Photochemistry

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Metal-Free Synthesis of Pharmaceutically Important Biaryls by Photosplicing

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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.*

Biaryls are important pharmacophoric groups found in a wealth of therapeutics including antibiotics, antiinflammatory, analgesic, neurological and antihypertensive drugs (Figure 1). The prevalence of the biaryl scaffold in pharmaceuticals has been rationalized by its ability to interact with a range of functional groups that are widespread in biological targets.[1] Because of its selective binding to proteins, the biaryl scaffold is regarded as a privileged structure.[2] The immense economic value of pharmaceuticals and other functional biaryls has consequently propelled the development of a vast array of synthetic methods. Unarguably, directed aryl cross-coupling reactions using late transition metal catalysts such as copper, nickel and palladium have revolutionized synthetic chemistry, which is reflected by the Nobel Prize in Chemistry 2010.[3] The huge success of Pd catalysis, in particular, is based on the fact that the intermediary metal complex directs the regio- and chemoselective fusion of two aryl groups with high accuracy (Figure 1). However, catalytic aryl couplings generally require the use of stoichiometric amounts of expensive organometallic compounds, which often require laborious synthesis and handling under inert conditions. Although it is sometimes possible to replace the organometallic part with redox-active carboxy

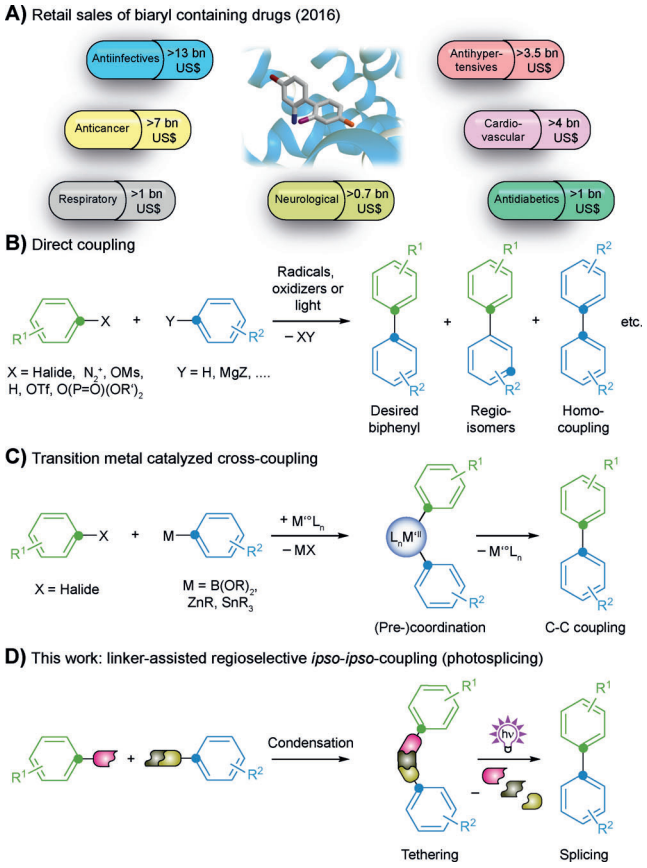

Figure 1. Impact and synthesis of biaryls. A) Biaryls are a privileged structure found in many clinically used drugs. B) General scheme for random direct coupling of aryls. C) Selective, catalytic cross-coupling by pre-coordination in transition-metal complexes. D) Selective, metal-free aryl coupling using a traceless linker for pre-coordination.

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groups[4] or triflates,[5] the coupling reactions involve harmful aryl halides and transition metals, which are scarce, expensive and toxic.

These limitations, which are unfavorable in the field of drug synthesis, have stimulated the development of a variety of metal-free biaryl syntheses.[6] Many expedient protocols have been reported, which involve photolysis to generate radicals or aryl cations,[7] Grignard reagents,[8] the oxidative coupling of electron-rich arenes,[9] and base-mediated coupling of aryl halides.[10] These methods, however, may require harsh conditions and large excess of the cross-coupling partner, and produce regioisomeric mixtures as well as homocoupling products in some cases. Current approaches to control selective oxidative aryl couplings involve metal catalysts.[11] In the absence of metals, regioselective biaryl syntheses have been achieved by intramolecular C–C bond formations and rearrangements,[12] but the linker or parts thereof remain in the product. Despite these promising developments, the currently available metal-free coupling methods still cannot outcompete the powerful metal-catalyzed cross-couplings. Here we report a novel metal-free approach to pharmaceutically relevant biaryls by a highly selective photochemical process termed photosplicing.

In the course of an attempted synthesis of an enzyme inhibitor, we serendipitously discovered a novel method that overcomes both the drawbacks of metal-catalyzed cross-couplings and the limitations of metal-free biaryl syntheses. Upon thin layer chromatographic (TLC) analysis and exposure to UV light for several minutes, the spot of an undesired sulfonamide side product (**1a**) started to show a strong fluorescence. Two-dimensional TLC suggested that the sulfonamide was transformed into a new product without any detectable side products (Figure 2A). High-resolution mass spectrometry (HRMS) of the fluorescent compound pointed at the molecular formula of $C_{14}H_{14}O_2$, indicating that the sulfur and nitrogen atoms disappeared. To elucidate the structure of the reaction product, the photoreaction was repeated on a larger scale. HPLC monitoring revealed that only a single product was formed. The structure of **2a** was fully elucidated by various NMR techniques and proved to be a *para*-substituted biaryl. Apparently, two aryl moieties were fused during traceless cleavage of the linker, which is reminiscent of biological splicing processes.

To develop this photosplicing process into a synthetic method, we tested and optimized a variety of conditions. We found that the reaction works well in methanol, ethanol, *n*-butanol, isopropanol, acetonitrile, tetrahydrofuran and acetone, while methanol and acetonitrile gave best results. The absorbance of the starting sulfonamide (**1a**) has a maximum at $\lambda = 233$ nm and declines towards the baseline at approximately 306 nm (Figure 2B). The emission of the low-pressure mercury lamp (maximum at $\lambda = 254$ nm) overlaps with the absorption of the sulfonamide (**1a**). Extensive kinetic studies on the reactivity of sulfonamide (**1a**) in relation to the UV wavelength showed that the rate of photosplicing is highest around $\lambda = 233$ nm and decreases towards 295 nm. This excitation range is in good agreement with the absorption spectrum of sulfonamide (**1a**). In addition, the selectivity of biphenyl (**2a**) formation slowly decreases with wavelength

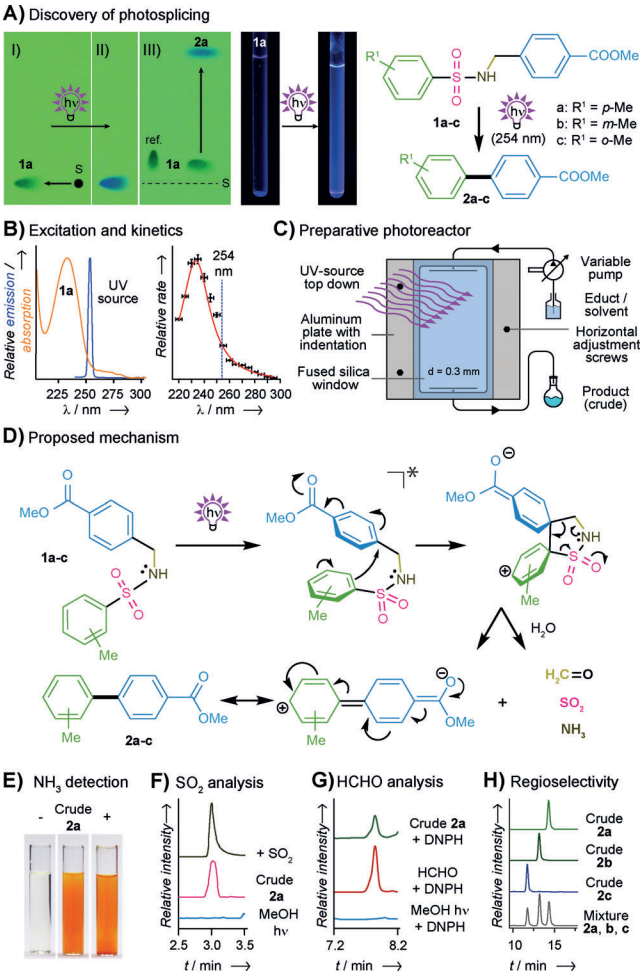

Figure 2. Discovery, design, wavelength dependency and mechanistic analysis of photosplicing reaction. A) Unexpected photoproduct on 2D-TLC, photoreaction in a quartz NMR tube, and structures of sulfonamide educts and biaryl products. B) Absorption of sulfonamide (**1a**) and emission of mercury lamp (left); wavelength dependency on the rate of photoreaction (right). C) Setup of flow photoreactor. D) Proposed reaction mechanism involving an intramolecular cyclization and a formal retro-[3+2] cycloaddition. E) Detection of ammonia released in the reaction. F) Gas chromatogram showing the formation of SO_2. G) HPLC profile (PDA) showing trapped formaldehyde (as hydrazone). H) HPLC profiles (PDA) from experiments involving regioisomeric sulfonamides that form distinct biaryls.

below $\lambda = 240$ nm, whereas higher wavelength have no influence (see the Supporting Information).

Since both the substrates and the biaryl products have strong UV absorbance the conversion rate is hampered in concentrated solutions ($> 1\ g\,L^{-1}$) and thick layers. To overcome these limitations we performed the reaction in flow and at reduced layer thickness (< 0.4 mm). Using a microfluidic system we demonstrated that it is possible to convert sulfonamide **1a** with continuous flow and a defined dwell time in the reactor. To upscale the reaction we constructed a two-channel flow chamber that is exposed to UV light emitted from low-pressure metal vapor lamps ($P_{sum} = 90$ W, $\lambda_{max} = 254$ nm) (Figure 2C). However, it should be highlighted that photosplicing can be performed in a standard

chemistry laboratory without the need of a flow photoreactor. Using a fused quartz glass vial, a magnetic stirrer and a UV lamp, yields are only slightly decreased (83 % instead of 92 % for **2a**), and reaction times increased.

The high regio- and chemoselectivities of the aryl coupling are striking, since previous studies indicated that the *S*–*N* bond of sulfonamides can be cleaved homolytically upon irradiation, followed by formation of carbon-centered radicals.[13] It is also known that the photochemical activation of aromatic sulfonamides can lead to radical Smiles rearrangements.[12b,14] A photochemical disruption and recombination is, however, unlikely. Biaryls that would arise from random radical recombination processes could not be detected in the reaction mixture. The outstanding regiocontrol can be better rationalized by an intramolecular reaction that may be initiated by a photo-induced charge transfer or polarization, thus leading to a cyclic transition state that would allow orbital interactions of both aryl residues. The instable five-membered intermediate would decompose in the fashion of a retro-[3+2] cycloaddition to yield the coupling product and the linker-derived *N*-sulfonylimine (Figure 2D).[15] The latter would readily fragment into sulfur dioxide, ammonia and formaldehyde (upon hydrolysis), thus exerting a driving force of the reaction.

To test this model we analyzed the side products of the coupling reaction. For the qualitative detection of ammonia we employed an alkaline solution of potassium tetraiodomercurate(II) (Nessler's reagent). Whereas the negative controls gave colorless solutions, irradiation of the sulfonamide solution followed by addition of Nessler's reagent resulted in a diagnostic orange coloration (Figure 2E). Sulfur dioxide formation was monitored by headspace GC-MS analysis. In contrast to the negative controls, the expected mass $m/z = 64$ (SO_2) was only detected in the biaryl-containing reaction mixture (Figure 2F). To trap the predicted formaldehyde we used 2,4-dinitrophenylhydrazine (Brady's reagent). By means of HPLC-HRMS we detected the formaldehyde-derived hydrazone from the photoreaction mixture. The identity of the product was verified by comparison of UV/Vis spectra, HRMS data, and retention times with a synthetic reference generated from a formalin-spiked solution (Figure 2G). Taken together, the photoreaction of the sulfonamide leads to a traceless cleavage of the linker and yields the biaryl product by an *ipso-ipso* substitution with very high regioselectivity. To validate the concept of *ipso-ipso*-substitution, we prepared regioisomeric sulfonamides with methyl residues in *para*-, *meta*- and *ortho*-position. In all cases we observed the specific formation of the *para*-, *meta*- and *ortho*-substituted biaryls (**2a**, **b**, **c**) (Figure 2H).

This clean, metal-free, and highly selective reaction appeared to be particularly suitable for the synthesis of pharmaceuticals. Diverse sulfonamides are readily available by nucleophilic substitution reactions using sulfonyl chlorides and benzyl amines (Figure 3A). Preliminary experiments revealed that a broad range of substituents, ranging from methoxy-, benzyloxy, cyano-, chloro-, fluoro-, carboxyalkyl-, dimethylamino- and alkyl-, is tolerated by the method. Only photolabile substituents such as bromide, iodide and nitro groups give no photoproducts, and photoactive substituents like thioethers, ketones and aldehydes give substantially lower yields.

To evaluate the utility of the metal-free photoreaction we synthesized a range of biaryl pharmacophores found in important lead compounds and clinically used drugs (Figure 3B). Biphenylcarboxylic ester **2d** and the corresponding alkoxy-substituted biphenyl **2e**, components of a novel antibiotic and of a potent histamine H3 receptor antagonist A-349821, were prepared in 76 % and 89 % yield, respectively. The fluorinated biaryl **2f**, an important building block of an inhibitor of the antiapoptotic protein Bcl-xL, was obtained in 66 % yield. Notably, besides biphenylcarboxy esters it is also possible to synthesize biphenylacetic ester **2g** from the corresponding sulfonamide (48 %). Biaryl **2g** is a precursor of the important antiarthritic non-steroidal antiinflammatory drugs (NSAID) felbinac and xenbucin.

Next, we envisaged the use of the photochemical aryl coupling method in a total synthesis of cannabinol. Because of its analgesic and antiemetic properties this non-psychoactive cannabinoid is a valuable therapeutic, yet it is only produced in trace amounts by *Cannabis*.[16] A photosplicing route to the cannabinol biaryl scaffold required a highly substituted sulfonamide precursor that was readily accessible starting from olivetol (see the Supporting Information). Irradiation provided the corresponding biaryl (**2h**) in excellent yield (93 %). Subsequent demethylation, nitrile hydrolysis and lactonization were achieved in a one-pot reaction (67 %). The obtained benzochromenone was quantitatively converted into cannabinol by reaction with methyllithium.[17]

Finally, we prepared the biaryl pharmacophore of the top-selling antihypertensive agents (sartans) such as losartan (Cozaar®), valsartan (Diovan®), and telmisartan (Micardis®).[18] According to the patent literature, their synthesis is based on Pd-catalyzed cross-couplings and subsequent bromination at the benzylic position, followed by nucleophilic substitution with primary amines or imidazoles.[19] We established a metal-free synthesis of the sartane biaryl scaffold by irradiation of two different *o*-substituted sulfonamides, yielding nitrile- and carboxymethyl-substituted biphenyl building blocks (**2i** and **2j**), which represent valuable starting points to the synthesis of all important sartans. Whereas the tetrazole substituents are easily accessible by treatment with sodium azide, hydrolysis leads to the carboxy-substituted sartans (Figure 3).

These results show that the photoreaction tolerates a variety of substituents found in biaryls used for the preparation of pharmaceuticals with good to excellent yields (Figure 3B). Surprisingly, it is feasible to couple aryls with multiple *ortho*-substituents adjacent to the sulfonamide linker to produce highly substituted biaryls as shown in the cannabinol route in high yield.

In conclusion, we present an unprecedented type of carbon-carbon bond forming reaction via photogenerated intermediates.[20] With its high regio- and chemoselectivity the conceptually new photochemical method shares the advantages of metal-catalyzed cross-couplings without the need of inert conditions, halogenated aromatics, expensive organometallic reagents or toxic transition metals. It is a particularly valuable alternative for the synthesis of active pharmaceutical

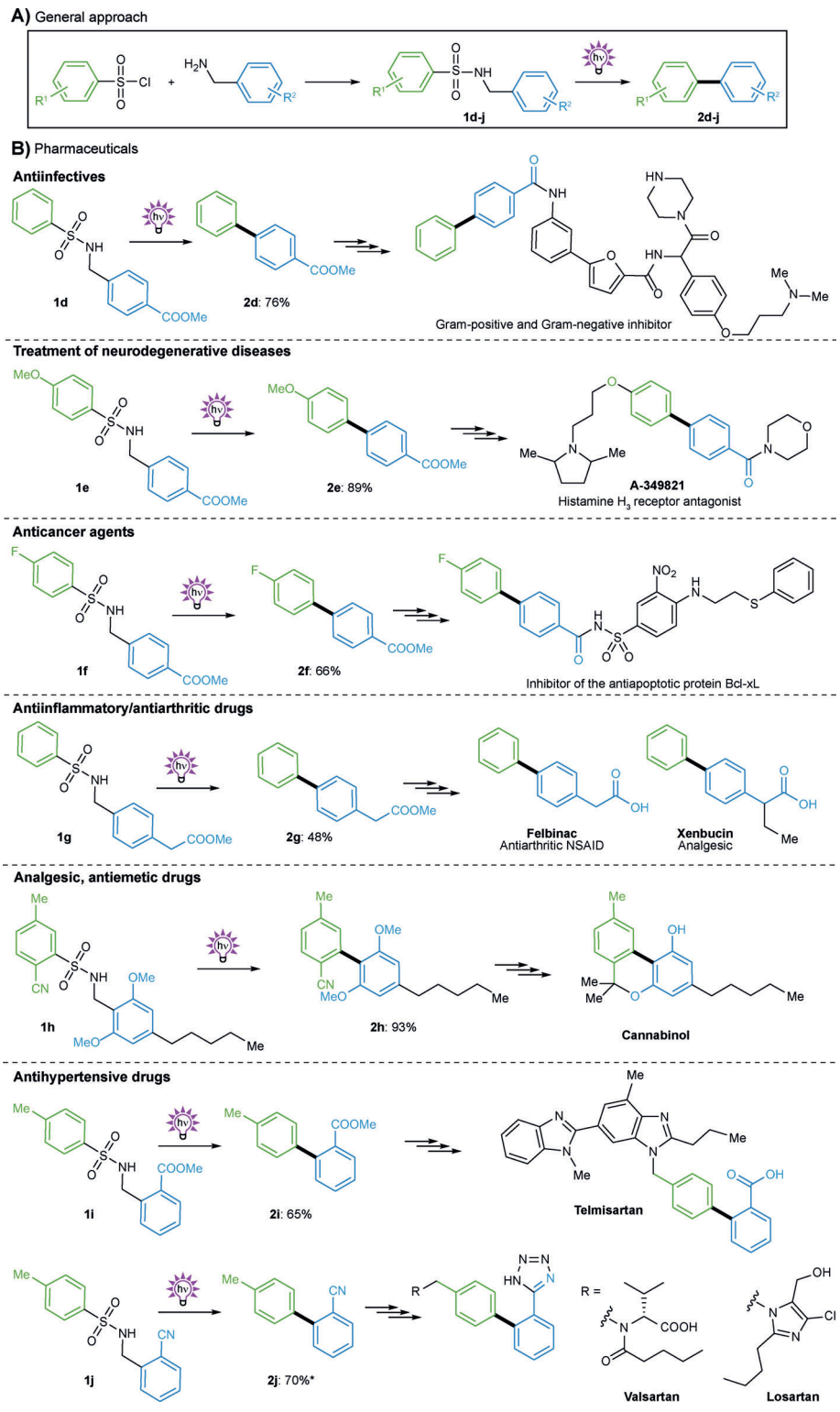

Figure 3. Metal-free synthesis of biaryl pharmacophores. A) General synthetic approach to sulfonamides and the derived biaryls. B) Synthesis of biaryl precursors of drug candidates and clinically used therapeutics. Total synthesis of cannabinol: 7 steps, total yield 15%.

ingredients or any application where trace impurities of heavy metals are critical for quality or product properties. The simple photochemical method even allows difficult, sterically demanding reactions with multiple *ortho*-substituents. Further advantages of the method are the straightforward syntheses of the sulfonamide precursors, which are often tailored from commercially available building blocks. These features combined with its broad scope and good yields render photosplicing an important addition to the synthetic toolbox of cross-coupling methodologies. Future work will address the full synthetic scope and exact mechanism of the novel aryl coupling method.

Experimental Section

General procedure of the photosplicing reaction: A substituted benzylsulfonamide (series **1**, prepared by any method available) is dissolved in methanol or acetonitrile (HPLC grade) to yield a concentration between 0.1 and 5 mg mL^{-1}. The solution is loaded on a continuous-flow thin-film photoreactor and irradiated with a 254 nm UV lamp. Average dwell times should be set in the range of 5–60 min, depending on the individual reaction speed. A typical silica window size of a photoreactor is 17 × 32 cm and suitable UV sources are six low-pressure metal vapor UV-C lamps (15 W power consumption each). The solvent feed of the photoreactor should be operated using an adjustable pump with appropriate flow rates. Reactor temperatures should be in the range of 0 to 25 °C. Throughout the reaction proper shielding of the setup must be warranted to protect the user from UV irradiation. The fractions containing the crude photoproducts are collected, the solvents are removed under reduced pressure and the residues are purified by silica gel filtration, flash chromatography or crystallization to yield the desired biaryls.

Full methods, detailed synthetic procedures and physicochemical characterization of new compounds including NMR spectra are available in the Supporting Information.

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Conflict of interest

A patent application on the synthetic method has been submitted.

Keywords: biaryls · cross-couplings · photochemistry · sulfonamides · synthetic methods

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Communications

Photochemistry

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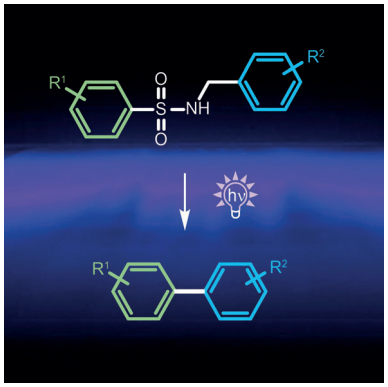
Metal-Free Synthesis of Pharmaceutically Important Biaryls by Photosplicing



Light on biaryls: A novel metal-free approach to biaryls is reported that involves the tethering and photochemical fusion of phenyl groups through sulfonamides. Using a flow reactor biaryl pharmacophores of numerous therapeutics, antibiotics, antitumor and neuroprotective agents, non-steroidal antiinflammatory drugs, sartans, and cannabinol, were prepared in excellent yields.