

# CAN-mediated tandem 5-*exo*-cyclisation of tertiary aminocyclopropanes: novel accelerative effect of an *N*-benzyl group for oxidative ring-opening

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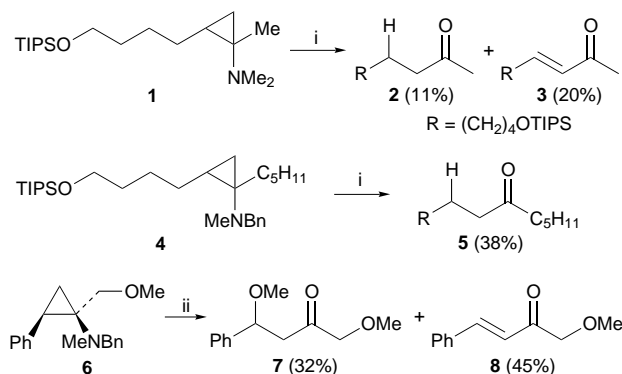
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Treatment of tertiary cyclopropylamines with cerium(IV) ammonium nitrate (CAN) gave ring-opened ketones and/or bicyclic secondary amines *via* an oxidative cyclopropane cleavage followed by a hydrogen abstraction or 5-*exo* radical cyclization: an *N*-benzyl group plays a crucial role in these reactions.

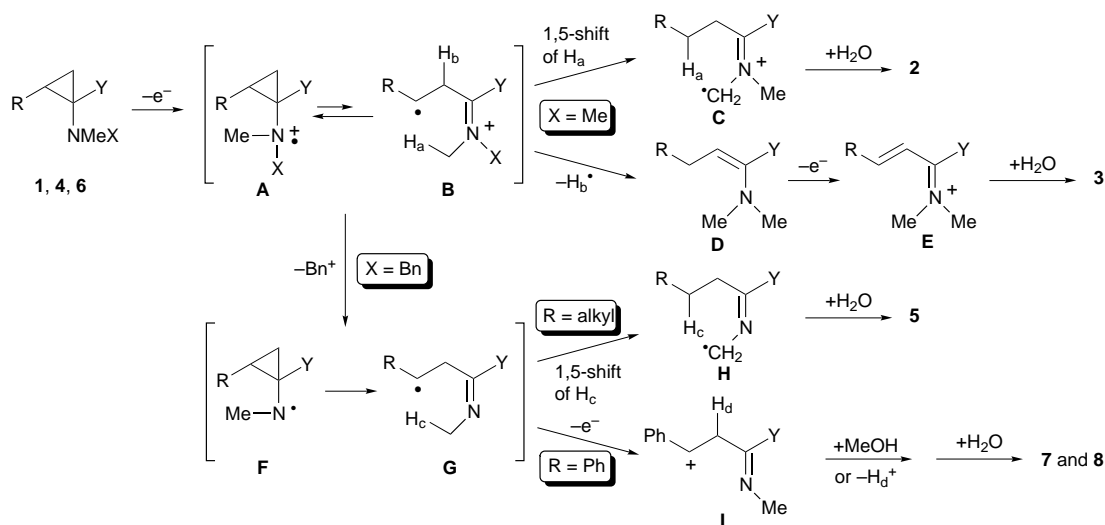
Cyclopropylamines have attracted considerable interest from organic and biological chemists as conformationally constrained amino acids<sup>1</sup> and mechanism-based inhibitors of cytochrome P-450 and monoamine oxidase.<sup>2</sup> Thus far many facile preparations of cyclopropyl amines, such as the Simmons–Smith cyclopropanation of enamines<sup>3</sup> and the Ti<sup>III</sup>-mediated coupling of *N,N*-dialkylamides and monosubstituted olefins,<sup>4</sup> have been developed. However, compared with these synthetic methods, few transformations of cyclopropylamines into more versatile synthetic intermediates have been reported.<sup>3,5</sup> Only the enzymatic oxidation of cyclopropylamines

to clarify the mechanism for the inactivation of cytochrome P-450<sup>6</sup> and monoamine oxidase,<sup>7</sup> and ethylene formation from 1-aminocyclopropane carboxylic acid<sup>8</sup> have been examined. In these studies, it has been proposed that the ring-opening reaction proceeds *via* cyclopropylamine radical cations, whose existence have been proven by an EPR study.<sup>9</sup> Recently, we developed an efficient synthetic method for cyclic ethers and spirocyclic compounds by a single electron transfer (SET) promoted ring-opening of cyclopropyl sulfides with cerium(IV) ammonium nitrate (CAN).<sup>10</sup> Our recent efforts have been directed to the oxidative ring-opening of the tertiary cyclopropylamines. Herein we report a convenient method for cleaving a cyclopropyl bond<sup>‡</sup> and an intramolecular [3 + 2]cycloaddition with a tethered olefin.<sup>11</sup>

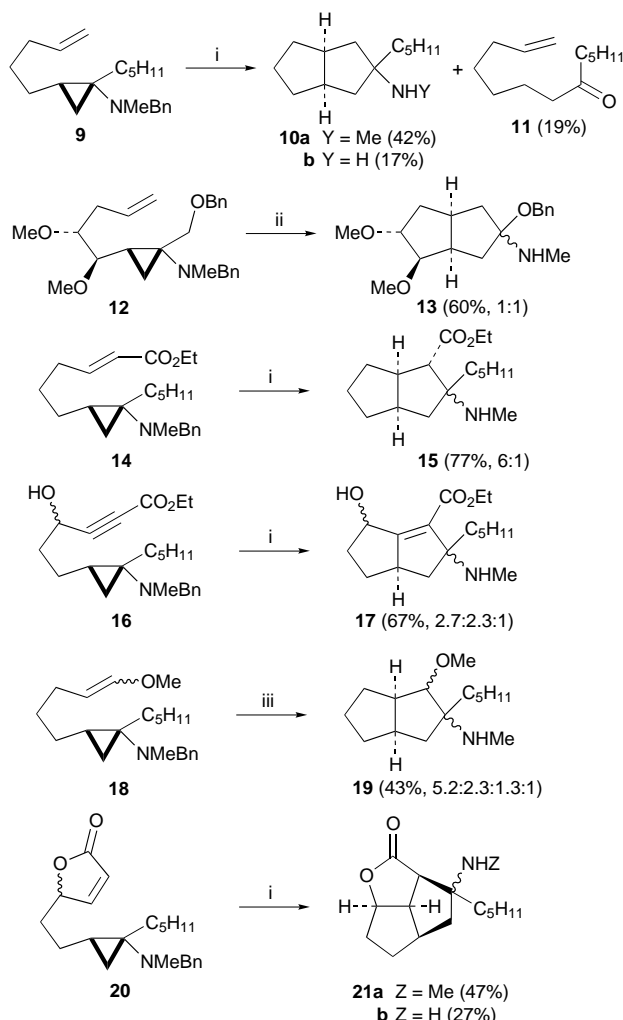
The ring-opening of *N,N*-dimethyl- and *N*-methyl-*N*-benzylcyclopropylamines **1**§ and **4**§ was studied as a model reaction (Scheme 1). The CAN-promoted oxidation of **1** proceeded slowly (20 h) in DMF in the presence of NaHCO<sub>3</sub> to give the ring-opened ketone **2** and  $\alpha,\beta$ -unsaturated ketone **3** in 11 and 20% yield, respectively. The use of MeOH as solvent in place of DMF slowed the reaction rate, resulting in the recovery of almost all the starting materials. On the other hand, the reaction of **4** under the same reaction conditions proceeded smoothly (2 h), irrespective to the reaction solvent, to give the ring-opened ketone **5** as the sole product in good yield. Although all products seem to be produced by cleaving the most substituted cyclopropyl bond of **1** and **4**, two-electron oxidation occurred simultaneously with single-electron oxidation in the former case. In addition, the oxidation of 2-phenylcyclopropylamine **6** took place only through two electron oxidation, giving the  $\beta$ -methoxy ketone **7** and the  $\alpha,\beta$ -unsaturated ketone **8** in 32 and 45% yield, respectively. These results indicate that the CAN-mediated oxidation of the tertiary cyclopropylamines is affected by substituents on both the nitrogen and the cyclopropane ring. The reaction pathway shown in Scheme 2 clearly explains these phenomena. The SET oxidation of **1** and **4** generates the radical-



**Scheme 1** Reagents and conditions: i, CAN, NaHCO<sub>3</sub>, DMF, room temp.; ii, CAN, K<sub>2</sub>CO<sub>3</sub>, MeOH, 0 °C



**Scheme 2**



**Scheme 3** Reagents and conditions: i, CAN, NaHCO<sub>3</sub>, DMF, room temp.; ii, CAN, NaHCO<sub>3</sub>, MeOH–THF (5:1), room temp.; iii, CAN, NaHCO<sub>3</sub>, DMF, 0 °C

cation **A**, which is equilibrated to the ring-opened iminium radical **B**. In the case of **1** (X = Me), the following 1,5-hydrogen shift (**B** → **C**) and successive deprotonation and second SET oxidation (**B** → **D** → **E**) might proceed slowly because the equilibrium lies so far to **A**. On the other hand, in the case of **4** (X = Bn), the benzyl group of the radical-cation species **A** and **B** was rapidly lost from the nitrogen atom, giving the aminyl radical **F** and/or iminyl radical **G**. Because the aminyl radical **F** undergoes a very rapid ring-opening to **G**,<sup>12</sup> the next 1,5-hydrogen shift (**G** → **H**) occurs at a reasonable rate to afford **5**. However, in the case of **6** (R = Ph), another SET oxidation of **G** takes place at a rate faster than the 1,5-hydrogen shift due to the stability of the radical, producing **7** and **8** via the cation intermediate **I**.

To achieve an intramolecular trapping of the presumed radical **G** by a tethered olefin, we next examined the CAN oxidation of *N*-benzyl-*N*-methylcyclopropylamines bearing a suitably situated radical acceptor, typically a double or triple bond (Scheme 3). The oxidation of **9** bearing a terminal olefin was carried out with 5 equiv. of CAN in DMF at room temperature. The reaction was completed in 2 h and gave the bicyclic products **10a** and **10b** in a total yield of 59% along with the ketone **11** as a minor product, while no monocyclic products were obtained.<sup>¶</sup> The cyclization of **12** was not influenced by the substituent on the tether, giving the desired products **13** in 60%

yield. More interestingly, the α,β-unsaturated ester **14** and the α,β-acetylenic ester **16** cyclized more efficiently to give the corresponding bicyclic products **15** and **17** without the ketones, whereas the oxidation of the methyl enol ether **18** afforded **19** in only moderate yield with several over-oxidation products. The α,β-unsaturated lactone **20** was also investigated to examine whether the chirality of the cyclopropylamine moiety influences the diastereoselectivity of the products obtained by the tandem cyclization. Because the CAN-mediated oxidation of **20** (diastereomeric mixture of 1.1:1) gave rise to the tricyclic products **21a** and **21b** in a total yield of 74% as a single isomer, the chirality of the cyclopropylamine moiety of **20** appears to have no effect on the diastereoselectivity of the tandem [3 + 2]-type cycloaddition.<sup>12</sup>

In conclusion, we have developed a novel tandem [3 + 2]-type cycloaddition using the CAN-mediated ring-opening reaction of the cyclopropylamines. This transformation allows for the utilization of aminocyclopropanes as the synthetic equivalents of γ-imino radicals. In addition, the present research demonstrates that the γ-imino radicals possess a totally different reactivity with γ-keto radicals, which can be prepared from cyclopropyl alcohols and α,β-unsaturated ketones by SET oxidation and Bu<sup>n</sup><sub>3</sub>SnH-mediated reduction, respectively.<sup>13</sup>

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## Notes and References

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‡ During our study, Cha reported the oxidative ring-opening of tertiary cyclopropylamines by photooxidation to give the corresponding ring-opened ketones (see ref. 11).

§ Syntheses of **1** and **4** were conducted according to the procedure of ref. 4.

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