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CAN-mediated stereoselective cyclization of epoxypropyl cinnamyl amines to 3,4,5-trisubstituted piperidines and supramolecular assembly of the latter aided by ethyl acetate

Vijay Nair,[a,*] Kishor Mohanan,[a] T. D. Suja[a] and Eringathodi Suresh[b]

[a]*Organic Chemistry Division, Regional Research Laboratory (CSIR), Trivandrum, India*
[b]*Central Salt and Marine Chemicals Research Institute (CSIR), Bhavnagar 364 002, India*

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Dedicated with best wishes to Professor Athelstan L. J. Beckwith, on the occasion of his 75th birthday

Abstract—The stereoselective intramolecular cyclization of epoxypropyl cinnamyl amines mediated by substoichiometric quantities of CAN leading to the synthesis of functionalized piperidines and the formation of a supramolecular assembly of the latter with ethyl acetate is described.

Recent work in our group and elsewhere has demonstrated the immense value of cerium(IV) ammonium nitrate (CAN) in a variety of carbon–carbon and carbon–heteroatom bond forming reactions.[1–7] Most of these investigations were primarily concerned with intermolecular reactions. In contrast, there are very few reports of CAN-mediated intramolecular cyclization reactions.[8–11] In general, CAN-mediated reactions require the use of this reagent in more than stoichiometric amounts. The catalytic use of CAN in ring opening of epoxides reported by Iranpoor[12] and some intermolecular C–C bond forming reactions using a catalytic process in which Ce(III) is oxidized to Ce(IV) in situ by oxygen are exceptional.[13] Recently our studies uncovered a novel oxidative cyclization mediated by CAN for the stereoselective synthesis of substituted tetrahydrofurans[14] and a process catalyzed by CAN for the oxidative cyclization of epoxypropyl cinnamyl ethers (Scheme 1).[15]

The synthetic potential inherent in the efficiency and stereoselectivity of the latter reaction combined with the advantageous substoichiometric use of CAN, inspired us to explore the construction of substituted piperidine frameworks by a CAN-mediated oxidative cyclization. Inter alia the piperidine ring system is present in many natural and synthetic compounds endowed with potent biological activities[16] and there has been substantial interest in devising efficient routes for the stereoselective synthesis of piperidines.[17]

The substrate selected for our studies was *N*-tosyl-*N*-cinnamyl-3-(4-fluorophenyl)-2,3-epoxypropyl amine **4**.[18] In an initial experiment, **4** was treated with a catalytic amount of CAN[19] in acetonitrile and the piperidine derivative **5a** was isolated in moderate yield (Scheme 2).[20]

The IR spectrum of compound **5a** displayed NH and OH stretching absorptions at 3324 and 3384 cm^{-1}, respectively. In the ^1H NMR spectrum, the acetamidomethyl group was detected as a sharp singlet at δ 1.96. The resonance signal at δ 169.2 in the ^{13}C NMR spectrum was attributed to the amide carbonyl group. All other signals were in good agreement with the assigned structure. Conclusive evidence for the structure and stereochemistry of **5a** was obtained from single crystal X-ray data (Fig. 1).

The reaction was found to be general and a number of substituted piperidines were synthesized from various epoxypropyl cinnamyl amines. The results are presented in Table 1.

Keywords: Cerium ammonium nitrate; Piperidine; One-electron oxidation; Radicals; Supramolecular assembly.
* Corresponding author. Tel.: +91 471 249 0406; fax: +91 471 249 1712; e-mail: vijaynair_2001@yahoo.com

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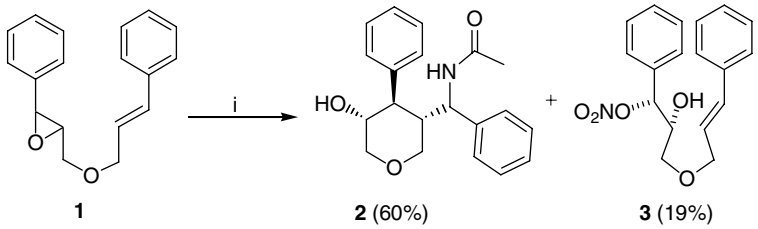
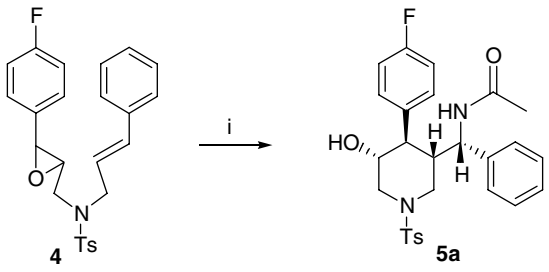


Scheme 1. Reagents and conditions: (i) CAN (0.5 equiv), dry CH_3CN, argon, rt, 16 h.



Scheme 2. Reagents and conditions: (i) CAN (0.8 equiv), dry CH_3CN, argon, 5 h, 55%.

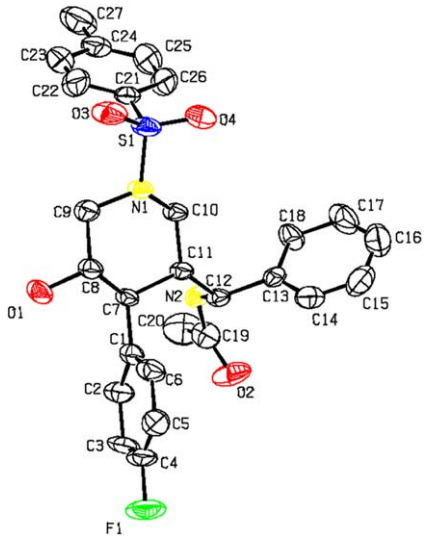
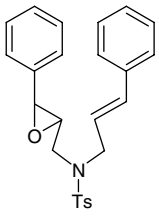
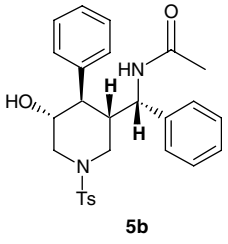
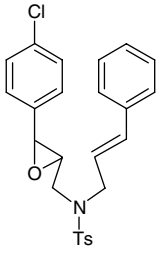
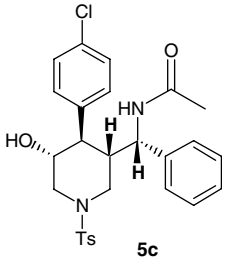
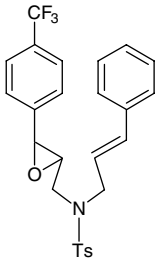
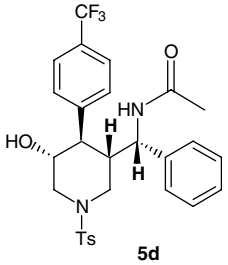
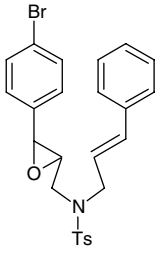
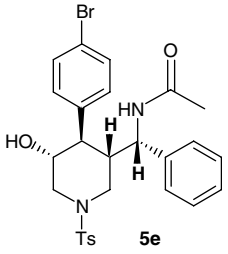
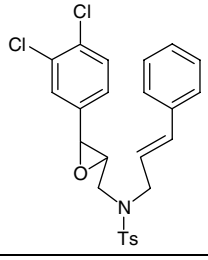
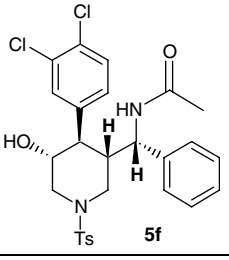


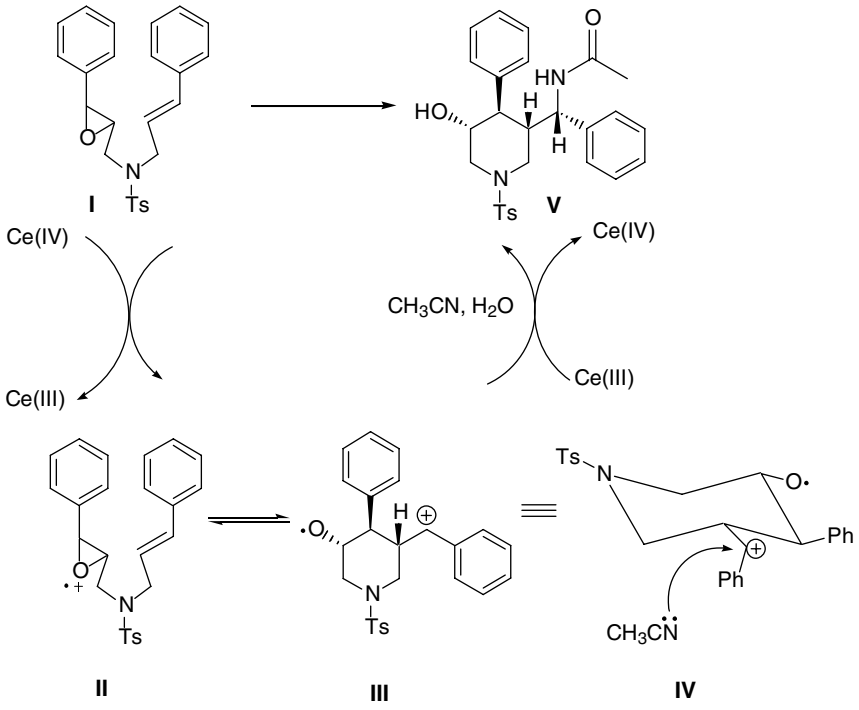
Figure 1. ORTEP diagram of the compound **5a** with 40% probability factor for the thermal ellipsoids. Hydrogen atoms are omitted for clarity.

A mechanistic rationalization for the formation of piperidines can be made along the following lines. The epoxy group of **I** undergoes single electron transfer oxidation by CAN to afford the radical cation **II**. It is conceivable that in a relatively less nucleophilic solvent like acetonitrile, it exists in equilibrium with its cyclic version **III**. The alkoxy radical thus formed reoxidizes Ce(III) to Ce(IV) and thereby is itself reduced to an alkoxide ion. Finally, the cationic centre is quenched by the solvent and the subsequent aqueous work up affords the piperidine derivative (Scheme 3).

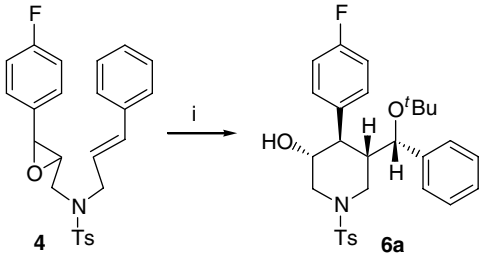
It is noteworthy that only one diastereomer is formed in the reaction. This was ascertained by spectroscopic analysis of the crude product. The remarkable stereoselectiv-

Table 1.

Entry	Substrate	Product	Yield (%)
1		 **5b**	62
2		 **5c**	63
3		 **5d**	32
4		 **5e**	71
5		 **5f**	40



Scheme 3.



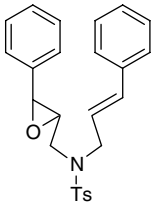
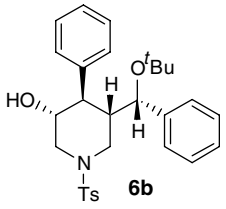
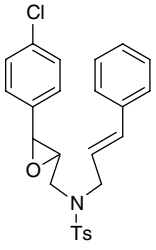
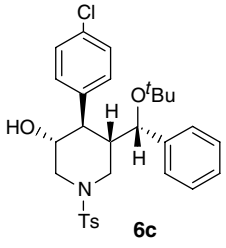
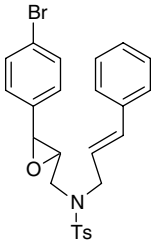
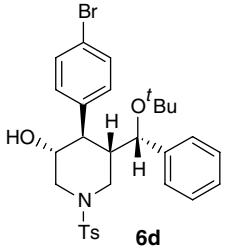
Scheme 4. Reagents and conditions: (i) CAN (0.8 equiv), *t*-BuOH, argon, 5 h, 52%.

ity of the reaction can be explained by invoking a chair-like geometry for the radical cation. The cycloisomerization of **II** to the distonic version **III** presumably takes place in such a way that the latter assumes a low energy chair conformation **IV**, thus rendering substituents at the 3-, 4- and 5-positions equatorial (Scheme 3). The resulting benzylic cation is then preferentially attacked by the nucleophile from the face opposite to the sterically demanding C-4 phenyl ring.

Incorporation of acetonitrile in the product was an interesting observation and to investigate the effect of the nucleophilicity of the solvent we carried out similar reactions in *tert*-butanol. Not surprisingly, the corresponding *tert*-butyl ethers were isolated in moderate yields (Scheme 4). A mechanistic pathway analogous to the one delineated for the amide formation is conceivable in this case also.

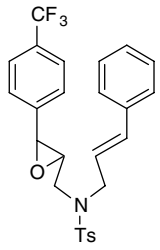
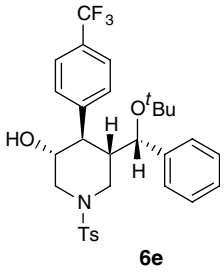
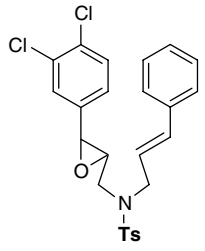
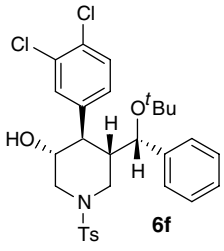
The reaction was found to be general and the results obtained are given in Table 2.

Table 2.

Entry	Substrate	Product	Yield (%)
1		 **6b**	56
2		 **6c**	58
3		 **6d**	55

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Product	Yield (%)
4		 **6e**	32
5	 **Ts**	 **6f**	35

During the crystallographic analysis, we found that ethyl acetate molecules were encapsulated in the lattice. On detailed analysis of packing and various intermolecular interactions, it was observed that the piperidine and ethyl acetate molecules were arranged in alternate layers by strong hydrogen-bonding interactions along all three axes. The hydroxyl group attached to the piperidine ring is strongly hydrogen bonded to the amide carbonyl oxygen forming a linear chain and these are cross linked by C–H···O interaction[21] between the methyl group and the amide oxygen and also, the C–H···F interaction[22] between the phenyl hydrogen and fluorine thereby creating a three dimensional network. This packing and hydrogen bonding created a cavity involving a pair of ligands from alternate layers thereby encapsulating ethyl acetate molecules as shown in Figure 2. There are several other recent reports on similar encapsulation of small molecules by supramolecular interactions.[23]

In conclusion, we have demonstrated that the oxidative cyclization of suitably substituted epoxypropyl cinnamyl amines by CAN can be used as an efficient protocol for the stereoselective synthesis of trisubstituted piperidines, which are structural units of important natural products.[16b] The supramolecular assembly of piperidine derivatives and the concomitant encapsulation of ethyl acetate is interesting and worthy of further studies.

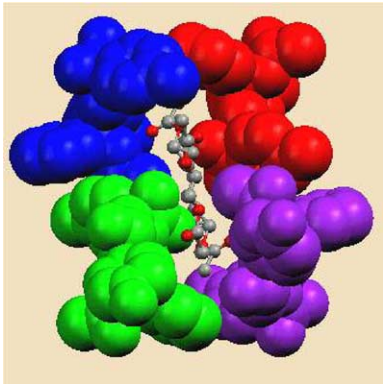


Figure 2. Supramolecular assembly of piperidine molecules with ethyl acetate.

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18. Strategy adopted for the synthesis of cyclization substrates: The epoxypropyl amine was synthesized by *m*-CPBA oxidation of *N*-cinnamyl toluenesulfonamide. Epoxypropyl amine was cinnamylated using the following procedure. A solution of amine (1 mmol) was added to a suspension of sodium hydride (3 mmol) in THF at reflux and allowed to stir for 10 min. Then a solution of cinnamyl bromide in THF was added dropwise and allowed to stir for a further 4 h. The solvent was removed and the residue diluted with water and extracted with dichloromethane (3×15 ml). The solvent was evaporated and column chromatographic separation (SiO_2) using hexane–ethyl acetate mixture (85:15) gave the pure compound.
19. In general, reactions mediated by CAN require 2.5 or more equivalents of the reagent. Therefore the use of 0.8 equiv can be regarded as substoichiometric.
20. All new compounds were fully characterized. *Typical experimental procedure and data for compound* **5a**: A completely deoxygenated solution of CAN (0.8 mmol) in acetonitrile was added dropwise to a completely deoxygenated solution of compound **4** (1 mmol) in acetonitrile and the mixture allowed to stir for 5 h under argon. On completion of the reaction as indicated by the TLC, the solvent was evaporated and the residue diluted with water. It was extracted with dichloromethane, washed with brine and dried over anhydrous sodium sulfate. The residue obtained after evaporation of the solvent was subjected to silica gel column chromatography and elution using $CHCl_3$–MeOH (95:5) furnished product **5a** in 55% yield as a colourless crystalline solid. Data for compound **5a**: Mp 157–159 °C. IR (KBr) ν_{max}: 3384, 3324, 3065, 2926, 1656, 1593, 1533, 1485, 1334, 1163 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$:CCl_4, 7:3 v/v) δ 7.58 (d, $J = 8.0$ Hz, 2H), 7.35–6.94 (m, 11H), 4.73–4.69 (m, 1H), 3.98–3.94 (m, 1H), 3.72–3.68 (m, 1H), 3.56–3.59 (m, 1H), 2.55–2.47 (m, 2H), 2.49 (s, 3H), 2.31–2.24 (m, 2H), 1.96 (s, 3H). ^{13}C NMR (75 MHz) δ 169.2, 163.6, 143.8, 140.1, 133.4, 130.3, 128.6, 127.0, 126.2, 124.9, 116.2, 96.1, 77.3, 71.2, 67.8, 53.1, 51.2, 46.6, 44.8, 29.6, 23.0, 21.5. X-ray data for compound **5a**: $C_{32.5}H_{32}FN_2O_7S$, $M = 613.66$, colourless plates, $0.18 \times 0.14 \times 0.10$ mm^3, monoclinic, space group $P21/c$, $a = 11.272(5)$, $b = 17.837(7)$, $c = 7.138(7)$ Å, $\beta = 101.208(8)°$, $V = 3380(2)$ $Å^3$, $Z = 4$, $D_c = 1.206$ g/cm^3, $F_{000} = 1288$, Mo Kα radiation, $\lambda = 71{,}073$, $T = 100(2)$ K, $2\theta_{max} = 25.0°$, 12,827 reflections collected, 4403 unique ($R_{int} = 0.0887$). Final GOF = 1.085, $R_1 = 0.1084$, $wR_2 = 0.2943$ indices based on 4403 reflections with $I > 2\sigma(I)$ (refinement on F^2), 392 parameters, 0 restraints. Lp and absorption corrections applied, $\mu = 0.147$ mm^{-1}. CCDC file no. 269991.
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