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Article

Metal-Free α-C(sp^3)–H Functionalized Oxidative Cyclization of Tertiary *N,N*-Diaryl Amino Alcohols: Theoretical Approach for Mechanistic Pathway

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Abstract: The mechanistic pathway of TEMPO/I_2-mediated oxidative cyclization of *N,N*-diaryl amino alcohols **1** is investigated in this study. Based on our direct empirical experiments, three key intermediates (the aminium radical cation **3**, the α-aminoalkyl radical **4**, and the iminium **5**), four kind reactive species (radical TEMPO, cationic TEMPO, TEMPO-I and iodo radical) and three kind pathways (1. SET/PCET mechanism, 2. HAT/1,6-H transfer mechanism, 3. Ionic mechanism) were assumed. Under the assumption, nine free energy diagrams are acquired through DFT calculation. From the comparison of the solution phase free energy, some possibility can be excluded and then the chosen plausible mechanisms are concretized with the more stable intermediate **7**.

Keywords: α-C(sp3)–H functionalization; oxidative cyclization; tertiary amine; 6-exo-trig; metal free

1. Introduction

Due to several reasons like costs and toxicity, metal-free C-H activation has been developed. [1] Even though iodine, itself is nonmetal, iodine can behave like a transition metal including ligand exchange, oxidative addition, reductive elimination, and ligand coupling. When three-center-four-electron (3c-4e) bond (L–I–L) (hypervalent bond) is formed by the overlap of the 5p orbital on iodine atom with the orbitals on the two ligands L, the transition metal like property can be observed well. Therefore, in the mostly reports, hypervalent iodine (III or V) were utilized for metal-free C-H functionalization. In particular, recently metal-free cross-dehydrogenative coupling (CDC) are feasible under hypervalent iodine (III). [2, 3] However, when compared with the versatile utilization of the metal-free reaction, the mechanism of metal-free reactions was not enough investigated and various plausible hypotheses has been reported with new reaction methodologies. Some papers appealed ionic mechanism and other described SET mechanism. [4-6]

In the case of 'TEMPO/BAIB' or 'TEMPO/I_2', they have been standard methods to oxidize alcohol to an aldehyde. While several leading reports report iodine as a catalyst, [7, 8] iodine as a co-oxidant is more general due to a cheap cost & benign byproduct. Recently, our research group published oxidative cyclization of *N,N*-diarylamino alcohol **1** through α-C(sp^3)–H functionalization of amines under the exact condition (**Fig1**). [9] Based on a literature search, we could explain that the CDC reaction resulted from the tert-amino effect. [10] However, in the study, we didn't get the clear conclusion on (1) 'what is direct reactive species for the functionalization', (2) 'which kind intermediate is dominant', (3) 'how the well-known radical trapping agent, TEMPO contribute to the reaction – direct catalyst or pre-catalyst, radical trapper or radical initiator, accelerator or controller to prevent undesired side reaction'.

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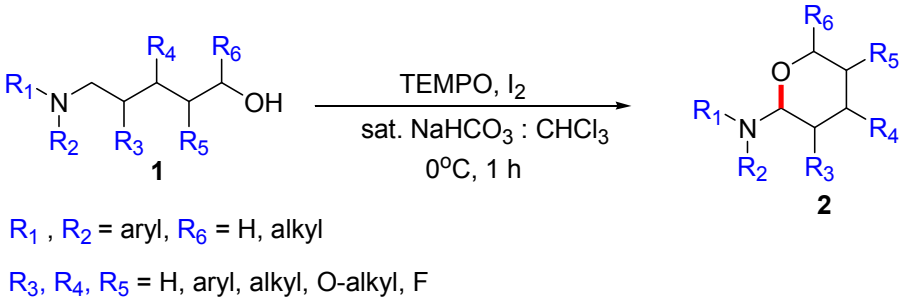

Fig 1. TEMPO/I_2 mediated oxidative cyclization of *N,N*-diarylamino alcohol **1**

In this study, we considered three kind pathways: (1) the aminium radical cation **3** and the SET/PCET mechanism, (2) the α-aminoalkyl radical **4** and the HAT mechanism, (3) the conventional ionic mechanism under basic condition. DFT calculation proposes energy diagrams so that more acceptable pathway among three mechanisms can be chosen. In addition, dominant reactive species can be proposed in three energy diagrams.

2. Initial Assumptions and Theoretical Background

First of all, we considered plausible catalytic cycles for the cross dehydrogenative coupling of amino alcohol using TEMPO catalyst in the combination with iodine as an oxidant/hydrogen acceptor. In our previous study, the reaction of azole derivatives bearing a sp^2 hybridized nitrogen (ex. benzimidazoyl amino alcohol or carbazoyl amino alcohol) couldn't show the cyclization product **2** at all so that we proposed that the key intermediate in the reaction is the iminium **5** requiring the loss of aromaticity of the azole ring in azole substrates. In sequence, how to generate the activated iminium **5** was considered. If the reaction follows a non-ionic mechanism, oxidants or reactive species from the oxidants can receive an e^- (via SET) or H^+/e^- (via radical transfer) from a substrate **1** to produce intermediates **3** or **4** in Fig**2**. In the first case, oxidants or a species generated from the oxidants (either TEMPO or BAIB) abstract an electron from nitrogen of the substrate (via SET) and leave the aminium radical cation **3**. Here, the radical cation **3** arising from the electron transfer must be stable. In the second case, a free radical removes a hydrogen atom from the α carbon of the substrate and produce the α-aminoalkyl radical **4**. The conversion percent yield of cyclization product **2** depends on the stability of the aminium radical cation ($R_3N^{\bullet+}$) **3**, and α-aminoalkyl radical intermediate **4**.

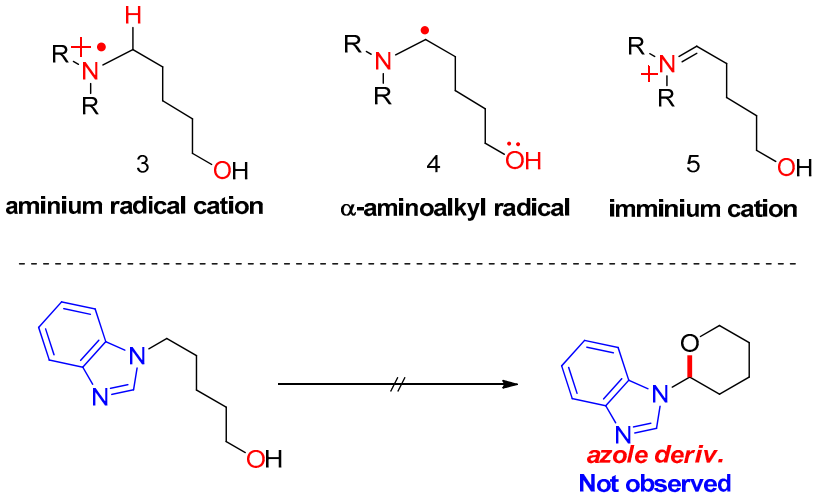

Fig 2. Initial assumed key intermediates of the oxidative cyclization

A TEMPO has been explained to be the active catalyst for hydrogen transfer in an oxidation and the radical scavenger in a radical chain reaction. [11-15] From the combination of TEMPO with iodine,

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the next reactive species were considered to generate intermediates **3** or **4** (two different mechanisms) in **Fig 3.** In addition, the typical regeneration of TEMPO from TEMPO-H was not considered in the ionic mechanism in **Fig 4**.

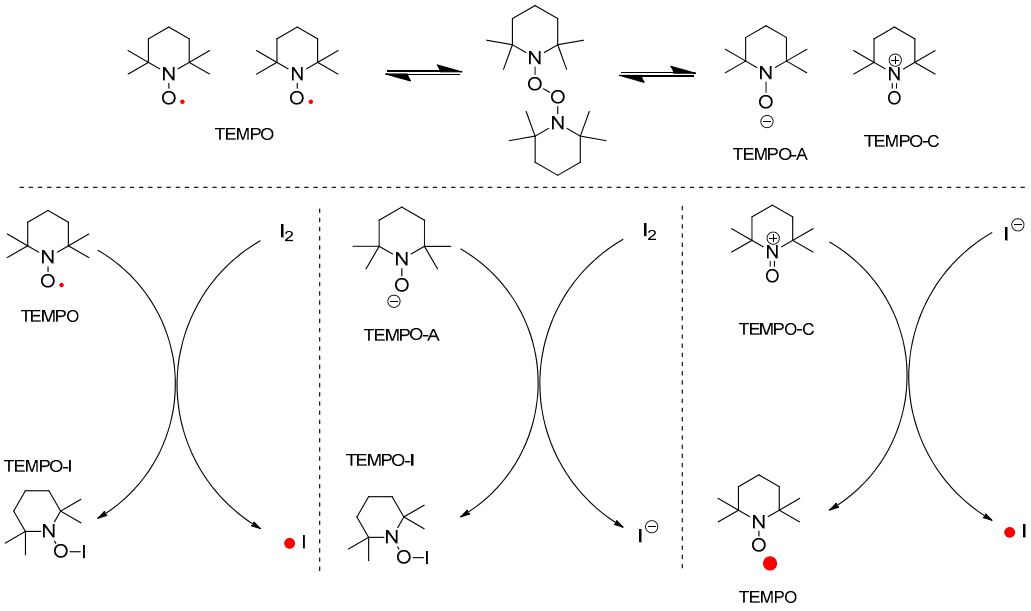

Fig 3 Plausible reactive species generated from TEMPO/I_2 in non-ionic mechanism

If the reaction follows an ionic mechanism like typical oxidation of an alcohol to an aldehyde, the next 4 kind ionic routes can be considered for the ionic mechanism in **Fig4**. The left cycle explains the new bond formation between TEMPO and nitrogen and the right cycle explain the bond formation between TEMPO and oxygen of the hydroxyl group in the substrate **2**. Every 'N-N', 'N-O', and 'O-O' formation commonly produce the activated iminium **5.**

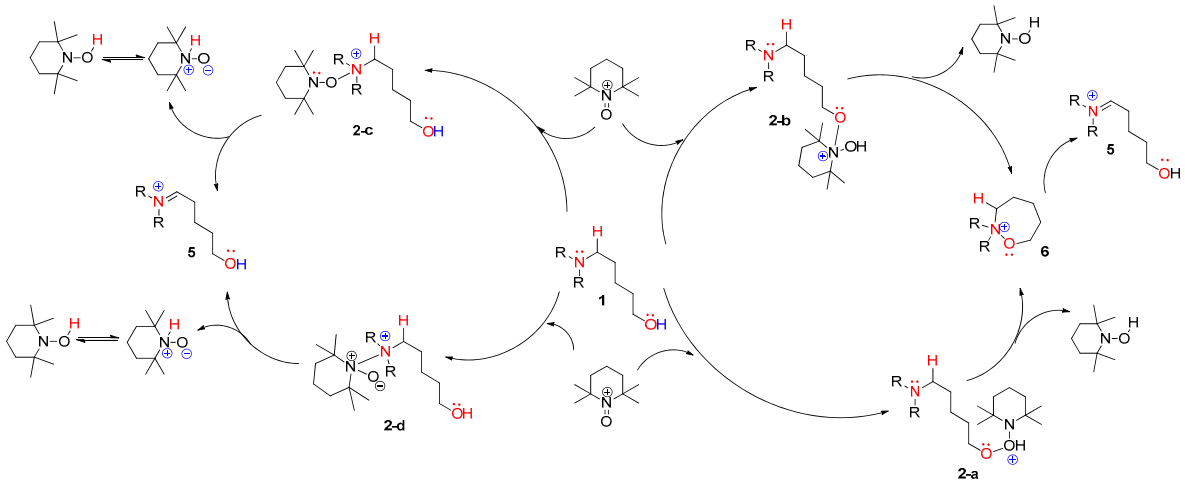

Fig 4. Plausible ionic mechanism of the oxidative cyclization

3. Computational Methods

All calculations were carried out using Density Functional Theory [16] as implemented in the Jaguar 8.0 suite of ab initio quantum chemistry programs. [17] Geometry optimizations were performed using the B3LYP [18-22] functional and the 6-31G** basis set. The energies of the optimized structures were reevaluated by additional single-point energy calculations of each optimized geometry using Dunning's correlation consistent triple-ζ basis set cc-pVTZ(-f) that includes a double set of polarization functions. [23] Solvation energies were evaluated using a self-consistent reaction

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field (SCRF) approach based on accurate numerical solutions of the Poisson-Boltzmann equation. [24-26] Solvation calculations were carried out with the 6-31G**/LACVP basis at the optimized gas-phase geometry employing a dielectric constant of ε = 8.93 for dichloromethane. For all continuum models, the solvation energies are subject to the empirical parameterization of the atomic radii which are used to generate the solute surface. We employed the standard set of optimized radii in Jaguar for H (1.150 Å), B (2.042 Å), C (1.900 Å), N (1.600Å), O (1.550Å), P (2.074Å), and I (2.250Å). Analytical vibrational frequencies within the harmonic approximation were computed with the 6-31G**/LACVP basis set to confirm proper convergence to well-defined minima or saddle points on the potential energy surface. The electron attachment energy in solution, ΔGEA, was calculated by computing the energy components:

$$\Delta GEA(sol) = \Delta GEA(GP) + \Delta Gsolv \quad (1)$$
$$\Delta GEA(GP) = \Delta HEA(GP) - T\Delta S(GP) \quad (2)$$
$$\Delta HEA(GP) = \Delta EEA(SCF) + \Delta ZPE \quad (3)$$

ΔGEA(GP) is the free energy in gas phase; ΔGsolv is the free energy of solvation as computed using the continuum solvation model; ΔHEA(GP) is the enthalpy in the gas phase; T is the temperature (298K); ΔS(GP) is the entropy in the gas phase; ΔEEA(SCF) is the self-consistent field energy, i.e. the "raw" electronic energy as computed from the SCF procedure; and ZPE is the zero point energy. The ZPE and entropy were retrieved from the vibrational frequency calculation. Note that by entropy we refer specifically to the vibrational/rotational/translational entropy of the solute(s); the entropy of the solvent is incorporated implicitly in the continuum solvation model.

3. Result & Discussion

3.1. Pathway A: aminium radical cation 3 and SET/PCET mechanism

In general, aminium radical cations ($R_3N^{\bullet+}$), particularly from arylamines, are involved in a proton-coupled electron transfer (PCET) reaction of amines to produce iminiums. [27-28] Therefore, homolytic cleavage of the α-C−H bond of aminium radical cation **3** via PCET can yield iminium ion **5**. From **Fig. 3**, TEMPO-I and iodo radical as well as TEMPO and cationic TEMPO (TEMPO-C) were considered as electron acceptors. In **Fig. 5-a**, a TEMPO molecule makes the catalytic mechanism begin through single electron transfer (SET) from the substrate, amino alcohol **1.** For the first time, the substrate forms a loosely bound complex **7-a** to proceed via a transition state (*) and then to form an adduct **7-b** at a relative solution phase free energy of 14.55 kcal/mol. The complex **2** takes 21.80 kcal/mol to produce the aminium radical cation **3** together with TEMPO-A. The $1H^+/1e^-$ transfer (PCET) from the aminium radical cation **3** into another TEMPO can produces the iminium **5** and TEMPO-H with -27 kcal/mol of solution phase free energy, showing high stability. The intermediate **5** leads to a more stable and neutral oxyaminal **7** via a transition state **7-TS** of 27 kcal/mol above the starting complex. Finally, the resulting product **2** is readily formed in an exergonic reaction of -15.20 kcal/mol with a barrier of 14 kcal/mol. The PCET reaction can be theoretically explained by homolytic bond dissociation free energy (BDFE). [21] The known BDFE from TEMPO-H into TEMPO is roughly 65 ~ 70 Kcal/moles according to deviation of solvent system. It seems that the decrease of the free energy gap (64.34 kcal/mol) between the aminium radical cation **3** into the iminium **5** can barely compensate the bond association energy from the second TEMPO into TEMPO-H.

In **Fig. 5-b**, TEMPO-C instead of free radical TEMPO in **Fig. 5-a**, initiated the SET from the substrate, amino alcohol **1**. As expected, rather than the complex of the substrate **1** and TEMPO (**Fig. 5-a**), the complex of the substrate **1** and TEMPO-C (**Fig. 5-b**) showed very smaller ΔΔG (36.55 kcal/mol in **Fig. 5-a** vs 5.11 kcal/mol in **Fig. 5-b**) between the aminium radical cation **3** and initial complex. In **Fig. 5-b**, we also consider the formation of the oxyaminal aminium radical cation **8** as well as the common key intermediate **5**. The radical cation **8** just showed 10.19 kcal/mol above **8-c**. Finally, generation of product **2** showed 0.38 kcal/mol above the starting complex **1**. In **Fig. 5-c**, iodo radical accepted $1e^-$ from the substrate **1** to produce the aminium radical cation **3** with 5.11 kcal/mol above

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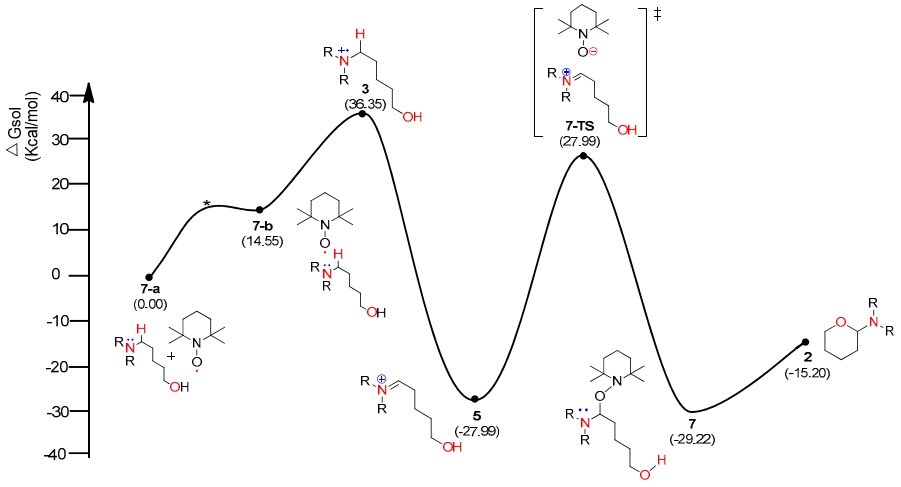
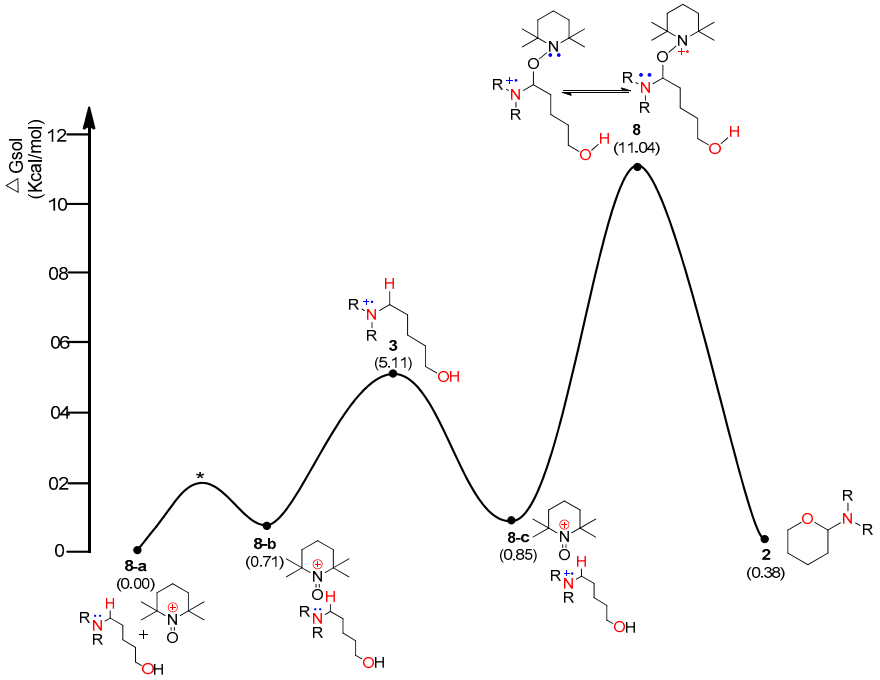
the complex **9-a.** After gaining the iminium intermediate **5**, the product **2** can be acquired through the more stable oxyaminal intermediate **7** than the iminium **5**. In **Fig. 5-d**, TEMPO-I initiated the reaction through ET and the aminium radical cation **3** can be produced with the increase of 5.11 kcal/mol above the starting complex.

(a)



(b)



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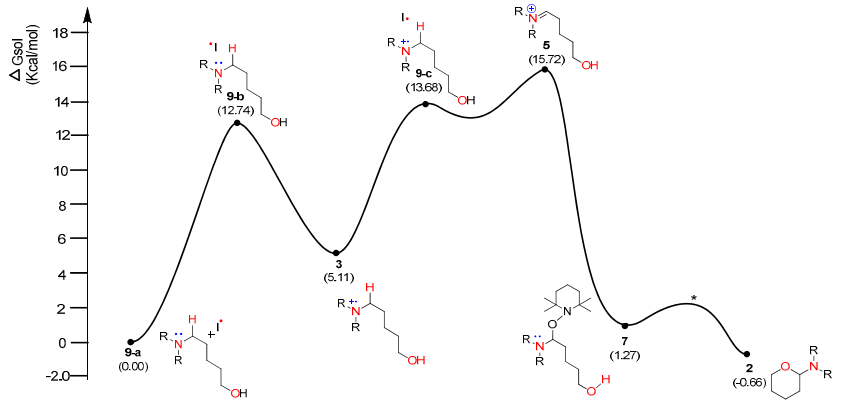
(c)



(d)

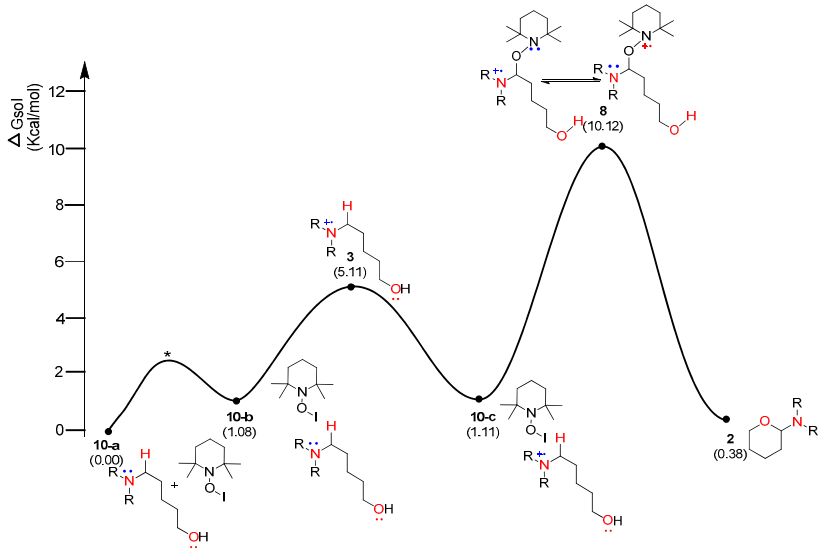


Fig 5. Calculated energy profile diagram for metal-free CDC reaction through the pathway A: (a) the intermediate **3** resulted from TEMPO, (b) the intermediate **3** resulted from TEMPO-C, (c) the intermediate **3** resulted from iodine radical, (d) the intermediate **3** resulted from TEMPO-I; R-group is phenyl; transition state marked by asterisk were not explicitly located.

3.2. Pathway B: α-aminoalkyl radical and HAT mechanism

The energy diagram of the second plausible mechanism was acquired, in which the imini um intermediate **5** is produced from the α-aminoalkyl radical **4** **(Fig. 6)**. In the diagram, the α-aminoalkyl radical **4** is generated through 1,6-H transfer following iodo radical elimination ('I-O' bond homolytic cleavage). TEMPO or iodo radical can be the initiators of the catalytic c ycle. In Fig. 6, an iodo radical makes the catalytic mechanism begin through HAT (hydrogen atom transfer) from the hydroxyl group in the substrate **1**. The O-radical **11-b** is located 22.34 kcal/mol above the starting complex **11-a**. The mechanism from the O-radical **11-b** into the 5-aminoalkyl hypoiodite **11-c** can be explained by the **11-TS-a** locating 15.52 kcal/mol above the O-radical **2** and 63.83 Kcal/mol below the hypoiodite **11-c**. The **11-TS-a** was similar with μ-o xo-bridged iodo derivatives to show 'I-O' bond length and angle of 'O-I-O' The stable and ne utral hypoiodite **11-c** can lead more stable α-iodo intermediate **11-d**. In the path, we can find that the location of the α-aminoalkyl radical **4** is 17.34 kcal/mol below the O-radical **11-b**. Ev

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en though the solution phase free energy of the α-aminoalkyl radical **4** is close to the free en ergy of **11-TS-b** within a barrier of 1.5 kcal/mol, it is more stable than the O-radical **11-b**. Thr ough the **11-TS-b**, the α-aminoalkyl radical **4** can abstract iodo radical from TEMPO-I generat ed from TEMPO and iodine (**Fig. 3**). After acquiring the α-iodo intermediate **11-d**, the reactio n proceeds via a transition state (*) and then forms the key intermediate **5** at a relative soluti on phase free energy of -68.39 kcal/mol.

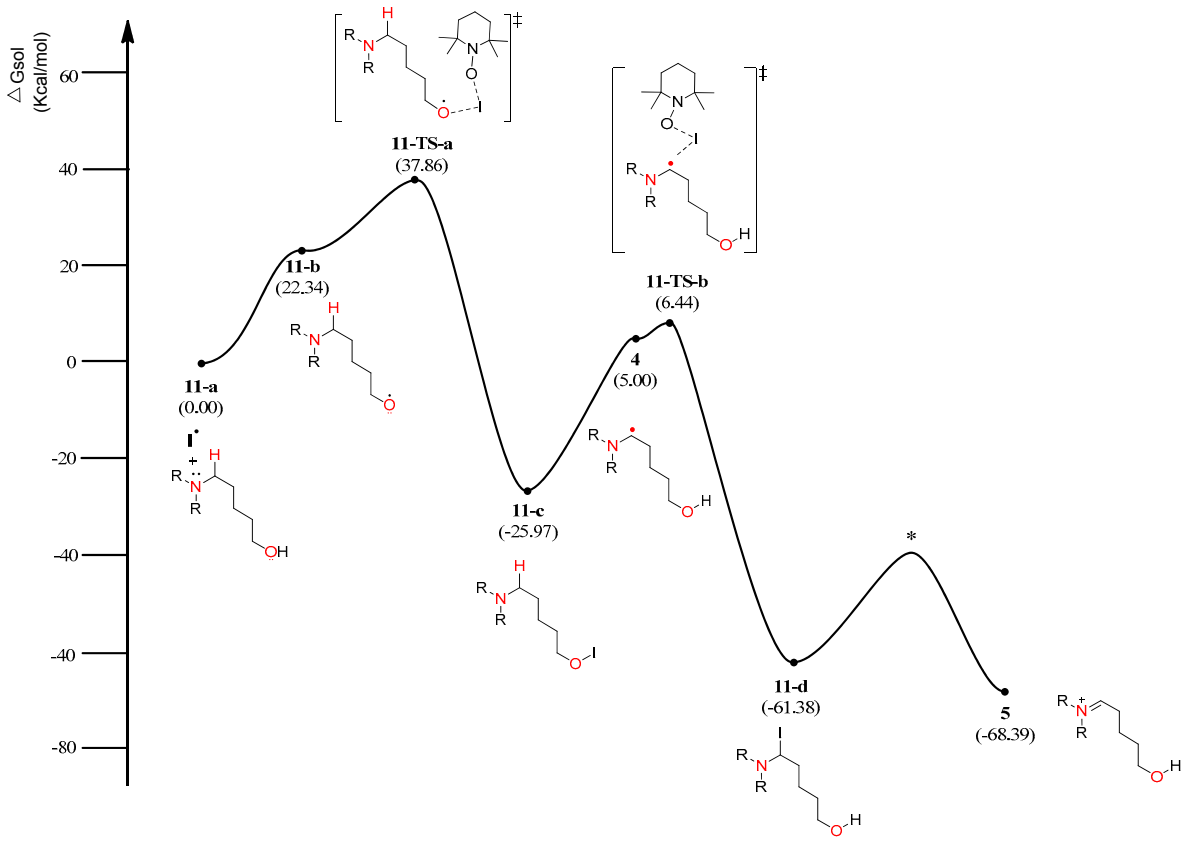

Fig 6. Calculated energy profile diagram for metal-free CDC reaction through the pathway B; R-group is phenyl; transition state marked by asterisk were not explicitly located.

3.3. Pathway C: conventional ionic mechanism

According to our assumed 4 kind routes, the energy diagram of the ionic mechanism was acquired. All catalytic cycles were proposed to be started from TEMPO-C approaching substr ate, amino-alcohol **1**. The each different colors in the **fig 7** means four kind routes having fou r kind initial intermediates after reacting TEMPO-C. The path **C-a** (A), as shown in red color is initiated via approaching of TEMPO-C to yield **2-a** with the free energy of -0.5 kcal/mol via an uncalculated transition state, described with a symbol *. The intra-molecular cyclization of the intermediate **2-a** gives the unstable oxazepanium intermediate **6** having the 'O-O' bond b reakage and the 'N-O' bond formation and the overall barrier for the step is calculated to be 1.7 kcal/mol. And then the oxidative elimination of α-proton can produce the iminium key int ermediate **5** locating 4.58 kcal/mol below the oxazepanium **6**. Finally, intra-molecular cyclizatio n of the resulting intermediate **5** for affording the 2-amino tetrahydropyran **2** was omitted in the calculation. In the path C-b (B), the starting complex **1** generates the intermediate **2-b** thro

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ugh the 'N-O' bond formation between cationic TEMPO and the sunbstrate **1** rather than the 'O-O' bond formation between them in path C-a. The calculated barrier of 2.17 kcal/mol of th e **2-b** showed that the intermediate **2-b** is more favored than the intermediate **2-a**. The barrier energy for the **2-b** due to high stearic hindrance is supposed to present backward reaction of the **2-b** into the complex **1**. Proposed path **C-c** and **C-d** also shows the less stable intermedia te **2-c** and **2-d** than the **2-a** but after the formation of them, the paths proceeds under lower f ree energy level than the path **C-a** or **C-b**. Therefore, it is supposed that the path **C-a** is favo red to form the first intermediate and in the thermodynamic equilibrium, existing ratio of **2-a** is largest among four intermediates (**2-a**, **2-b**, **2-c**, and **2-d**) but forward reaction into the imini um key intermediate **5** favor the path **C-c**.

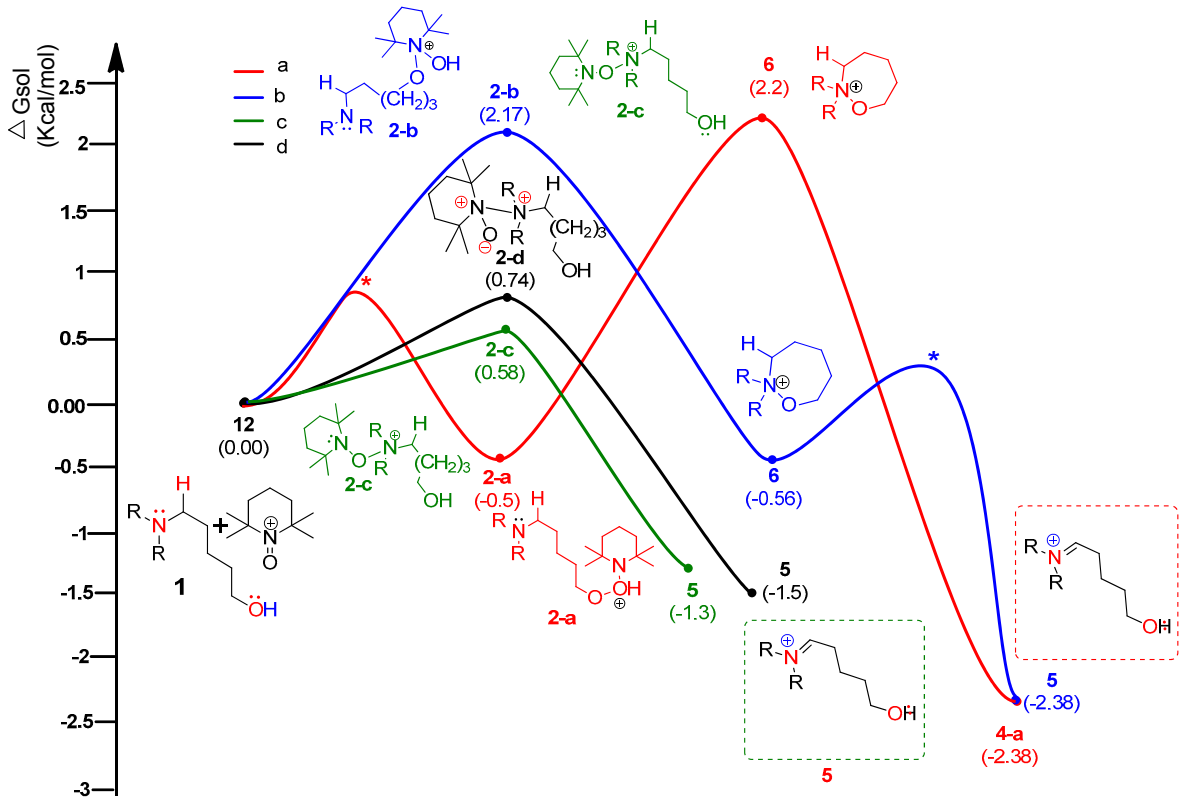

Fig 7. Calculated energy profile diagram for metal-free CDC reaction through the pathway **C** (ionic mechanism); R-group is phenyl; transition state marked by asterisk were not explicitly located.

3.4. Combined analysis of the mechanistic study

From the four kind path A, we can propose that the iminium intermediate **5** can be converted to slightly the more stable oxyaminal intermediate **7** resulting from the addition of TEMPO to the iminium **5**. Among four kind reactive species (TEMPO, TEMPO-C, TEMPO-I and iodo radical), despite comparative high energy transition state, TEMPO initiated cyclization shows the largest free energy gap between the starting complex and the product **2**. The result following commonly proposed plausible routes is neither surprising nor unexpected. The TEMPO initiated mechanism was described in **fig. 8** (left side). In the mechanism, two TEMPO produced two TEMPO-H after the dehydrogenative coupling and TEMPO radical can be regenerated under the BDFE from TEMPO-H into TEMPO. In the case of path B, similar to the modified Suárez hypoiodite oxidation, 1,6-H transfer in 5-aminoalkyl hypoiodite **11-c** can afford the α-aminoalkyl radical **4** with the increase of ca. 30 kcal/mol. [29] Although examples for the formation of aminoalkyl radicals by HAT are limited in photoredox catalysis,[30] the stabilizing effect by the *N*,*N*-diarylamino group prompted us to propose

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the formation of the α-aminoalkyl radical **4** and the sequenced formation of the α-iodo intermediate **11-d** showed -61.38 kcal/mol below the starting complex to support the possibility of the pathway. The overall concrete pathway can be described in **fig. 8** (right side). In addition, when TEMPO was replaced with a stable aminium radical cation (TBPA; tris-4-bromophenyl ammonium hexachloroantimonate) a reported initiator of the α-aminoalkyl radical, the corresponding cyclization product was observed in our synthetic experiment. [9] When considering three key intermediates (the aminium radical cation **3**, the α-aminoalkyl radical **4**, and the iminium **5**), the cation **3** was more stable than our expectation due to hyper-conjugation of substituted aromatic rings and free energy of the iminium **5** can explain why we didn't observe the intermediate at all. When comparing three paths, it seems that ionic pathway (path C) is more favored in the view of free energy of TS but can't exclude the possibility of two single electronic oxidations. In particular, the free energy gap between a starting complex and the key intermediate iminium **5** was the largest in the path **B**.

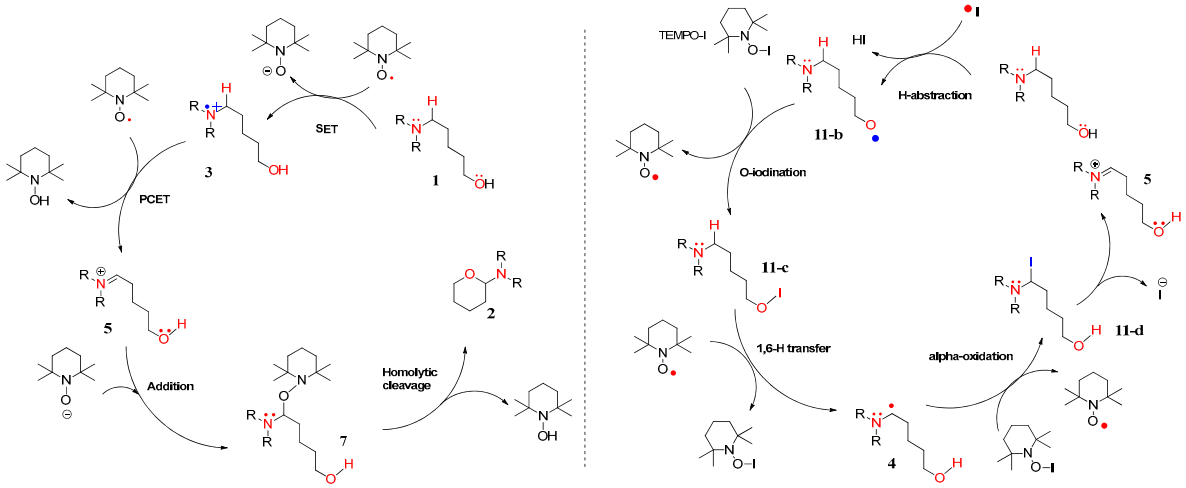

Fig 8. The plausible non-ionic mechanisms for metal-free CDC reaction of the compound **1**: pathway A & B

Conclusions

In summary, TEMPO/I_2 mediated oxidative cyclization of 1,5-amino alcohol **1** as a metal-free CDC reaction was described with DFT calculated energy diagrams. As general expectations, TEMPO showed more favored rather than TEMPO-I or iodo radical in SET/PCET pathway. With the evidence of our catalytic radical reaction, iodo radical initiated HAT pathway showed larger free energy gap between the starting complex and the iminium intermediate **5**. The free energy of TS was the lowest in ionic pathway. In the future, we hope to develop our metal-free CDC methodology to other substrates based on our understanding acquired this study.

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Author Contributions: M.K. opened her research project and prepared funding source; as a part of the project, M.K. proposed the idea; M.K. and Z.U. conceived and designed the experiments; Z.U. performed the experiments; M.K. and Z.U. analyzed the data; M.K. and Z.U. wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

CDC: Cross-dehydrogenative coupling
PCET: Proton-coupled electron transfer
SET: Single electron transfer
HAT: Hydrogen atom transfer
GEA: Electron attachment free energy
SCF: Self-consistent field
ZPE: Zero point energy
BDFE: Homolytic bond dissociation free energy

References

1. Narayan, R.; Matcha, K.; Antonchick, A. P. Metal-Free Oxidative C-C Bond Formation through C-H Bond Functionalization. *Chem-Eur J* **2015**, *21*, 14678-14693.
2. Samanta, R.; Matcha, K.; Antonchick, A. P. Metal-Free Oxidative Carbon-Heteroatom Bond Formation Through C-H Bond Functionalization. *Eur J Org Chem* **2013**, *2013*, 5769-5804.
3. Yoshimura, A.; Zhdankin, V. V. Advances in Synthetic Applications of Hypervalent Iodine Compounds. *Chem Rev* **2016**, *116*, 3328-3435.
4. Nicolaou, K. C.; Mathison, C. J.; Montagnon, T. *o*-Iodoxybenzoic acid (IBX) as a viable reagent in the manipulation of nitrogen- and sulfur-containing substrates: scope, generality, and mechanism of IBX-mediated amine oxidations and dithiane deprotections. *J Am Chem Soc* **2004**, *126*, 5192-5201.
5. Funes-Ardoiz, I.; Sameera, W. M.; Romero, R. M.; Martinez, C.; Souto, J. A.; Sampedro, D.; Muniz, K.; Maseras, F. DFT Rationalization of the Diverse Outcomes of the Iodine(III)-Mediated Oxidative Amination of Alkenes. *Chemistry* **2016**, *22*, 7545-7553.
6. Zhang, N.; Cheng, R.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. Hypervalent iodine-mediated oxygenation of N,N-diaryl tertiary amines: intramolecular functionalization of sp3 C-H bonds adjacent to nitrogen. *J Org Chem* **2014**, *79*, 10581-10587.
7. Tang, S.; Liu, K.; Long, Y.; Gao, X.; Gao, M.; Lei, A. Iodine-catalyzed radical oxidative annulation for the construction of dihydrofurans and indolizines. *Org Lett* **2015**, *17*, 2404-2407.
8. Matsumoto, S.; Shibata, H.; Akazome, M. alpha-Diketone formation accompanied by oxidation of sulfur functional group by the reaction of o-alkynylarenesulfoxide with iodine. *J Org Chem* **2013**, *78*, 1650-1654.
9. Afzal, S.; Venkanna, A.; Park, H. G.; Kim, M. H. Metal-Free α-C(sp^3))-H Functionalized Oxidative Cyclization of Tertiary *N*,*N*-Diarylamino Alcohols: Construction of *N*,*N*-Diarylaminotetrahydropyran Scaffolds. *Asian J Org* Chem **2016**, 5, 232-239.
10. Nijhuis, W. H. N.; Verboom, W.; Abu El-Fadl, A.; Van Hummel, G. J.; Reinhoudt, D. N. Stereochemical aspects of the "tert-amino effect". 2. Enantio- and diastereoselectivity in the synthesis of quinolines, pyrrolo[1,2-a]quinolines, and [1,4]oxazino[4,3-a]quinolines. *J Org Chem* **1989**, *54*, 209-216.
11. Haidasz, E. A.; Meng, D.; Amorati, R.; Baschieri, A.; Ingold, K. U.; Valgimigli, L.; Pratt, D. A. Acid Is Key to the Radical-Trapping Antioxidant Activity of Nitroxides. *J Am Chem Soc* **2016**, *138*, 5290-5298.
12. Wang, T.; Jiao, N. TEMPO-catalyzed aerobic oxygenation and nitrogenation of olefins via C horizontal lineC double-bond cleavage. *J Am Chem Soc* **2013**, *135*, 11692-11695.
13. Bogart, J. A.; Lee, H. B.; Boreen, M. A.; Jun, M.; Schelter, E. J. Fine-tuning the oxidative ability of persistent radicals: electrochemical and computational studies of substituted 2-pyridylhydroxylamines. *J Org Chem* **2013**, *78*, 6344-6349.
14. Yan, H.; Rong, G.; Liu, D.; Zheng, Y.; Chen, J.; Mao, J. Stereoselective intermolecular nitroaminoxylation of terminal aromatic alkynes: trapping alkenyl radicals by TEMPO. *Org Lett* **2014**, *16*, 6306-6309.
15. Shibuya, M.; Osada, Y.; Sasano, Y.; Tomizawa, M.; Iwabuchi, Y. Highly efficient, organocatalytic aerobic alcohol oxidation. *J Am Chem Soc* **2011**, *133*, 6497-6500.
16. Parr, R. G.; Yang, W. Density Functional Theory of Atoms and Molecules; Oxford University Press: New York, **1989**
17. Jaguar, version 8.1 Schrödinger, LLC, New York, NY, **2013**.
18. Slater, J. C. Quantum Theory of Molecules and Solids, Vol. 4: The Self-Consistent Field for Molecules and Solids; McGraw-Hill: New York, **1974**.

19. Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, 58, 1200.
20. Becke, A. D. *Phys. Rev. A* **1988**, 38, 3098.
21. Becke, A. D. *J. Chem. Phys.* **1993**, 98, 5648.
22. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, 37, 785.
23. Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, 90, 1007.
24. Marten, B.; Kim, K.; Cortis, C.; Friesner, R. A.; Murphy, R. B.; Ringnalda, M. N.; Sitkoff, D.; Honig, B. *J. Phys. Chem.* **1996**, 100, 11775.
25. Friedrichs, M.; Zhou, R.; Edinger, S. R.; Friesner, R. A. *J. Phys. Chem. B* **1999**, 103, 3057.
26. Edinger, S. R.; Cortis, C.; Shenkin, P. S.; Friesner, R. A. *J. Phys. Chem. B* **1997**, 101, 1190.
27. Warren, J. J.; Tronic, T. A.; Mayer, J. M., Thermochemistry of proton-coupled electron transfer reagents and its implications. *Chem. Rev.* **2010**, 110, 12, 6961-7001]
28. Haidasz, E. A.; Shah, R.; Pratt, D. A. The catalytic mechanism of diarylamine radical-trapping antioxidants. *J Am Chem Soc* **2014**, 136, 16643-16650.
29. Lee, S.; Fuchs, P. L. An efficient C-H oxidation protocol for alpha-hydroxylation of cyclic steroidal ethers. *Org. Lett.* **2004**, 6, 1437-1440.
30. Miyake, Y.; Nakajima, K.; Nishibayashi, Y. Visible-Light-Mediated Utilization of alpha-Aminoalkyl Radicals: Addition to Electron-Deficient Alkenes Using Photoredox Catalysts. *J Am Chem Soc* **2012**, *134*, 3338-3341.