl,], [5.43 (s) (major isomer) + 5.60 (d, *J* = 6.3 Hz) (minor isomer), 1H, CHCl], 7.32 (t, 1H, *J* = 4.8 Hz, CH), 7.73 (t, 1H, *J* = 7.5 Hz, CH), 8.16 (d, 1H, *J* = 6.6 Hz, CH), 8.64 (d, 1H, *J* = 4.2 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 42.1 (CH_2), 45.0 (CH_2), 46.9 (CH), 50.1 (CH), 60.6 (CH), 61.1 (CH), 62.8 (CH_2), 63.5 (CH_2), 122.6 (CH), 122.9 (CH), 125.3 (CH), 125.4 (CH), 136.59 (CH), 136.62 (CH), 149.3 (CH), 149.4 (CH), 150.4 (C), 171.4 (C), 173.0 (C) ppm: IR (KBr);ν_{max}3064(m), 2953(s), 2855(s), 1620(s), 1579(s), 1467(s), 1440(s), 1344(s), 1294(m), 1042(m), 981(m), 987(m), 799(s), 742(s) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{10}H_{10}Cl_2N_2H$ 229.0294, found 229.0294.

3,3-Dichloro-4-(chloromethyl)-2-(thien-2-yl)pyrrolidine 3b: Colorless liquid, 83 % yield; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.84 (s, br, 1H, *N*H, D_2O-exchangeable), 3.15-3.18 (m, 2H, NCH_2 and

CHCH$_2$), 3.63-3.75 {m, 2H, (1H, CH$_2$N and 1H, CH$_2$Cl)}, 3.96-3.99 (m, 1H, CH$_2$Cl), 4.63 (s, 1H, CH), 7.00 (t, 1H, *J* = 4.5 Hz, CH), 7.27 (d, 1H, *J* = 4.5 Hz, CH), 7.34 (d, 1H, *J* = 4.8 Hz, CH) ppm; ^{13}C NMR (CDCl$_3$, 75 MHz): δ 43.5 (CH$_2$), 48.8 (CH$_2$), 54.9 (CH), 75.3 (CH), 94.3 (C), 127.0 (CH), 127.1 (CH), 128.5 (CH), 137.3 (C) ppm; IR (KBr): ν_{max} 3353(br, m), 2962(s), 1610(m), 1503(w), 1430(s), 1252(m), 1152(s), 1070(m), 1011(s), 927(m), 807(s), 709(s) cm^{-1};HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_9H_{11}Cl_3NS$ 269.9672, found 269.9682.

The side chain functionalized *N*H-pyrrolidines 9a-e were prepared from the corresponding amines **8a-e** as above, except that 60 mol % each of CuCl and PMDETA were taken and the reaction mixture was stirred at 0˚C for 6-10 h.

1-(3,3-dichloro-4-(chloromethyl)pyrrolidin-2-yl)propan-2-one 9a-a': Reddish liquid, 83 % yield as diastereomeric mixture (70:30); ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.19 (s, 4.5H, CH$_3$, major and minor isomers), 2.30 (br, s, 1.5 H, NH, D$_2$O-exchangeable), 2.60 (dd, 0.5H, *J* = 9.0, 1.5 Hz, CH$_2$CO, minor isomer), 2.69 (dd, 1H, *J* = 7.8, 1.2 Hz, CH$_2$CO, major isomer), 2.80-2.92 (m, 1.5H, COCH$_2$, major and minor isomer), 2.94-3.01(m, 3H, (1.5H, CHCH$_2$ and 1.5H, NCH$_2$)(major + minor isomer}], 3.38-3.50 (m, 1.5H, CH$_2$Cl(major + minor isomer)}, 3.59 (t, 1H, *J* = 10.4 Hz, NCH$_2$ major isomer), 3.76 (dd, 0.5H, *J* = 9.6, 3.0 Hz, NCH$_2$ minor isomer), 3.82-3.95 [(m, 3H, NCH (major and minor isomer) and CH$_2$Cl (major and minor isomer)] ppm; ^{13}C NMR (CDCl$_3$, 75 MHz): δ 30.2 (CH$_3$), 30.4 (CH$_3$), 42.0 (CH$_2$), 43.4 (CH$_2$), 44.0 (CH$_2$), 44.6 (CH$_2$), 47.6 (CH$_2$), 48.4 (CH$_2$), 55.4 (CH), 55.8 (CH), 67.1 (CH), 67.3 (CH), 92.6 (C), 93.9 (C), 205.6 (C), 205.8 (C) ppm; IR (KBr): ν_{max} 3367 (m, br), 2923(m), 1715 (s), 1558(s), 1421(m), 1377(s), 921(s), 832(s), 764(m) cm^{-1}; HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_8H_{13}Cl_3NO$ 244.0057, found 244.0047.

1-(3,3-dichloro-4-(2-chloropropan-2-yl)pyrrolidin-2-yl)propan-2-one 9b-b': Reddish liquid, 80 % yield as diastereomeric mixture (72:28); ^{1}H NMR (CDCl$_3$, 300 MHz): δ 1.94 (s, 7.5H, CH$_3$, major and minor isomers), 2.22 (br, s, 1.25H, NH, D$_2$O-exchangeable, major and minor isomers), 2.25 (s, 3.75H, CH$_3$, major and minor isomers), 2.80 (dd, 0.25H, *J* = 10.8, 2.4 Hz, CH$_2$CO minor isomer), 2.88 (dd, 1H, *J* = 17.1, 8.1 Hz, CH$_2$CO major isomer), 2.92-3.11 (m, 1.25H, CH$_2$CO major and minor isomer), 3.17-3.40 (m, 3.75H, (1.25H, CHCH$_2$ and 2.50H, NCH$_2$)(major + minor isomer}], 4.12 (dd, 0.25H, *J* = 10.8, 4.8 Hz, NCH, minor isomer), 4.18 (dd, 1H, *J* = 13.2, 7.8 Hz, NCH, major isomer) ppm; ^{13}C NMR (CDCl$_3$, 75 MHz): δ 29.2 (CH$_2$), 29.9 (CH$_2$), 30.2 (CH$_3$), 30.3 (CH$_3$), 30.6 (CH$_3$), 34.3 (CH$_3$), 34.5 (CH$_3$), 44.9 (CH$_2$), 49.8 (CH$_2$), 55.6 (CH), 57.6 (CH), 63.9 (CH), 64.3 (CH), 71.2 (C), 71.5 (C), 93.3 (C), 93.6 (C), 202.7 (C), 202.8 (C) ppm; IR (KBr): ν_{max} 3367 (m, br), 2923(m), 17.16 (s), 1558(s), 1421(m), 1377(s), 921(s), 832(s), 764(m) cm^{-1}; HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{10}H_{17}Cl_3NO$ 272.0370, found 272.0380.

2-(3,3-Dichloro-4-(chloromethyl)pyrrolidin-2-yl)-1-phenylethanone 9c[5a] : Colorless liquid, 85%; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.24 (s, br, 1H, *N*H, D$_2$O-exchangeable), 2.92 (d, 1H, *J* = 10.5, 9.6 Hz, COCH$_2$), 3.02-3.13 (m, 1H, CHCH$_2$), 3.20-3.32 (m, 1H, COCH$_2$), 3.48-3.62 (m, 2H, NCH$_2$), 3.68 (t, 1H, *J* = 10.4 Hz, CH$_2$Cl), 4.01 (dd, 1H, *J* = 11.1, 4.2 Hz, CH$_2$Cl), 4.11 (dd, 1H , *J* = 9.6, 1.8 Hz, CHN), 7.49 (t, 2H, *J* = 7.5 Hz, aromatic CH), 7.60 (t, 1H, *J* = 7.5 Hz, aromatic CH), 8.00 (d, 2H, *J* = 7.2 Hz, aromatic CH) ppm; ^{13}C NMR (CDCl$_3$, 75 MHz): δ 39.3 (CH$_2$), 42.4 (CH$_2$), 47.9 (CH$_2$), 56.1 (CH), 67.7 (CH), 93.2 (C), 128.1 (CH), 128.2 (CH), 133.5 (CH), 136.3 (C), 197.3 (C) ppm; IR (KBr): ν_{max} 3326 (m, br), 2924(s), 2854(s), 1682(s), 1627(s), 1580(s), 1398(s), 1283(s), 1072(s), 1005(m), 827(s), 756(s) cm^{-1};HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{13}H_{14}Cl_3NONa$ 328.0038, found 328.0033.

2-(3,3-dichloro-4-(chloromethyl)pyrrolidin-2-yl)-N,N-dimethylacetamide 9d-d': Reddish liquid, 81 % yield as diastereomeric mixture (74:26); ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.0 (br, s, 1.25 H, NH, D$_2$O-exchangeable), 2.47-2.58 (m, 1.25 H, CH$_2$CON, major and minor isomer), 2.86-2.93 (m, 1.25H, CH$_2$CON, major and minor isomer), 3.0-3.11 (m, 10H 2xCH$_3$, CHCH$_2$ andNCH$_2$, major and minor isomer), 3.45-3.61 (m, 2.5H, NCH$_2$ and CH$_2$Cl)(major + minor isomer}], 3.64-3.72 (m, 1.25H, ClCH$_2$ major and minor isomers), 3.82 (dd, 1H, *J* = 16.8, 5.7 Hz, NCH major isomer), 4.00 (dd, 0.25H, *J* = 12.9, 4.8 Hz, NCH (minor isomer) ppm; ^{13}C NMR (CDCl$_3$, 75 MHz): δ 30.2 (CH$_2$), 30.4 (CH$_2$), 38.7 (CH$_3$), 38.9 (CH$_3$), 41.9 (CH$_2$), 51.17 (CH$_2$), 51.20 (CH$_2$), 54.3 (CH), 54.6 (CH), 57.8 (CH), 58.8 (CH), 95.3 (C), 95.4 (C), 164.7 (C), 164.9 (C) ppm; IR (KBr): ν_{max} 3367 (m, br), 2923(m), 1705 (s), 921(s), 832(s), 764(m) cm^{-1}; HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_9H_{16}Cl_3N_2O$ 273.0323, found 273.0330.

3,3-dichloro-4-(chloromethyl)-2-(nitromethyl)pyrrolidine 9e-e': Reddish liquid as diastereomeric mixture of diastereomers (22:78), 79 % yield; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 2.08 (s, br, 1H, NH, D$_2$O-exchangeable), 2.97-3.13 [m, 2H, (1H, CHCH$_2$ and 1H, NCH$_2$)(major and minor isomer}], 3.49-3.68 [m, 2H, (1H, NCH$_2$ and 1H, CH$_2$Cl)(major and minor isomer)], 3.95 (m, 1H, CH$_2$Cl)(major and minor isomer), 4.29-4.47 (m, 1H, NCH)(major and minor isomer), [4.38-4.46 (m, CH$_2$NO$_2$)(minor isomer) + 4.56 (dd, 1H, *J* = 13.5, 9.3 Hz)(major isomer), 1H, CH$_2$NO$_2$)], [4.79-4.90 (m)(major isomer) + 4.90-5.02 (m)(minor isomer), 1H, CH$_2$NO$_2$) ppm; ^{13}C NMR (CDCl$_3$, 75 MHz): δ 41.5 (CH$_2$), 42.8 (CH$_2$), 48.1 (CH$_2$), 48.3 (CH$_2$), 55.3 (CH), 56.4 (CH), 68.7 (CH), 69.2 (CH), 76.1 (CH$_2$), 77.1 (CH$_2$), 90.1 (C), 90.9 (C) ppm; IR (KBr): ν_{max} 3367 (m, br), 2923(m), 1558(s), 1421(m), 1377(s), 921(s), 832(s), 764(m) cm^{-1}; HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_6H_{10}Cl_3N_2O_2$ 246.9802, found 246.9806.

N-protected Pyrrolidine 11a: The amine precursor **10a** was cyclized with 25 mol % CuCl/PMDETA at RT in MeCN under N$_2$ atmosphere for 12 hrs.[9b]

Methyl 3,3-dichloro-4-(chloromethyl)pyrrolidine-1-carboxylate 11a: Colorless liquid, 88% yield; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 3.02-3.29 (m, 1H, CH), 3.32-3.51 (m, 1H, CH$_2$), 3.55-3.60 (m, 1H, CH$_2$), 3.82-3.86 (2xs, 5H, CH$_2$ & CH$_3$), 3.96-4.03 (m, 1H, CH$_2$), 4.04-4.10 (m, 1H, CH$_2$) ppm; ^{13}CNMR (CDCl$_3$, 75 MHz): δ 43.0 (CH$_2$), 51.2 (CH$_2$), 56.1 (CH), 56.2 (CH$_3$), 67.1 (CH$_2$), 90.7 (C) 156.0 (CO) ppm; IR (KBr): ν_{max} 2976(s), 1690(s), 1368(m), 1150(s), 1070(s), 807(s), 718(s) cm.$^{-1}$; HRMS (ESI+): m/z (M+ Na)$^+$calcd for $C_7H_{10}Cl_3NO_2$ 267.9669, found 267.9675.

Preparation of Pyrrolines 4c-d: These were obtained by stirring an equimolar mixture of crude NH-pyrrolidines **3c-d**[5a] (1 mmol) with DBU (1 mmol) base at room temperature in toluene (30 mL) for 3-6 h, followed by filtration, washing the

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filtrate with brine (2x25 mL) and purification by column chromatography on small pad of neutral alumina using 10-20 % ethyl acetate/n-hexane (v:v) as eluent.

4-Chloro-3-(chloromethyl)-5-(4-nitrophenyl)-3,4-dihydro-2H-pyrrole 4c: Yellow solid, 78 % yield; mp 84 ˚C (*n*-hexane): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.09-3.11 (m, 1H, methine CH), 3.51 (dd, 1H, *J* = 11.4, 7.5 Hz, NCH_2), 3.71 (dd, 1H, *J* = 11.4, 5.4 Hz, NCH_2), 4.07 (dd, 1H, *J* = 17.7, 2.1 Hz, CH_2Cl), 4.45 (dd, 1H, 17.7, 7.2 Hz, CH_2Cl), 5.19 (s, 1H, CHCl), 8.09 (d, 2H, *J* = 8.4 Hz, aromatic CH), 8.28 (d, 2H, *J* = 8.4 Hz, aromatic CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 44.8 (CH_2), 50.4 (CH), 61.1 (CH), 63.1 (CH_2), 123.7 (CH), 129.2 (CH), 137.0 (C), 149.1 (C), 168.2 (C) ppm; IR (KBr): ν_{max}2962(w), 1591(m), 1521(s), 1441(w), 1347(s), 1108(w), 1012(m), 973(w), 864(m), 844(w), 713(m), 713(m) cm^{-1};HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{11}H_{11}Cl_2N_2O_2$ 273.0196, found 273.0200.

4-Chloro-3-(chloromethyl)-5-phenyl-3,4-dihydro-2H-pyrrole 4d:yellow solid, 62 % yield, mp 48-49 ˚C (*n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.01-3.10 (m, 1H, C<u>H</u>CH_2), 3.35 (dd, 1H, *J* = 11.7, 7.5 Hz, NCH_2), 3.56 (dd, 1H, *J* = 11.7, 5.7 Hz, NCH_2), 3.83 (dd, 1H, *J* = 15.0, 3.0 Hz, CH_2Cl), 4.25 (dd, 1H, *J* = 15.0, 7.2 Hz, CH_2Cl), 5.27 (s, 1H, CHCl), 7.26-7.38 (m, 5H, phenyl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz):δ 43.8 (CH_2), 49.5 (CH), 60.1 (CH), 62.1 (CH_2), 126.3 (CH), 128.3 (CH), 130.3 (CH), 132.8 (C), 162.2 (C) ppm; IR (KBr): ν_{max}2962(w), 2955(m), 2924(m), 1520(s), 1440(w), 1346(s), 1010(w), 973(w), 865(m), 700(m), 670(m) cm^{-1};HRMS (ESI+): m/z [M + H]$^+$ calcd for $C_{11}H_{12}Cl_2N$ 228.0241, found 228.0250.

Halogen atom transfer radical cyclization (ATRC) of β-lactam fused precursor 10d-e: Preparation of 1-aza-bicyclo[4.2.0]octan-8-one 11d*-e*

A flame-dried, two-necked, round-bottom flask was charged with CuCl (40 mg, 0.4 mmol), and degassed DCE (30 mL) under a N_2 atmosphere using Schlenk techniques. Into this suspension were injected TMEDA (0.093 g, 0.8 mmol), starting material **10d-e** (0.320 g, 1 mmol) was added and the mixture was stirred at reflux. After completion of reaction as indicated by TLC monitoring after 6 hrs, the reaction mixture was evaporated under reduced pressure and the residual mass was added ethyl acetate(100 mL) and washed with brine (2x20 mL), dried (anhydrous Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (neutral alumina, *n*-hexane / Ethylacetate = 70:30 v/v) followed by recrystallization from n-hexane-DCM gave β-lactam fused piperidines**11d*-e*** in high isolated yields (75-80 %).

3,5,5-trichloro-7-phenoxy-1-aza-bicyclo[4.2.0]octan-8-one 11d*: Light pink crystal(*n*-hexane-DCM), Mp 78.5 °C, 80 % yield; ^{1}H NMR ($CDCl_3$, 300MHz):δ 2.51 (dd, 1H, *J* = 14.1, 11.7 Hz, CH_2), 2.98 (dd, 1H, *J* = 13.8, 11.4 Hz, CH_2), 3.13-3.18 (m, 1H, NCH_2), 3.93 (s,1H, $CHCCl_2$), 4.19-4.33 (m, 2H, CHCl+NCH_2), 5.51 (s,1H, CH-O), 7.05-7.11 (m, 3H, CH), 7.27-7.36 (m, 2H, CH) ppm;^{13}C NMR ($CDCl_3$, 75 MHz): δ 44.8 (CH_2), 48.3 (CH), 52.1 (CH_2), 66.0 (CH), 83.2 (C), 84.5 (CH), 115.6 (CH), 122.8 (CH), 129.7 (CH), 156.9 (C.), 162.1 (C) ppm. IR(KBr) vmax 2974(s), 1775(s), 1595(s), 1491(s), 1446(s), 1398(s), 1284(s), 1237(s), 892(s), 753(s)cm^{-1}.HRMS(ESI+): m/z (M+ Na)$^+$calcd for $C_{13}H_{12}C_3NO_2$ 341.9826, found 341.9832

X-ray crystal structure data of lactam 11d*

Formula sum:$C_{13}H_{12}Cl_3NO_2$,Formula weight:110.54 g/mol; Crystal system: monoclinic; Space group: P 21/c; Unit cell dimensions: a = 12.302(3) Å b = 13.884(3) Å c = 8.368(2) Å, α = 90.00(0)°β = 101.188(4)°γ = 90.00(0)°; Cell volume = 1402.1(6) Å^3, Z = 4; Density calculated = 1.519 g/cm^3; R_{All} = 0.086. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 1504483).

3,5,5-trichloro-7-phenyl-1-aza-bicyclo[4.2.0]octan-8-one 11e*: LightPink crystal (*n*-hexane-DCM), mp 58.5 °C, 75 % yield; ^{1}H NMR ($CDCl_3$, 300MHz): δ 2.47-2.55 (m, 1H, CH_2), 2.94-3.02 (m, 1H, CH_2CCl_2), 3.01-3.18 (m, 1H, CH_2CCl_2), 3.71 (s, 1H, NCH), 4.19-4.33 (m, 2H, CHCl+NCH_2), 4.27 (s, 1H, CHCO), 7.25-7.38 (m, 3H, aryl CH), 7.48-7.57 (m, 2H, aryl CH) ppm;^{13}C NMR ($CDCl_3$, 75 MHz): δ 44.7 (CH_2), 48.3 (CH), 52.9 (CH_2), 59.0 (CH), 65.9 (CH), 83.4 (C), 128.3 (CH), 129.1 (CH), 129.3 (CH), 161.6 (C) ppm; IR(KBr):ν_{max} 2974(s), 1775(s), 1595(s), 1491(s), 1446(s), 1398(s), 1284(s), 1237(s), 892(s), 753(s)cm.$^{-1}$ HRMS(ESI+): m/z [M + Na]$^+$ calcd for $C_{13}H_{12}C_{l3}NO_2$ 325.9877, found 325.9880.

Preparation of 3,3-dichloro-4-(chloromethyl)-2-(nitromethyl)-1-tosylpyrrolidine 12: Tosylation of the crude product **9e** was done using a method reported in the literature[5a] for tosylation of 2-cyanomethylene–*N*H-pyrrolidine under a mild condition. A mixture of pyrrolidines (1 mmol), Tosyl chloride (1 mmol) and K_2CO_3 (1.5 equiv) in dry THF (50 mL) was stirred for 16 hrs at 10-15 ˚C. After disappearance of starting material as indicated by TLC, the reaction mixture was concentrated under rotary evaporator. Ethylacetate (100 mL) was added to the reaction mixture and washed with brine (2x25 mL), dried (anhydrous Na_2SO_4), concentrated and recrystallized (DCM: *n*-hexane) to obtain tosylatedpyrrolidine**12** (58 %).

3,3-Dichloro-4-(chloromethyl)-2-(nitromethyl)-1-tosylpyrrolidine 12: White crystals, 58 % yield, mp 78 ˚C (DCM: *n*-hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.40-2.47 (m, 1H, C<u>H</u>CH_2), 2.49 (s, 3H, CH_3), 3.40 (t, 1H, *J* = 11.4 Hz, CHCl), 3.50-3.58 (m, 1H, CH_2Cl), 3.78-3.87 (m, 2H, CH_2N), 4.70 (dd, 1H, *J* = 4.8, 3.2 Hz, CHN), 4.93-5.11 (m, 2H, CH_2NO_2), 7.44 (d, 2H, *J* = 7.8 Hz, CH), 7.76 (d, 2H, *J* = 7.8 Hz, CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): 21.6 (CH_3), 39.6 (CH_2), 50.9 (CH_2), 54.4 (CH), 69.9 (CH_2), 75.3 (CH), 88.9 (C), 127.9 (C), 130.4 (CH), 131.8 (CH), 145.4 (C) ppm; IR (KBr): ν_{max} 3049(m), 2996(m), 15976(w), 1552(s), 1420(m), 1358(s), 1164(s), 1099(s), 1048(m), 999(m), 778(m), 665(s), 559(s) cm^{-1};HRMS (ESI+): m/z [M + Na]$^+$ calcd for $C_{13}H_{15}Cl_3N_2O_4SNa$ 422.9710, found 422.9715.

X-ray crystal structure data of 12

Formula sum: $C_{13}H_{15}Cl_3N_2O_4S$, Formula weight:401.69 g/mol; Crystal system: triclinic; Space group: P-1; Unit cell dimensions: a = 8.1177(13) Å b = 13.574(2) Å c = 16.277(3) Å α = 107.443(3)° β = 90.128(3)° γ = 90.166(3)°; Cell volume = 1711.1(5) Å^3, Z = 4; Density calculated = 1.559 g/cm^3; R_{All} = 0.085. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC 1504482).

Synthesis of β-lactam fused piperidine 11e* in the presence of AIBN and its Synthetic application towards Ritalin 14. The *N*H-pyrrolidines**11e***was prepared from the corresponding amines **10e** using general ATRC procedure as above for **10d-e**, except that 5 mol % each of CuCl and 10 mol% of TMEDA were taken in DCE along with 20 mol % AIBN and the reaction mixture was stirred at reflux 6 hrs. The reaction mixture was evaporated under reduced pressure and to the residual mass was added ethyl acetate (100 mL), washed with brine (2x20 mL), dried (anhydrous Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (neutral alumina, *n*-hexane / Ethylacetate = 70:30 v/v) to obtain **11e*** in high isolated yields (75%) which was used in the next step as such for dehalogenative reduction. Dehalogenative reduction of**11e*** to **13** was done using a reported method for reduction of trichlorinated *N*-heterocycles.[15] Bu_3SnH (1.32 g, 1.22 mL, 4.5 mmol) and AIBN (80 mg, 0.5 mmol) were added to a stirred solution of piperidine **11e*** (0.305 g, 1 mmol) in dry, degassed toluene (40 mL) under nitrogen atmosphere. The reaction was heated to reflux and then maintained the temperature for 1 h. The reaction mass was cooled to room temperature. The solvent was removed in vacuum on rotary evaporator. The resultant residue was triturated with diethyl ether (40x2 mL) and stirred vigorously with an aqueous potassium fluoride solution (10 % by weight, 50 mL) for 12 hours. The organic and aqueous layers were then separated. The aqueous layer was then extracted with ethyl acetate (60 mL). The combined organic layer was washed with water (30 mL), brine (30 mL), dried (anhydrous Na_2SO_4) and concentrated in vacuum. The purification of the crude product with silica gel column chromatography using *n*-hexane-ethylacetate) gave a previously known compound **13** (80 mg, 40 %) as solid, m.p. 88 °C. This compound on reaction with methanolic hydrochloric acid is known in literature to give Ritalin **14**in single step, was used as such in the next step for preparation of **14** with slight modifications.[16-17] A solution of β-lactam **13** (80 mg) in MeOH (20 mL) was cooled to 0 °C. Then anhydrous HCl gas was purged into the solution for 10 minutes till its saturation. The reaction mass was then stirred at 0-5 °C for 15 min. The temperature of the reaction mixture was raised to room temperature and stirred further till the complete disappearance of starting material on TLC plate in 6hrs. The solvent was removed under vacuum to obtain the solid hydrochloride salt. This was triturated twice with diethyl ether (25 mL). The solid was filtered and washed with diethyl ether (10 mL). This solid was further recrystallized in MeOH-diethyl ether to obtain previously known compound **14** as white crystals in 80 % yield having mp 220 °C matching with ^{1}H NMR spectrum reported in literature.[16-17]

Synthesis of 1-heteroarylsubstituted *N*H-pyrrolidine 3b and 17 in the presence of AIBN and their synthetic application in the preparation of 3-chloro-*N*H-pyrroles 15 and 18.

The *N*H-pyrrolidines **3b**and **17** was prepared from the corresponding amines **2b**or **16**[5a] which was previously synthesized by us using same route for **2a**, respectively using general ATRC procedure as above for **3a-b**, except that 10 mol % each of CuCl and PMDETA were taken along with 30 mol% AIBN and the reaction mixture was stirred at reflux 6 hrs. Next the crude product after usual work up was taken up as such for next step of aromatization step. This reaction was performed by following a method reported in our previous work[9h-l] in which 3,3-dichloro-4-chloromethyl-tetrahydrofurans were aromatized by DBU. A solution of the chlorinated pyrrolidine **3b or 17**[5a] (1mmol) and DBU (0.38 mL, 2.5 mmol) in dry toluene (30 mL) was heated at reflux for 24 h. The reaction mass was cooled to room temperature and ethyl acetate (100 mL) was added. The solution was washed successively with saturated solution of NH_4Cl (20 mL) and with brine (2x20 mL). The organic phase was dried (anhydrous Na_2SO_4), filtered and evaporated to obtain the crude product. The purification of the crude product by column chromatography on a neutral alumina column using a mixture of ethyl acetate and *n*-hexane (10-20 %, *v*:*v*) as the mobile phase gave the pure product **15** and **18** in good yield (45-46 %).

3-Chloro-4-(chloromethyl)-2-(thiophen-2-yl)-1H-pyrrole 15: Viscous liquid, 45 % yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.21 (s. 3H, CH_3), 6.51 (d, 1H, *J* = 1.2 Hz, pyrrolic CH), 7.20 (t, 1H, *J* = 4.5 Hz, thienyl CH), 7.39 (d, 1H, *J* = 5.1 Hz, thienyl CH), 7.49 (s, 1H, thienyl CH), 8.67 (br, s, 1H, *N*H, D_2O-exchangeable) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 9.9 (CH_3), 109.8 (C), 118.2 (CH), 124.3 (C), 126.3 (CH), 126.7 (CH), 127.7 (C), 128.3 (C), 138.5 (C) ppm; IR (KBr): ν_{max} 3363(s, br), 2927(m), 1697(s), 1576(m), 1526(s), 1451(s), 1248(s), 1097(m), 1027(s), 830(s), 723(m) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_9H_8Cl_1N_1ONa$ 219.9958, found 219.9970.

3-Chloro-4-(chloromethyl)-2-(furan-2-yl)-1H-pyrrole 18: Viscous liquid in 46 % yield; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.11 (s. 3H, CH_3), 6.42 (s, 1H, pyrrole CH), 6.54-6.57 (m, 2H, furyl CH), 7.08 (br, s, 1H, *N*H, D_2O-exchangeable), 7.38-7.39 (m, 1H, furyl CH) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 10.3 (CH_3), 108.8 (C), 111.2 (CH), 112.2 (CH), 116.5 (CH), 124.3 (C), 126.3 (C), 140.0 (CH), 150.3 (C) ppm; IR (KBr): ν_{max} 3363(s, br), 2927(m), 1697(s), 1576(m), 1526(s), 1451(s), 1248(s), 1097(m), 1027(s), 830(s), 723(m) cm^{-1}; HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_9H_8Cl_1NNa$ 204.0187, found 204.0190.

Conflicts of interest

There are no conflicts of interests to declare.

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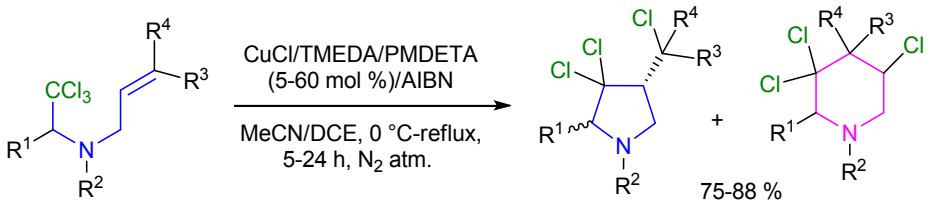

R^1 = N & S-heteroaryls, CO_2Me, CH_2EWG (EWG = $CONMe_2$, COR, NO_2), H
R^1-R^2 = RCHCO, R^2 = H, CO_2Me, R^3 & R^4 = H, alkyl

Chelation, rigidity and carbon-radical positions in aminoalkyl precursors disturb the usual 2,4-*trans* diastereoselectivity and 5-*exo* mode in Cu(I)-catalyzed ATRC