Photosensitization enables Pauson–Khand–type reactions with nitrenes

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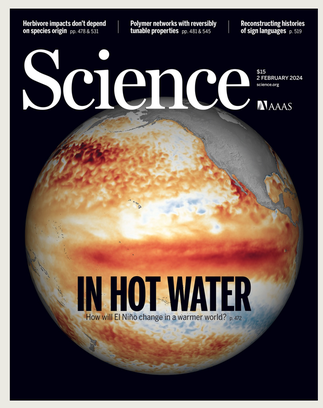
Introduction

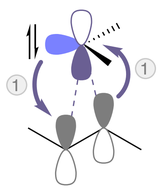
The Pauson-Khand reaction has in the past 50 years become one of the most common cycloaddition reactions in chemistry. Coupling two unsaturated bonds with carbon monoxide, the transformation remains limited to CO as a C_1 building block. Herein we report analogous cycloaddition reactions with nitrenes as an N_1 unit. The reaction of a nonconjugated diene with a nitrene precursor produces bicyclic bioisosteres of common saturated heterocycles such as piperidine, morpholine, and piperazine. Experimental and computational mechanistic studies support relaying of the diradical nature of triplet nitrene into the π-system. We showcase the reaction's utility in late-stage functionalization of drug compounds and discovery of soluble epoxide hydrolase inhibitors.



Combining Fundamentals and Applications

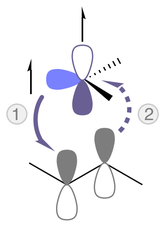
General reactivity of singlet and triplet reagents

Singlet reagents
[2+1] cycloaddition with singlet species



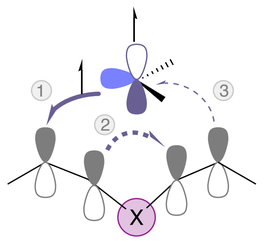
favorable interactions
(n) indicates sequence of reaction steps

Triplet reagents
[2+1] cycloaddition with triplet species



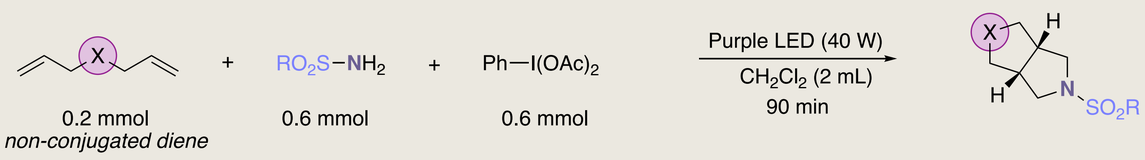
stepwise mechanism

This work: [2+2+1] cycloaddition with triplet species

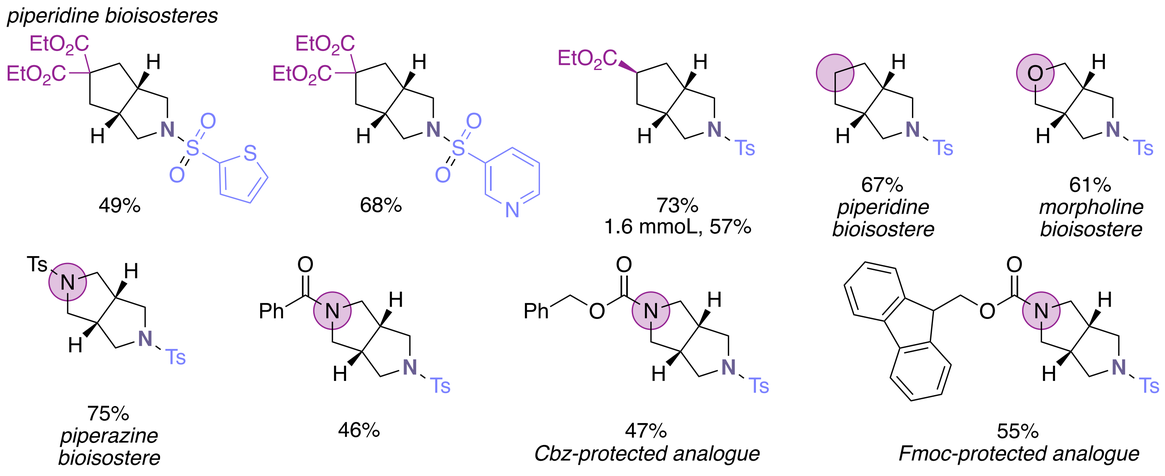


relay of the triplet reactivity

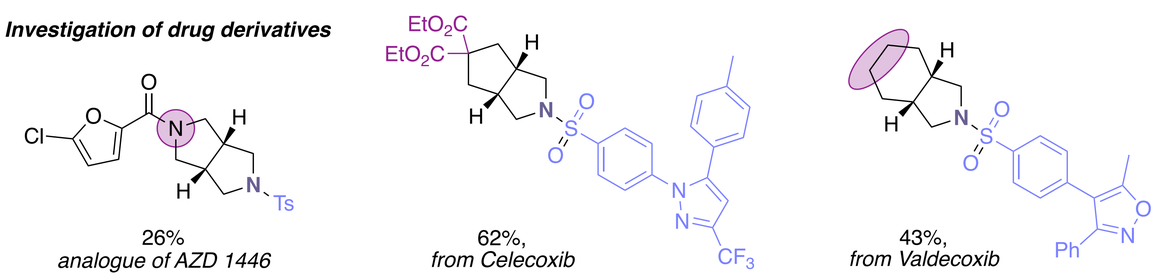
In situ synthesis of bioisosteres



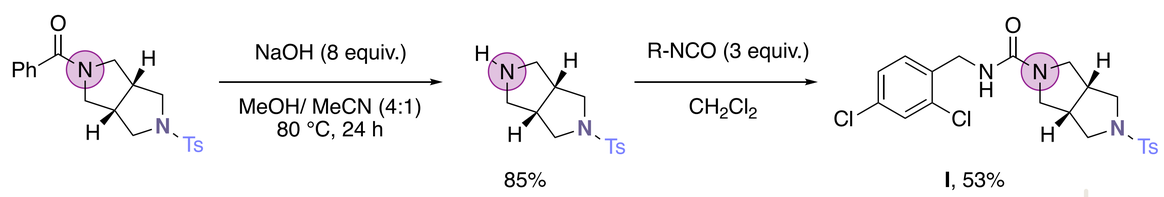
piperidine bioisosteres



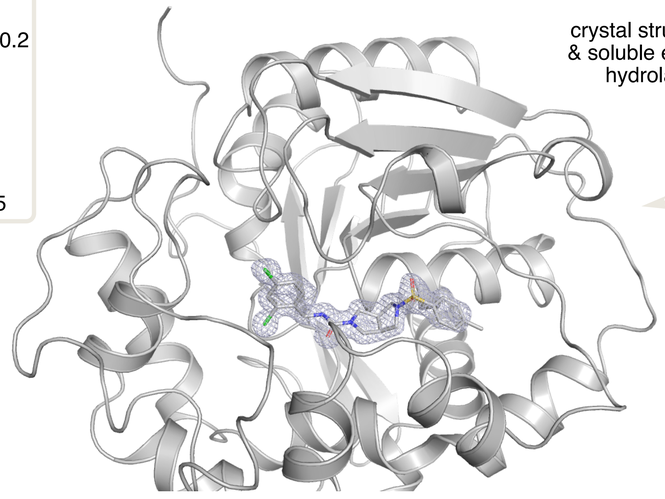
Investigation of drug derivatives



Synthesis of soluble Epoxid Hydolase (sEH) inhibitors

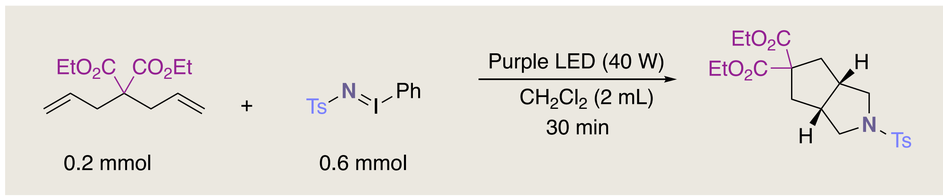


evaluation for applications in medicinal chemistry	
IC_{50} (sEH) [nM]	2.4±0.2
solubility [μM]	20
CL_{int} [mg μL^{-1} min^{-1}]	303
lgP_e (PAMPA)	-4.45

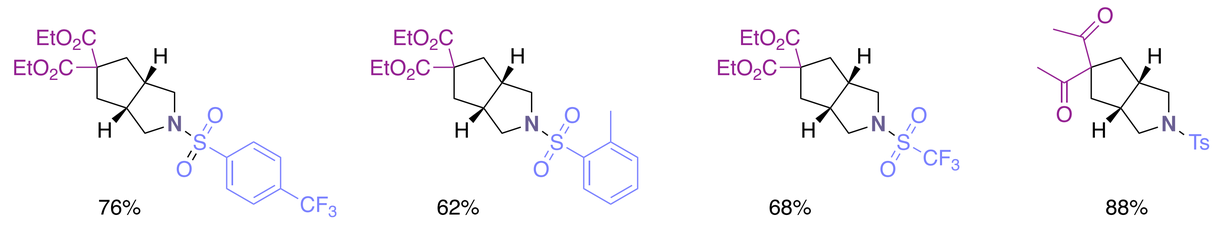


crystal structure **I** & soluble epoxide hydrolase

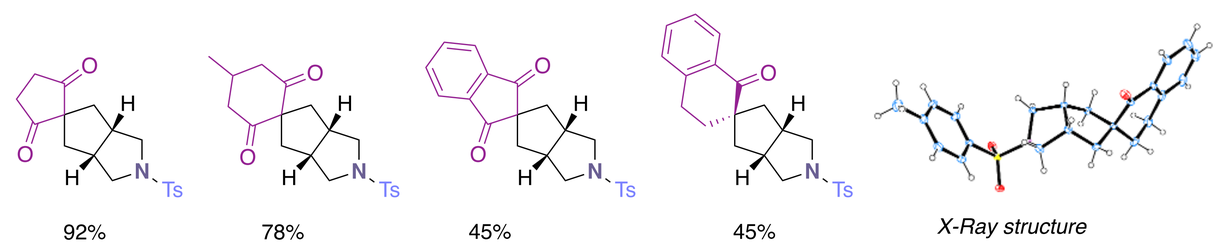
Photochemical synthesis of 3-aza-bicyclo-[3.3.0]-octane derivatives



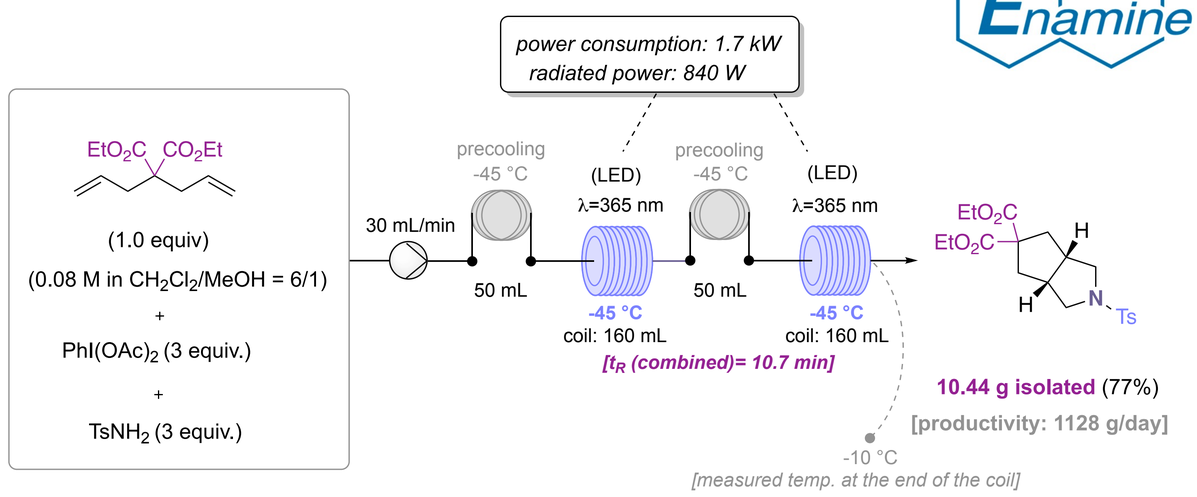
synthesis of substituted piperidine bioisosteres



synthesis of spirocyclic piperidine bioisosteres



Reaction scale up – Flow synthesis



Understanding the reaction mechanism