

**The I.S.H.C. Bulletin**

**Recent Publications of Members**

**Issue 78     June 2023**

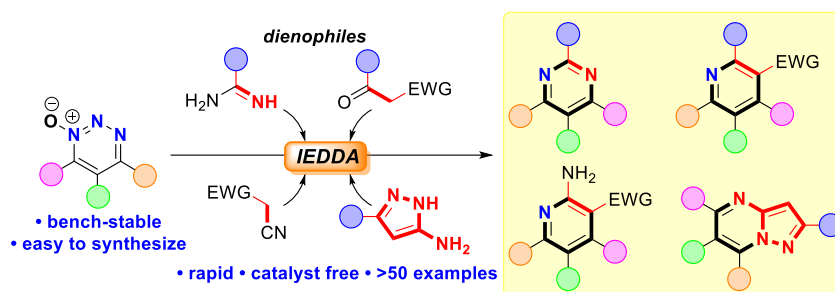
Please send any articles for inclusion in future publications to [ishc@surrey.ac.uk](mailto:ishc@surrey.ac.uk)

If you wish to advertise any conferences or vacant positions, please email [ishc@surrey.ac.uk](mailto:ishc@surrey.ac.uk)

**Inverse Electron Demand Diels-Alder-type Heterocycle Syntheses with 1,2,3-Triazine 1-Oxides - Expanded Versatility**

Soumen Biswas, Luca De Angelis, Gildardo Rivera, Hadi Arman, Michael P. Doyle\*

*Org. Lett.* **2023**, 25, 1104-1108    DOI:10.1021/acs.orglett.2c04360

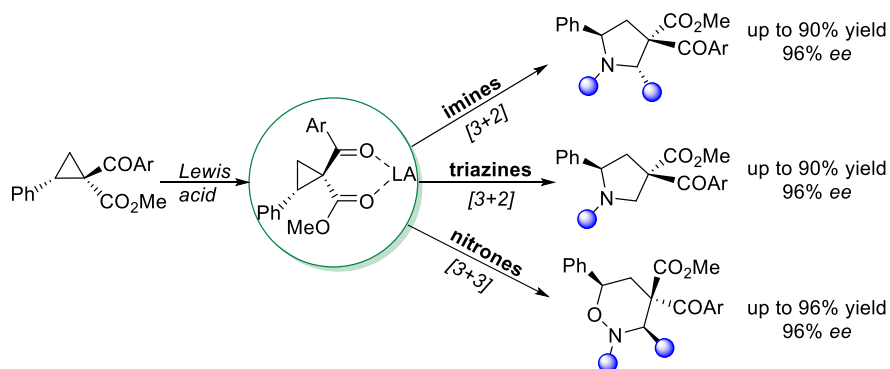


1,2,3-Triazine 1-oxides are remarkably effective substrates for inverse electron demand Diels-Alder reactions. Formed from vinyldiazoacetates via reaction with *tert*-butyl nitrite, these stable heterocyclic compounds undergo clean nucleophilic addition with amidines to form pyrimidines, with β-ketocarbonyl compounds and related nitrile derivatives to form polysubstituted pyridines, and with 3/5-aminopyrazoles to form pyrazolo[1,5-*a*]pyrimidines, in high yield. These practical reactions are rapid at room temperature, base catalyzed, and offer a diversity of structural modifications.

**Stereoretentive Catalytic [3 + 2]/[3 + 3]-Cycloaddition of Nonracemic Donor–Acceptor Cyclopropanes: Synthesis of Substituted Pyrrolidines and 1,2-Oxazinanes**

Ming Bao, Michael P. Doyle\*

*Org. Lett.* **2023**, 26, 3029-3033    DOI:10.1021/acs.orglett.3c00831



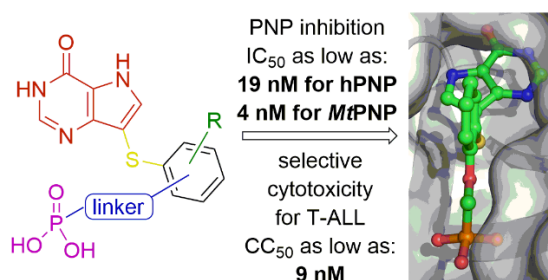
A highly enantioselective preparation of substituted pyrrolidines and 1,2-oxazinanes has been achieved *via* stereoretentive [3+2]/[3+3]-cycloaddition of non-racemic donor-acceptor cyclopropanes with imines, triazines and nitrones in good to high yields with broad scope under mild reaction conditions. In comparison with the well-documented approach to donor-acceptor

cyclopropane reactions using racemic cyclopropane reactants and a catalyst with chiral ligands, this report features applications of enantioenriched donor-acceptor cyclopropanes as cycloadduct reactants with achiral catalysts.

## Design, Synthesis, Biological Evaluation, and Crystallographic Study of Novel Purine Nucleoside Phosphorylase Inhibitors.

Jan Skácel, Stefan Djukic, Ondřej Baszczyński, Filip Kalčic, Tadeáš Bílek, Karel Chalupský, Jaroslav Kozák, Alexandra Dvořáková, Eva Tloušťová, Zuzana Král'ová, Markéta Šmídková, Jan Voldřich, Michaela Rumlová, Petr Pachl, Jiří Brynda, Tereza Vučková, Milan Fábry, Jan Snášel, Iva Pichová, Pavlína Řezáčová, Helena Mertlíková-Kaiserová, Zlatko Janeba

*Journal of Medicinal Chemistry* **66**: 6652–6681, 2023. <https://doi.org/10.1021/acs.jmedchem.2c02097>

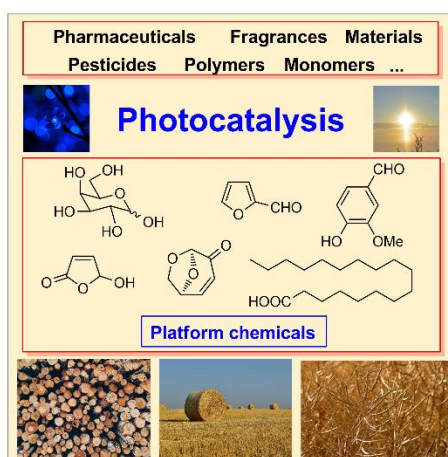


Purine nucleoside phosphorylase (PNP) is a well-known molecular target with potential therapeutic applications in the treatment of T-cell malignancies and/or bacterial/parasitic infections. Here, we report the design, development of synthetic methodology, and biological evaluation of a series of 30 novel PNP inhibitors based on acyclic nucleoside phosphonates bearing 9-deazahypoxanthine nucleobase. The strongest inhibitors exhibited  $IC_{50}$  values as low as 19 nM (human PNP) and 4 nM (*Mycobacterium tuberculosis* (*Mt*) PNP), and highly selective cytotoxicity towards various T-lymphoblastic cell lines with  $CC_{50}$  values as low as 9 nM. No cytotoxic effect was observed on other cancer cell lines (HeLa S3, HL60, HepG2) or primary PBMCs for up to 10  $\mu$ M. We report the first example of PNP inhibitor exhibiting over 60-fold selectivity for the pathogenic enzyme (*Mt*PNP) over hPNP. The results are supported by a crystallographic study of eight enzyme-inhibitor complexes and by ADMET profiling *in vitro* and *in vivo*.

## Photocatalytic Transformation of Biomass and Biomass Derived Compounds – Application to Organic Synthesis

Mario Andrés Gómez Fernández, Norbert Hoffmann\*

*Molecules* **2023**, *28*, 4746. DOI: <https://doi.org/10.3390/molecules28124746>



Biomass and biomass-derived compounds have become an important alternative feedstock for chemical industry. They may replace fossil feedstocks such as mineral oil and related platform chemicals. These compounds may also be transformed

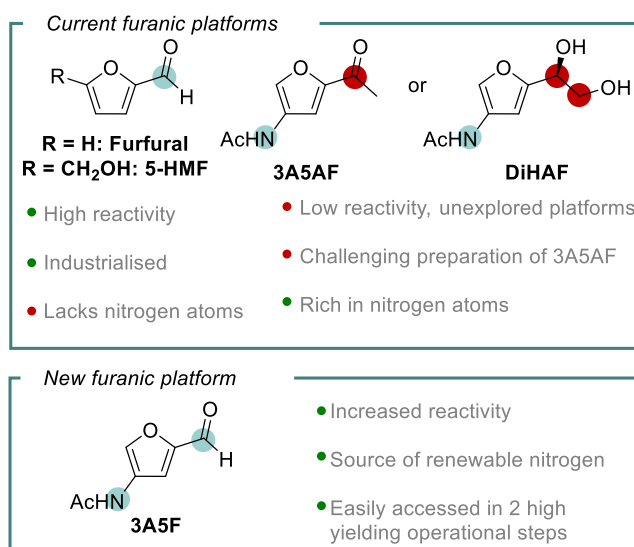
conveniently into new innovative products for the medicinal or the agrochemical domain. The production of cosmetics or surfactants as well as materials for different applications are examples for other domains where new platform chemicals obtained from biomass can be used. Photochemical and especially photocatalytic reactions have recently been recognized as being important tools of organic chemistry as they make compounds or compound families available that cannot be or are difficultly synthesized with conventional methods of organic synthesis. The present review gives a short overview with selected examples on photocatalytic reactions of biopolymers, carbohydrates, fatty acids and some biomass-derived platform chemicals such as furans or levoglucosenone. In this article, the focus is on application to organic synthesis.

## Unlocking the Potential of Bio-Based Nitrogen-Rich Furanic Platforms as Biomass Synthons

Rafael F. A. Gomes, Bruno M. F. Gonçalves, Késsia H. S. Andrade, Bárbara B. Sousa, Nuno Maulide, Gonçalo J. L. Bernardes, Carlos A. M. Afonso,

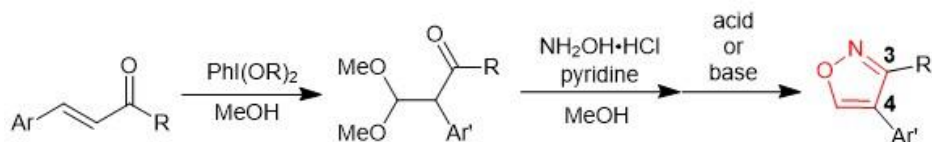
*Angewandte Chemie*, **2023**, e202304449 DOI: 10.1002/anie.202304449.

The demand for new biomass-derived fine and commodity chemicals propels the discovery of new methodologies and synthons. Whereas furfural and 5-hydroxymethylfurfural are cornerstones of sustainable chemistry, 3-acetamido-5-acetyl furan (3A5AF), an N-rich furan obtained from chitin biomass, remains unexplored, due to the poor reactivity of the acetyl group relative to previous furanic aldehydes. Here we developed a reactive 3-acetamido-5-furfuryl aldehyde (3A5F) and demonstrated the utility of this heterocyclic synthon as a source of bio-derived nitrogen-rich heteroaromatics, carbocycles, and as a bioconjugation reagent.



## Regioselective Synthesis of 3,4-Disubstituted Isoxazoles by Using a Chalcone-Rearrangement Strategy

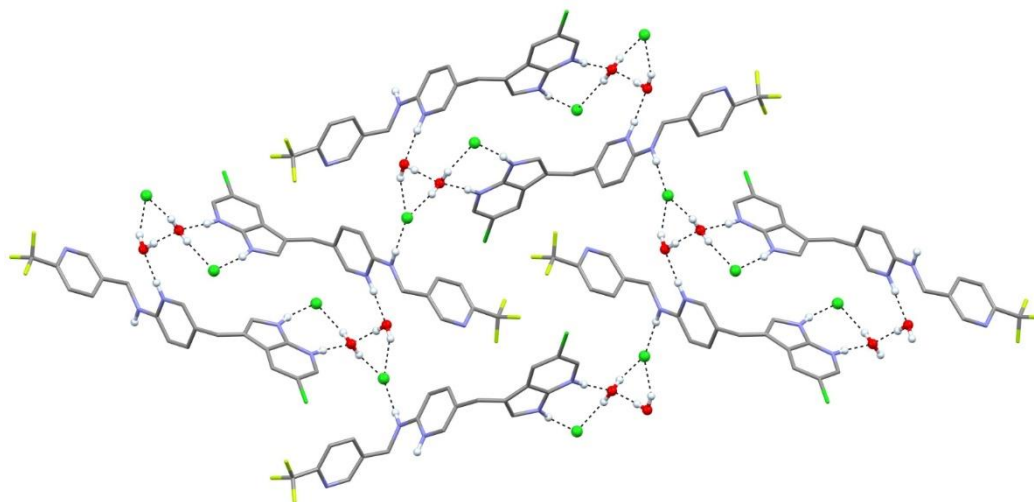
Akira Nakamura, Tohko Kine, Haruna Uenishi, Yuri Maki, Yasuhito Kase, Mayo Takagi, Tomohiro Maegawa\*  
*Synlett*, **2023**, 34,1253 DOI: [10.1055/a-2028-9454](https://doi.org/10.1055/a-2028-9454)



We have developed a regioselective synthesis of 3,4-disubstituted isoxazoles by using a chalcone-rearrangement strategy. The reaction of  $\beta$ -ketoacetals with hydroxylamine hydrochloride and pyridine afforded the corresponding 3,4-disubstituted isoxazoles via isoxazolines or oximes. Depending on the substrate, another disubstituted isomer was also obtained under our optimized conditions, and a reaction mechanism for each transformation is proposed.

## 5-[(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-N-[[6-(trifluoromethyl)pyridin-3-yl]methyl]pyridin-2-amine Dihydrochloride Dihydrate

Weronika Kozanecka-Okupnik, Klaus Wurst, Sandro Neuner, Sven Nerdinger and Thomas Gelbrich \*  
*Molbank* **2023**, 2023(2), M1673. DOI: <https://doi.org/10.3390/M1673>



The dihydrochloride salt of pexidartinib was synthesized and the crystal structure of its dihydrate was determined from single crystal data. The asymmetric unit consists of one formula unit. In the pexidartinib molecule, the N atom of the central pyridine ring and the pyridine-N atom of the pyrrolopyridine group are both protonated. The pexidartinib molecule forms N–H···O and N–H···Cl interactions with neighboring water molecules and chloride ions, respectively. Water/chloride (O–H···Cl) and water/water (O–H···O) interactions are also observed. Collectively, these intermolecular interactions result in a complex H-bonded framework structure.