Triaryl Carbonium Ion-Pair Mediated Cooperative Aerobic Dehydrogenation of *N*-Heterocycles

Zhenguo Zhang[a,b,c], Jun Gu[d], Liang Ji[b], Xiaoxiao Liu[b], Ting Zhang[b], Yongheng Lv[b], Fang Liu[d]*, Zhenhua Jia[a,b,c]*, Teck-Peng Loh[a,b,c]*

[a]College of Advanced Interdisciplinary Science and Technology, Henan University of Technology, Zhengzhou, 450001, China.

[b]Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Jiangsu National Synergetic Innovation Center for Advanced Materials, Nanjing Tech University, Nanjing, 211816, China.

[c]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore.

[d]College of Sciences, Nanjing Agricultural University, Nanjing, 210095, China.

*E-mail: iaszhjia@njtech.edu.cn; Email: acialiu@njau.edu.cn; E-mail: teckpeng@ntu.edu.sg

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ABSTRACT: Triphenylmethyl radical was discovered by Moses Gomberg in 1900 and has been shown as a persistent radical species. Surprisingly, this radical is rarely used in organic synthesis since its discovery over a century ago. Here, we report a metal-free aerobic dehydrogenation of *N*-heterocycles mediated by triphenylmethyl radical generated from triaryl carbonium ion-pair as the pre-catalyst in the presence of TEMPO. This protocol exhibits broad substrate scope and excellent functional group tolerance. The practicability has also been demonstrated with gram-scale preparation of key intermediates of small molecule drugs and late-stage functionalization of various dipine drugs. Mechanistic studies and DFT calculation revealed that triphenylmethyl radical was involved in the catalytic cycle and was essential for the aerobic dehydrogenation process.

Triphenylmethyl radical (trityl radical), was discovered by Moses Gomberg in 1900 during the preparation of hexaphenylethane from the reaction of triphenylmethyl chloride with a metal, like silver or zinc in benzene or diethyl ether *via* Wurtz reaction.[1-3] This serendipity was then confirmed as a novel species after trapping with iodine or oxygen molecule and shown to be more reactive than expected.[4-7] Subsequently, with the development of electron spin resonance (ESR) technology, the structure of trityl radical was finally determined.[8,9] Despite this discovery and in contrast to trityl carbocation,[10-15] trityl radical has not attracted much attention in organic synthesis. More recently, Gabbaï *et al.* described the reduction of O_2 into H_2O_2 with a bifunctional carbenium dications as the catalyst under metal-free conditions.[16] As far as we know, there is still very rare report on the application of trityl radical in organic synthesis (Fig. 1A).

Oxidases are powerful enzymes that play crucial roles in our biological system by helping to maintain the fundamental metabolism. They participate in the oxidation-reduction reaction using O_2 as the terminal electron acceptor with the formation of water (H_2O) or hydrogen peroxide (H_2O_2) as the by-product.[17-22] Inspired by this enzymatic transformation, numerous catalytic systems have been developed to mimic this aerobic oxidation process. Various transition metals, such as Pd, Ru, Ir, Cu, Fe, Co, Ni and Zn *etc.*, have been successfully utilized for the aerobic oxidation of organic molecules.[23-37] The catalytic models could be summarized into three general categories, including single-electron redox, two-electron oxidation and four-electron oxidation to produce water as the sole by-product (Fig. 1B).[27] However, the involvement of transition metals inevitably produced chemical wastes and potentially introducing toxic contaminants into the target products.

Aromatic *N*-heterocycles are prevalent in natural products and bioactive molecules and are attrctive scaffolds in the design of new drugs.[38] An important access to these compounds is the aerobic dehydrogenation of their saturated precursors.[39-41] In connection with our interest in the development of bioinspired reactions, *herein* we explore the use of trityl radical featured as the metal-free catalytic species to mediate this biological process.[42-45]

The catalytic cycle was proposed as shown in Fig. 1C. First, the ion-pair II was generated from trityl tetrakis-(pentafluorophenyl)-borate with TEMPO *via* a single-electron transfer process, affording trityl radical, which could trap O_2 molecule efficiently to form the triphenyl-methyl peroxide.[46] Then, the reactive oxygen-centered radical was generated *in-situ via* the homolysis process,

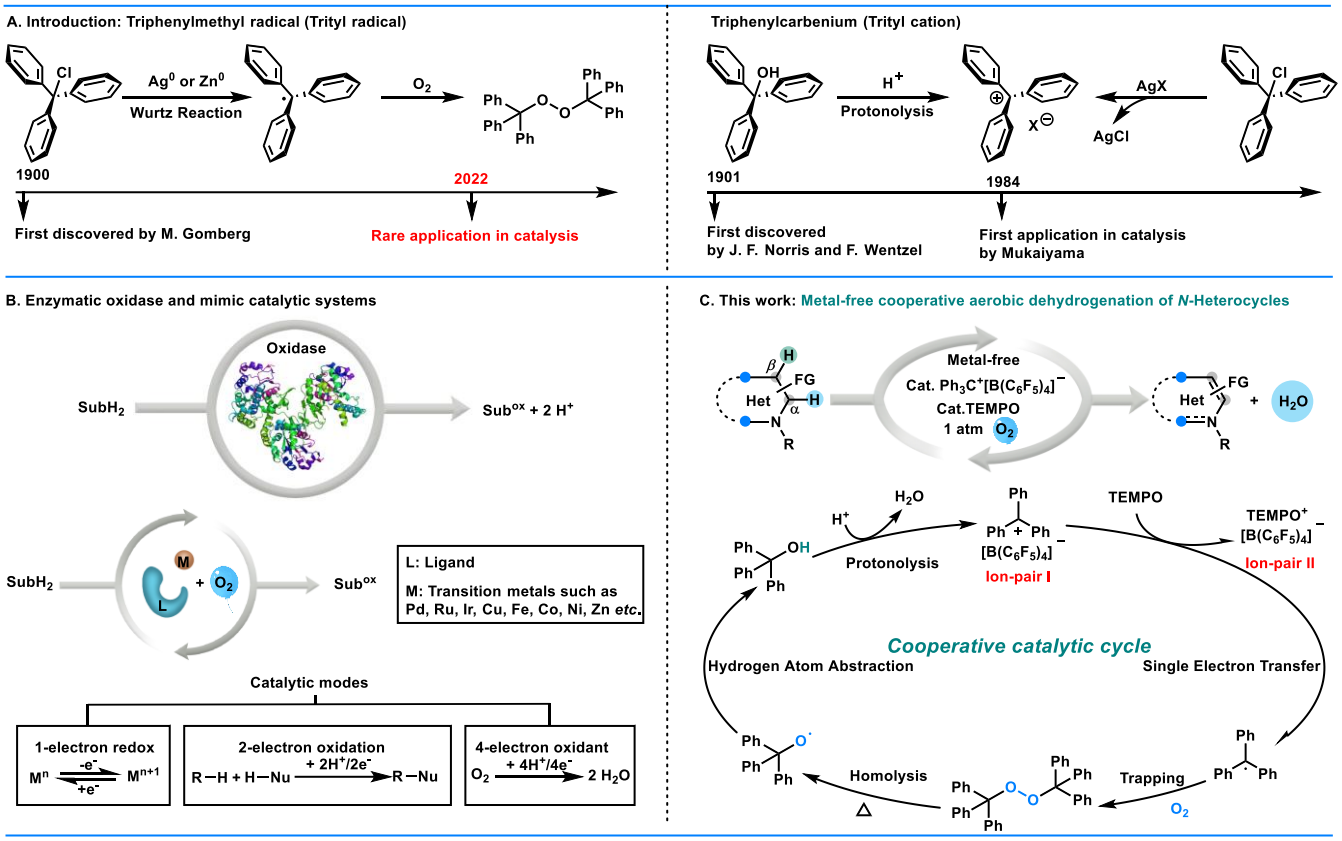
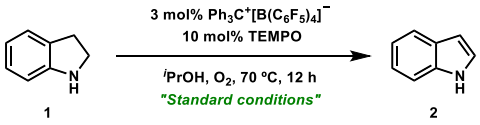


Figure 1. Aerobic dehydrogenation. (A) The introduction of triphenyl carbocation and triphenylmethyl radical. (B) Enzymatic oxidase and mimic catalytic systems. (C) Metal-free cooperative aerobic dehydrogenation of *N*-heterocycles.

Table 1. Selected Optimization of Reaction Conditions[a]



Entry	Change from the 'standard conditions'	Yield of 2 (%)
1	none	99 (94[b])
2	without $Ph_3C^+[B(C_6F_5)_4]^-$	21
3	without TEMPO	13
4	$K^+[B(C_6F_5)_4]^-$ instead of $Ph_3C^+[B(C_6F_5)_4]^-$	9
5	air instead of O_2	31
6	in Argon	5
7	60 °C instead of 70 °C	80
8	11 h instead of 12 h	93

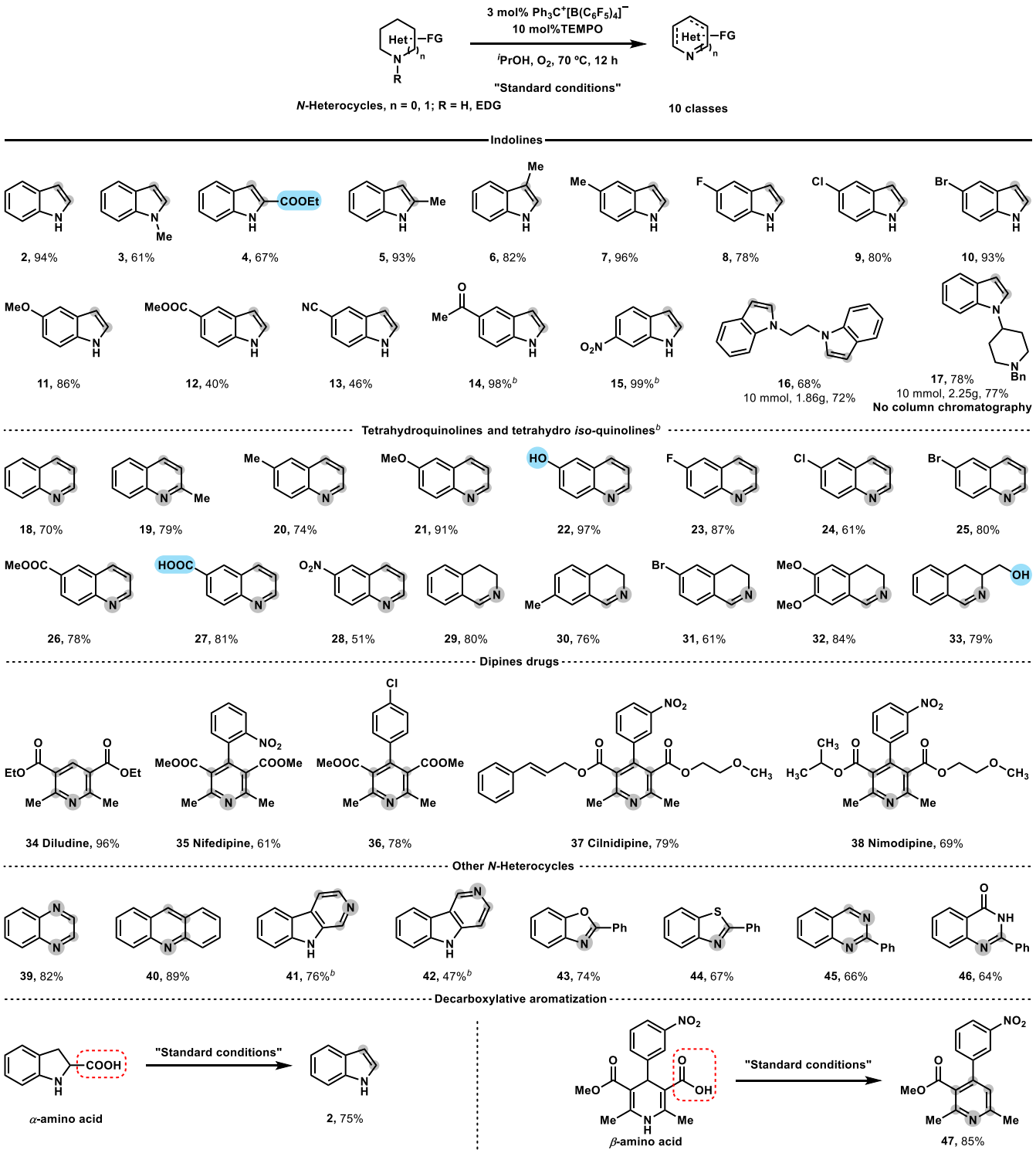
[a]Reactions performed at 0.2 mmol of **1**. Yield is based on **1** and was determined by ^1H NMR analysis by using CH_3NO_2 as an internal standard. [b]Isolated yield.

which could abstract hydrogen atom from the substrate to afford the triphenylmethanol.[4,5,47] Finally, the catalyst was regenerated from triphenylmethanol by protonolysis with the formation of H_2O as the by-product.

Inspired by the recent advances in aerobic dehydrogenation reaction, we started our study with indoline as the model substrate using trityl tetrakis-(pentafluorophenyl)-borate ($[Ph_3C]^+[B(C_6F_5)_4]^-$) as the catalyst and tetramethylpiperidine *N*-Oxyl (TEMPO) as the co-catalyst to optimize the metal-free aerobic oxidative reactions (See supporting information for details). After extensive investigations, we found that the desired indole product **2** could be obtained in 99% yield, when the reaction was carried out using 3 mol% $[Ph_3C]^+[B(C_6F_5)_4]^-$ together with 10 mol% TEMPO in ^{i}PrOH at 70 °C under O_2 atmosphere (Table 1, entry 1). Control experiments indicated that the combination of ion-pair with TEMPO was essential for the aerobic dehydrogenation reaction. In the absence of $[Ph_3C]^+[B(C_6F_5)_4]^-$, the efficiency of the reaction decreased substantially, yielding **2** in 21% yield, whereas the desired product was obtained in only 13% yield without the use of TEMPO (Table 1, entries 2-3). It was worth noting that only 9% of **2** was detected when potassium pentafluorophenyl-borate was used to replace the triphenyl carbocation catalyst (Table 1, entry 4). When the reaction was conducted in air, the target product **2** was also obtained in 31 % yield (Table 1, entry 5).

However, only 5% yield of **2** was obtained under argon atmosphere (Table 1, entry 6), indicating that oxygen molecule was necessary for the successful transformation. When the temperature was adjusted to 60 °C, **2** was obtained in 80% yield (Table 1, entry 7). When the reaction time was shorten to 11 h, the yield of **2** increased to 93% (Table 1, entry 8). Other parameters were also screened and the results

Scheme 1. Scope of *N*-heterocycles[a]



[a]Reaction conditions: Substrates (0.2 mmol), $Ph_3C^+[B(C_6F_5)_4]^-$ (3 mol%), TEMPO (10 mol%), ^{i}PrOH (1 mL), 70 °C, 1 atm O_2, 12 h. All yields are isolated yields. [b]5 mol% $Ph_3C^+[B(C_6F_5)_4]^-$ was used at 90 °C.

were summarized in the supporting information (Table S1-S8).

As illustrated in Scheme 1, diverse classes of *N*-Heterocycles were examined under this metal-free conditions (**2**-**46**). A broad range of indolines were found to work well under the standard conditions to generate the corresponding indole products in good to excellent yields (**2**-**17**). *N*-methyl indoline was also suitable in our protocol to afford the *N*-methyl indole in 61% yield (**3**). The ester group at *α* position of Nitrogen atom was well tolerated and remained intact after the reaction (**4**). Moreover, when indolines containing

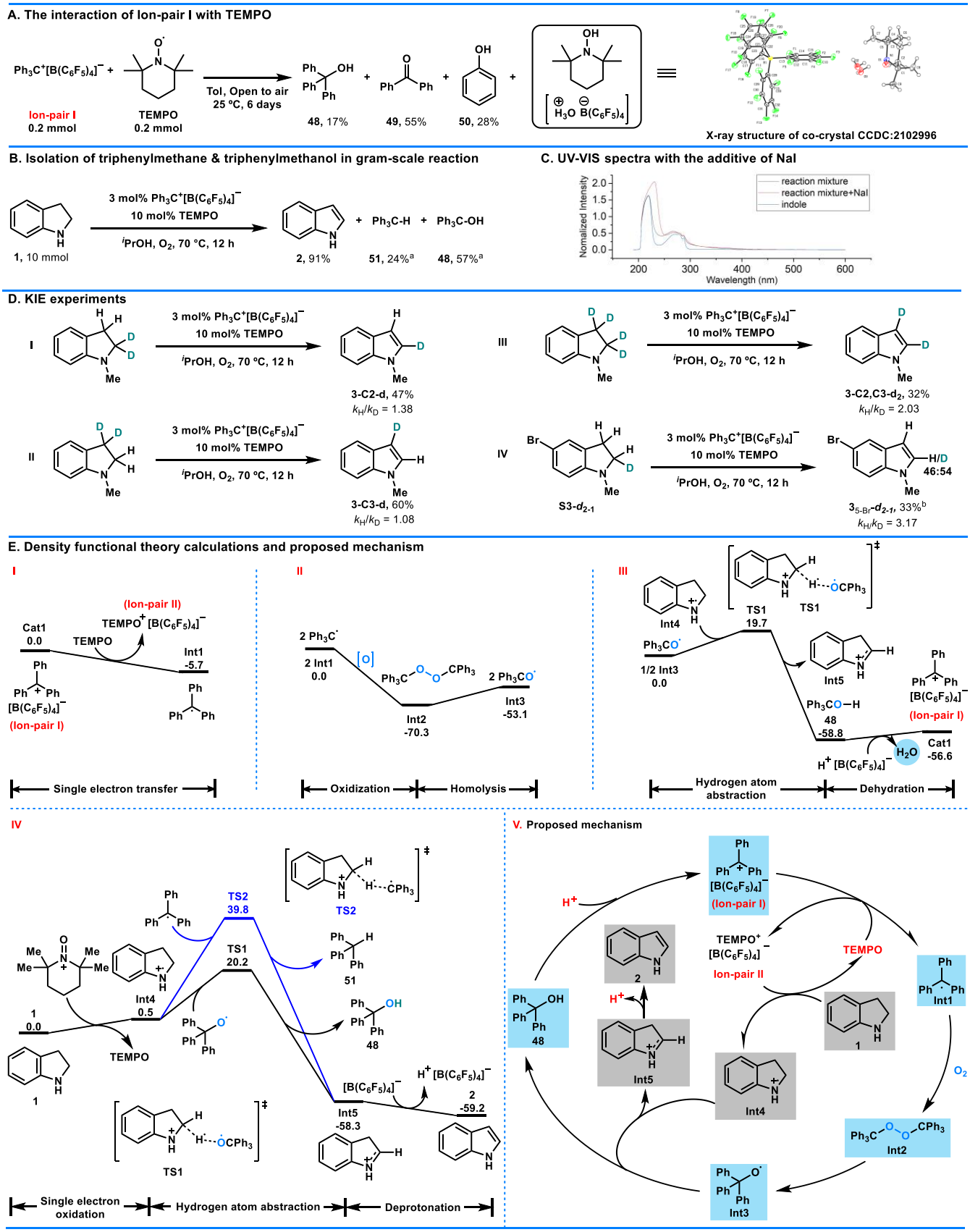


Figure 2. Mechanistic studies. (A) The interaction of Ion-pair I with TEMPO. (B) Isolation of triphenylmethane and triphenylmethanol in gram-scale model reaction. (C) UV-Vis spectra with the additive of NaI. (D) KIE experiments and Kinetic analysis of model reaction. (E) The Gibbs free energy (in kcal/mol) profiles of trityl radical-mediated aerobic dehydrogenation and proposed mechanism. [a]Isolated yield was calculated based on the amount of $Ph_3C^+[B(C_6F_5)_4]^-$. [b]Isolated yield was given.

methyl substituent at diverse positions were subjected to the current protocol, the desired products were obtained in good yields (61-96% yields) (**5**-**7**). Halogen groups, such as fluoride (**8**), chloride (**9**) and bromide (**10**) were also tolerated, which would provide handles for further manipulation of the indole products. Methoxyl group (**11**) as an electron donating group, substituted with indoline at C5 position was also applicable in this reaction, whereas the electron withdrawing groups, for instance ester (**12**), cyano (**13**) and acetyl group (**14**), decreased the yields under the standard conditions. To our surprise, the nitro group substituted indoline at C6 position could be introduced into the indole product in 99% yield (**15**). Furthermore, we showcased the synthetic utility of this method by applying it to the synthesis of key intermediates of drugs. The product **16** was obtained in 68% yield, which was further transformed into CDK4/cyclin D1 inhibitor, avoiding the use of excess MnO_2 as the terminal oxidant in reported procedure.[48] When the reaction was scaled up to 10 mmol, 1.86-gram desired product **16** could be obtained in 72% yield. Enzastaurin and its analogs, exhibiting various bio-activities, could be synthesized in 6 steps from the key intermediate **17**, which was produced in 78% yield *via* our metal-free protocol.[49,50] In addition, the gram scale synthesis of **17** was also realized by direct recrystallization without column chromatography. Subsequently, the scope of tetrahydroquinolines was explored systematically under slightly modified conditions and the corresponding quinolones bearing diverse functional groups were isolated in 51-97% yields (**18**-**28**). In particular, the unprotected hydroxyl group of phenol (**22**) and the carboxylic acid group (**27**) were found to be compatible with the oxidation conditions. When various tetrahydro-*iso*-quinolines were subjected to the optimal conditions, dihydro-*iso*-quinolines were generated in 61-84% yields with the loss of one molecule of H_2 (**29**-**33**). In addition, the hydroxyl moiety at the adjacent position of nitrogen atom was retentive in the dihydro-*iso*-quinoline product (**33**). Next, dipine compounds, a class of well-known prodrugs for the clinical treatments, were applied for the synthesis of corresponding pyridine derivatives *via* metal-free aerobic dehydrogenation, which are always treated as crucial impurities for the analysis of the drugs on the market. For instance, diludine (**34**), nifedipine (**35**) and its derivatives (**36**), cilnidipine (**37**) nimodipine (**38**) were successfully transformed into the pyridine products in 61-96% yields without any metal contaminant.

Considering that the aromatic *N*-heterocycles are ubiquitous in pharmaceutical compounds, we next demonstrated the generality of our protocol with one-pot synthesis of functional molecules. Quinoxaline, acridine, *β*-carbolines, *γ*-carbolines, benzoxazole, benzothiazole, quinazoline and quinazolone were obtained in 47-89% yields from their precursors under mild and sustainable conditions (**39**-**46**). Notably, our strategy was also suitable for the decarboxylation of *α*-amino acid and *β*-amino acid to access the aromatic indole and pyridine products respectively (**2**, **47**).

As shown in Table 1, the cooperative catalysis was necessary for the efficient aerobic dehydrogenation. To further elucidate the possible mechanism, we mixed the stoichiometric $[Ph_3C]^+[B(C_6F_5)_4]^-$ with TEMPO in toluene open to air at 25 ºC. Excitingly, a co-crystalline was obtained in 6 days, which was provided one key evidence for the involvement of cooperative catalytic process. Moreover, we carefully purified the crude residue and found that triphenylmethanol (**48**), benzophenone (**49**), and phenol (**50**) were obtained in 17%, 55%, and 28% respectively, which most probably resulted from the decomposition of the triphenylmethyl peroxide (Fig. 2A).[51] When the model reaction was scaled up to 10 mmol, the desired product **2** was isolated in 91% yield. Simultaneously, the triphenylmethane (**51**) and triphenylmethanol (**48**) were obtained in 24% yield and 57% yield respectively, calculated based on the amount of Ion-pair (Fig. 2B).

To identify the possible formation of hydrogen peroxide, we also compared UV-vis absorption spectra of the samples, including the indole product (blue), the crude sample of the model reaction (black) and the mixture of reaction sample with NaI as the additive (red). As shown in Fig. 2C, there's no obvious absorption peak of triiodide anion at 361 nm before and after the reaction, which indicated that H_2O_2 was not likely generated during this aerobic dehydrogenation process.[16]

A series of kinetic isotope effect (KIE) experiments was conducted independently to compare the rates of dehydrogenation with **3a**, **3a-C2-*d*$_2$**, **3a-C3-*d*$_2$**, and **3a-*d*$_4$** (Fig. 2D). The results revealed that a significant KIE was observed at C2 position of *N*-methyl indoline (KIE = 1.38, Fig. 2D-I), but no obvious KIE (KIE = 1.08, Fig. 2D-II) at the C3 position. In addition, when **3a-*d*$_4$** was treated to measure the KIE, the value was obtained as 2.03 (Fig. 2D-III). The intramolecular competition deuterium KIE was 3.17, observing at C2 position by the isolation of $\mathbf{3}_{\mathbf{5\text{-}Br}}$**-*d*$_{2\text{-}1}$** in 33% yield (Fig. 2D-IV). The kinetic analysis of the model reaction also suggested that a hydride transfer process was excluded (Fig. S7), which could be also rationalized by a single-electron transfer pathway.[25] Furthermore, the radical scavenging experiment was also performed by adding AIBN under standard conditions, the model reaction was inhibited as expected (see Supporting Information for details).

Density functional theory (DFT) calculations were carried out (for detailed information, see the Supporting Information) to investigate the mechanism of trityl radical-mediated aerobic dehydrogenation at the level of (U)M062x/6-311+G(d,p)/SMD-(2-Propanol)// (U)ωb97xd /6-31g(d).[52-54] As shown in Fig. 2E-I, a single electron transfer process was illustrated between TEMPO and triaryl carbonium (**Cat1**) to generate trityl radical (**Int1**) and ion-pair II. In the presence of oxygen molecule, trityl radical could be oxidized to form the peroxide **Int2**, which led to the triphenylmethoxyl radical species **Int3** *via* the homolysis process (Fig. 2E-II).

The possible pathway of triaryl carbonium ion-pair mediated aerobic dehydrogenation process with indoline was shown in Fig. 2E-IV and the probable mechanism was also depicted in Fig. 2E-V. Triaryl carbonium ion-pair I reacted with TEMPO to generate trityl radical (Int1) and TEMPO cation ion-pair II, which oxidized the substrate **1** to regenerate TEMPO and the corresponding intermediate **Int4**.[55] Hydrogen atom abstraction at the C2 position of **Int4** occurred through **TS1** or **TS2** with the triphenylmethoxyl radical or the trityl radical, respectively. However, the energy barriers of these two different pathways (20.2 kcal/mol *vs*

39.8 kcal/mol) suggested that the hydrogen atom abstraction with trityl radical was unlikely (Fig. 2E-IV). Finally, the deprotonation at the C3 position of **Int5** with $[B(C_6F_5)_4]^-$ was followed to result in the indole product and $H^+[B(C_6F_5)_4]^-$, which was subsequently involved in the regeneration of **Cat1** (Fig. 2E-III).[12-14] The spin density plot of **Int4** was also given in Fig. S9 (with Multiwfn software package),[56] confirming the radical character of **Int4** from single electron transfer process.

In summary, we have demonstrated that trityl radical generated *in-situ* from the corresponding triaryl carbonium ion-pair, which could mediate the aerobic dehydrogenation of various *N*-heterocycles efficiently under metal-free conditions. This method represents a novel approach to generate trityl radical with TEMPO *via* a single-electron transfer process. We anticipate that this unprecedented strategy relying on the overlooked trityl radical in organic synthesis could have broad applications despite its discovery over a century ago.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge at

Detailed experimental procedures and characterization data for all isolated compounds

AUTHOR INFORMATION

Corresponding Author

Zhenhua Jia - College of Advanced Interdisciplinary Science and Technology, Henan University of Technology, Zhengzhou, 450001, China; Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering Nanjing Tech University, 30 South Puzhu Road, Nanjing, 211816, China; Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore; orcid.org/ 0000-0002-5154-4839; E-mail: iaszhjia@njtech.edu.cn

Fang Liu - College of Sciences, Nanjing Agricultural University, Nanjing, 210095, China; orcid.org/0000-0002-0046-8434; E-mail: acialiu@njau.edu.cn

Teck-Peng Loh – College of Advanced Interdisciplinary Science and Technology, Henan University of Technology, Zhengzhou, 450001, China; Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering Nanjing Tech University, 30 South Puzhu Road, Nanjing, 211816, China; Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore; orcid.org/0000-0002-2936-337X; E-mail: teckpeng@ntu.edu.sg

Authors

Zhenguo Zhang - College of Advanced Interdisciplinary Science and Technology, Henan University of Technology, Zhengzhou, 450001, China; Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing, 211816, China; Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore; orcid.org/ 0000-0001-7872-4947

Jun Gu - College of Sciences, Nanjing Agricultural University, Nanjing, 210095, China

Liang Ji - Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing, 211816, China

Xiaoxiao Liu - Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing, 211816, China

Ting Zhang - Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing, 211816, China

Yongheng Lv - Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing, 211816, China

Complete contact information is available at:

Notes

The authors declare no competing financial interest.

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