



Formal carbene insertion into C=O double bond: A facile approach to the synthesis of 2*H*-chromenes

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ABSTRACT

A formal carbene insertion into C=O double bonds of 2-hydroxycinnamaldehydes catalyzed by Rh₂(esp)₂ with Na₂CO₃ as additive has been disclosed by using aryldiazoacetates as carbene precursors. 2*H*-chromenes with a quaternary carbon at C-2 position were readily obtained from simple starting materials in good yields with excellent diastereoselectivity under mild reaction conditions in one pot. The reaction mechanism was investigated and proposed as the formation of epoxide intermediate from Rh(II)-associated carbene and (*E*)-2-hydroxycinnamaldehyde and followed by a cascade epoxide ring-opening procedure in which the (*E*)-intermediate was converted into the (*Z*)-intermediate to give (*Z*)-products.

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1. Introduction

Metal-associated carbenes, which are frequently generated from diazo compounds or *N*-tosylhydrazones [1], are well-known as versatile and powerful intermediates for the construction of new chemical bonds [2]. Especially, carbenes are commonly used in the cycloaddition reaction and insertion reactions, such as C=X (X=C, O) cycloaddition [3,4] and X-H (X=C, N, O, Si, S) [5,6] or C-X (X=C, Si, S) [7] insertion. However, carbenes insertion into double bonds, including C=C and C=O double bonds, has remained a formidable challenge and has been limitedly established mainly owing to the strength of such double bonds.

The general transformation of metal-associated carbenes with C=C or C=O double bonds is cycloaddition reaction to yield cyclopropanes [3] (Scheme 1a) or epoxides [4] (Scheme 1b). Only a few examples for the insertion reaction of carbenes into C=C double bonds were developed [8]. Buchner reaction is a typical example of insertion reaction for the carbene into the C=C double bonds, in which the cyclopropanation of a C=C double bond in the phenyl ring is followed by an electrophilic ring open to afford cycloheptatrienes (Scheme 1c) [9]. To the best of our knowledge, no

example of carbene insertion into C=O double bonds has been developed. Herein, we report a formal carbene insertion reaction into C=O double bonds in cinnamaldehydes for the rapid construction of 2*H*-chromenes with a quaternary carbon at C-2 position from simple starting materials (Scheme 1d).

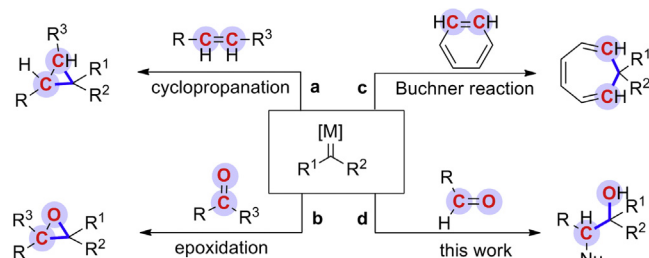
Recently, we successfully established a transition-metal and iminium-ion co-catalyzed strategy for asymmetric multicomponent reaction, in which chiral-amine-activated enals enantioselectively trapped zwitterionic intermediate derived from aryldiazoacetates and indoles via a selective 1,4-addition, giving 3-substituted indole derivatives in good yields (Scheme 2a) [10]. On the basis of this chemistry, we envisioned to design an intramolecular oxonium ylide trapping process by the similar transition-metal/iminium co-catalysis strategy via a 1,4-addition manner of enal to rapidly construct biologically active 2,3-dihydrobenzofurans (Scheme 2b).

2. Result and discussion

The reaction was carried out by reacting methyl phenyldiazoacetate **1a**, 2-hydroxycinnamaldehyde **2a** in CH₂Cl₂ using Rh₂(OAc)₄ (5 mol %) and 2-(diphenyl((trimethylsilyl)oxy)-methyl)pyrrolidine **race-4a** (20 mol %) as a co-catalyst and, *p*-nitrobenzoic acid (*p*-NBZA, 40 mol %) as an additive. Gratifyingly, the product with the targeting molecular mass (detected by HPLC-MS) was

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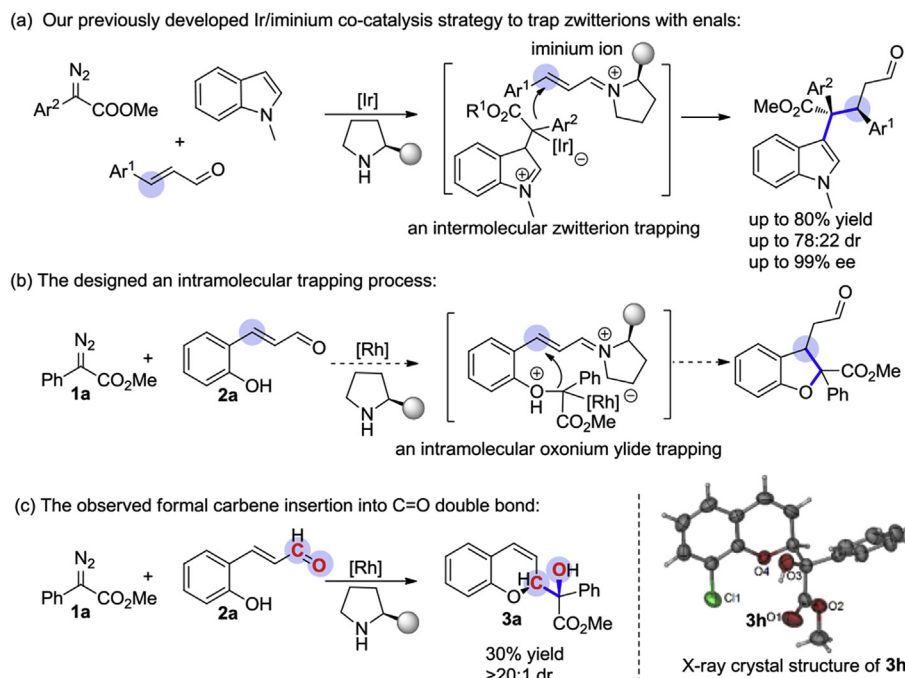
Scheme 1. Schematic representation of carbene generated from diazo compounds insertion into various bonds.

obtained and isolated in 30% yield with >20:1 dr. We then turned our attention to improve efficiency of the reaction. To our surprise, it was found that the reaction could go smoothly even without amine *rac*-**4a** as co-catalyst to give the same product in even better yield of 51% (Table 1, entries 1 vs 2), indicating the reaction may not involve iminium ion intermediate process as expected. Further investigations showed that no intramolecular trapping product 2,3-dihydrobenzofuran ring was formed (Scheme 2b), instead, a product of a formal carbene insertion into C=O double bond, 2*H*-chromene derivative **3a** was obtained in 30% yield with >20:1 dr (Scheme 2c). The specific chemical structure was assigned in analogy with **3h** as determined by single-crystal X-ray diffraction (Scheme 2c).

Modulating the rate of the decomposition of diazo compounds by utilizing other different transition metal complexes such as [PdCl(η^3 -C₃H₅)]₂, Cu(hfacac)₂, [Ru(*p*-cymene)Cl₂]₂, [Ir(COD)Cl]₂ had no improvement in the yield (see supporting information (SI), Table S1). Lewis acids ZnCl₂ and InCl₃, which might activate the carbonyl group of **2a**, were employed to improve the yield. But instead, the yield was destroyed from 51% to 35% and 42%, respectively (Table 1, entries 3–4). Next, brønsted acid **4b** was used to activate carbonyl group of **2a**, but the yield was not improved

(Table 1, entry 5). Then, organic or inorganic base was introduced to enhance nucleophilicity of the oxygen atom in phenol group of **2a**. Organic base 1,4-diazabicyclooctane (DABCO) afforded no any product because Rh₂(OAc)₄ was poisoned by the coordination interaction of DABCO (Table 1, entry 6). To our delight, additive Na₂CO₃ improved the yield to 60% (Table 1, entry 7). Adjusting the ratio of **1a** and **2a** from 1.5:1.0 to 2.0:1 obviously improved the yield to 70% with a remaining excellent diastereoselectivity of >20:1 (Table 1, entry 8). Further increasing the ratio to 3.0:1 gave a similar result (Table 1, entry 9). In return, decreasing the ratio to 1.0:1 gave a lower yield of 48% (Table 1, entry 10). Increasing basicity to K₂CO₃ gave lower yield of 61%, and Cs₂CO₃ only gave moderate yield of 40% (Table 1, entries 11–12). Screening of other bases like NaOAc, NaHCO₃, Na₂HPO₄ showed they were less efficient (SI, Table S1). The exploration on various solvents and different temperatures for the formal carbene insertion reaction into C=O double bonds was fruitless (SI, Table S1). It is well known that Rh₂(esp)₂, a dirhodium complex with tethered carboxylate ligands, developed by Du Bois [11] is an efficient catalyst for decomposition of diazo compounds and it often showed a high level similarity to Rh₂(OAc)₄. When it was introduced to the reaction, it did give a same good result as Rh₂(OAc)₄ in 69% yield with >20:1 dr, but a more clear reaction mixture (Table 1, entry 13). Matched with additive K₂CO₃, the same good yield was obtained, but Cs₂CO₃ decreased yield dramatically (Table 1, entries 14–15). Based on this point, Rh₂(esp)₂ was chosen as the catalyst for the substrate scope investigation.

The general applicability of the protocol was investigated under the optimal reaction conditions (Table 1, entry 13), and the results are summarized in Table 2. With different 3-, 4-, 5- or 6-substituents on 2-hydroxycinnamaldehydes (Table 2, entries 1–8), reactions proceeded smoothly with excellent dr values in good yields although electron rich alkoxy 2-hydroxycinnamaldehydes gave relative lower yields (Table 2, entries 4–5, 7), probably because weak acidity of electron-donating phenol unit is harmful to the reaction with base Na₂CO₃. The reaction was extended to other different substituents on



Scheme 2. Discovery of Rh(II)-catalyzed formal C=O double bonds carbene insertion reaction.

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