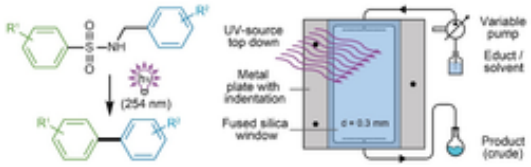
Technology Offer

Biaryl coupling by Photosplicing

Reference Number 10-00105

Challenge

Biaryl compounds are key building blocks in a broad spectrum of organic substances, particularly pharmaceutical or agrochemical active ingredients. Prominent examples are the angiotensin II receptor antagonists losartan and valsartan for treatment of cardiovascular diseases, the nonsteroidal anti-inflammatory drug diflunisal, the antiinfective radezolid, the virostatic ledipasvir, or GABA receptor modulators such as zolpidem. Current synthesis methodologies used for these compounds involve transition metal catalyzed cross-coupling reactions (e.g. Pd catalyzed cross coupling such as Suzuki reaction). Owing to the use of heavy metals, undesired trace impurities remain in the products which are quality-limiting. Moreover, recycling of the catalysts is complicated and expensive.
Thus, recent research focuses on the development of metal-free approaches for the synthesis of biaryls. However, all metal-free strategies so far discovered suffer from different disadvantages like homocoupling, limited regioselectivity or remaining linker residues in the product. Therefore, the currently available metal-free coupling methods cannot compete with the powerful metal-catalyzed cross-couplings in terms of chemo- and regioselectivity. Thus, there is a need for novel approaches for metal-free synthesis of biaryl compounds overcoming the named drawbacks.



Schematic representation of the metal-free biaryl coupling by photosplicing (left) and photosplicing reactor setup (right).

Technology

The invention comprises a novel method for a regiocontrolled, metal-free biaryl coupling reaction achieved by a highly selective method termed *photosplicing*. A precursor molecule, consisting of two aryl moieties linked by a temporary traceless sulfonamide, undergoes a UV-light mediated aryl-fusion at room temperature leading to a single and metal-free coupling product. The suggested reaction mechanism implies a labile five-membered transition state, which decomposes sequentially. All detected extrusion products are volatile (sulfur dioxide, ammonia, formaldehyde), therefore the desired biaryl product remains. Radical formation and homocoupling does not occur. The inventive *photosplicing* approach provides a safe and convenient method for the production of biaryl building blocks in the field of pharmaceuticals, agrochemicals, organic polymers or redox active materials, particularly when trace metal impurities are critical. The method is a valuable alternative cross-coupling protocol which combines the advantages of classical metal catalyzed procedures and metal-free biaryl synthesis strategies known so far.

Commercial Opportunity

The invention is offered for licensing.

Development Status

Proof of concept has been obtained for the total synthesis of cannabinol, precursors of a variety of active ingredients of the sartan family (antihypertensives) and anti-inflammatory drugs (NSAIDs such as felbinac and xenbucin) among others. Current research focuses on production scale photoreactor designs as well as technical optimization of reaction parameters.

Patent Situation

A European priority application has been filed in November 2017 (EP17202739).

Further Reading

Kloss F., Neuwirth T., Haensch V., Hertweck C. *Metal-Free Synthesis of Pharmaceutically Important Biaryls by Photosplicing* (published online, https://doi.org/10.1002/anie.201805961).

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