Carbenium Catalysis Towards β-Carbolines

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SUMMARY

In this preview, we highlight the recent findings of Liu, Jia, Loh, and co-workers on the synthesis of β-carbolines in good to excellent yields catalyzed by the $[Ph_3C]^+[B(C_6F_5)_4]^-$ ion pair. The aerobic dehydroaromatization mechanism is proposed to proceed via a possible radical mechanism.

β-Carboline alkaloids are an important class of naturally occurring and synthetic heterocyclic amines whose core structure is a pyridine-fused indole framework (pyrido[3,4-*b*]indole) in which the pyridine ring can exist in varying oxidation states leading to unsaturated, dihydro, or tetrahydro systems. β-Carboline alkaloids are widely found in nature in plants, marine organisms, insects, and mammals, and possess many important pharmacological and biological activities. Such compounds have been found to have anticancer, antimicrobial, anti-inflammatory, and antiviral activities amongst others.[1,2] The biological importance of these compounds has led to widespread interest in their synthesis through novel and efficient routes. The laboratory synthesis of β-carbolines is well-reported.[3] Commonly, a stoichiometric oxidant is employed for the oxidative dehydrogenation and aromatization of the pyridine ring in the tetrahydro-β-carboline precursor. Alternatively, a precious metal such as palladium, iridium, or ruthenium can be used. Both of these methods have drawbacks including stoichiometric waste or the use of toxic metals and potential contamination of the target product. The latter is particularly important in the synthesis of pharmaceuticals where the concentration of toxic metals in the end product must be limited to ppm levels. The desire to remove toxic precious metals from catalytic processes has led to interest in the utilisation of 1st-row TM congeners, such as iron-based catalysts for β-carboline synthesis and C–C coupling.[4] Recently there has also been an increased interest in the use of metal-free catalysis as an alternative to the use of transition metals. For example, the field of organocatalysis has grown in popularity over the last few decades and was awarded the Nobel prize in 2021.[5] Carbocations R_3C^+ are good Lewis acids owing to their positive charge and vacant *p*-orbital. In particular, the trityl cation (Ar_3C^+) is one of the most well-known systems owing to its more stable nature arising from the electronic and steric protection of the positive charge by the three aryl rings. Such systems have been used in catalysis to activate substrates for instance in aldol and Diels–Alder reactions.[6] The counter anion (X^-) is also very important in these reactions since ion-pairing effects can influence the solution-state properties and activity of the system. The perfluorophenyl borate anion $[B(C_6F_5)_4]^-$ is a popular choice of counter anion being only weakly coordinating. Recently the trityl tetrakis-(pentafluorophenyl)-borate ($[Ph_3C]^+[B(C_6F_5)_4]^-$) ion pair has been employed in organic synthesis, however its applications in catalysis have been mostly limited to its roles as either an acid catalyst or a counter anion.[7–9]

In a recent publication in *Cell Reports Physical Sciences*, Liu, Jia, Loh and co-workers disclose an elegant metal-free strategy to access β-carbolines using the $[Ph_3C]^+[B(C_6F_5)_4]^-$ ion pair as a catalyst.[10] In this study, β-carbolines were synthesized from the reaction of tryptamines and aromatic aldehydes using an ion-pair as a catalyst (Figure 1A). Interestingly, the $[Ph_3C]^+[B(C_6F_5)_4]^-$ ion pair was found to be superior to other ion pairs including $[Ph_3C]^+[BF_4]^-$, $[Ph_3C]^+[PF_6]^-$, and $K^+[B(C_6F_5)_4]^-$ which all gave negligible yields of the desired β-carboline product. Importantly, the reaction needed to be performed under an O_2 atmosphere with significantly reduced yields being obtained in air, and negligible conversion under argon. To explore the synthetic utility and applicability of the trityl carbenium ion catalysis in β-carboline synthesis, 20 mol% $[Ph_3C]^+[B(C_6F_5)_4]^-$ was tested for β-carboline formation with various aromatic aldehydes and tryptamines. For this reaction, various aromatic aldehydes and tryptamines were tolerated giving 31 different products in 32–89% yield. Of note is the synthesis of the natural product Eudistomin U in one-pot on gram scale in 47% yield (Figure 1A). This methodology was also evaluated for its applicability to the late-stage modification of six small drug molecules and natural products. For example, the benzyl protected Helicid derivative could be reacted with tryptamine under the optimum conditions to give the β-carboline product in 73% yield

(Figure 1A). Further transformations of the resulting β-carboline products from the substrate scope was also demonstrated. The reaction of tryptamine with 4-ethynylbenzaldehyde generated the corresponding β-carboline product in 76% yield on a 0.3 mmol scale, and 46% on an 5 mmol scale. The resulting product could be further transformed by reaction of the alkyne functionality through Sonogashira coupling, click chemistry, the Eglinton reaction, or hydrogenation.

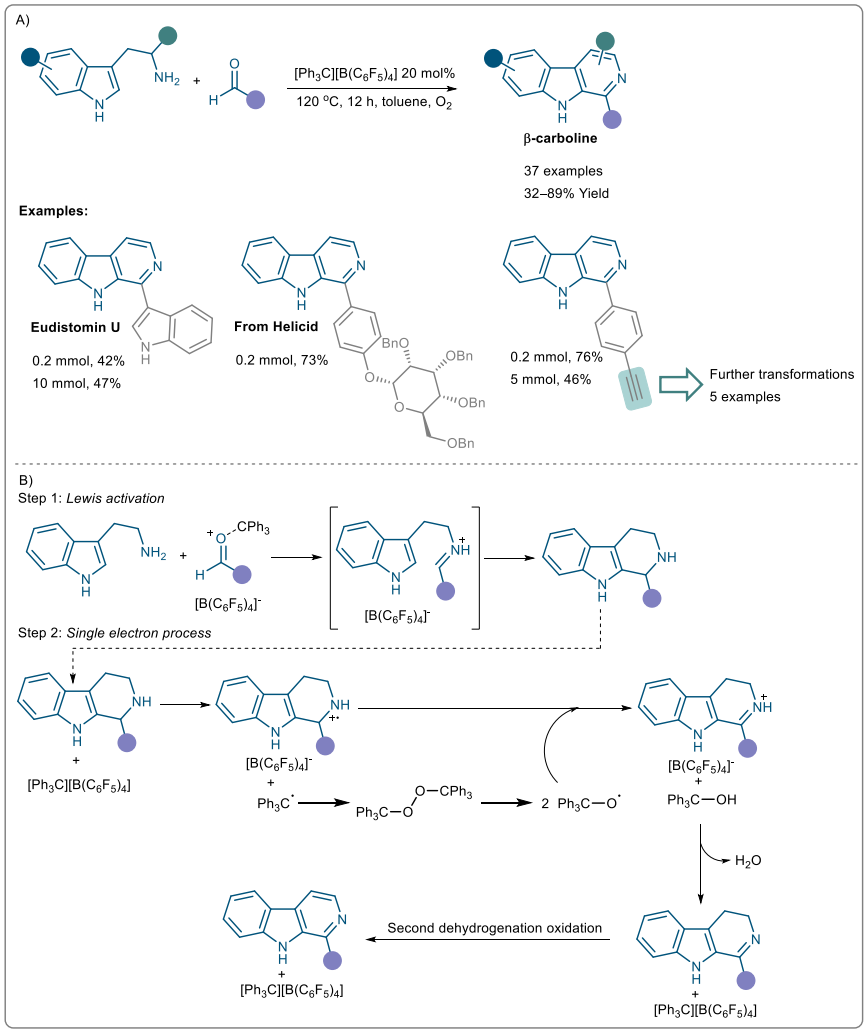

Figure 1. Synthesis of β-Carbolines

(A) Synthesis of β-carbolines and further functionalization; (B) Simplified reaction mechanism.

An understanding of the mechanistic pathway and the role of the ion pair was then undertaken by the authors by detailed DFT and EPR studies. Initially, the tetrahydro-β-carboline is proposed to be formed from the tryptamine and benzaldehyde through the Pictet-Spengler reaction involving condensation of the amine with the aldehyde (activated by the Lewis acidic trityl carbenium) to give an imine followed by ring closure (Figure 1B). Control reactions of both the imine and tetrahydro-β-carboline both lead to the product under the reaction conditions. The tetrahydro-β-carboline is then proposed to lead to the product β-carboline through a radical oxidative dehydroaromatization. Initially a single electron transfer (SET) process between the tetrahydro-β-carboline and trityl carbenium is proposed generating nitrogen radical cation and the trityl radical. The latter can then trap the oxygen radical generating the peroxide $Ph_3C–O–O–CPh_3$ which undergoes homolytic cleavage giving $Ph_3C–O^{\bullet}$. Hydrogen atom abstraction by $Ph_3C–O^{\bullet}$ yields an intermediate iminium and triphenylmethanol. Deprotonation of the iminium and protonolysis of triphenylmethanol yields the intermediate dihydro-β-carboline, and regenerates the trityl carbenium ion. A second dehydrogenation step then leads to the final product (Figure 1B). The role of O_2 was confirmed by the reduced yields in air or under argon, and radical scavenging using AIBN provided evidence for oxygen and carbon based radicals. EPR spectroscopy provided direct evidence for the generation of the trityl cation under O_2 conditions in the presence of the $[Ph_3C]^+[B(C_6F_5)_4]^-$ ion pair, and a second intense signal characterized by triplet hyperfine coupling could potentially be attributed to the nitrogen radical cation (step 2, Figure 1B), although was not explicitly stated by the authors. As the involvement

of radicals and single-electron transfer processes in metal-free, main group chemistry is becoming more prevalent, the utilization of EPR spectroscopy in elucidating mechanistic details of radical-pathways should be strongly considered by researchers working in these fields.

In summary, Liu, Jia, Loh and co-workers have demonstrated an efficient metal-free procedure for the synthesis of a range of biologically important β-carboline products using catalytic amounts of the $[Ph_3C]^+[B(C_6F_5)_4]^-$ ion pair. A wide range of β-carbolines were afforded in good to excellent yields which could be synthesized on a gram scale, and which could be further functionalized. Mechanistic studies revealed that the aerobic dehydroaromatization likely proceeds through a single electron transfer process using catalytic $[Ph_3C]^+[B(C_6F_5)_4]^-$. This exciting result further demonstrates the use of metal-free catalysts in the synthesis of synthetically relevant compounds and adds to the increasing field of radical reactions in organic synthesis.

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AUTHOR CONTRIBUTIONS

E.R. and R.L.M. jointly wrote and edited the article.

DECLARATION OF INTERESTS

The authors declare no competing financial interests. R.L.M. is a member of the journal's advisory board.

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