PHOTOCATALYTIC TRANSFORMATIONS OF THE ANOMERIC CARBON OF SUGARS

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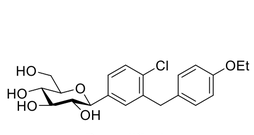
1. PHOTOCATALYSIS AND CARBOHYDRATES

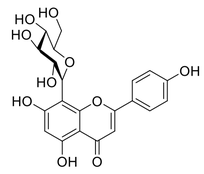
Carbohydrates are known to be involved in almost all the aspects of life. For this reason, the naturally occurring carbohydrates and their derivatives have been largely studied for the treatment of different diseases, with 54 carbohydrate-based drugs approved as drugs or diagnostic agents between 2000 and 2021.[1] Nevertheless, **this class of molecules is quite difficult to functionalize**, relying on tedious (protecting groups), quite sensible (e.g., glycosylation) and often heavy metal-based (e.g., deoxygenation) reactions. In this context, **photocatalysis has proved to be a valid instrument to overcome the classic problems related to functionalization of carbohydrates, enabling new pathways of reactivity and leading to high-value intermediates.**[2] In this contribution, we present two types of photo-mediated structural modifications for the synthesis of **C-aryl glycosides** (**deoxygenative arylation**)[3] and **1-deoxy sugars** (**reduction of OH groups**)[4].

2. C-ARYLGLYCOSIDES

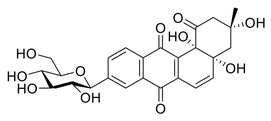
C-arylglycosides are widespread in Nature and several of them show excellent biological activities. Moreover, the ***C*-glycoside bond is more stable towards enzymatic and chemical hydrolysis than the *O*- or *N*-glycoside ones**.[5] Hence, *C*-glycosides are increasingly exploited in pharmaceutical chemistry and biochemistry.



Depagliflozin
type-II diabete drug



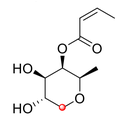
Vitexin
anti-tumor drug



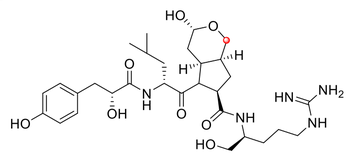
Aquayamycin
anctibacterial drug

3. 1-DEOXYSUGARS

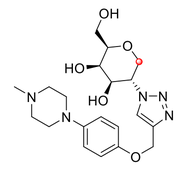
1-deoxysugars are present in naturally occurring compounds. **The lack of a hydroxy group at the C-1 position makes them metabolically inert and thus they have been employed as short term markers for several illnesses.** These substrates have been also used as synthetic intermediates for the preparation of biologically active natural product analogues.[6]



Ophiocerin D
from the genus Ophioceras

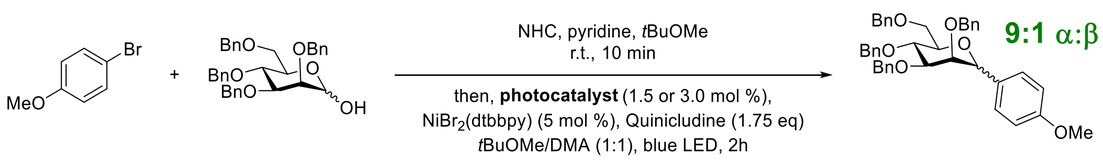


Aeruginosin 298-A analogue
inhibitor of thrombin

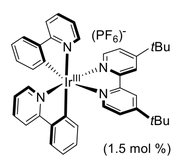


ASGP-R ligand
potential target for anticancer therapy development

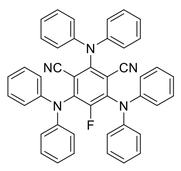
4a. MECHANISM



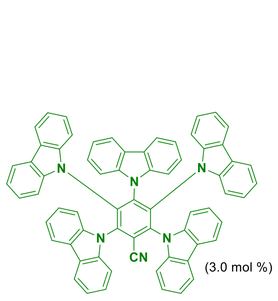
Scope of the photocatalysts



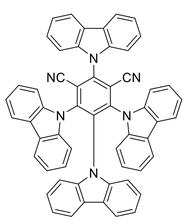
$[Ir(ppy)_2(dtbbpy)](PF_6)$
E (PC*/PC⁻) = +0.66 V
E (PC/PC⁻) = -1.51 V
y = 61 %
(1.5 mol %)



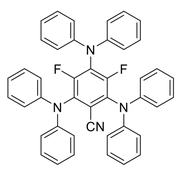
3DPAFIPN
E (PC*/PC⁻) = +1.09 V
E (PC/PC⁻) = -1.59 V
y = 41 %



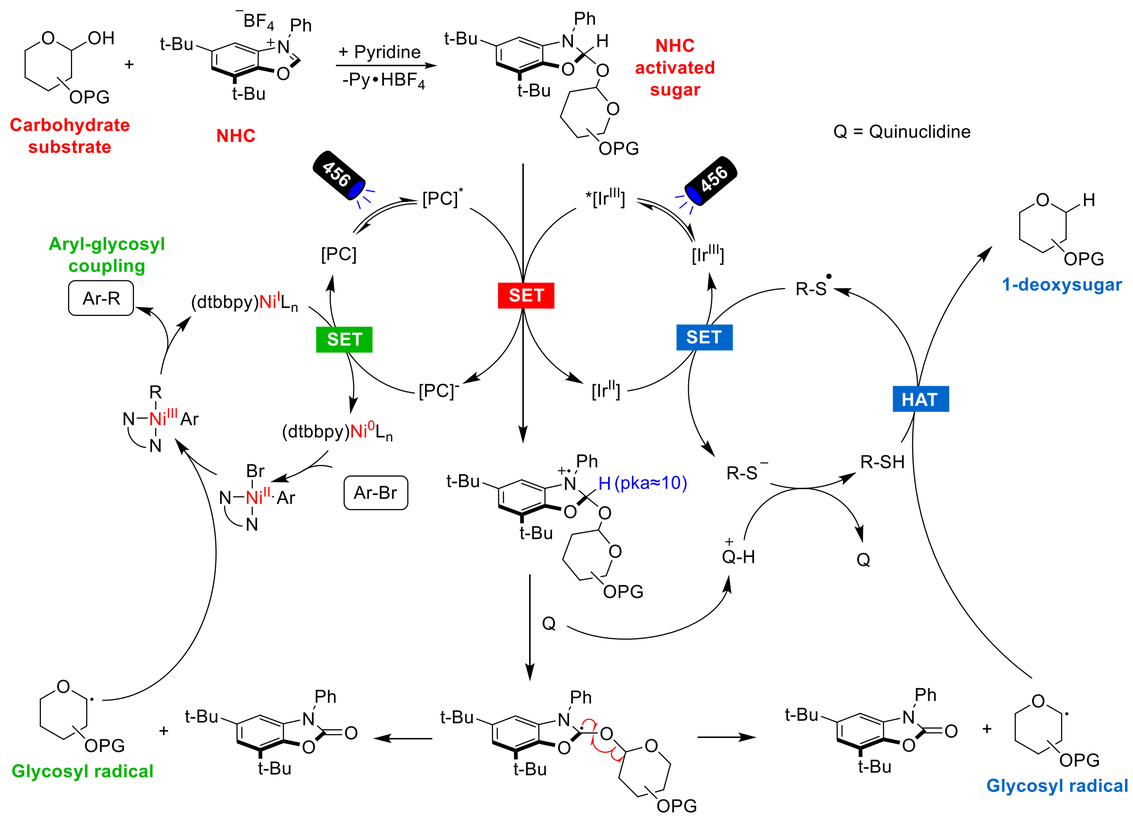
5CzBN
E (PC*/PC⁻) = +1.31 V
E (PC/PC⁻) = -1.51 V
y = 71 %
(3.0 mol %)



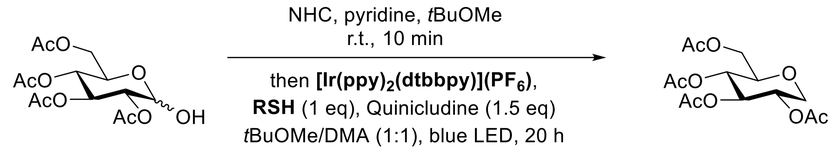
4CZIPN
E (PC*/PC⁻) = +1.43 V
E (PC/PC⁻) = -1.24 V
y = 42 %



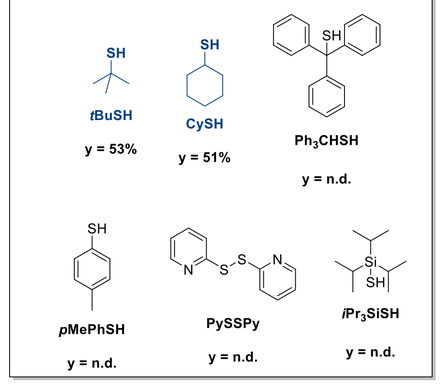
3DPA2FBN
E (PC*/PC⁻) = +0.92 V
E (PC/PC⁻) = -1.54 V
y = 14 %



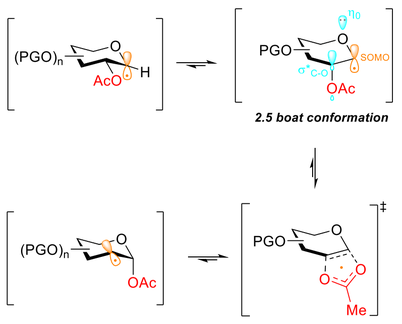
4b. MECHANISM



Scope of thiols



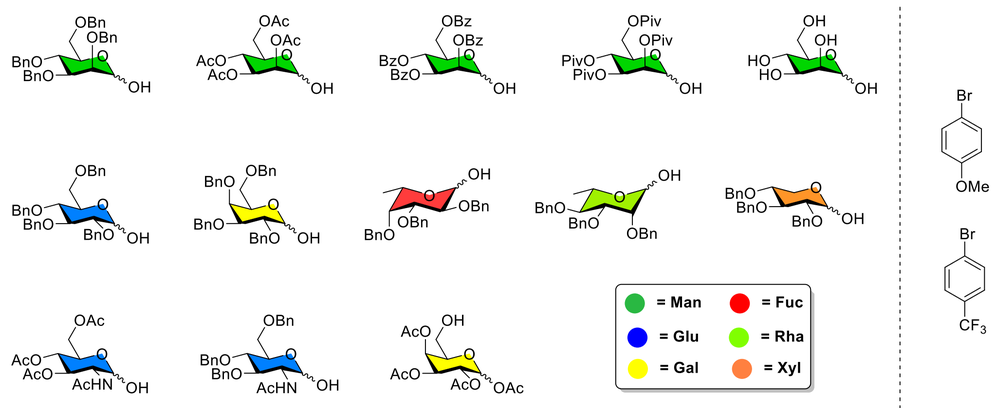
Possible side pathway (leading to 2-deoxysugars)



5a. PRELIMINARY RESULTS AND DISCUSSION

A wide scope on several carbohydrate substrates is currently ongoing. Preliminary results show that benzyl-protected substrates react better than acetate or benzoate protected-ones. Mannose and Rhamnose react, preferentially giving the α-anomer (α:β > 9:1).

Extended scope on carbohydrates and aryl halides



5b. PRELIMINARY RESULTS AND DISCUSSION

The presented approach represents a faster and greener alternative compared to the classic stannane-based Barton-McCombie deoxygenation, to get important carbohydrate derivatives. Our preliminary results underline that alkyl thiols are better HAT-agents than aryl-containing ones and disulfide. Other HAT-agents (new alkyl-thiols and silanes) are under investigation. Moreover, additional studies on the amount of HAT-agent and Quinuclidine are undergoing.

6. CONCLUSIONS

In conclusion, we have here reported two photo-mediated functionalisations of carbohydrates, both proving to be greener and cheaper alternatives to the classic procedures. In particular, the possibility to substitute iridium-based photocatalysts with organic dyes (with 5CzBN giving higher yields than Ir) is an added value. Moreover, these methods could be employed for the synthesis of highly expensive substrates.

7. REFERENCES

[1] X. Cao et al., *Acta Pharm. Sin.*, **2022**, 12 (10), 3783; [2] D. J. Gorelik et al., *Chem. Sci.*, **2024**, 15, 1204; [3] Z. Dong et al., *Nature*, **2021**, 598, 451; [4] Y. Wang et al., *Nature*, **2020**, 578, 403; D. Stokmaier et al., *Bioorg. Med. Chem.*, **2009**, 17, 7254; M. G. Adlington et al., *Tet. Lett.*, **1976**, 17, 2955; [5] X. Gou et al., *Chem. Eur. J.*, **2023**, 29 (32), e202203351; [6] G. Li et al., *Tetrahedron Lett.*, **2018**, 59, 3428.