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► **To cite this version:**

Norbert Hoffmann. Paternò-Büchi pathways. *Nature Synthesis*, 2023, 2, pp.9-10. 10.1038/s44160-022-00200-7. hal-03865892

HAL Id: hal-03865892

<https://cnrs.hal.science/hal-03865892v1>

Submitted on 22 Nov 2022

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PHOTOCHEMISTRY

Paternò-Büchi pathways

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The Paternò-Büchi reaction is a useful approach in organic synthesis to prepare oxetanes. Understanding the mechanism of this reaction is required for the prediction and control of the diastereoselectivity of the products.

Photochemical reactions are an important tool in organic synthesis and in the chemical and pharmaceutical industry, these reactions are particularly useful in the search for biologically active compounds. The reason for this success in different applications is that upon electronic excitation by light absorption, or by energy transfer in the case of photochemical sensitization, the electronic configuration of a compound changes and thus the chemical reactivity changes.¹ This means that compounds or compound families that are difficult to, or cannot be, synthesized by conventional methods become available under photochemical conditions. Traditionally, organic photochemistry is closely linked to physical chemistry.² This is because techniques such as time resolved spectroscopy are often used for mechanistic studies, for example, to understand electron transfer processes or to detect and characterize intermediates in these reactions. In recent years, the technology of photochemical reactors has been developed to increase the efficiency of photochemical reactions, such as by reducing the optical trajectory to increase the concentration of the chromophore as well as through the development of continuous flow to further optimize the reactions.

Now, writing in *Nature Synthesis*, Dell'Amico and co-workers report a comprehensive investigation of the Paternò-Büchi reaction between indole derivatives, such as **1** and aromatic ketones, such as **2** (Fig. 1a).³ The Paternò-Büchi reaction^{4,5} is one of the most intensively investigated reactions in organic photochemistry. This [2+2] cycloaddition reaction between a carbonyl and an alkene yields oxetanes, which are important synthesis intermediates. The role of this reaction in target oriented syntheses, has been compared to that one of an aldol reaction.⁶ As in the case of many organic photochemical reactions, only a few systematic investigations on the Paternò-Büchi reaction scope have been reported. In particular, extended studies using heterocyclic compounds are rare. In terms of the reaction mechanism, generally the carbonyl reaction partner is photochemically excited, however, various intermediates may be involved in the reaction depending on the substrate structure.⁷ The formation of these intermediates and their behaviour have a significant influence on the outcome of the reaction, for example, on the regio- and stereoselectivity.

Indole derivatives (**2**) and aromatic ketones (**1**), as well as similar compounds, form electron-donor-acceptor (EDA) complexes **3** at the ground state (Fig. 1a) and UV/vis spectra show that such species absorb at $\lambda > 425$ nm. Dell'Amico and co-workers characterize the EDA complexes by computational methods.

When irradiation is carried out at 405 nm, these complexes are electronically excited (**4**), which favours the formation of the *exo* diastereoisomer **6**. In contrast, when the irradiation of the reaction mixture is carried out at 370 nm, the excitation of the non-complexed ketone **1** is strongly favoured. In this case, an exciplex intermediate **7** is formed. Generally in such cases, for example, in reactions between benzophenone as the carbonyl reaction partner and less electron-rich alkenes, a 1,4-diradical intermediate is generated via the formation of a C-O bond (Fig. 1b). In the reaction between **1** and **2**, however, an electron transfer occurs in the exciplex **7**, yielding the corresponding radical ion pair or charge transfer complex **8** (Fig. 1a). Complex **8** is a regioisomer of complex **5**. This is a typical reaction step in the transformation of particularly electron-rich alkenes and electron-poor carbonyl partners. From this intermediate the *endo* diastereoisomer **9** is formed. The reaction intermediates are characterized by laser flash photolysis and computational methods.

Because polar intermediates and electron transfer processes are involved, the influence of the redox potential on the stereoselectivity is studied using derivatives of **1** and **2** carrying electron-donating or withdrawing substituents. Steric effects are also studied using the corresponding α -ketoester substrates and Charton parameters and these studies provide a first insight into the reaction scope. Additionally, the reaction is carried out under microfluidic conditions with irradiation of 370 nm or 456 nm. Furthermore, from the view of industrial-scale production, such studies provide information on how to establish these processes safely.

This study by Dell'Amico and co-workers of the Paternò-Büchi reaction, with a focus on diastereoselectivity, nicely combines a large methodology spectrum of physical and theoretical chemistry. As a consequence, a large amount of the mechanistic aspects of this reaction are discussed and presented and the interest for application to organic synthesis is clearly shown. Additionally, perspectives for an industrial application in connection with medicinal chemistry are indicated. This comprehensive investigation therefore covers almost all aspects of the reaction, as such, is also of particular educational value. Starting from basic studies of the chemical reactivity and selectivity, it is demonstrated how a photochemical reaction can be applied to organic synthesis including the industrial scale. Thus the present study can be used for teaching organic photochemistry in academia. It increases the acceptance of photochemical reactions in the field of synthetic organic chemistry and in the chemical and pharmaceutical industry.

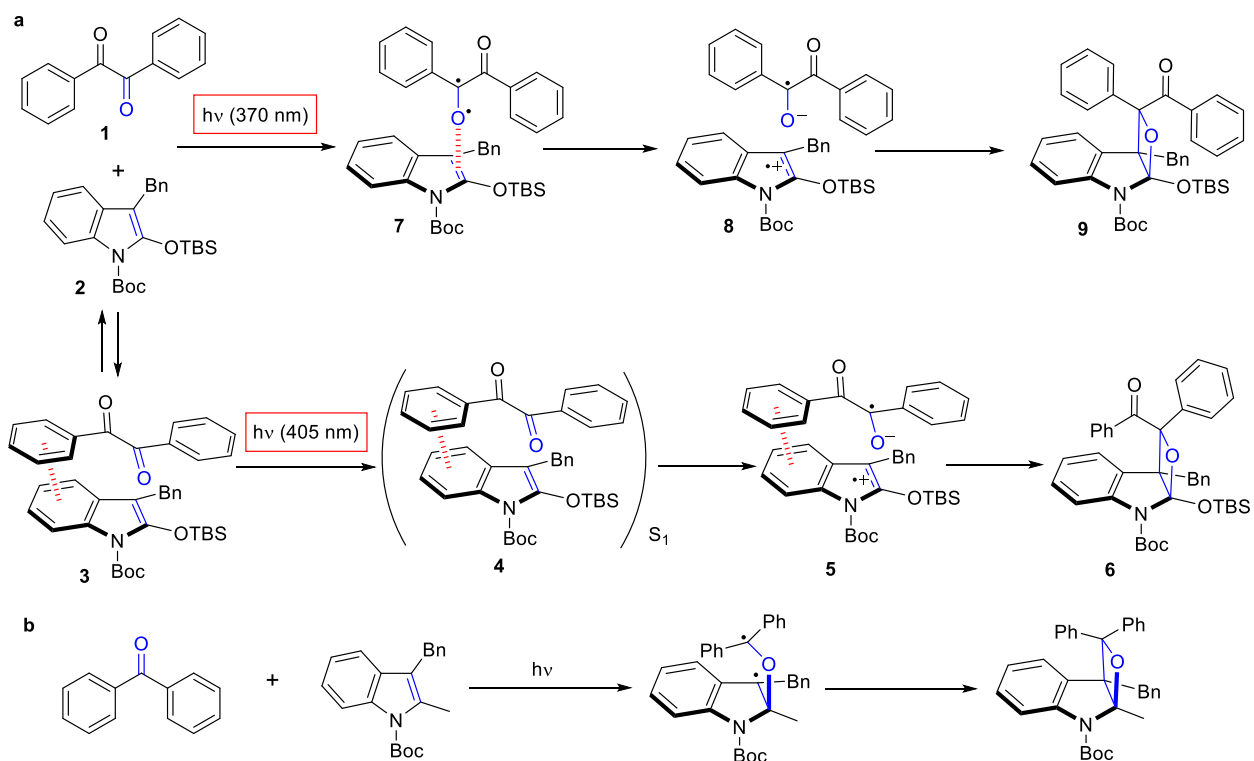


Figure 1. Mechanisms of the Paternò-Büchi reaction. a. Two different pathways involving electron transfer. b. Classical mechanism of the Paternò-Büchi reaction of benzophenone with a less electron-deficient indole derivative. (Bn: benzyl, Boc: t-butoxycarbonyl, Ph: phenyl, TMS: t-butyldimethylsilyl, S₁: first excited singlet state)

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Competing interests

The author declares no competing interests.

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