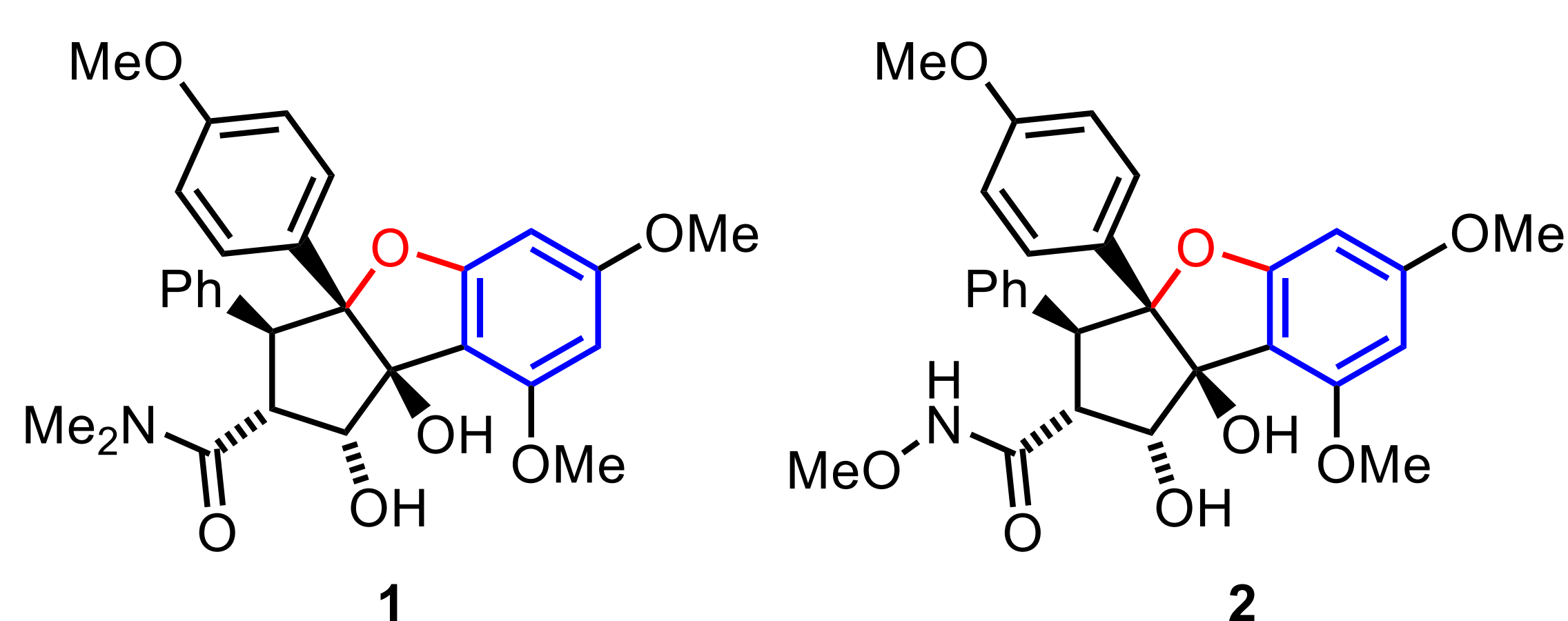


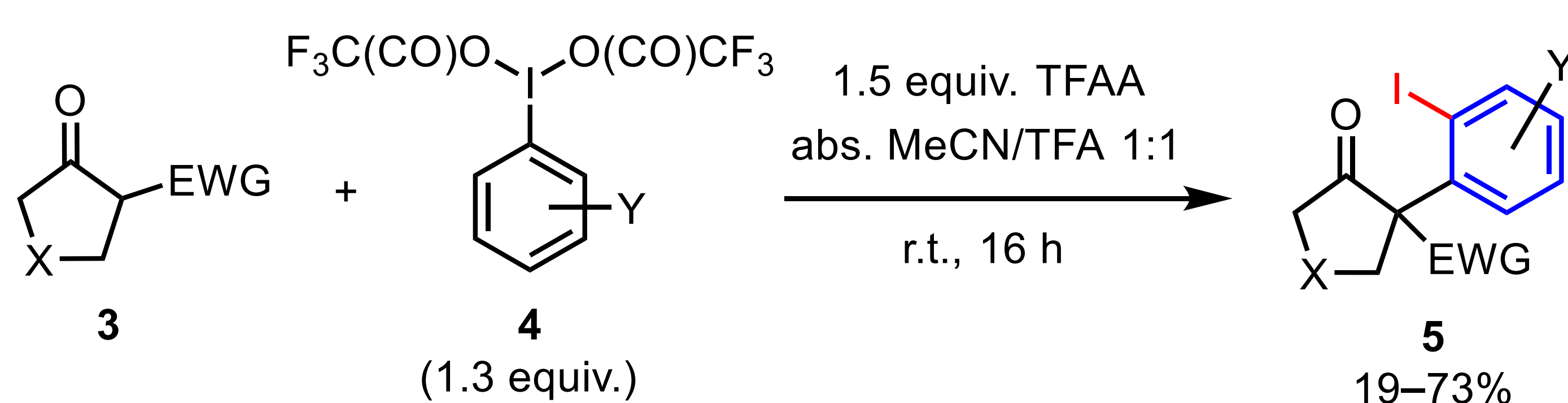
The [b]-annulated 2,3-dihydrobenzofuran ring system is a characteristic scaffold of the flavaglines, a natural product class. Due to the antiviral activities of some flavaglines against SARS-CoV-2 and many other viruses, the development of a synthetic route to structural analogues of these compounds is a central goal. In this study, we present a new method to construct the scaffold via an Ullmann-like, copper-catalyzed C–O-coupling reaction of various α -arylated β -oxoesters.

Introduction

Several natural products with a [b]-annulated 2,3-dihydrobenzofuran ring system are known.^[1] Most of these belong to the natural product class of the flavaglines. Two examples are Rocaglamid (**1**) as well as the synthetic CR-31-B (**2**). Due to recent publications on the antiviral activities of some flavaglines against SARS-CoV-2 and many other viruses, the development of a synthetic route to structural analogues of these compounds is a central goal of organic chemistry in the context of the ongoing corona pandemic.^[2]

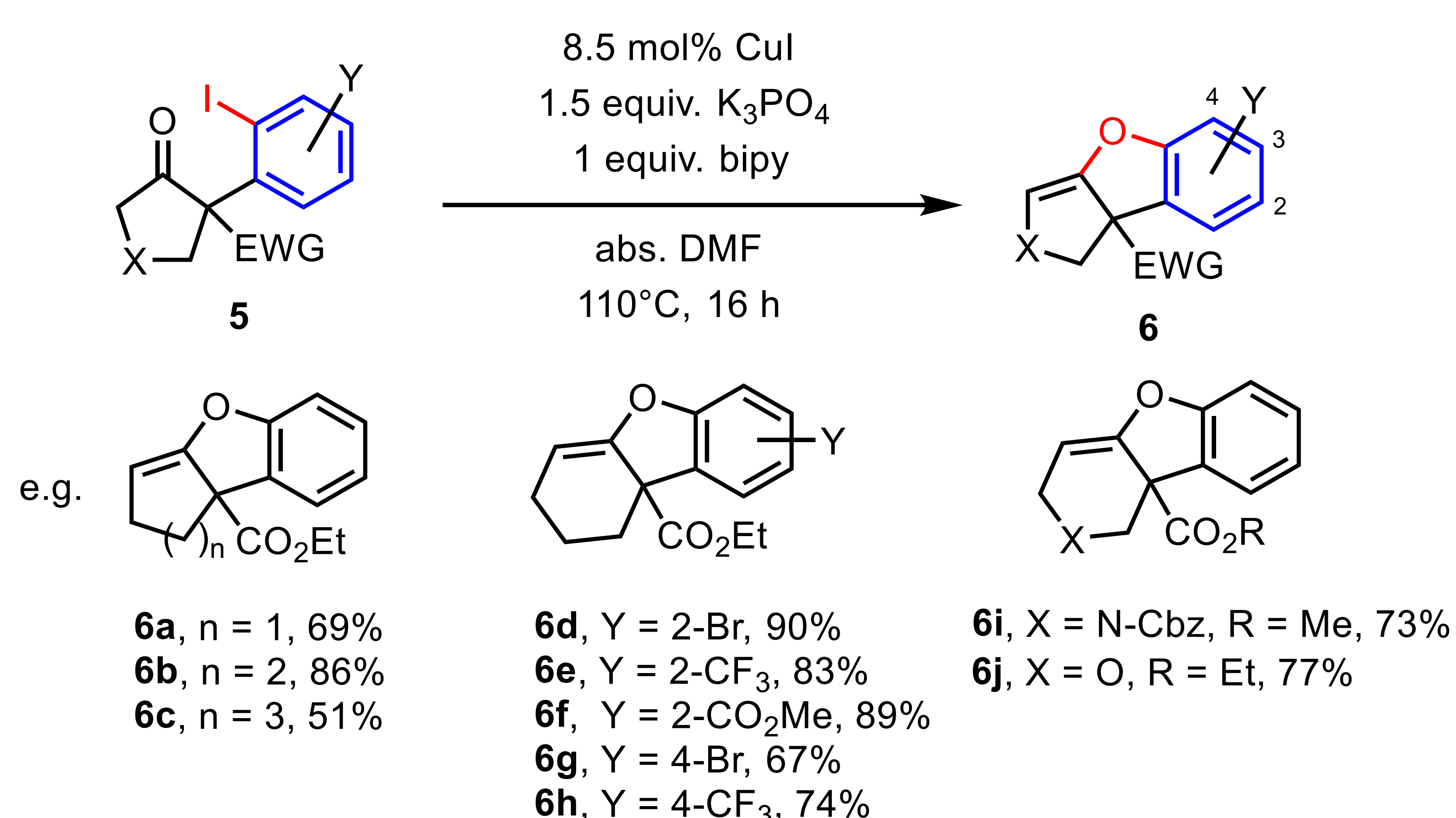


We have developed a new method to construct the scaffold of the flavaglines. Here, an Ullmann-like, copper-catalyzed C–O-coupling reaction of various α -arylated β -oxoesters **5** was investigated and optimized. The synthesis of these α -arylated β -oxoesters **5** was previously established by our group via an iodo-Claisen-type rearrangement of β -oxoesters **3** with several PIFA-Derivatives **4**.^[3,4]



Copper-catalyzed C–O-coupling

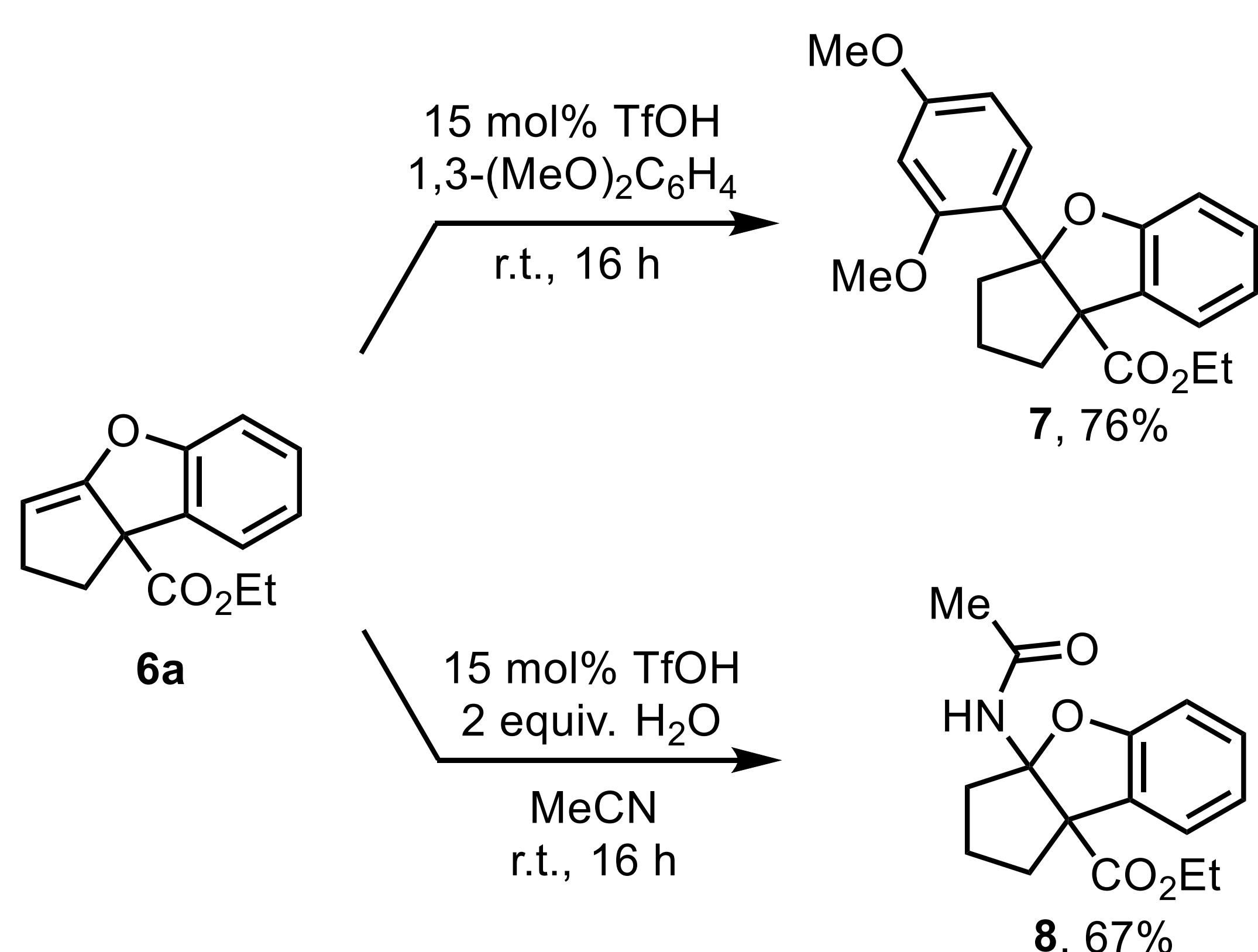
After an extensive screening the Ullmann-like, copper-catalyzed C–O-coupling reaction of α -arylated β -oxoesters **5** could be optimized and the yield of the annulated benzofuran **6a** has been raised from the initial 9% to 69%. With the optimized reaction conditions in hand, we investigated the scope of the transformation to the annulated benzofuran derivatives **6**.



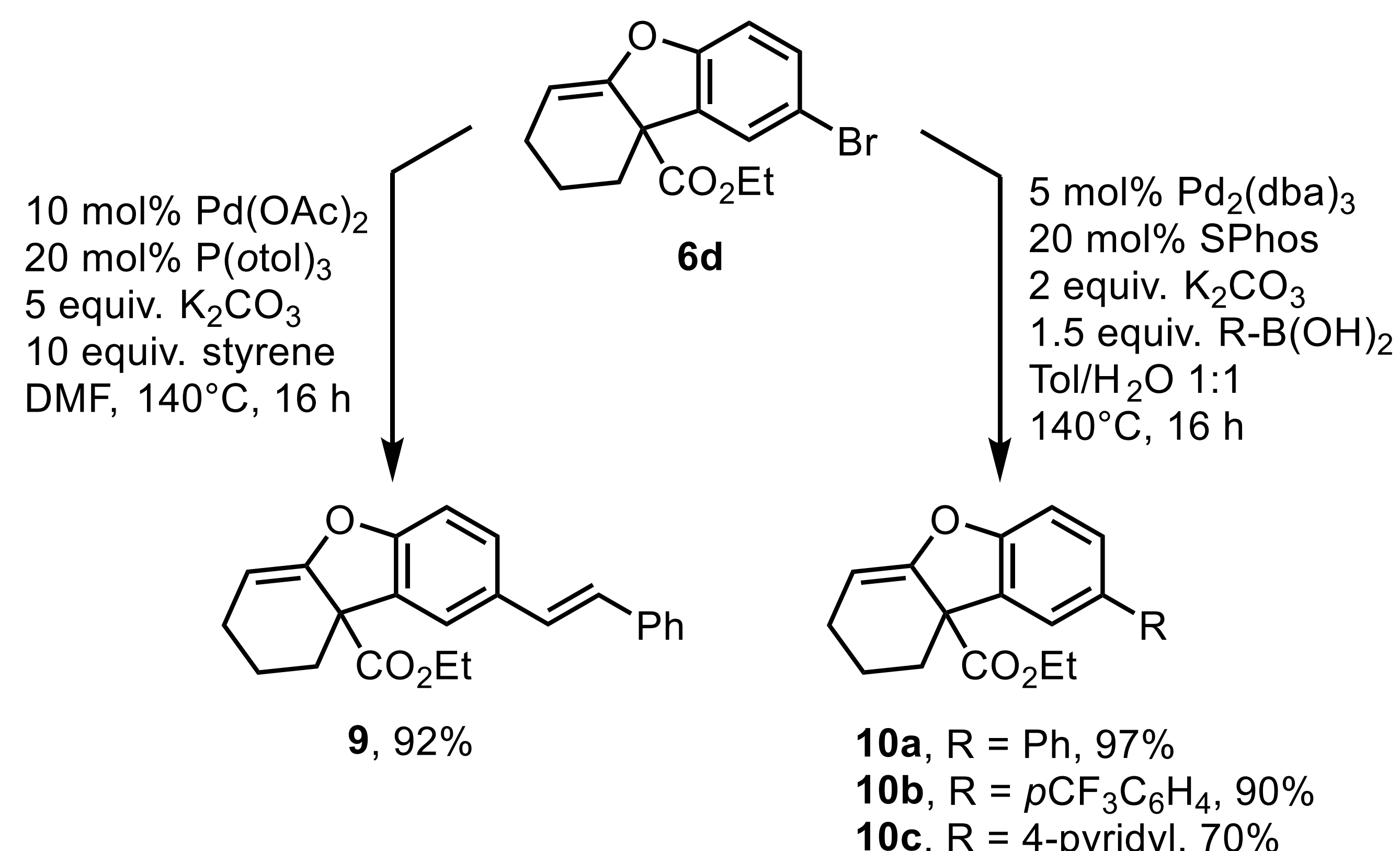
In order to explore the scope of the reaction, the ring size was varied (**6a–6c**). Furthermore, electron withdrawing substituents in the aromatic ring (**6d–6h**) as well as heteroatoms in the [b]-annulated ring (**6i–6j**) were introduced. Yields of up to 90% could be obtained by this method, thus the copper-catalyzed C–O-coupling reaction has a potentially broad range of application.

Examples for further Derivatization

To get closer to our goal of the preparation of structural analogues of flavaglines we further derivatized benzofuranes **6**, for example through the introduction of an electron rich aromatic ring or a Ritter reaction in the enol ether position both by acid catalysis to obtain compounds **7** and **8** in yields of 76% and 67%, respectively. Further examples of derivatization comprise of coupling reactions.



A Heck reaction of the brominated annulated benzofuran **6d** with styrene resulted in the corresponding product **9** with a yield of 92%. Suzuki coupling reactions of benzofuran **6d** with different boronic acids led to the products **10a–10c** in yields of 70–97%. This is just a glimpse at the versatility and possible reactions of the annulated benzofuranes **6**.



[1] H. Greger, *Phytochem. Rev.* **2022**, *21*, 725–764.

[2] C. G. Nebigil, C. Moog, S. Vagner, N. Benkirane-Jessel, D. R. Smith, L. Desaubry, *Eur. J. Med. Chem.* **2020**, *203*, 112653.

[3] A. Dierks, J. Tönjes, M. Schmidtman, J. Christoffers, *Chem. Eur. J.* **2019**, *25*, 14912–14920.

[4] J. Strehl, C. Kahrs, T. Müller, G. Hilt, J. Christoffers, *Chem. Eur. J.* **2020**, *26*, 3222–3225.