International Society of Heterocyclic Chemistry
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Issue 56; June 2021

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Recent Publications of ISHC Members

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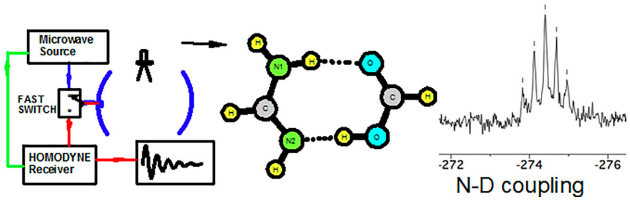
Measurements of Microwave and NMR Spectra for ^{15}N Substituted Formamidinium Formate

Zunwu Zhou, Coralyse Peureux, R. Alan Aitken, Stephen G. Kukolich* (kukolich@arizona.edu)

J. Mol. Spectrosc. **2021**, *378*, 111478 (1–5). **DOI:** 10.1016/j.jms.2021.111478

^{15}N Formamidine Formate Microwave and NMR Spectra

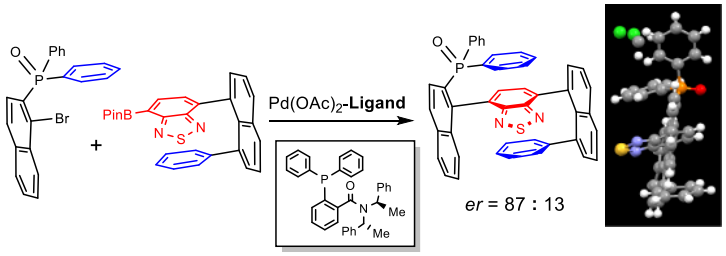


Abstract: A sample of doubly-substituted ^{15}N formamidinium formate was synthesized and the microwave spectrum was measured in the 5.6–14.2 GHz frequency range using a Flygare-Balle type pulsed beam Fourier transform microwave (MW) spectrometer. A total of 13 a-type rotational transitions were measured and fitted to obtain the rotational constants and centrifugal distortion constants for the ^{15}N substituted isotopologue. The rotational constants and centrifugal distortion constants determined have the following values: A=5808.02(18) MHz, B=2127.008(2) MHz, C=1557.615(2) MHz, D_J=0.60(11) kHz, D_{JK}=4.95(71) kHz and δ_J=–0.138(24) kHz. Tunneling splittings were searched for, but not observed. NMR spectra for this compound are reported including values of δ_C, δ_N, $^1J_{CH}$, $^1J_{CN}$ and $^2J_{NH}$ in CD_3SOCD_3, CD_3OD and D_2O. The occurrence of NH to ND exchange in D_2O allowed the fortuitous measurement of $^1J_{ND}$.

Asymmetric Catalytic Approach to Multilayer 3D Chirality

Guanzhao Wu, Yangxue Liu, Hossein Rouh, Liulei Ma, Yao Tang, Sai Zhang, Peng Zhou, Jia-Ying Wang, Shengzhou Jin, Daniel Unruh, Kazimierz Surowiec, Yanzhang Ma, and Guigen Li* (guigen.li@ttu.edu)

Chem. Eur. J. **2021**, *27*, 8013–8020. **DOI:** 10.1002/chem.202100700



Asymmetric Catalysis and X-Ray Assignment

Abstract: The first asymmetric catalytic approach to multi-layer 3D chirality has been achieved *via* Suzuki-Miyaura cross-couplings. New chiral catalysts were designed and screened under various catalytic systems that proved chiral amide-phosphines to be more efficient ligands than other candidates. The multi-layer 3D framework was unambiguously determined by X-ray structural analysis showing a parallel pattern of three layers consisting of top, middle and bottom aromatic rings. X-ray structure of a catalyst complex, dichloride complex of Pd-phosphine amide, was obtained revealing an interesting asymmetric environment nearby the Pd metal center. Three rings of multi-layer 3D products can be readily changed by varying aromatic ring-anchored starting materials. The resulting multi-layer products displayed strong luminescence under UV irradiation and strong aggregation-induced emission (AIE). This work would benefit not only asymmetric chemistry but also materials science, particularly, polarized organic electronics, optoelectronics and photovoltaics.

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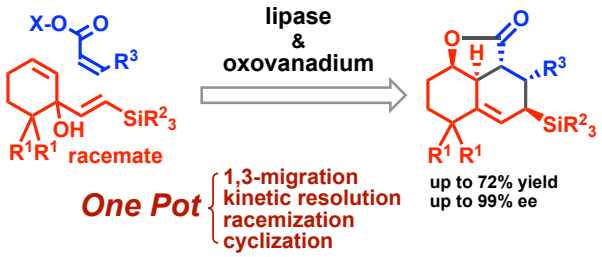
Four-Step One-Pot Catalytic Asymmetric Synthesis of Polysubstituted Tricyclic Compounds: Lipase-Catalyzed Dynamic Kinetic Resolution Followed by an Intramolecular Diels–Alder Reaction

Izuru Tsuchimochi, Shuhei Hori, Yasuo Takeuchi, Masahiro Egi, Tomo-o Satoh, Kyohei Kanomata, Takashi Ikawa, Shuji Akai* (akai@phs.osaka-u.ac.jp)

Synlett **2021**, *32*, 822–828. **DOI:** 10.1055/a-1344-8713

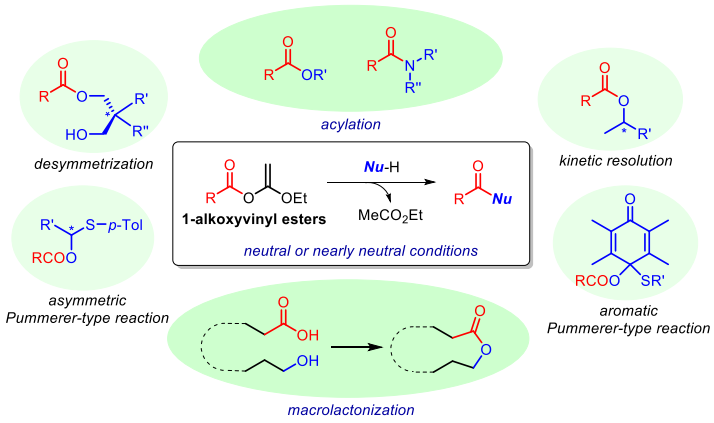


Abstract: Starting from readily available tertiary alcohols, four different reactions (a 1,3-migration of a hydroxy group, kinetic resolution, racemization, and an intramolecular Diels–Alder reaction) took place under co-catalysis by lipase and oxovanadium compounds in a one-pot process to produce polysubstituted tricyclic carbon frameworks in high yields and with high enantioselectivities. The key to the success of this process was the discovery that a silyl group attached to the terminal carbon of the vinyl moiety completely controls the direction of hydroxy group migration.

1-Alkoxyvinyl Ester as an Excellent Acyl Donor: Efficient Macrolactone Synthesis

Yasuyuki Kita,* Shuji Akai, Hiromichi Fujioka, and Tohru Kamitanaka (kita@ph.ritsumei.ac.jp)

J. Org. Chem. **2021**, *86*, 3683–3696. **DOI:** 10.1021/acs.joc.0c02677

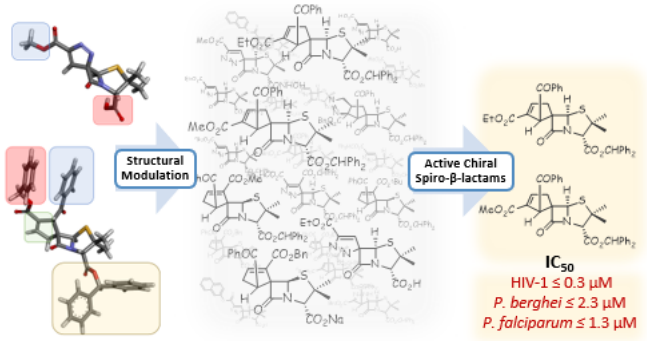


Abstract: Ketene acetal derivatives, such as 1-alkoxyvinyl esters and *O*-silyl ketene acetals, belong to the category of *O*-substituted enols of esters, which easily react with various types of nucleophiles, Nu–H, under neutral conditions to give the corresponding acylated and silylated products in excellent yields only by evaporation of the generated volatile esters. Silyl ketene acetals can be easily synthesized by various simple procedures, whereas 1-alkoxyvinyl esters require an equimolar or catalytic amount of a mercury salt to synthesize them. This drawback prevented the advancement of the chemistry of 1-alkoxyvinyl esters. In 1993, we developed a useful synthetic method of 1-alkoxyvinyl esters using a small amount of a ruthenium catalyst, subsequently developed various reactions and applied them to the synthesis of biologically useful natural products and macrolactones. Additionally, several new reactions using 1-alkoxyvinyl esters or their analogs as key intermediates on the basis of our methods were recently reported. In this paper, we introduce our efforts from the synthesis of 1-alkoxyvinyl esters to the application such as natural product syntheses and recent advancements.

Synthesis and Structure-Activity Relationships of New Chiral Spiro-β-Lactams Highly Active Against HIV-1 and *Plasmodium*

Nuno Guerreiro Alves, Inês Bártolo, Américo J. S. Alves, Diana Fontinha, Denise Francisco, Susana M. M. Lopes, Maria I. L. Soares, Carlos, J. V. Simões, Miguel Prudêncio, Nuno Taveira, Teresa M. V. D. Pinho e Melo* (tmelo@ci.uc.pt)

Eur. J. Med. Chem. **2021**, *219*, 113439 (1–16). **DOI:** 10.1016/j.ejmech.2021.113439

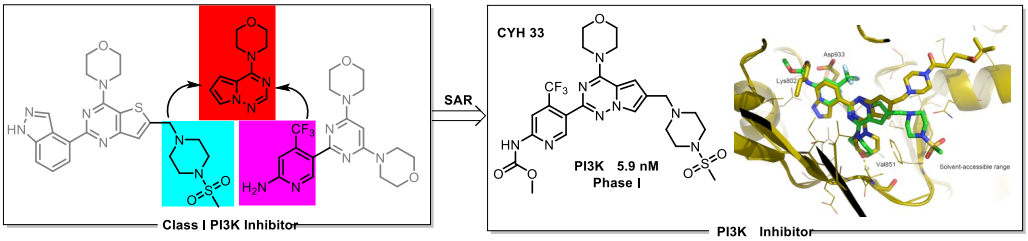


Abstract: The synthesis and antimicrobial activity of new spiro-β-lactams is reported. The design of the new molecules was based on the structural modulation of two previously identified lead spiro-penicillanates with dual activity against HIV and *Plasmodium*. The spiro-β-lactams synthesized were assayed for their *in vitro* activity against HIV-1, providing relevant structure-activity relationship information. Among the tested compounds, two spirocyclopentenyl-β-lactams were identified as having remarkable nanomolar activity against HIV-1. Additionally, the same molecules showed promising antiplasmodial activity, inhibiting both the hepatic and blood stages of *Plasmodium* infection.

Identification of Methyl (5-(6-((4-(Methylsulfonyl)piperazin-1-yl)methyl)-4-morpholinopyrrolo[2,1-*f*][1,2,4]triazin-2-yl)-4-(trifluoromethyl)pyridine-2-yl)carbamate (CYH33) as an Orally Bioavailable, Highly Potent, PI3K Alpha Inhibitor for the Treatment of Advanced Solid Tumors

Hao-Yue Xiang, Xiang Wang, Yan-Hong Chen, Xi Zhang, Cun Tan, Yi Wang, Yi Su, Zhi-Wei Gao, Xiao-Yan Chen, Bing Xiong, Zhao-Bing Gao, Yi Chen, Jian Ding,* Ling-Hua Meng,* Chun-Hao Yang* (jding@simm.ac.cn or lhmeng@simm.ac.cn or chyang@simm.ac.cn)

Eur. J. Med. Chem. **2021**, *209*, 112913 (1–10). **DOI:** 10.1016/j.ejmech.2020.112913

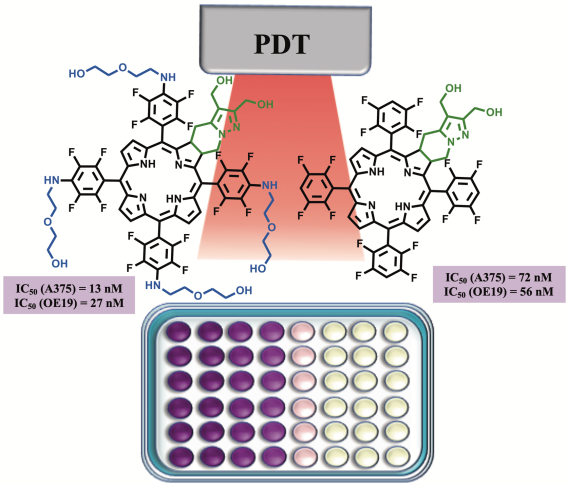


Abstract: In various human cancers, PI3Ks pathway is ubiquitously dysregulated and thus become a promising anti-cancer target. To discover new potent and selective PI3K inhibitors as potential anticancer drugs, new pyrrolo[2,1-*f*][1,2,4]triazines were designed, leading to the discovery of compound **37** (**CYH33**), a selective PI3Kα inhibitor (IC_{50} = 5.9 nM, β/α, δ/α,γ/α = 101-, 13-, 38-fold). Western blot analysis confirmed that compound **37** could inhibit phosphorylation of AKT in human cancer cells to modulate the cellular PI3K/AKT/mTOR pathway. And further evaluation *in vivo* against SKOV-3 xenograft models demonstrated that a dose-dependent antitumor efficacy was achieved.

Novel Fluorinated Ring-Fused Chlorins as Promising PDT Agents Against Melanoma and Esophagus Cancer

Nelson A. M. Pereira, Mafalda Laranjo, Bruno F. O. Nascimento, João C. S. Simões, João Pina, Bruna D. P. Costa, Gonçalo Brites, João Braz, J. Sérgio Seixas de Melo, Marta Pineiro, Maria Filomena Botelho, and Teresa M. V. D. Pinho e Melo (tmelo@ci.uc.pt)

RSC Med. Chem. **2021**, *12*, 615–627. **DOI:** 10.1039/d0md00433b

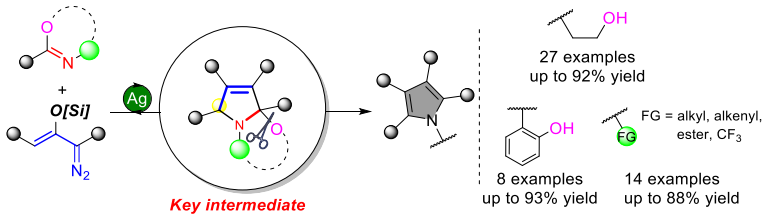


Abstract: Investigation of novel 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyridine-fused chlorins, derived from 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin, as PDT agents against melanoma and esophagus cancer is disclosed. Diol and diester fluorinated ring-fused chlorins, including derivatives with 2-(2-hydroxyethoxy)ethanamino groups at the phenyl rings, were obtained via a two-step methodology, combining SNAr and [8π + 2π] cycloaddition reactions. The short-chain PEG groups at the para-position of the phenyl rings together with the diol moiety at the fused pyrazole ring promote a red-shift of the Soret band, a decrease of the fluorescence quantum yield and an increase of the singlet oxygen formation quantum yield, improving the photophysical characteristics required to act as a photosensitizer. Introduction of these hydrophilic groups also improves the incorporation of the sensitizers by the cells reaching cellular uptake values of nearly 50% of the initial dose. The rational design led to a photosensitizer with impressive IC_{50} values, 13 and 27 nM against human melanoma and esophageal carcinoma cell lines, respectively.

Ag^{I}-Catalyzed Reaction of Enol Diazoacetates and Imino Ethers: Synthesis of Highly Functionalized Pyrroles

Kuiyong Dong, Ahmad Humeidi, Wendell Griffith, Hadi Arman, Xinfang Xu,* and Michael P. Doyle* (xuxinfang@mail.sysu.edu.cn or michael.doyle@utsa.edu)

Angew. Chem. Int. Ed. **2021**, *60*, 13394–13400. **DOI:** 10.1002/anie.202101641

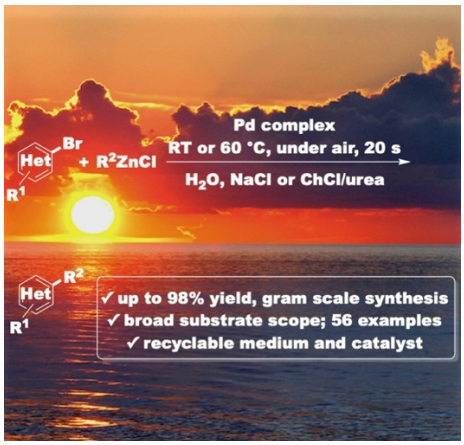


Abstract: An unprecedented Ag^{I}-catalyzed efficient method for the coupling of imino ethers and enol diazoacetates through a [3+2]-cycloaddition/C–O bond cleavage/[1,5]-proton transfer cascade process is reported. The general class of imino ethers that includes oxazolines, benzoxazoles and benzimidates are applicable substrates for these reactions that provide direct access to fully substituted pyrroles with uniformly high chemo- and regioselectivity. High variability in substitution at the pyrrole 2-, 5- and *N*-positions characterizes this methodology that also presents an entry point for further pyrrole diversification via facile modification of resulting *N*-functional pyrroles.

Scalable Negishi Coupling Between Organozinc Compounds and (Hetero)Aryl Bromides Under Aerobic Conditions When Using Bulk Water or Deep Eutectic Solvents With No Additional Ligands

Giuseppe Dilauro, Claudia S. Azzollini, Paola Vitale, Antonio Salomone, Filippo M. Perna,* and Vito Capriati* (filippo.perna@uniba.it or vito.capriati@uniba.it)

Angew. Chem. Int. Ed. **2021**, *60*, 10632–10636. **DOI:** 10.1002/anie.202101571

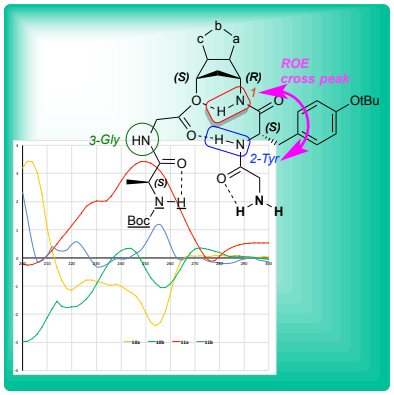


Abstract: Pd-catalyzed Negishi cross-coupling reactions between organozinc compounds and (hetero)aryl bromides have been reported when using bulk water as the reaction medium in the presence of NaCl or the biodegradable choline chloride/urea eutectic mixture. Both C(sp3)-C(sp2) and C(sp2)-C(sp2) couplings have been found to proceed smoothly, with high chemoselectivity, under mild conditions (room temperature or 60 °C) in air, and in competition with protonolysis. Additional benefits include very short reaction times (20 s), good to excellent yields (up to 98%), wide substrate scope, and the tolerance of a variety of functional groups. The proposed novel protocol is scalable, and the practicability of the method is further highlighted by an easy recycling of both the catalyst and the eutectic mixture or water.

Turn-Folding in Fluorescent Anthracene-Substituted Cyclopenta[*d*]isoxazoline Short Peptides

Marco Leusciatti, Barbara Mannucci, Teresa Recca, and Paolo Quadrelli* (paolo.quadrelli@unipv.it)

RSC Adv. **2021**, *11*, 19551–19559. **DOI:** 10.1039/d1ra03685h



Abstract: Cyclopenta[*d*]isoxazoline aminols were used for the synthesis of the β-turn mimics. The peptide chains choice ascertained the influence of their structural features on the applicability/reliability/robustness of these scaffolds as β-turn inducers and their limitations. The amino acid selection as well as steric demands can favor or disfavor the structure folding and the correct design of the peptide chains deeply influence the potential use of these nitrosocarbonyl-based compounds as turn-inducers.

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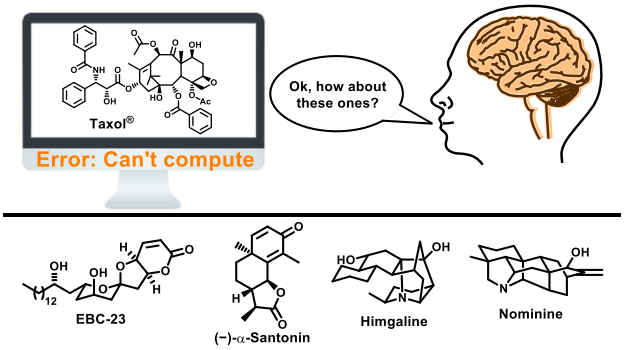
The Future of Retrosynthesis and Synthetic Planning: Algorithmic, Humanistic or the Interplay?

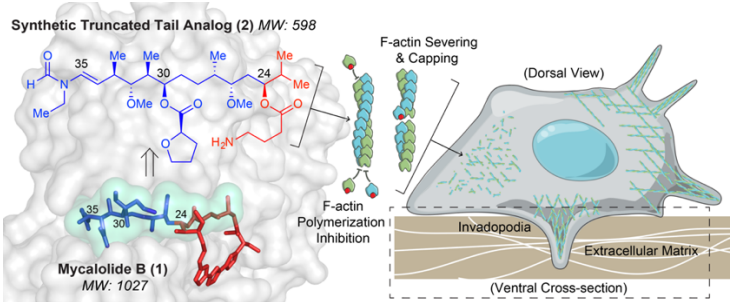
Craig M. Williams* and Madeleine A. Dallaston (c.williams3@uq.edu.au)
Aust. J. Chem. **2021**, *74*, 291–326. **DOI:** 10.1071/CH20371



Abstract: Will the computer ever compete with human retrosynthetic design and the art of organic synthesis? An overview is presented that covers the concept of retrosynthesis, along with exemplified methods and theories, and an attempt to comprehend the impact of artificial intelligence in an era when freely and commercially available retrosynthetic and forward synthesis planning programs are increasingly prevalent. Classical and historical methods and practices of retrosynthesis are briefly overviewed, along with an assessment of currently available retrosynthesis programs. Combined, this assessment will hopefully generate philosophical debate around the pros and cons of AI introduction and contemplation on the future of organic synthesis design.

Truncated Actin-Targeting Macrolide Derivative Blocks Cancer Cell Motility and Invasion of Extracellular Matrix

Bhavin V. Pipaliya, Daria N. Trofimova, Rebecca L. Grange, Madhuy Aeluri, Xu Deng, Kavan Shah, Andrew W. Craig, John S. Allingham,* and P. Andrew Evans* (allinghj@queensu.ca or andrew.evans@chem.queensu.ca)
J. Am. Chem. Soc. **2021**, *143*, 6847–6854. **DOI:** 10.1021/jacs.0c12404



Abstract: Cancer metastasis is a complex process involving highly motile tumor cells that breach tissue barriers, enter the bloodstream and lymphatic system, and disseminate throughout the body as circulating tumor cells. The primary cellular mechanism contributing to these critical events is the reorganization of the actin cytoskeleton. Mycalolide B (MycB) is an actin-targeting marine macrolide that can suppress proliferation, migration, and invasion of breast and ovarian cancer cells at low nanomolar doses. Through structure-activity relationship studies focused on the actin-binding tail region (C24–C35) of MycB, we identified a potent truncated derivative that inhibits polymerization of G-actin and severs F-actin by binding to actin's barbed end cleft. Biological analyses of this miniature MycB derivative demonstrate that it causes a rapid collapse of the actin cytoskeleton in ovarian cancer cells and impairs cancer cell motility and invasion of extracellular matrix (ECM) by inhibiting invadopodia-mediated ECM degradation. These studies provide essential proof-of-principle for developing actin-targeting therapeutic agents to block cancer metastasis and establish a synthetically tractable barbed end-binding core that can be further improved by adding targeting groups for precision drug design.