Metal-Free Synthesis of Pharmaceutically Important Biaryls by Photosplicing.

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Projects

Investigation of new photochemical reactions
Details

Abstract

Many pharmaceuticals feature biaryl motifs that are crucial for their binding to the target. Yet, benchmark methods for selective cross-couplings rely on highly toxic heavy metal catalysts, which are unfavorable in the synthesis of pharmaceuticals. Metal-free coupling reactions, on the other hand, may require harsh conditions and lack selectivity. We report a novel, metal-free cross-coupling reaction that involves the tethering of two phenyl groups by a temporary, traceless sulfonamide linker that directs a photochemical aryl fusion into a single coupling product. The perfect regio- and chemoselectivity of the reaction could be rationalized by a cyclic intermediate, which fragments into the biaryl and volatile side products. Using a flow reactor, we synthesized numerous substituted biaryl building blocks for important therapeutics in high yields, such as antibiotics, antitumor, neuroprotective and cholesterol-lowering agents as well as antiarthritic non-steroidal antiinflammatory drugs (NSAIDs). The new method was successfully employed in a total synthesis of cannabinol, an important analgesic and antiemetic therapeutic. We also report a metal-free synthesis of key building blocks used for the preparation of sartans, antihypertensive agents that rank among the top blockbuster drugs worldwide. This safe and convenient protocol is a valuable alternative for the widely used metal-dependent aryl cross-coupling methods.

Identifier

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