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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801184

Link to VoR: http://dx.doi.org/10.1002/adsc.201801184

10.1002/adsc.201801184

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Catalytic Oxidative Coupling Cyclization for Construction of Benzofuroindolenines under Mild Reaction Conditions

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract. We describe iron-catalyzed oxidative coupling cyclization of tetrahydrocarbazoles or THβCs or THγCs to form benzofuroindolenines as fused polycyclic indoles. This mild, efficient and simple approach afforded a library of more than 52 complex compounds across a range of substrate classes with good to excellent yields.

Keywords: catalytic oxidative coupling cyclization; benzofuroindolenines; fused polycyclic indoles; open flask

During the past few decades, oxidative coupling reactions had developed into an essential branch of organic synthesis.[1] Diverse elegant methods extensively complemented the fields of traditional coupling reactions and provided widely applicable approaches for new bond formation.[2] Efficient oxidative coupling protocols for functionalized indoles have been developed by the groups of Harran,[3] Danishefsky,[4] Trost,[5] Nicolaou,[6] Overman,[7] Muniz,[8] MacMillan,[9] Xiao,[10] Lei,[11] Vincent,[12] You,[13] Stephenson,[14] and others.[15] While, the synthetic utility of catalytic oxidative coupling cyclization for construction of complex benzofuroindolenines has not been fully developed.

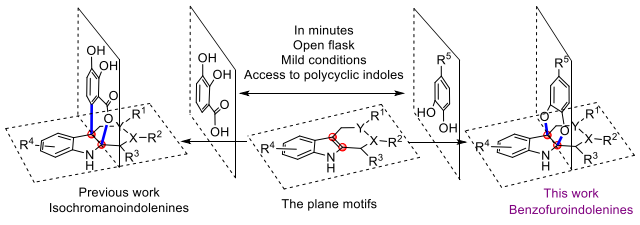

Figure 1. Recent work for the construction of fused polycyclic indoles.

Tetrahydrocarbazoles, tetrahydro-β-carbolines (THβCs) and tetrahydro-γ-carbolines (THγCs) with attractive pharmacological potentials,[16] are common core motifs in natural products and pharmaceuticals.[17] These scaffolds have become an interesting starting point for direct functionalization in organic and medicinal chemistry.[18] Recently, we reported a biomimetic oxidative coupling cyclization for rapid construction of isochromanoindolenines via efficient functionalization of THβCs or THγCs with 2,3-bishydroxybenzoic acid.[19] Herein, we present the oxidative coupling cyclization using commercial available iron(II) phthalocyanine (FePc) as an efficient catalyst via a radical type catalytic oxidation reaction, allowing for the rapid access to complex benzofuroindolenines (Figure 1).

Treatment of THβC with 3,4-dihydroxybenzoic acid in the presence of FePc (2.5 mol%) and *t*-BuOOH (3 eq) at 0 °C for 10 min afforded two easily separated products **1a** and **1b** in excellent yield (**1a** and **1b** are diastereomers with 43% + 43% isolated yield, respectively). The significantly distinct NMR data indicated that these novel structures are completely different from our earlier report.[19] Through X-ray crystallographic analysis, we assigned the chemical structures of these complex products as benzofuroindolenines (Figure 2).

This interesting result encouraged us to test the generality of catalytic oxidative coupling cyclization. Various substrates were investigated to construct valuable complex molecules. As shown in Figure 2, we first investigated the reactions of a variety of THβCs or THγCs with 3,4-dihydroxybenzoic acid. The desired products were isolated in good to excellent yields. Different *N*-substituted THβCs, including Ts, Ac, SO_2Me, SO_2Ph, COOMe, and COOEt, afforded the desired products **2-7** in satisfactory yields. Other THβCs or THγCs with

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10.1002/adsc.201801184

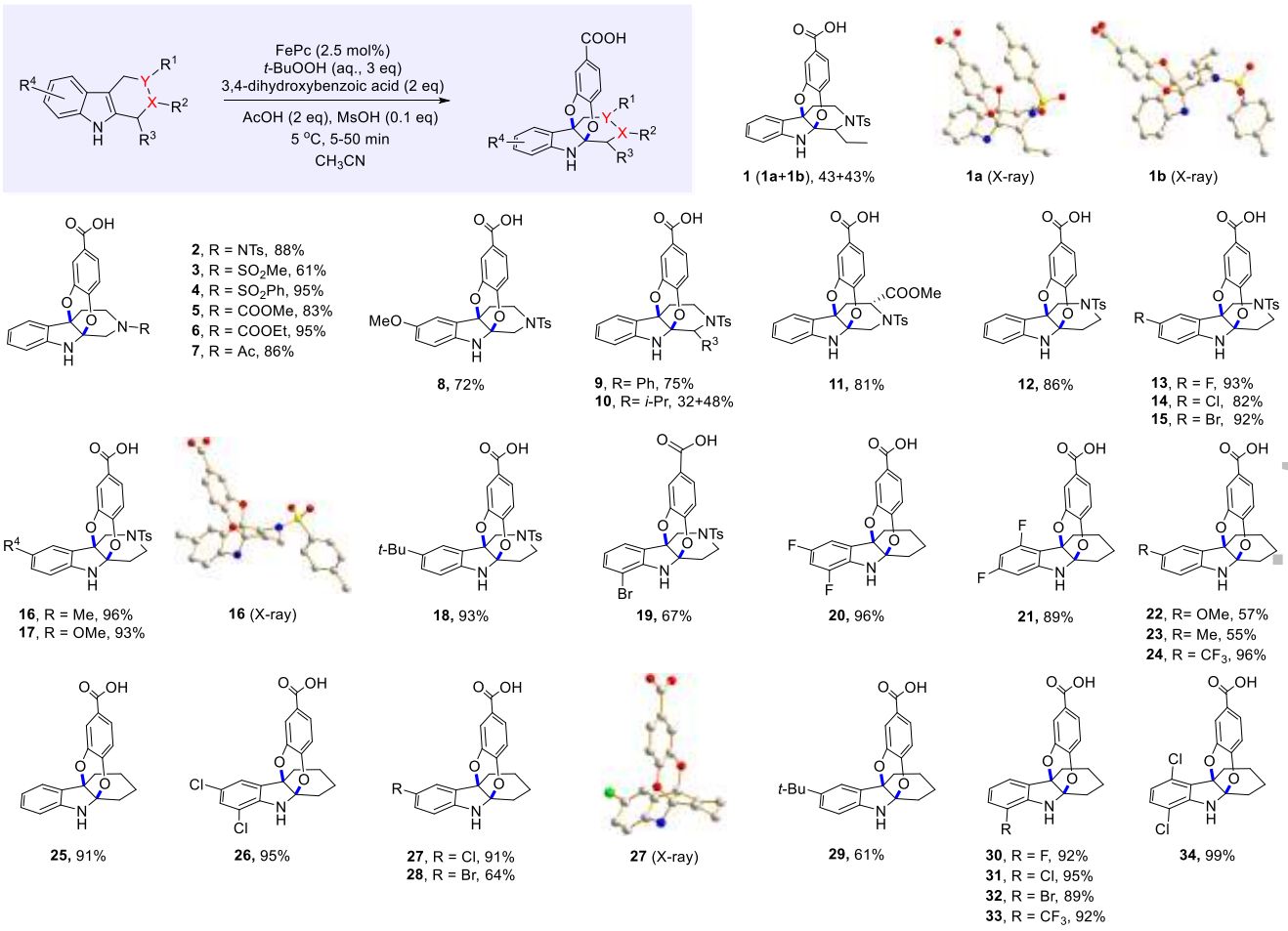

Figure 2. Scope of the catalytic oxidative coupling cyclization.

different substituents, such as F, Cl, Br, Me, OMe, were well-tolerated, and the corresponding products **8**-**19** were obtained in 67-96%. Notably, the reaction was also suitable for tetrahydrocarbazoles. By using various tetrahydrocarbazoles with different substituents, the corresponding products **20**-**34** were obtained in 55–99% yields. The structures of **16** and **27** were further established by X-ray crystallographic analysis.[20]

The extensive substrate scope and broad functional-group compatibility of this transformation encouraged us to further explore more catechols derivatives (Figure 3). 3,4-Dihydroxyphenyl derivatives containing electron-withdrawing groups, such as NO_2, CN, COOMe or COPh, were tolerable to afford the corresponding products **35**-**49** in moderate to excellent yields. The structure of **37** was established by X-ray crystallographic analysis.[20] It is worth mentioning that compound **44** could be performed on gram scale without a significant deterioration in yield (98% versus 99%), indicating the practical utility of this transformation in organic synthesis.

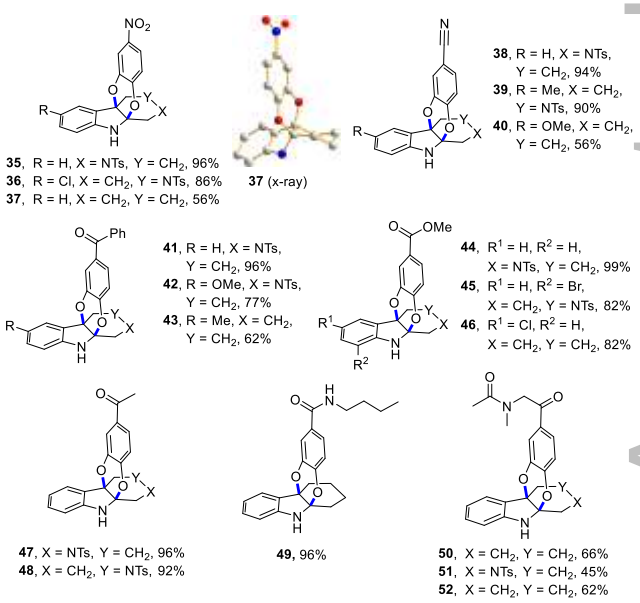

Figure 3. Application of catalytic oxidative cyclization coupling reaction.

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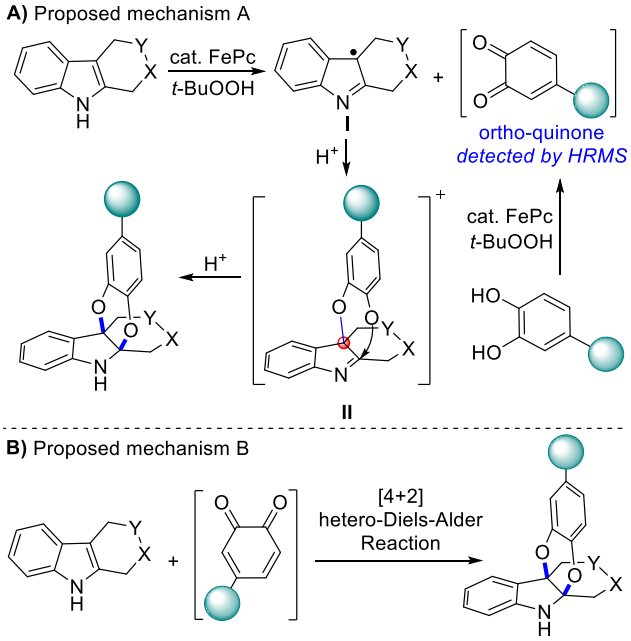

Figure 4. Mechanistic investigation of catalytic oxidative coupling cyclization.

However, it is worth to mention that indoles fused with five-membered ring or seven-membered ring and catechols with electron-donating substituents were not well-tolerated, and the products were obtained in extremely low yields.

To further demonstrate the value of this general strategy, we focused on the desired pharmaceutically drug-likeness molecules. *N*-Ac-adrenalone as one of the catecholics with extensive pharmacological properties can be successfully functionalized to afford the corresponding products **50-52** in reasonable yields (Figure 3).[21] Notably, the suitable drug-likeness properties of all final compounds indicated that these molecules are worth for further biological evaluation.[22]

To explore the reaction mechanism of this catalytic oxidative coupling cyclization, radical trapping experiment was performed. In the presence of various radical inhibitors, no product was obtained under the standard condition.[22] Based on previous mechanistic investigation[19] and our experimental observations,[23] two plausible mechanisms were proposed as follows. As shown in Figure 4A, the starting material was catalyzed by FePc/*t*-BuOOH to form a radical intermediate **I**, while catechol was catalyzed by FePc/*t*-BuOOH to form a unstable ortho-quinone (detected by HRMS, see Figure S1). Upon protonation by Bronsted acid, this unstable ortho-quinone combined with excited state intermediate **I** to form the key intermediate **II**, which undergoes coupling cyclization to afford the final product. A plausible [4+2] hetero-Diels-Alder reaction between starting material and the ortho-quinone generated in situ is depicted in Figure 4B.[24]

In conclusion, we have developed an efficient FePc-catalyzed oxidative coupling cyclization for rapid construction of benzofuroindolenines in an open flask. This protocol provides a library of benzofuroindolenines which accessing undeveloped chemical space for further structural modification. The pharmacological characterizations of these compounds will be outlined in due course.

Experimental Section

General Procedure for rapid construction of benzofuroindolenines. To a solution of starting material (tetrahydrocarbazoles or THβCs or THγCs, 1.0 equiv) and 3,4-dihydroxyphenyl derivatives (2.0 equiv) in CH_3CN (0.2 M) was added FePc (2.5 mol%), AcOH (2.0 equiv), MsOH (0.1 equiv) and *t*- BuOOH (aq. 65%, 3.0 equiv) at 5 °C. The reaction mixture was stirred at the same temperature. After the reaction was completed (monitored by TLC analysis), silica gel was added to the mixture and then the solvent was removed *in vacuo*. The crude product was purified by chromatography on silica gel to give the desired product**.**

Acknowledgements

This work was supported by Joint research project of health and education of Fujian Province (No. WKJ2016-2-06) and the National Natural Science Foundation of China (No. 81571802).

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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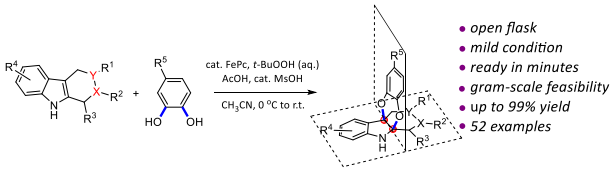

Catalytic oxidative coupling cyclization for rapid construction of benzofuroindolenines was described.

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