Issue 89 August 2024

The I.S.H.C. Bulletin

Recent Publications of Members

Issue 89 August 2024

Please send any articles for inclusion in future publications to ishc@surrey.ac.uk

If you wish to advertise any conferences or vacant positions, please email ishc@surrey.ac.uk

ISHC Congress July 2024

Thank you to everyone who came to the 29th Congress of the Society.
In particular, we sincerely and deeply thank our hosts, Prof Teresa Pinho e Melo and Prof Artur Silva and all of their team for the excellent organisation and hospitality. A great time was had by all attendees and Aveiro (Portugal) was a fantastic location.
Many congratulations to all the award and prize winners:

E.C. Taylor Senior Award in Heterocyclic Chemistry
Professor Mark Lautens
(University of Toronto, Canada)

A.R. Katritzky Junior Award in Heterocyclic Chemistry
Professor Ryan Shenvi
(Scripps Institute)

ISHC Industrial Award
Dr Jeffrey T. Kuethe
(Merck)

Best Oral Presentation Prizes:

João R. Vale (*Total synthesis of (-)-agelastatin A from pyridine: Improving scalability*)
Willi M. Amberg (*Photo- and cobalt-catalyzed synthesis of heterocycles via cycloisomerization of unactivated olefins*)

Best Poster Presentation Prizes:

Kazuho Ban (*Development of various deuterated alkylating reagents using D2O for drug discovery*)
Phillip S. Grant (*Remote proton elimination: C–H activation enabled by distal acidification*)

International Society of Heterocyclic Chemistry
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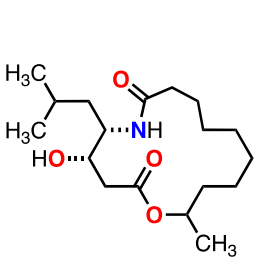
Now here are this month's latest articles from the membership.

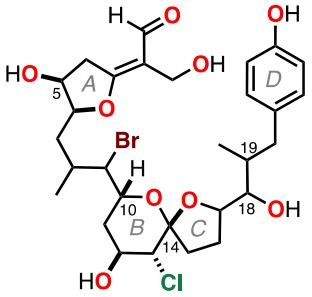
Small molecule *in situ* resin capture provides a compound first approach to natural product discovery

Bogdanov, A.; Salib, M.N.; Chase, A.B.; Hammerlindl, H.; Muskat, M.N.; Luedtke, S.; da Silva, E.B.; O'Donoghue, A.J.; Wu, L.F.; Altschuler, S.J.; Molinski, T.F.*; Jensen, P.R.*

Nat. Commun. **2024**, *15*, 5230-5244. **DOI:** https://doi.org/10.1038/s41467-024-49367-x



Cabrillostatin A (**1**)



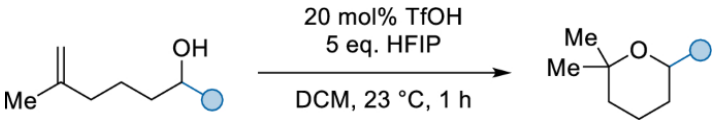
Cabrillospiral A (**2**)

Culture-based microbial natural product discovery strategies fail to realize the extraordinary biosynthetic potential detectable across earth's microbiomes. Here we introduce Small Molecule *In situ* Resin Capture (SMIRC), a culture- independent method to obtain natural products directly from the environments in which they are produced. We use SMIRC to capture numerous natural products including representatives of two new carbon skeletons; cabrillostatin (**1**) and cabrillospiral A (**2**). The molecular structures, characterized by microcryoprobe NMR, MS and ECD, include the first example of a dihydrofuran-2(3*H*)-ylidene vinylogous formate ester, **2**. This compound-first approach to natural product discovery provides access to poorly explored chemical space and has implications for drug discovery and the detection of chemically mediated biotic interactions.

Tetrahydropyran synthesis mediated by catalytic triflic acid and hexafluoroisopropanol

Bogdan R. Brutiu, Le Tang, Daniel Kaiser and Nuno Maulide*

Monatsh. Chem. – Chem. Monthly **2024**, *155*, 709–713; **DOI**: 10.1007/s00706-024-03214-3



A Brønsted acid-catalyzed regioselective intramolecular hydroalkoxylation is described. This reaction proceeds via a carbocation intermediate and enables the preparation of 1,1,1'-trisubstituted tetrahydropyran derivatives under mild conditions using catalytic triflic acid (TfOH) and hexafluoroisopropanol (HFIP) as a mediator.

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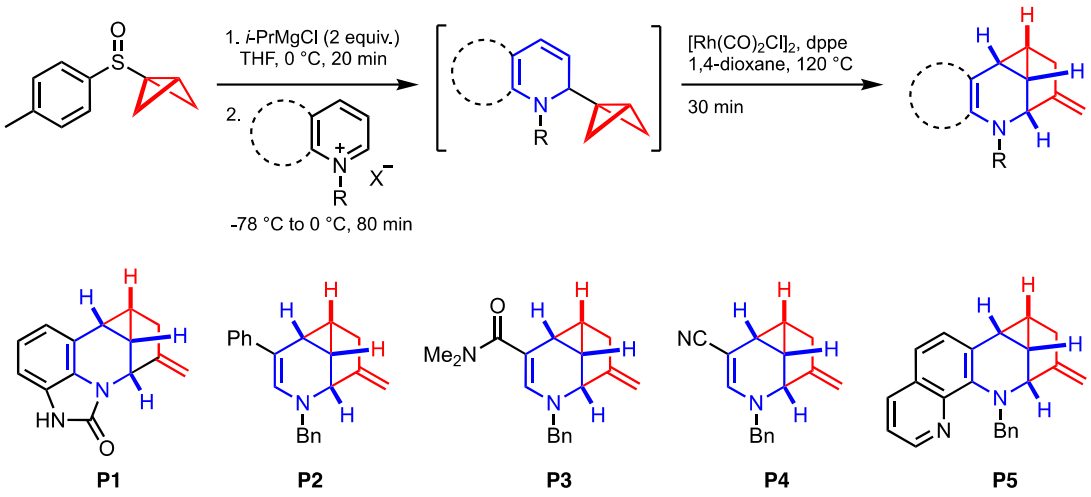
Rhodium(I)-Catalyzed Annulation of Bicyclo[1.1.0]butyl-Substituted Dihydroquinolines and Dihydropyridines

Matteo Borgini, Qi-Nan Huang, Pan-Pan Chen, Steven J. Geib, K. N. Houk, and Peter Wipf

J. Am. Chem. Soc. ***2024****, 146, 14927−14934* **DOI**: 10.1021/jacs.4c04081

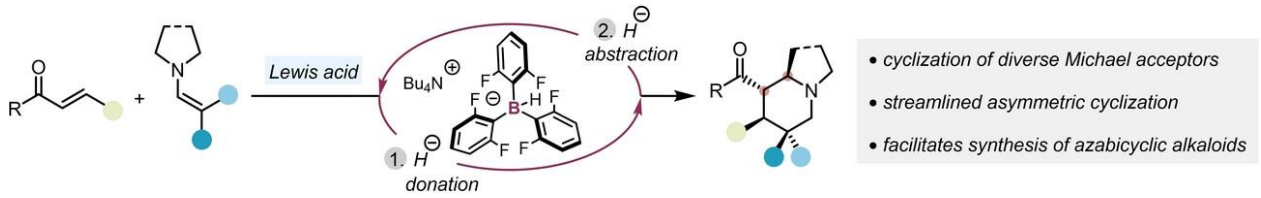


Bicyclo[1.1.0]butane-containing compounds feature a unique chemical reactivity, trigger “strain-release” reaction cascades, and provide novel scaffolds with considerable utility in the drug discovery field. We report the synthesis of new bicyclo[1.1.0]butane-linked heterocycles such as **P1**-**P5** by a nucleophilic addition of bicyclo[1.1.0]butyl anions to iminium cations derived from quinolines and pyridines. The resulting bicyclo[1.1.0]butanes are converted in a rhodium(I)-catalyzed annulative rearrangement to structurally unprecedented bridged heterocycles. The addition/rearrangement process tolerates a surprisingly large range of functional groups. Subsequent chemo- and stereoselective synthetic transformations of urea, alkene, cyclopropane, and aniline moieties of the 1-methylene-5-azacyclopropa[*cd*]indene scaffolds provide several additional new heterocyclic building blocks.

Lewis Acid-Driven Inverse Hydride Shuttle Catalysis

Benjamin T. Jones and Nuno Maulide*

Angew. Chem. Int. Ed. **2024**, *63*, e202320001; **DOI**: 10.1002/anie.202320001



Inverse hydride shuttle catalysis provides a multicomponent platform for the highly efficient synthesis of alkaloid frameworks with exquisite diastereoselectivity. However, a number of limitations have thus far hindered this method, primarily the strict requirement for highly electron-deficient acceptors. Herein, we present a general Lewis acid-driven approach to address this constraint, and have developed two broad strategies enabling the modular synthesis of complex azabicycles that were entirely unattainable using the previous method. The enhanced synthetic flexibility facilitates a streamlined asymmetric cyclization, leading to a concise total synthesis of the alkaloid (−)-tashiromine.

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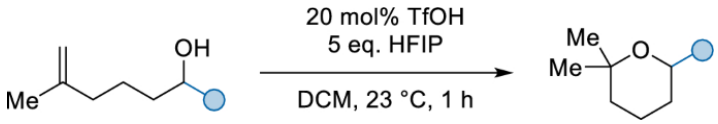
Tetrahydropyran synthesis mediated by catalytic triflic acid and hexafluoroisopropanol

Bogdan R. Brutiu, Le Tang, Daniel Kaiser and Nuno Maulide*

Monatsh. Chem. – Chem. Monthly **2024**, *155*, 709–713; **DOI**: 10.1007/s00706-024-03214-3

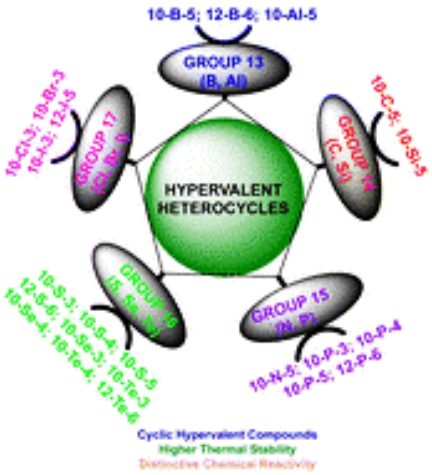


A Brønsted acid-catalyzed regioselective intramolecular hydroalkoxylation is described. This reaction proceeds via a carbocation intermediate and enables the preparation of 1,1,1'-trisubstituted tetrahydropyran derivatives under mild conditions using catalytic triflic acid (TfOH) and hexafluoroisopropanol (HFIP) as a mediator.

Organohypervalent Heterocycles

Ravi Kumar,* Toshifumi Dohi,* and **Viktor V. Zhdankin***

Chem. Soc. Rev. **2024**, *53*, 4786- 4827. **DOI**: 10.2174/1570178620666230803123511

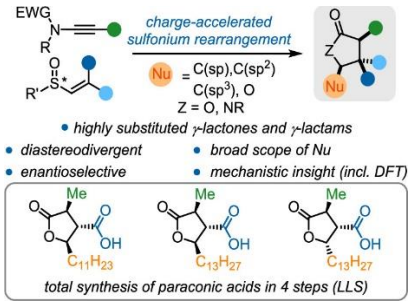


This review summarizes the structural and synthetic aspects of heterocyclic molecules incorporating an atom of a hypervalent main-group element. The term "hypervalent" has been suggested for derivatives of main-group elements with more than eight valence electrons, and the concept of hypervalency is commonly used despite some criticism from theoretical chemists. The significantly higher thermal stability of hypervalent heterocycles compared to their acyclic analogs adds special features to their chemistry, particularly for bromine and iodine. Heterocyclic compounds of elements with double bonds are not categorized as hypervalent molecules owing to the zwitterionic nature of these bonds, resulting in the conventional 8-electron species. This review is focused on hypervalent heterocyclic derivatives of nonmetal main-group elements, such as boron, silicon, nitrogen, carbon, phosphorus, sulfur, selenium, bromine, chlorine, iodine(III) and iodine(V).

Stereodivergent Synthesis of 1,4-Dicarbonyl Compounds through Sulfonium Rearrangement: Mechanistic Investigation, Stereocontrolled Access to γ-Lactones and γ-Lactams, and Total Synthesis of Paraconic Acids

Nicolas G.-Simonian, Philipp Spieß, Margaux Riomet, Boris Maryasin, Immo Klose, Alexander Beaton Garcia, Laurin Pollesböck, Dainis Kaldre, Uroš Todorovic, Julia Minghua Liu, Daniel Kaiser, Leticia González, and Nuno Maulide*

J. Am. Chem. Soc. **2024**, *146*, 13914–13923; **DOI**: 10.1021/jacs.4c01755



Although simple γ-lactones and γ-lactams have received considerable attention from the synthetic community, particularly due to their relevance in biological and medicinal contexts, stereoselective synthetic approaches to more densely substituted derivatives remain scarce. The in-depth study presented herein, showcasing a straightforward method for the stereocontrolled synthesis of γ-lactones and γ-lactams, builds on and considerably expands the stereodivergent synthesis of 1,4-dicarbonyl compounds by an ynamide/vinyl sulfoxide coupling. A full mechanistic and computational study of the rearrangement was conducted, uncovering the role of all of the reaction components and providing a rationale for stereoselection. The broad applicability of the developed tools to streamlining synthesis is demonstrated by concise enantioselective total syntheses of (+)-nephrosteranic acid, (+)-rocellaric acid, and (+)-nephromopsinic acid.