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Deconstructive Oxygenation of Unstrained Cycloalkanamines

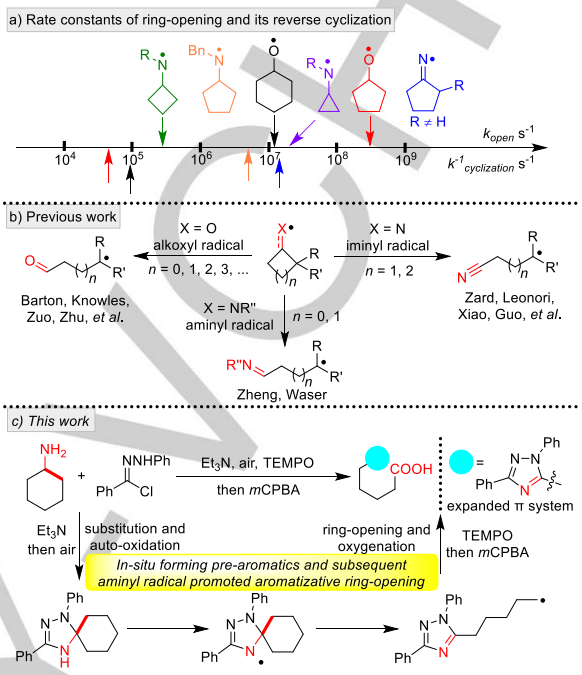
Jian-Wu Zhang, Yuan-Rui Wang, Jia-Hao Pan, Yi-Heng He, Wei Yu, and Bing Han*

***Abstract**: A deconstructive oxygenation of unstrained primary cycloalkanamines has been developed for the first time via an auto-oxidative aromatization promoted C(sp^3)-C(sp^3) bond cleavage strategy. This metal-free method involves the substitution reaction of cycloalkanamines with hydrazonyl chlorides and subsequent auto-oxidative annulation to in-situ generate pre-aromatics, followed by N-radical-promoted ring-opening and further oxygenation by 2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) and m-cholorperoxybenzoic acid (mCPBA). Consequently, a series of 1,2,4-triazole-containing acyclic carbonyl compounds were efficiently produced. This protocol features one-pot operation, mild conditions, high regioselectivity and ring-opening efficiency, broad substrates scope, and is compatible with alkaloids, osamines, peptides as well as steroids.*

Aliphatic rings are a vital structural element in various kinds of organic compounds including drugs, natural products, and functional materials.[1] The deconstruction of such cycloalkane derivatives via ring-opening constitutes a highly attractive scaffold hopping strategy in organic synthesis.[2] However, the C-C bond cracking of unstrained aliphatic rings has long been viewed as an extremely challenging problem owing to the high C-C bond dissociation energy.[3,4] One promising strategy to solve this problem is to take advantage of the high reactivity of oxygen radicals to facilitate the ring-opening via C-C bond cleavage. In this context, elegant methods have been developed based on the cycloalkoxy radical-promoted ring opening.[5] The ring-opening rates of alkoxy radicals are several orders of magnitude higher than those of the reverse cyclization (Scheme 1a, $k_{open} \approx 10^8$ s^{-1} >> $k^{-1}_{cyclization} \approx 10^4$ s^{-1} and $k_{open} \approx 10^7$ s^{-1} >> $k^{-1}_{cyclization} \approx 10^5$ s^{-1} for 5- and 6-membered ring, respectively),[6] and thus their ring-opening process is thermodynamically favorable as well as kinetically favorable. Besides cycloalkoxy radicals, it is also possible other types of radicals can also be exploited to cleavage the unstrained aliphatic rings, but so far, few effective methods have been reported in this line.

Cycloalkyliminyl and cycloalkylaminyl radicals-involved ring-opening reactions have attracted much attention in recent years.[7-9] For example, the groups of Zard,[7a,7c] Leonori,[7f] Xiao,[7e] and Guo[7g] have developed iminyl radical-mediated ring-opening of strained rings by using oxime esters or ethers as the substrates (Scheme 1b). Meanwhile, Zheng[8a-c] and Waser[8e] have independently reported ring-opening reconstruction and functionalization of strained cyclopropylamines and cyclobutylamines. However, different from alkoxyl radicals, those reactions are limited to strained rings, while the ring-opening of unstrained ring still remains a big challenge. This situation can be attributed to their high reverse 5-exo cyclization rate constant onto nitrile and imine ($k^{-1}_{cyclization} \approx 10^7$ s^{-1}), [10] respectively.

Cyclic amines are widely found in drugs and natural products.[11] However, to the best of our knowledge, the ring-opening of unstrained cycloalkanamines has not been reported. We report herein for the first time an aminyl radical-mediated ring-opening of unstrained primary cycloalkanamines by introducing aromatization as both dynamic and thermodynamic driving forces (Scheme 1c). Aromatization has been applied in C-C bond cleavage as a momentous thermodynamic driving force,[12] but this strategy is still unappreciated because of the difficulty in generating pre-aromatics in situ.[4f] In this context, the present one-pot protocol employs a convenient mean for the in-situ formation of heterocyclic pre-aromatics 3,4-dihydro-1,2,4-trizoles by the substitution reaction of cycloalkanamines with hydrazonyl chloride followed by subsequent auto-oxidative annulation using air as the terminal oxidant. The further auto-oxidation of such pre-aromatics by air realizes the aminyl radical-promoted C-C bond cleavage ring-opening. Thus, a series of 1,2,4-triazole-featured acyclic carboxylic acids/carbonyls are efficiently produced by the oxygenation of the C-centered radical by TEMPO and *m*CPBA (Scheme 1c).



Scheme 1. Heteroatom radical-mediated ring-opening of naphthenes and rate constants.

The study commenced by stirring the mixture of cyclohexylamine **a1** (0.3 mmol), N-phenylbenzohydrazonoyl chloride **b1** (0.39 mmol), and Et_3N (0.45 mmol) in dimethylacetamide (DMA) (2 mL) under Ar at RT for 1 h, and then the mixture was stirred for additional 72 h under air. Indeed, the desired auto-oxidative ring-opening took place and gave the self-coupling product **c1** in 20% yield as the only separable product (Figure 1a). Apparently, **c1** was produced through trapping the ring-opened C-radical by unopened aminyl radical $\mathbf{R_N}$ (Figure 1a). This result was attributed to the high stability of the formed aminyl radical $\mathbf{R_N}$,

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which could be directly detected by using the reaction mixture in (1a) via electron paramagnetic resonance (EPR) (Figure 1b).[13] Data analysis verifed that N-centered radical was generated (g = 2.0037; hpfc: 0.65 G (2H); 1.95 G (1H); 3.23 G (1N); 6.45 G (1N); 7.74 G (1N)). In addition, the formation of stable radical $\mathbf{R_N}$ was also confirmed by HRMS measurement (see Supporting Information (SI)). This high stability was due to the delocalization of single-electron spin density over three N-atoms, which was also validated by DFT calculation (Figure 1c).

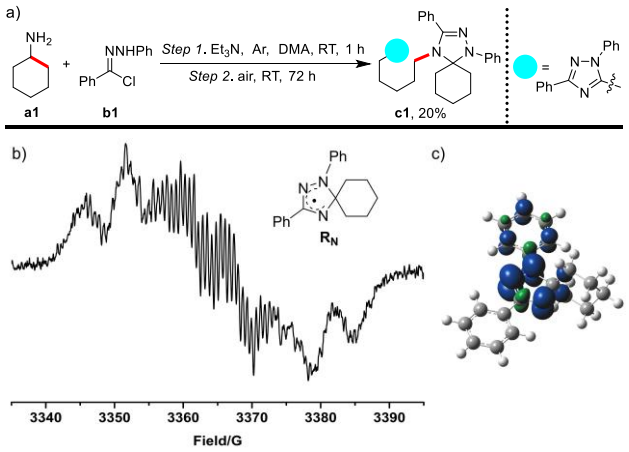
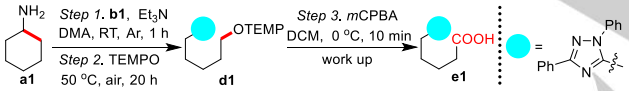


Figure 1. (a) **a1** (0.3 mmol), **b1** (0.39 mmol), and Et_3N (0.45 mmol) in DMA (2 mL) was stirred under Ar at RT for 1 h, and then stirred for additional 72 h under air. (b) EPR spectrum (X band, 9.4 GHz, RT): the reaction mixture in (a) was derectly used for EPR measurement. (c) The caculated spin density of $\mathbf{R_N}$.

To prevent the formation of **c1**, a well-known C-centered radical scavenger TEMPO[14] was employed in the reaction. To our delight, when TEMPO (3.5 equiv.) was charged in the auto-oxidative stage, the self-coupling was totally inhibited and the TEMPO-trapped ring-opening product **d1** was afforded in 74% yield. Significantly, **d1** could be easily converted to the desired

Table 1. Optimization of the Reaction Conditions.[a]

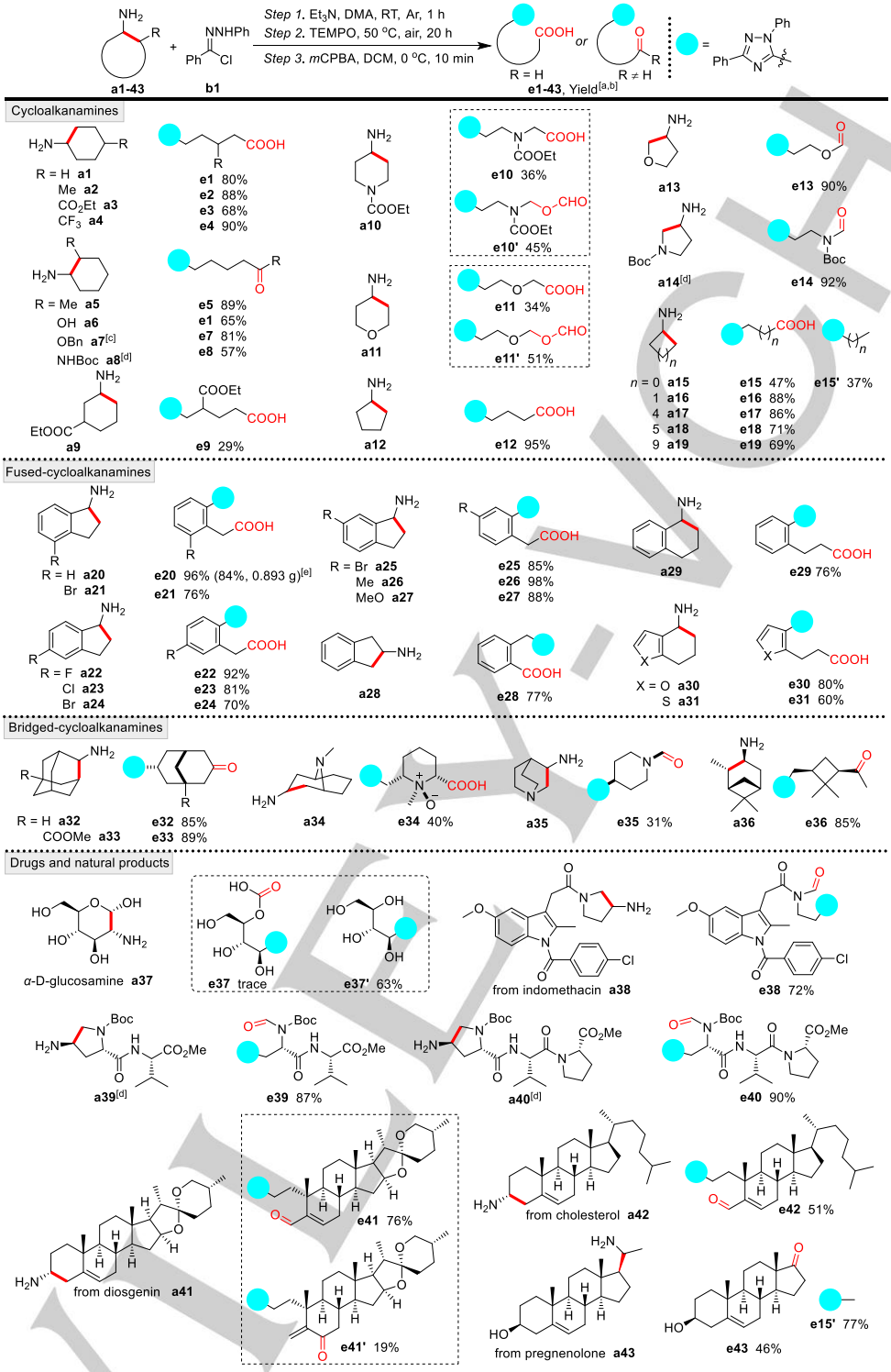


Entry	Variation of conditions of *Step 2*	Yield (**d1**, %)[b,c]	Yield (**e1**, %)[b]
1	RT, 72 h	74	67
2	40 °C, 64 h	83	75
3	none	92	80
4	TEMPO (1.5 equiv.)	68	60
5	TEMPO (2.5 equiv.)	76	70
6	TEMPO (5 equiv.)	86	72
7	under Ar	16	-
8	CH_3CN instead of DMA		53
9	DCE instead of DMA		36
10	toluene instead of DMA		trace
11	CH_3OH instead of DMA		39

[a] A mixture of **a1** (0.3 mmol), **b1** (0.39 mmol), and Et_3N (0.45 mmol) in DMA (2 mL) was stirred under Ar at RT for 1 h, and then TEMPO (3.5 equiv.) was added in the reaction mixture and stirred at 50 °C under air for additional 20 h. After remove DMA, the miture was treated with *m*CPBA (3 equiv.) in DCM (10 mL) at 0 °C for 10 min. [b] Isolated yield. [c] Without step 3. TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, *m*CPBA = *m*-Cl-peroxybenzoic acid, DMA = *N,N*-dimethylacetamide, DCE = 1,2-dichloroethane, DCM = dichloromethane.

oxygenated product 1,2,4-triazole-featured acyclic carboxylic acid **e1** in 67% yield after the treatment with *m*CPBA in a sequential one-pot process (Table 1, Entry 1). Increasing the reaction temperature of auto-oxidative stage would reduce the reaction time and improve the product yields (Table 1, Entries 2 and 3). The usage amount of TEMPO was essential for an efficient reaction (Table 1, Entries 4-6). When the reaction was conducted under Ar, the product **e1** was remarkably reduced to 16% yield (Table 1, Entry 7). Solvent screening results showed that DMA was a better choice than CH_3CN, dichloroethane (DCE), toluene, and methanol (Table 1, Entries 8-11).

With the optimal conditions established, we proceeded to evaluate the scope of the protocol with respect to primary cycloalkanamines. As shown in Scheme 2, a large variety of cycloalkanamines including monocyclic, bicyclic, bridged, and complex natural product derivatives were efficiently ring-opened and oxygenized. First, the regioselectivity of C-C bond cleavage as well as the substituent tolerance were investigated by introducing various functional groups at different sites on cyclohexylamine. 4-Substituted symmetric cyclohexylamines **a2-4** bearing Me, COOEt, and CF_3 groups were well compatible in the transformation, affording acyclic acids **e2-4** in good yields. Incorporation of substituents such as Me, OH, OBn (Bn = Benzyl), and NHBoc (Boc = *t*Butyloxycarbonyl) at the 2-position of cyclohexanamine significantly increased the diversity of deconstructive products, as demonstrated in the cases of **a5-8**, the corresponding linear ketone **e5**, carboxylic acid **e1**, ester **e7**, and amide **e8** were produced in good yields. 3-Substituted cyclohexanamine was also suitable for this conversion and the C–C bond was selectively cut at the less steric hindrance side (**e9**). Notably, six-membered heterocyclic amines embedding heteroatoms such as N- and O-atoms were also good candidates, providing the desired ring-opening products **e10** and **e10'** in a combined yield of 81% and **e11** and **e11'** in a combined yield of 85%, respectively. When cyclopentanamine **a12** participated in the procedure, **e12** was produced in 95% yield. Similarly, heteroatoms O- and N-substituents could also be incorporated into the 5-membered heterocyclic alkanamines, delivering formiate **e13** and formamide **e14** in excellent yields and high regioselectivity. Cycloalkanamines of the varying of ring sizes could also be transformed to the corresponding chain carboxylic acids **e15-19**. Except **e15** was easy to decarboxylate to **e15'** during column chromatograph, **e16-19** were formed in excellent yields. Next, aryl-fused bicyclic alkanamines were explored for this protocol. 1-Indanamines **a20-27** bearing substituents with a variety of electronic properties at 4-, 5-, and 6- position on the phenyl ring were all compatible in this tactic, producing biaryl carboxylic acids **e20-27** in 70-98% yields. The reaction of 2-indanamine was also performed well, giving rise to **e28** in 77% yield. This process also made promise for benzo-, furo- and thieno-cyclohexylamines and gave the acyclic carboxylic acids bearing biaryl and biheteroaryl in decent yields over one-pot (**e29-31**). In addition, a variety of bridged cyclic amines, such as 2-amantadine, tropine amine, 3-pinanamine, and 3-amino-quinuclidine, were all smoothly converted to the desired products with good regioselectivity and yields (**e32-36**). After successfully converting simple unstrained cycloamines, we turned our attention to drugs and natural product derivatives containing cycloamine moiety. D-glucosamine was

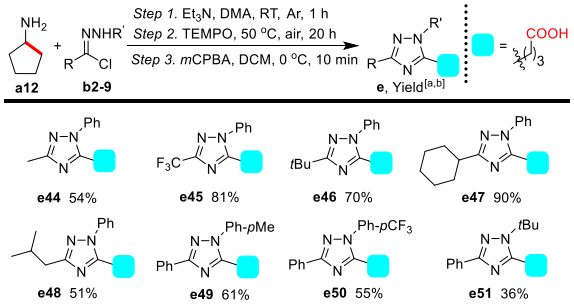


Scheme 2. Scope of cycloalkanamines. [a] Isolated yields. [b] Reaction conditions, see note [a] in Table 1. [c] Bn = Benzyl. [d] Boc = *t*Butyloxycarbonyl. [e] The reaction was conducted on 3 mmol scale.

regioselectively deconstructed to the corresponding acid **e37**, despite the latter is easy to decarboxylate to **e37'**. Indomethacin derivative **a38** can also be readily transformed the corresponding product **e38** in 72% yield. Bi- and tri-peptides containing aminoproline were deconstructed very well in this tactic (**e39** and **e40**). The reaction enables the efficient and regioselective cleavage of A ring of steroids in diosgenin and cholesterol derivatives (**e41** and **e42**). This C-C bond dissociation can also be used on acyclic substrates containing ethylamine moiety, as demonstrated in the case of pregnenolone derivative **a43**, providing **e43** and methyl-1,2,4-trizole **e15'** in good yields. Notably, this protocol can be conducted on a gram-scale without any difficulty, as demonstrated in the case of **e20** in 84% yield (0.893 g). By utilizing decarboxylative functionalization, **e20** can be easily

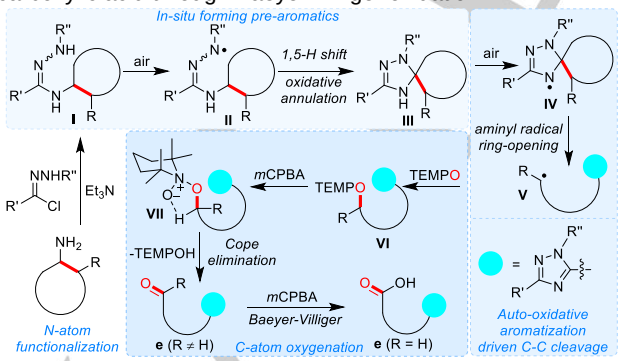
transformed to diversified molecules (see SI).

Considering that 1,2,4-triazole scaffold possesses good biocompatibility and tissue bioactivity,[15] which are found in antimicrobial agents such as terconazole, fluconazole, and itraconazole as well as in aromatase inhibitors anastrozole and letrozole, we also explored the scope of hydrazonyl chlorides for the tactics. Gratifyingly, as depicted in Scheme 3, a series of aryl and alkyl substituted hydrazonyl chlorides are all suitable for this conversion, affording 1,3,5-trisubstituted-1,2,4-triazoles in moderate to excellent yields.



Scheme 3. Scope of hydrazonyl chlorides. [a] Isolated yield. [b] Reaction conditions, see note [a] in Table 1.

Based on literatures and our observations, a plausible mechanism for the protocol was postulated as shown in Scheme 4. Cycloalkanamine first reacts with hydrazonyl chloride to produce hydrazonamide **I** via nucleophilic substitution. **I** is subsequently auto-oxidized by air to generate the hydrazonyl radical **II** [16] which then experiences a cascade 1,5-H-atom transfer and further oxidation/ annulation process to form the pre-aromatics **III** (see SI for the isolation and identification of intermediates **I-1** and **III-1**). The succeeding auto-oxidation of **III** by air yields the aminyl radical **IV**. The latter undergoes radical C-C bond cleavage enabled by the aromatization driving force to afford the distal alkyl radical **V** which is immediately intercepted by TEMPO to give ring-opening product **VI**. The treatment of **VI** with *m*CPBA to produce the intermediate N-oxide **VII** which immediately experiences Cope-elimination to give 1,2,4-triazole-containing acyclic carbonyl compound **e**.[17] Under the present conditions, acyclic aldehyde can be further transformed to acyclic carboxylic acid through Baeyer-Villiger oxidation.[18,19]



Scheme 4. Proposed Mechanism.

In summary, we have developed a deconstructive oxygenation of unstrained primary cycloalkanamines through an aromatization driven C(sp^3)-C(sp^3) single-bond cleavage ring opening for the first time. The present tactic not only exploits in-situ forming pre-aromatics as the source of the aromatization driving force but also realizes auto-oxidative ring-opening of unstrained aliphatic rings under mild conditions. The synthetic practicability of this strategy has been demonstrated by regioselective deconstructive oxygenation of a great variety of substrates including mono-, fused, and bridged cyclic alkanamines as well as alkaloids, osamines, peptides, and steroids. Consequently, a series of 1,2,4-triazole-featured acyclic carbonyl compounds have been efficiently produced. Further research about deconstructive functionalization of unstrained aliphatic rings is ongoing in our laboratory.

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Keywords: *aminyl radical • auto-oxidation • cycloalkanamines • C-C bond cleavage • oxygenation*

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[19] For the final step Baeyer-Villiger oxidation of aldehydes, the acyclic acids **e1-4**, **e9, e12,** and **e15-31** were formed because the migration tendency of the H group is higher than the alkyl group. Formamide **e10'** and formate **e11'** were produced along with the formation of acyclic acids **e10** and **e11** due to the similar migration ability of the groups H- and R-N-CH_2- and R-O-CH_2-. In the cases of **e13**, **e14**, **e35**, and **e38-42**, the reaction stopped at aldehydes because themselves were already formates/formamides/allylaldehydes which cannot be further transformed under the standard conditions.

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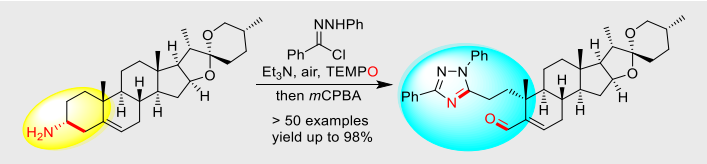

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Deconstructive Oxygenation of Unstrained Cycloalkanamines

A regioselective deconstructive oxygenation of unstrained cycloalkanamines has been developed for the first time. This metal-free method involves the substitution reaction of cycloalkanamines with hydrazonyl chlorides and subsequent auto-oxidative annulation to in-situ generate pre-aromatics, followed by N-radical-promoted aromatizative ring-opening and further oxygenation by TEMPO and *m*CPBA.