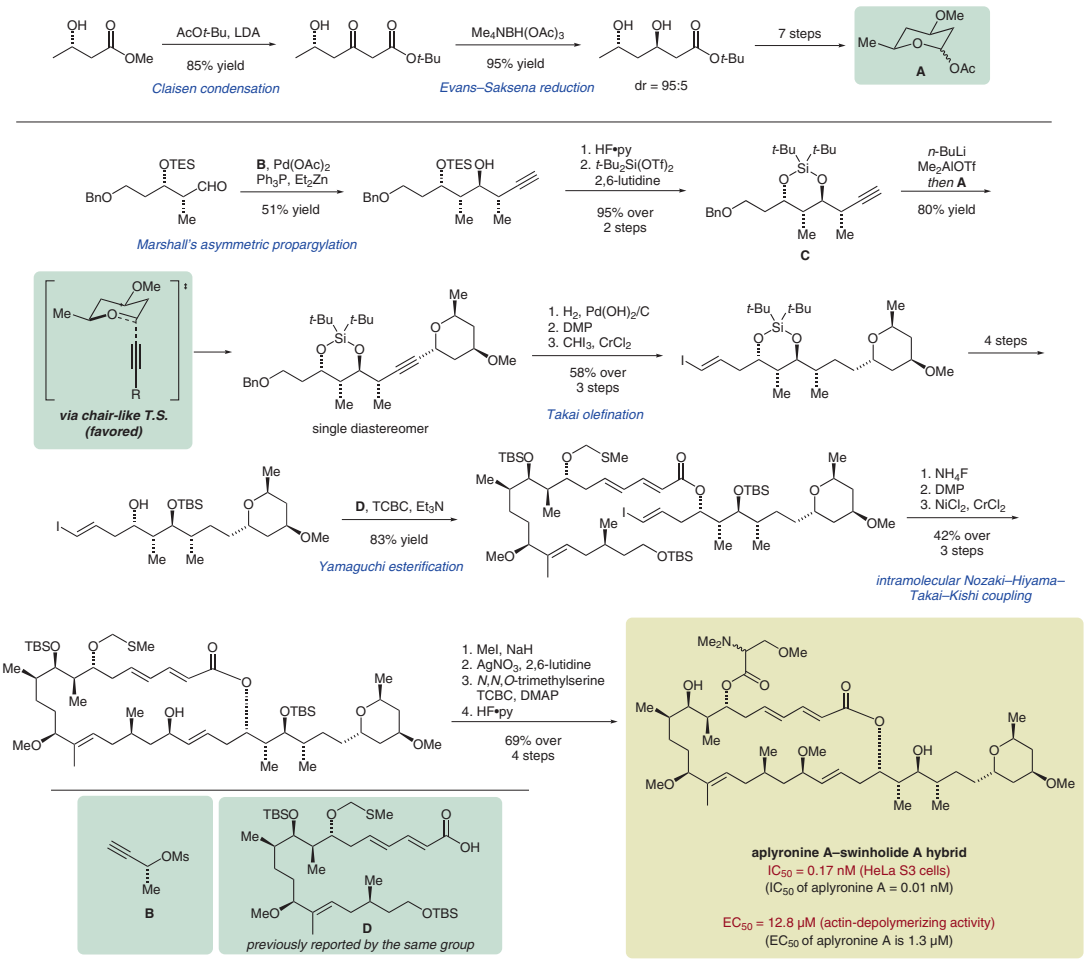
T. OHYOSHI*, A. TAKANO, I. KIKUCHI, T. OGURA, M. NAMIKI, Y. MIYAZAKI, T. HIRANO, S. KONISHI, Y. EBIHARA, K. TAKENO, I. HAYAKAWA, H. KIGOSHI* (UNIVERSITY OF TSUKUBA, JAPAN)

Structure–Activity Relationship Studies on an Antitumor Marine Macrolide using Aplyronine A–Swinholide A Hybrid
Org. Biomol. Chem. **2022**, *20*, 2922–2938, DOI: 10.1039/d2ob00118g.

A Natural Product Hybrid with Potent Antitumor Activity



Significance: Bioactive natural products are promising resources in drug development. The authors report a natural product hybrid approach by combining aplyronine A and swinholide A. By synthetically combining the structures of these two marine macrolides, the group has developed an aplyronine A–swinholide A hybrid, which showed comparably potent cytotoxicity and actin depolymerizing activity against HeLa S3 cells.

Comment: Synthesis of pyran **A** involves a Claisen condensation and an asymmetric Evans–Saksena ketone reduction. Pyran **A** and acetylene **C** were coupled using a highly diastereoselective reaction governed by a kinetically favored chair-like transition state over a twist-boat conformation. Other key reactions used in the synthesis are Takai olefination, a modified Yamaguchi esterification, and an intramolecular Nozaki–Hiyama–Takai–Kishi coupling.

SYNFACTS Contributors: Dirk Trauner, Tufan K. Mukhopadhyay
Synfacts 2022, 18(07), 0797 Published online: 15.06.2022
DOI: 10.1055/s-0041-1737647; **Reg-No.:** T08822SF

Category

Chemistry in Medicine and Biology

Key words

Marshall's asymmetric propargylation

Takai olefination

Nozaki–Hiyama–Takai–Kishi coupling

aplyronine A–swinholide A hybrid

Synfact of the Month

Category

Chemistry in Medicine and Biology

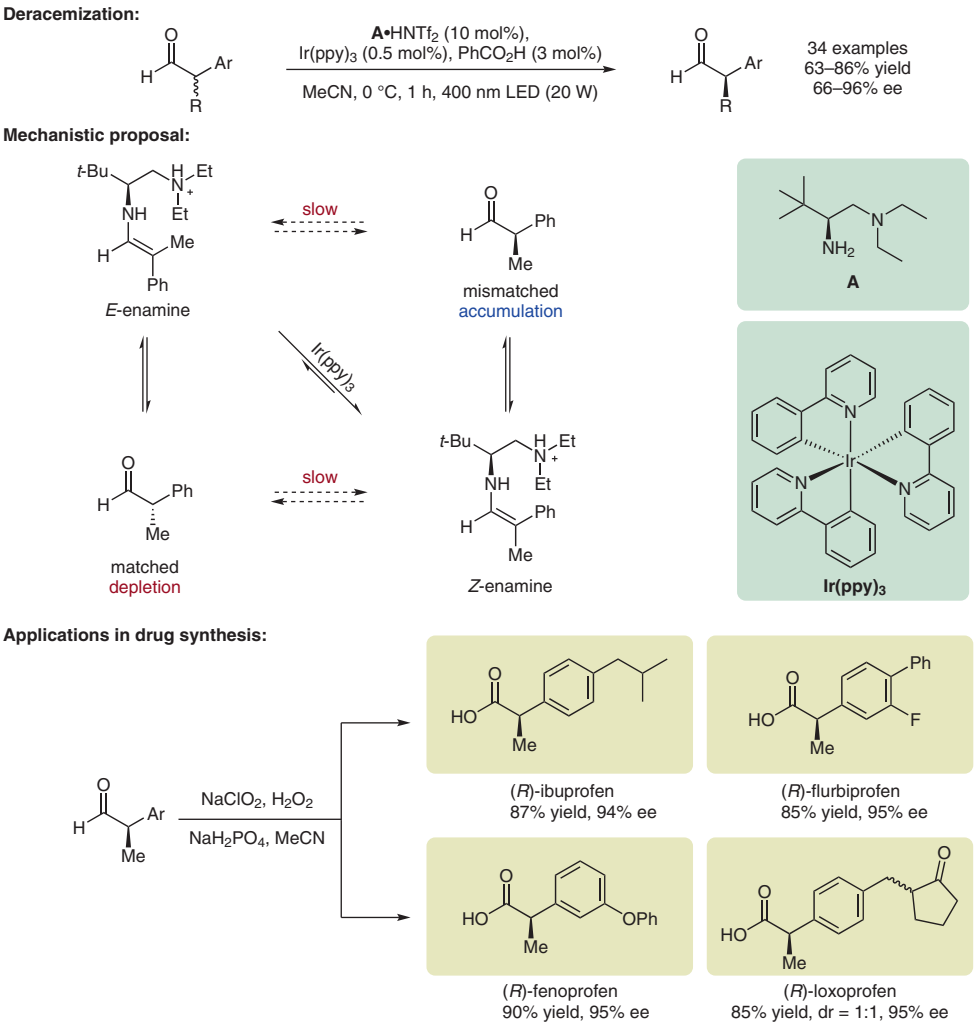
Key words

aminocatalysis
organocatalysis
photocatalysis
deracemization

M. HUANG, L. ZHANG, T. PAN, S. LUO* (TSINGHUA UNIVERSITY, BEIJING, P. R. OF CHINA)

Deracemization through Photochemical *E*/*Z* Isomerization of Enamines
Science **2022**, *375*, 869–874, DOI: 10.1126/science.abl4922.

Breaking the Mirror: Deracemization of α-Branched Aldehydes



Significance: Deracemizations are endergonic processes due to a negative entropy change; therefore, such phenomena demand an exogenous source of energy. Bach (*Nature* **2018**, *564*, 240), Knowles and Miller (*Science* **2019**, *366*, 364) demonstrated that light could operate as the exogenous driving force to push the racemic system out of equilibrium. In this work, the authors demonstrated a deracemization of α-stereogenic aldehydes based on a photocatalytic *E*/*Z* isomerization of enamines formed in situ and applied this to the enantioselective synthesis of commercial anti-inflammatory drugs.

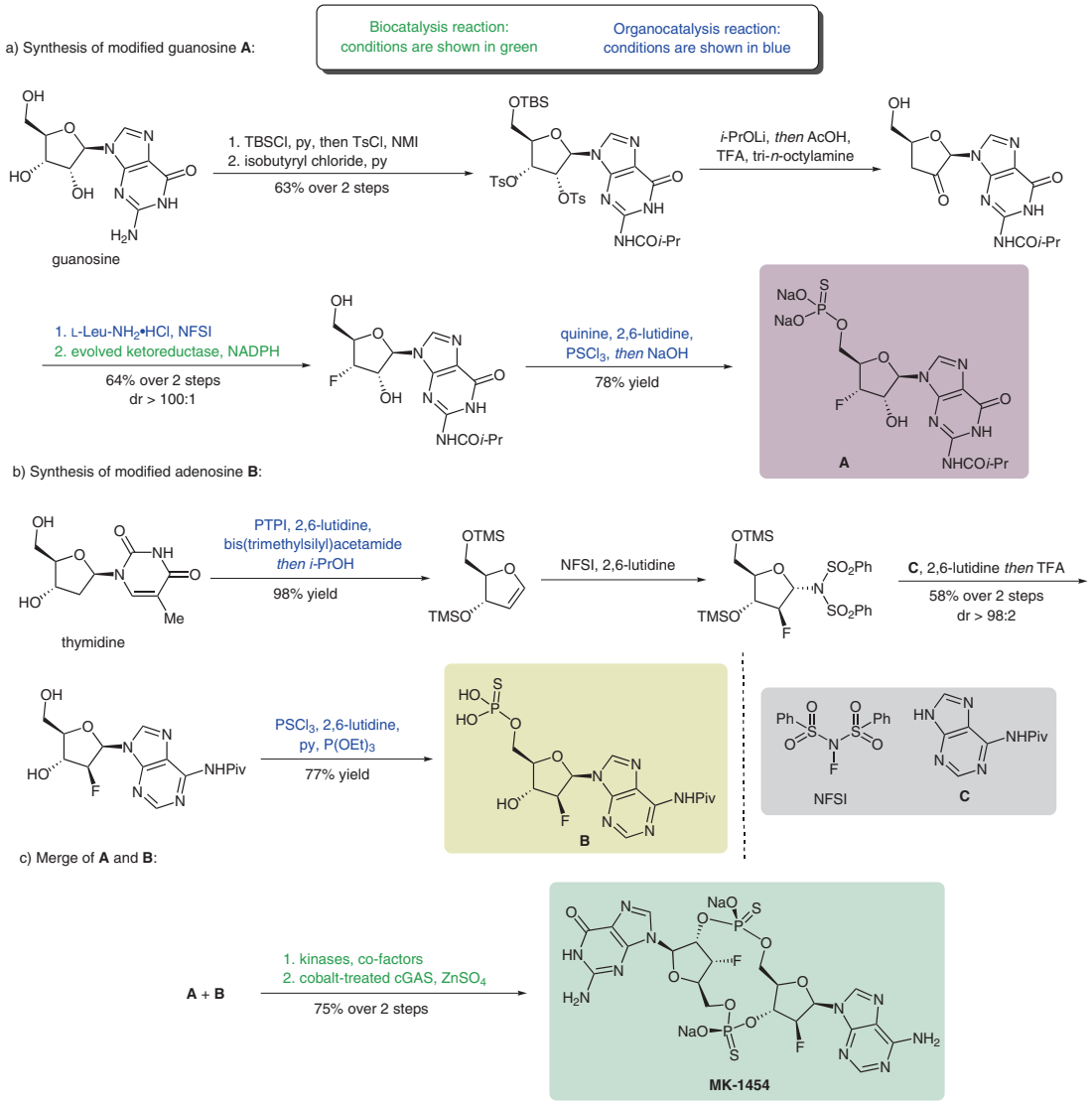
Comment: In the presence of a chiral primary aminocatalyst, *E*- and *Z*-enamines form stereoselectively from each enantiomer of an α-branched aldehyde due to facial selective deprotonation (*Angew. Chem. Int. Ed.* **2011**, *50*, 11451). In the presence of visible light (400 nm), an iridium photocatalyst converts the *E*-enamine into the disfavored *Z* isomer. The overall effect is the depletion of one of the enantiomers, which affords enantioenriched aldehydes with up to 96% ee within one hour. A modified Pinnick oxidation converts the aldehyde products into α-aryl-propionic acid derived drugs.

SYNFACTS Contributors: Dirk Trauner, Bruno Matos Paz
Synfacts 2022, 18(07), 0798 Published online: 15.06.2022
DOI: 10.1055/s-0041-1737640; **Reg-No.:** T08122SF

F. PENG*, E. M. PHILLIPS*, ET AL. (MERCK & CO., INC., RAHWAY, USA)

Diverse Catalytic Reactions for the Stereoselective Synthesis of Cyclic Dinucleotide MK-1454
J. Am. Chem. Soc. **2022**, *144*, 5855–5863, DOI: 10.1021/jacs.1c12106.

Harnessing the Power of Organo- and Biocatalysis to Synthesize STING Agonist MK-1454



Significance: The stimulator of interferon gene (STING) protein is part of the innate immune system, which is responsible for the upregulation of interferons and cytokines. There is a huge interest in agonism of STING for cancer treatment. **MK-1454**, a complex cyclic di-nucleotide, is a potent agonist of STING protein and is currently under clinical development.

Comment: The synthesis leveraged conventional organocatalysis and novel biocatalysis reactions, which are well-orchestrated into a concise and highly efficient stereoselective synthesis of **MK-1454**. Highlights are two stereoselective fluorination reactions using NFSI and the optimization of two biocatalysis reactions by directed evolution.

SYNFACTS Contributors: Dirk Trauner, Ruiyang Bao
Synfacts 2022, 18(07), 0799 Published online: 15.06.2022
DOI: 10.1055/s-0041-1737646; **Reg-No.:** T08722SF

Category
Chemistry in Medicine and Biology

Key words
STING agonist
organocatalysis
biocatalysis
directed evolution

Category

Chemistry in Medicine and Biology

Key words

histone deacetylase

HDAC6 inhibitors

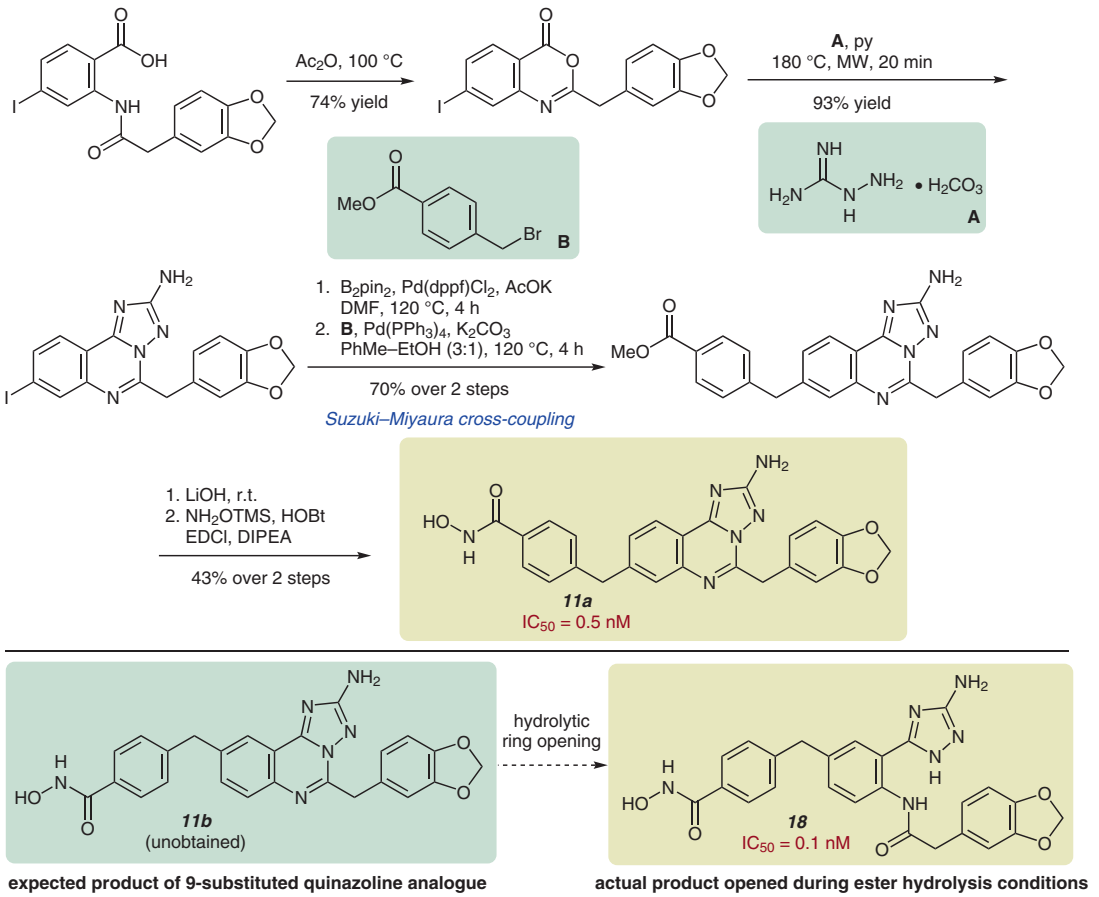
triazoloquinazolines

D. MOI, A. CITARELLA, D. BONANNI, L. PINZI, S. PASSARELLA, A. SILVANI, C. GIANNINI, G. RASTELLI* (UNIVERSITY OF MODENA AND REGGIO EMILIA, ITALY)

Synthesis of Potent and Selective HDAC6 Inhibitors led to Unexpected Opening of a Quinazoline Ring

RSC Adv. **2022**, *12*, 11548–11556, DOI: 10.1039/d2ra01753a.

Unexpected Hydrolytic Triazoloquinazoline Ring Opening Leads to a Potent HDAC6 Inhibitor



Significance: Histone deacetylases (HDACs) play a key role in the epigenetic regulation of gene function, and their overexpression has been found in several tumor types. HDAC6 specifically has been established as a target for anticancer agents, and many structurally diverse inhibitors have been reported. Expanding on known quinazoline-capped HDAC inhibitors, the authors designed **11a** and **11b** and demonstrated potent in vivo HDAC inhibition of **11a** with an original aminotriazoloquinazoline-based scaffold. In attempting to synthesize **11b**, an unexpected quinazoline ring opening generated **18**, which was also demonstrated to be a novel aminotriazole-based HDAC6 inhibitor.

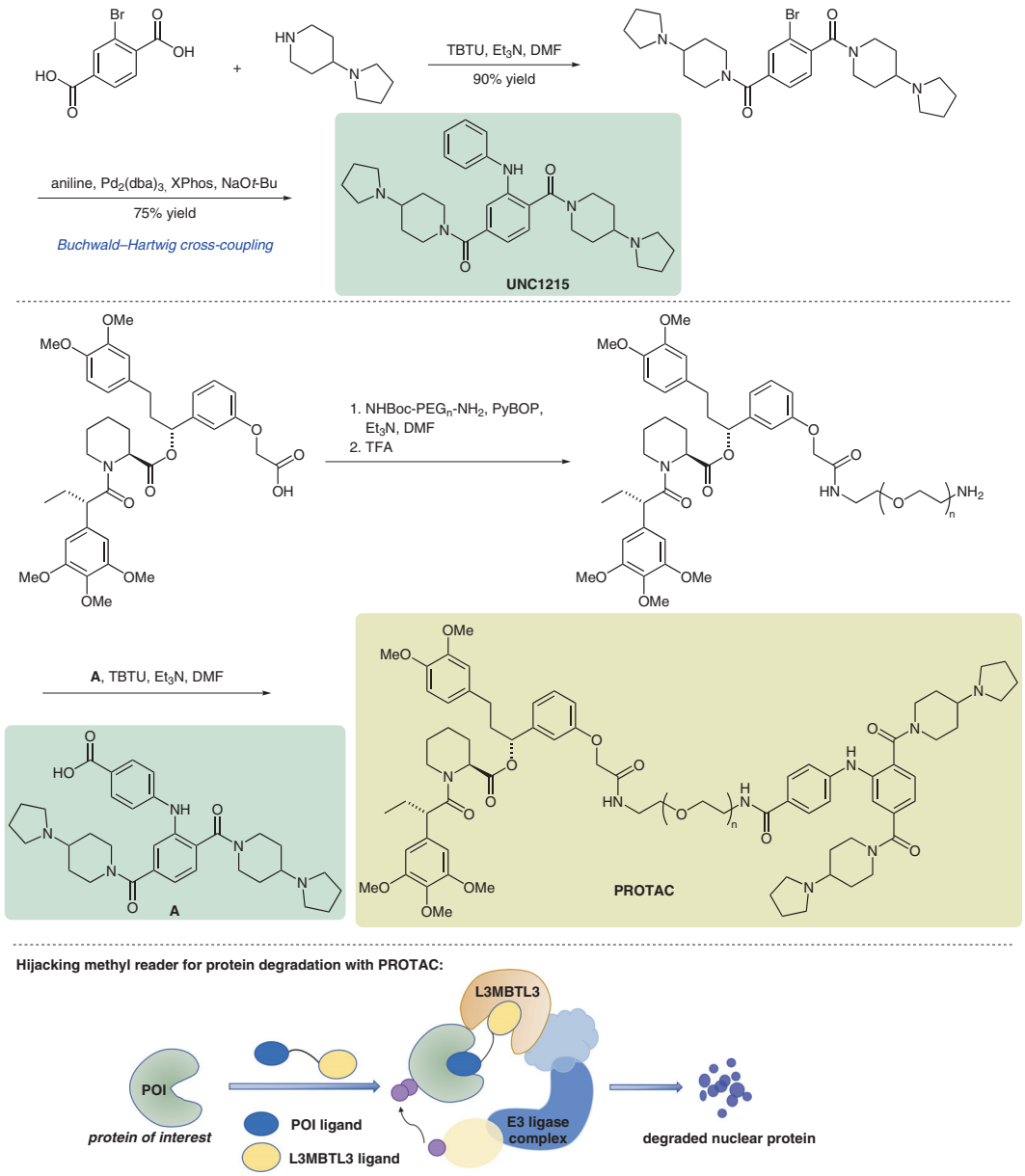
Comment: Anthranilic anilide was converted into a benzoxazinone by an intramolecular annulation, and the resulting fused heterocycle was condensed with aminoguandine **A** to obtain the desired tricyclic aminotriazoloquinazoline. Changing the substitution of the benzoate group to generate **11b** led to hydrolytic opening of the pyrimidine ring upon ester hydrolysis, which is a reactivity that is unreported for triazoloquinazolines in the absence of carbon nucleophiles. Interestingly, the unanticipated product **18** demonstrated five-fold more potent inhibition compared to the designed product **11a**, offering an additional scaffold for further HDAC inhibitor design.

SYNFACTS Contributors: Dirk Trauner, Joseph A. Flores
Synfacts 2022, 18(07), 0800 Published online: 15.06.2022
DOI: 10.1055/s-0041-1737642; **Reg-No.:** T08322SF

D. A. NALAWANSHA, K. LI, J. HINES, C. M. CREWS* (YALE UNIVERSITY, NEW HAVEN, USA)

Hijacking Methyl Reader Proteins for Nuclear-Specific Protein Degradation
J. Am. Chem. Soc. **2022**, *144*, 5594–5605, DOI: 10.1021/jacs.2c00874.

Expanding the E3 Ligase Toolbox by Co-opting Methyl Readers



Significance: Proteolysis targeting chimeras (PROTACs) are tools for targeted protein degradation. The authors use L3MBTL3, a methyl reader protein that binds to the E3 ligase complex, to induce nuclear-specific protein degradation of FKBP12 and BRD2.

Comment: The authors use **UNC1215**, a potent antagonist of L3MBTL3 synthesized via Buchwald–Hartwig cross-coupling, as a handle to recruit the E3 ligase complex. The L3MBTL3-recruiting PROTACs promote nuclear-specific protein degradation.

SYNFACTS Contributors: Dirk Trauner, Xiang Ji
Synfacts 2022, 18(07), 0801 Published online: 15.06.2022
DOI: 10.1055/s-0041-1737649; **Reg-No.:** T09022SF

Category

Chemistry in Medicine and Biology

Key words

PROTAC

methyl reader protein

Buchwald–Hartwig cross-coupling

Category

Chemistry in Medicine and Biology

Key words

tropomyosin receptor kinase

macrocyclic kinase inhibitor

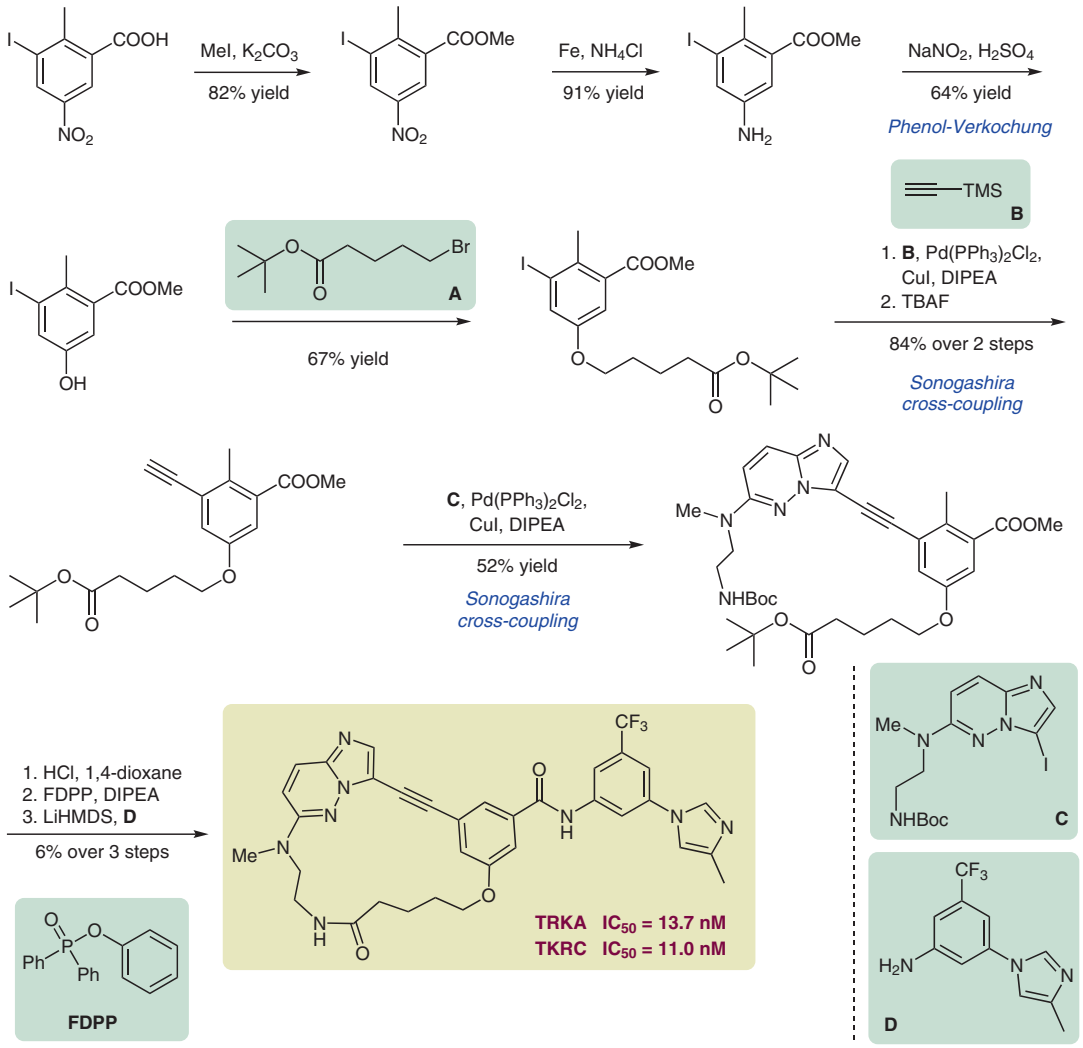
Sonogashira cross-coupling

Z. WANG, J. WANG, Y. WANG, S. XIANG, X. SONG, Z. TU, Y. ZHOU, Z.-M. ZHANG*, Z. ZHANG*, K. DING*X. LU* (JINAN UNIVERSITY, GUANGZHOU, P. R. OF CHINA)

Discovery of the First Highly Selective and Broadly Effective Macrocycle-Based Type II TRK Inhibitors that Overcome Clinically Acquired Resistance

J. Med. Chem. **2022**, *65*, 6325–6337, DOI: 10.1021/acs.jmedchem.2c00308.

Novel Macrocycle-Based Type-II TRK Inhibitors



Significance: Tropomyosin receptor kinases (TRK) are considered targets for anticancer drug discovery, but mutations at the solvent-front (SF) and the DFG motif render type-I inhibitors sensitive to drug resistance. A highly selective macrocyclic TRK inhibitor with a unique type II binding mode was synthesized that was able to overcome any DFG mutation related resistance.

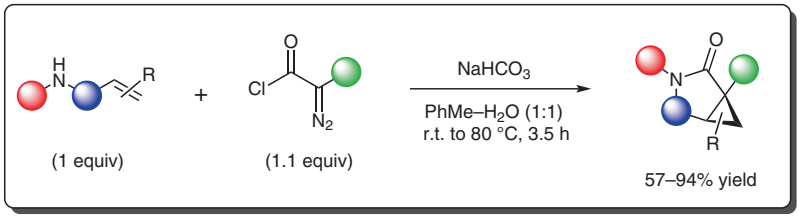
Comment: The synthesis started from the commercially available 3-iodo-2-methyl-5-nitrobenzoic acid. Conversion of the nitro group into a phenol ether, followed by two consecutive Sonogashira reactions, formed the precursor for the macrocyclic core. Acidic deprotection followed by macrolactamization completed the macrocycle.

SYNFACTS Contributors: Dirk Trauner, Zisis Peitsinis
Synfacts 2022, 18(07), 0802 Published online: 15.06.2022
DOI: 10.1055/s-0041-1737651; **Reg-No.:** T09222SF

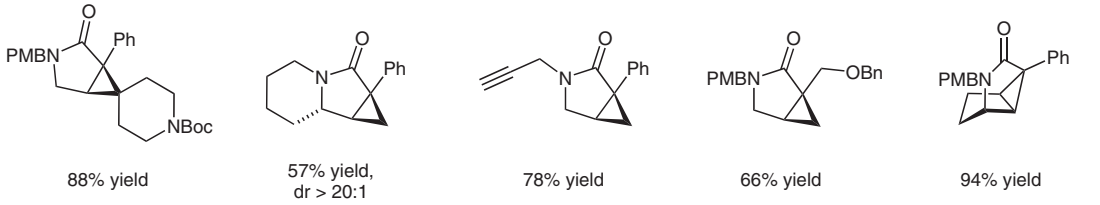
M. J. R. RICHTER, F. J. ZÉCRI*, K. BRINER*, S. L. SCHREIBER* (NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, HARVARD UNIVERSITY, BROAD INSTITUTE OF MIT AND HARVARD, CAMBRIDGE, USA)

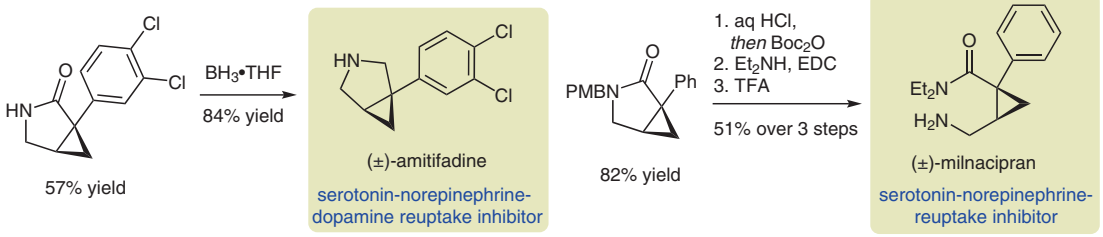
Modular Synthesis of Cyclopropane-Fused *N*-Heterocycles Enabled by Underexplored Diazo Reagents
Angew. Chem. Int. Ed. **2022**, e202203221 DOI: 10.1002/anie.202203221.

A Rapid Approach to Cyclopropane-Fused Lactams

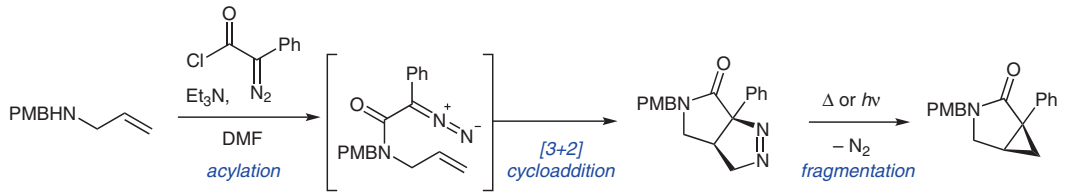


Substrate scope:





Reaction mechanism:



Significance: The medicinally attractive scaffold of cyclopropane-fused *N*-heterocycles finds application in many biologically active compounds. Facilitating their synthetic access, the authors developed a mild, rapid, and modular approach implementing novel bench- and thermally stable α-diazo acyl chloride reagents. Reaction with readily available allyl amines via an acylation, intramolecular [3+2] cycloaddition, fragmentation sequence afforded cyclopropane-fused lactams.

Comment: The developed methodology tolerates a broad scope of functional groups in various positions and is suitable for the construction of complex fused ring systems. The usefulness of this transformation has been demonstrated with the efficient syntheses of the two antidepressants, amitifadine and milnacipran.

SYNFACTS Contributors: Dirk Trauner, Klaus-Peter Ruehmann
Synfacts 2022, 18(07), 0803 Published online: 15.06.2022
DOI: 10.1055/s-0041-1737645; **Reg-No.:** T08622SF

Category
Chemistry in Medicine and Biology

Key words
α-diazo acyl chloride
cyclopropanation
[3+2] cycloaddition

Category

Chemistry in Medicine and Biology

Key words

iron chelators

fluorescence

aggregation-induced emission

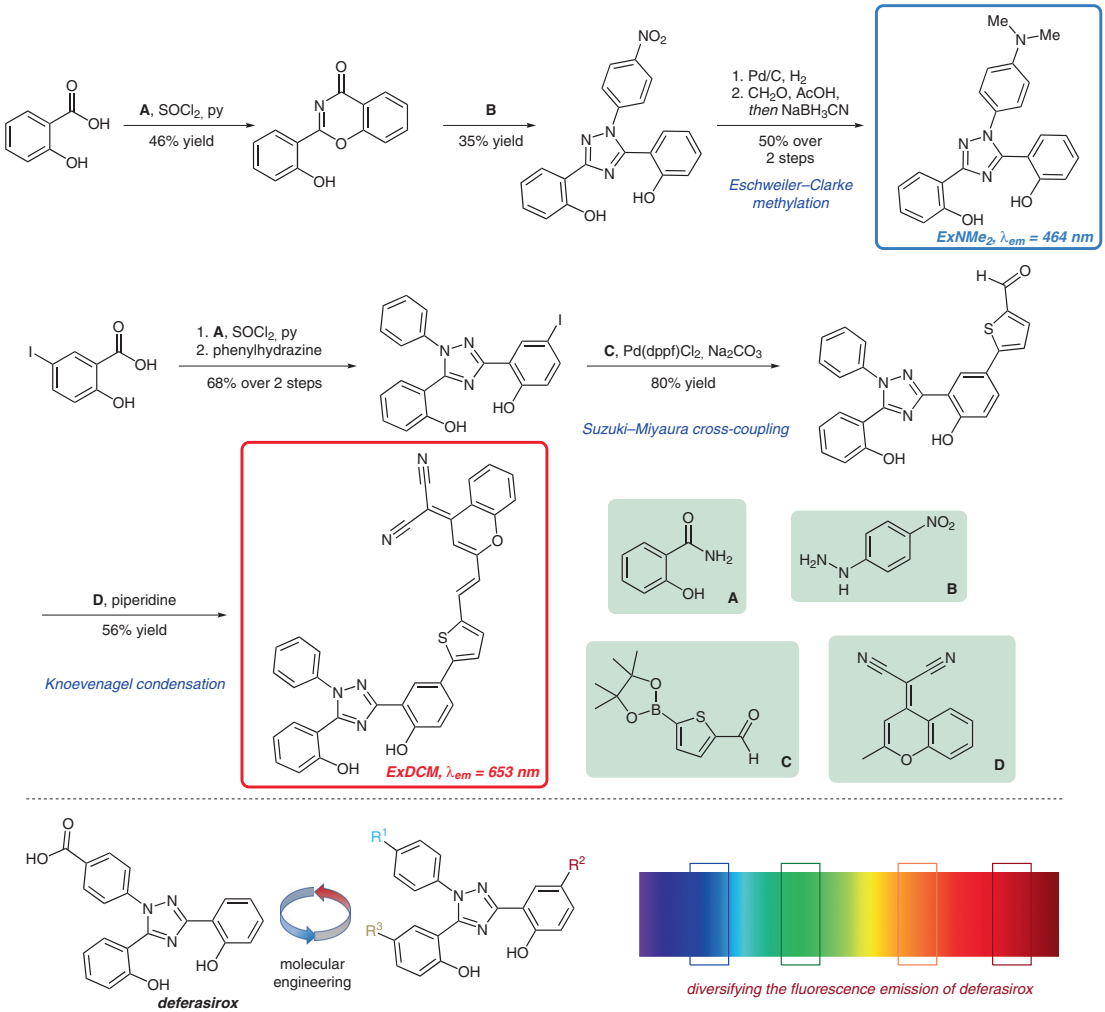
Suzuki–Miyaura cross-coupling

X-L. HU, A. C. SEDGWICK*, D. N. MANGEL, Y. SHANG, A. STEINBRUECK, K-C. YAN, L. ZHU, D. W. SNELSON, S. SEN, C. V. CHAU, G. JUAREZ, V. M. LYNCH, X-P. HE*, J. L. SESSLER* (EAST CHINA UNIVERSITY OF SCIENCE AND TECHNOLOGY, SHANGHAI, P. R. OF CHINA; THE UNIVERSITY OF TEXAS AT AUSTIN, USA; UNIVERSITY OF OXFORD, UK)

Tuning the Solid- and Solution-State Fluorescence of the Iron-Chelator Deferasirox

J. Am. Chem. Soc. **2022**, *144*, 7382–7390, DOI: 10.1021/jacs.2c01155.

Tuning Colors of the Drug: A Systematic Study of the Emissive Features of the Deferasirox Scaffold



Significance: Deferasirox, an FDA-approved iron chelator, is shown to have anticancer and antimicrobial activities. Its core has been identified as a novel scaffold for an easy-to-visualize aggregation-induced emission platform with similar therapeutic effects as deferasirox (*J. Am. Chem. Soc.* **2021**, *143*, 1278). A broad library of deferasirox derivatives is synthesized with various fluorescent emission profiles, which shows promise in bioimaging applications.

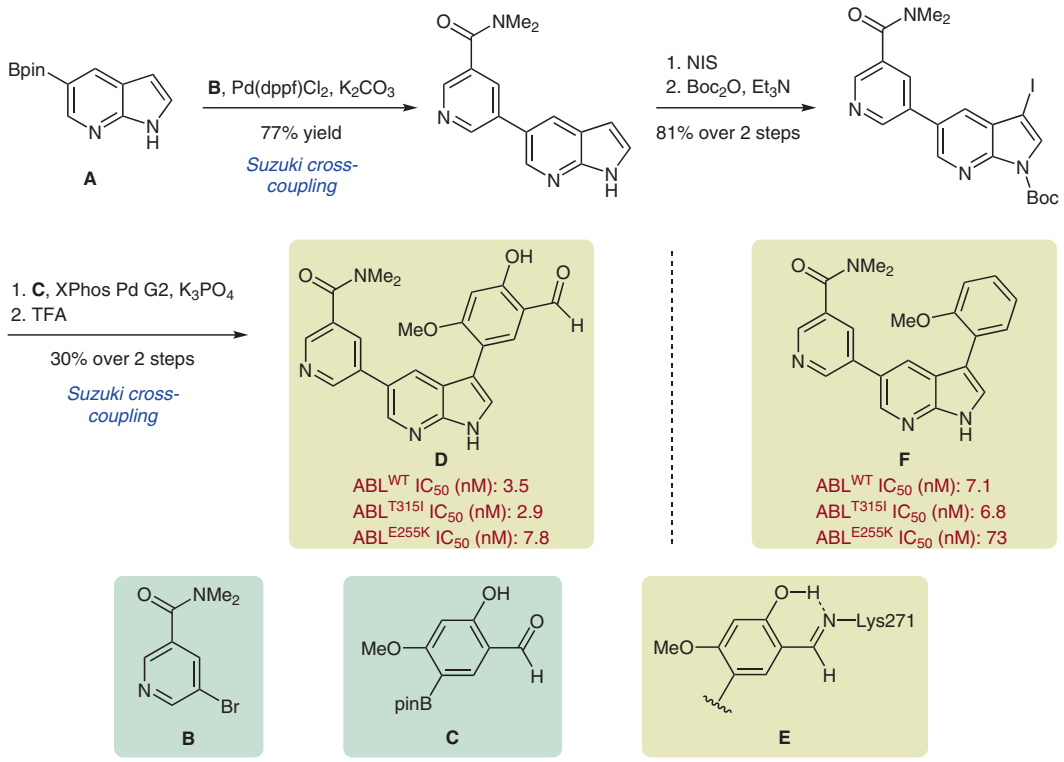
Comment: The fluorescent deferasirox derivatives retain the iron-dependent antibiotic activity while permitting bioimaging in the presence of commonly used imaging agents. **$ExNMe_2$**, emitting in the blue channel with no overlap emission with green and red channels, proves useful for *in vivo* and *in vitro* imaging. The simultaneous use of several fluorescent derivatives maximizes the information gained during a single imaging experiment.

SYNFACTS Contributors: Dirk Trauner, Xiang Ji
Synfacts 2022, 18(07), 0804 Published online: 15.06.2022
DOI: 10.1055/s-0041-1737650; **Reg-No.:** T09122SF

P. CHEN, J. SUN, C. ZHU, G. TANG*, W. WANG, M. XU, M. XIANG, C.-J. ZHANG, Z.-M. ZHANG*, L. GAO*, S. Q. YAO* (NATIONAL UNIVERSITY OF SINGAPORE, SINGAPORE; SUN YAT-SEN UNIVERSITY, SHENZHEN, GUANGDONG YOUMEI INSTITUTE OF INTELLIGENT BIO-MANUFACTURING FOSHAN, AND JINAN UNIVERSITY, GUANGZHOU, P. R. OF CHINA)

Cell-Active, Reversible, and Irreversible Covalent Inhibitors That Selectively Target the Catalytic Lysine of BCR-ABL Kinase
Angew. Chem. Int. Ed. **2022**, e202203878 DOI: 10.1002/anie.202203878.

A Reversible Covalent Inhibitor Targeting the BCR-ABL Active-Site Lysine



Significance: Permanent activity of the BCR-ABL kinase causes certain types of leukemia such as chronic myeloid leukemia. Various noncovalent inhibitors targeting the ATP-binding site of this protein have been clinically investigated and they greatly reduce the tumor burden in patients. The leukemia cells however often develop a resistance against the treatment, which is, in many cases, caused by point mutations in the kinase. Targeted covalent inhibitors represent a possibility to overcome the resistance problem. In the highlighted publication the development of the first cell-active covalent BCR-ABL inhibitor is described based on previous work (*Angew. Chem. Int. Ed.* **2021**, *60*, 17131).

Comment: The synthesis of inhibitor **D** proceeded via functionalization of azaindole **A** featuring two Suzuki cross-coupling reactions with fragments **B** and **C**. Upon binding of **D** to the BCR-ABL protein, the salicylaldehyde moiety forms an imine (**E**) with the active site lysine 271, which is stabilized by a hydrogen-bond with the neighboring hydroxyl group. In vitro inhibition experiments revealed a high potency of **D** against the wild-type kinase as well as against various drug-resistant mutants. In comparison, the inhibitory activity of compound **F**, which lacks the salicylaldehyde moiety, was significantly lower. Compound **D** showed 50 nM cellular activities in a chronic myeloid leukemia cell line but low metabolic stability in mouse liver microsomes.

SYNFACTS Contributors: Dirk Trauner, Julian Maximilian Feilner
Synfacts 2022, 18(07), 0805 Published online: 15.06.2022
DOI: 10.1055/s-0041-1737643; **Reg-No.:** T08422SF

Category
Chemistry in Medicine and Biology

Key words
BCR-ABL kinase
reversible covalent inhibitors
salicylaldehyde

Category

Chemistry in Medicine and Biology

Key words

bioconjugation

cyclopropenone

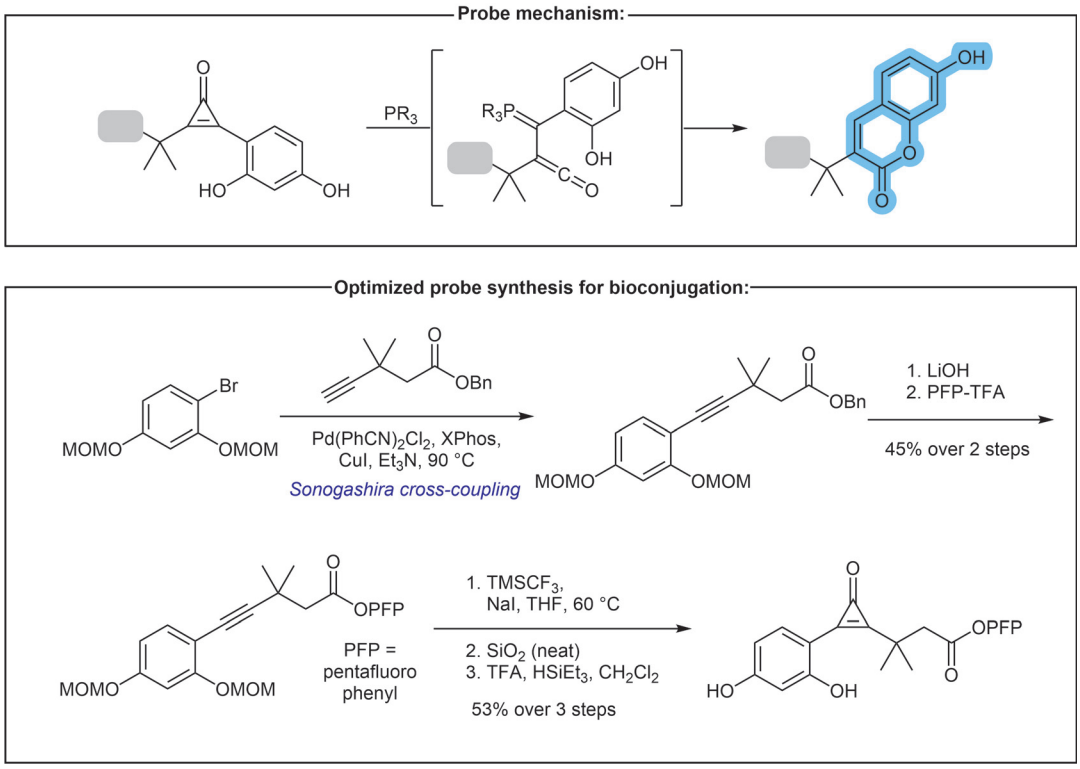
Sonogashira cross-coupling

T. K. HEISS, R. S. DORN, A. J. FERREIRA, A. C. LOVE, J. A. PRESCHER* (UNIVERSITY OF CALIFORNIA, IRVINE, USA)

Fluorogenic Cyclopropenones for Multicomponent, Real-Time Imaging

J. Am. Chem. Soc. **2022**, *144*, 7871–7880, DOI: 10.1021/jacs.2c02058.

Fluorogenic Cyclopropenones for Cellular Imaging



Significance: Fluorogenic bioorthogonal reactions that can be used to image cellular features are highly sought after. These reactions are attractive because they 'light up' only in the presence of the required reagents and remove the need to wash-out unreactive probe and reagents. In the highlighted paper, the authors describe first-in-class cyclopropenone-based probes that cyclize to form fluorescent coumarins upon reaction with a bioorthogonal phosphine. The pentafluorophenyl ester probes can be conjugated to primary amines in biomolecules. Additionally, the authors show that this reaction is compatible with strain-promoted click chemistry in cellular imaging experiments.

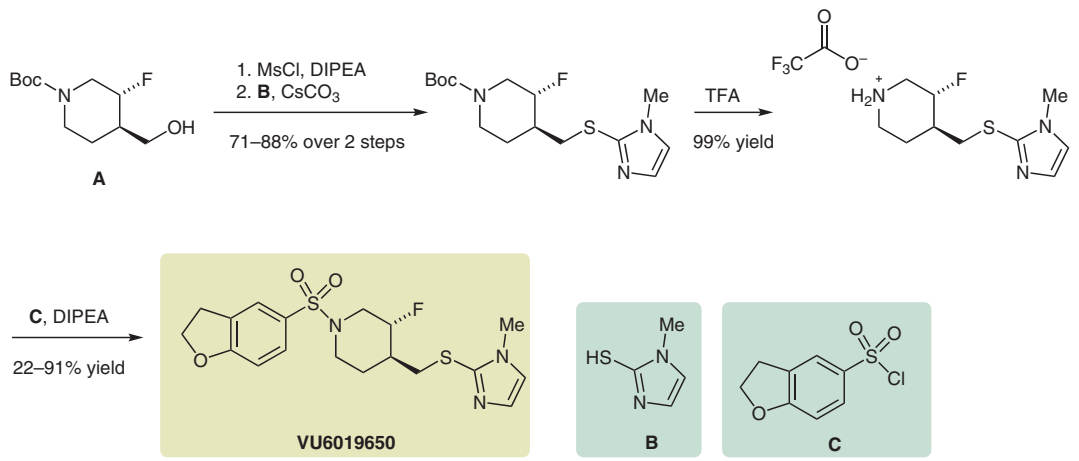
Comment: Upon reaction with a bioorthogonal phosphine, the cyclopropenone forms a ketene ylide that reacts with an intramolecular nucleophile to yield a fluorescent coumarin. Significant synthetic and design efforts were made to favor the formation of the fluorogenic coumarin product over the non-fluorescent furanone and to determine the best phosphine for the reaction. Reactions with the optimized probe molecule provided a >1600-fold increased signal turn-on response compared with the unreacted probe. The optimized probe synthesis for bioconjugation experiments features a Sonogashira cross-coupling, followed by the installation of the cyclopropenone via a difluorocarbene insertion, hydrolysis and finally, acidic deprotection to yield the desired probe.

SYNFACTS Contributors: Dirk Trauner, Anna C. Impastato
Synfacts 2022, 18(07), 0806 Published online: 15.06.2022
DOI: 10.1055/s-0041-1737639; **Reg-No.:** T08022SF

C. K. JONES*, C. HAN*, ET AL. (VANDERBILT UNIVERSITY, NASHVILLE, USA)

Development of VU6019650: A Potent, Highly Selective, and Systemically Active Orthosteric Antagonist of the M_5 Muscarinic Acetylcholine Receptor for the Treatment of Opioid Use Disorder
J. Med. Chem. **2022**, *65*, 6273–6286, DOI: 10.1021/acs.jmedchem.2c00192.

An Improved Orthosteric Antagonist of the M_5 Muscarinic Acetylcholine Receptor



Significance: The M_5 muscarinic acetylcholine receptor is a G_q-coupled GPCR expressed in the mesolimbic reward pathway. One hypothesis is that M_5 antagonists could mitigate the rewarding effects of opioids and thus serve as a potential treatment for opioid use disorder. A selective and potent M_5 orthosteric antagonist, **ML375**, was previously developed but suffered from poor pharmacokinetic properties. The authors report a new M_5 orthosteric antagonist, **VU6019650**, that displays favorable brain penetration to serve as a tool compound for investigating M_5 antagonism.

Comment: An efficient synthesis of **VU6019650** starts with mesylation of primary alcohol **A**, followed by substitution with imidazole **B**. Deprotection of the Boc group and substitution with sulfonyl chloride **C** yields **VU6019650**. Antagonist **VU6019650** has an IC_{50} of 36 nM against human M_5 receptor and was demonstrated to inhibit oxycodone self-administration in rat models. Efforts are underway to improve the poor metabolic stability of the antagonist, likely arising from the thioether linkage.

SYNFACTS Contributors: Dirk Trauner, Christopher J. Arp
Synfacts 2022, 18(07), 0807 Published online: 15.06.2022
DOI: 10.1055/s-0041-1737641; **Reg-No.:** T08222SF

Category

Chemistry in Medicine and Biology

Key words

muscarinic acetylcholine receptor (mAChR)

M_5 receptor

opioid use disorder

Category

Chemistry in Medicine and Biology

Key words

cyclopropanol

cyclopropylamine

titanium-catalyzed cyclopropanation

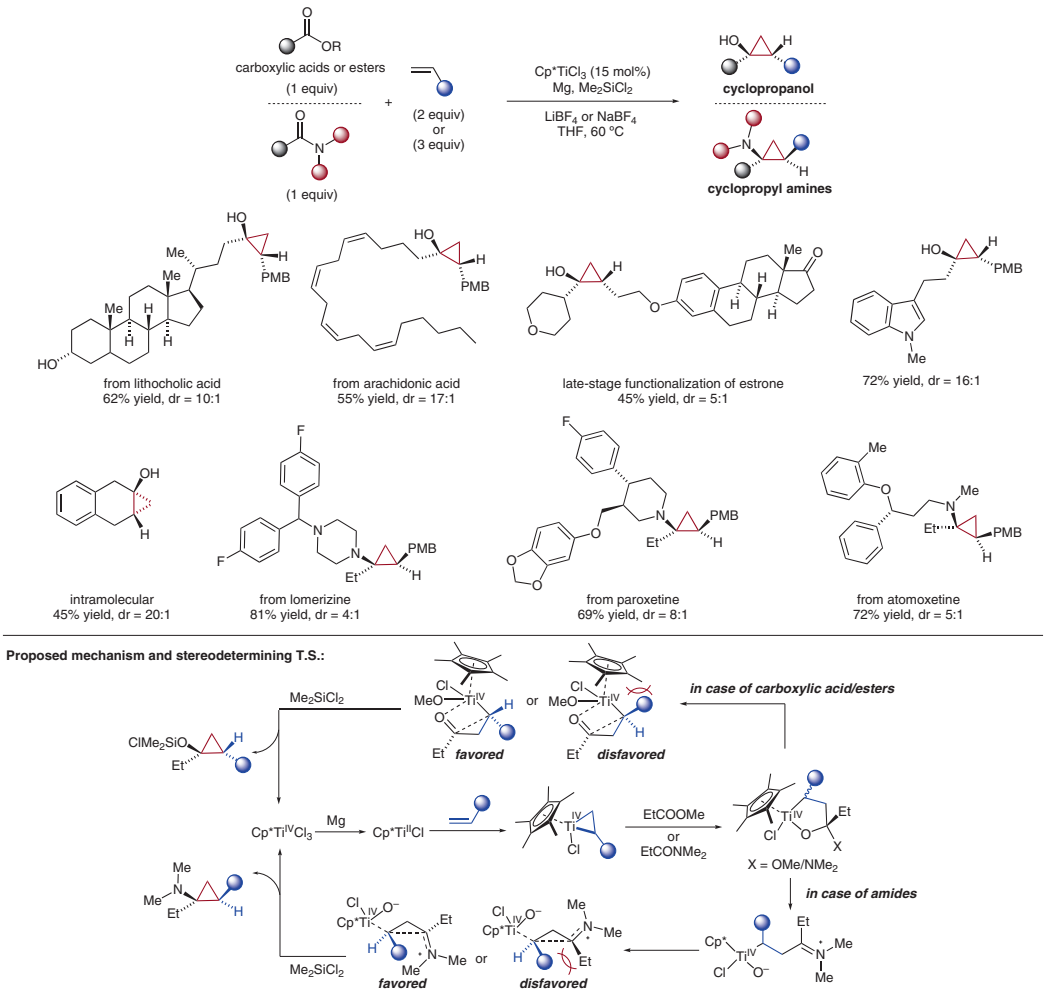
titanacyclopropane

J. NI, X. XIA, W.-F. ZHENG, Z. WANG* (WESTLAKE UNIVERSITY, HANGZHOU, P. R. OF CHINA)

Ti-Catalyzed Diastereoselective Cyclopropanation of Carboxylic Derivatives with Terminal Olefins

J. Am. Chem. Soc. **2022**, *144*, 7889–7900, DOI: 10.1021/jacs.2c02360.

A Diastereoselective Cyclopropanation Strategy



Significance: While cyclopropanols and cyclopropylamines are interesting synthetic equivalents, they are also important pharmacophores in medicinal chemistry. Despite the existing cyclopropane synthesis, diastereoselective cyclopropanation strategies remained less studied. Here, the authors report a Ti-catalyzed diastereoselective cyclopropanation method that couples alkenes with carboxylic acids or amides. This method has been shown to be widely compatible across a broad range of substrates.

Comment: Unlike Kulinkovich cyclopropanation, this protocol does not require stoichiometric Grignard reagent and the catalyst is regenerated by using dichlorodimethylsilane. The proposed mechanism involves the formation of a titanacyclopropane intermediate. In case of carboxylic acid esters, the diastereoselectivity is governed by the steric hindrance between the alkene substituent and the methyl groups of Cp*. The 1,3-alkyl interaction, in case of amides, dictates the diastereoselectivity.

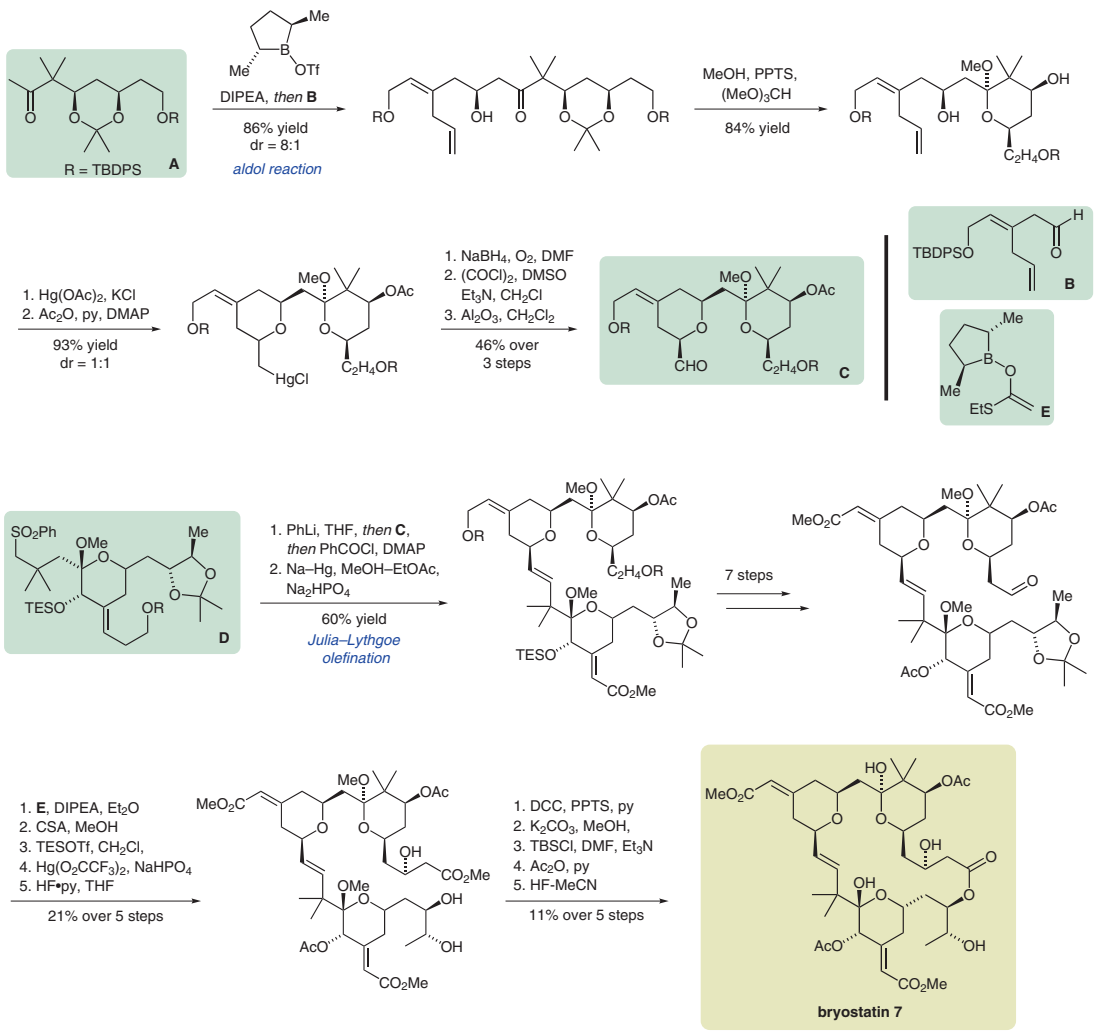
SYNFACTS Contributors: Dirk Trauner, Tufan K. Mukhopadhyay
Synfacts 2022, 18(07), 0808 Published online: 15.06.2022
DOI: 10.1055/s-0041-1737648; **Reg-No.:** T08922SF

M. KAGEYAMA, T. TAMURA, M. H. NANTZ, J. C. ROBERTS, P. SOMFAI, D. C. WHRITENOUR, S. MASAMUNE* (MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE, USA)

Synthesis of Bryostatin 7

J. Am. Chem. Soc. **1990**, *112*, 7407–7408, DOI: 10.1021/ja00176a058.

The First Total Synthesis of Bryostatin 7



Significance: The bryostatins are a family of 21 marine natural products boasting a wide range of biological activities. They have been explored as anticancer agents, treatments for Alzheimer's disease, and as antivirals against HIV. Of this family, the first to succumb to total synthesis was bryostatin 7 in a heroic synthesis by the Masamune group requiring a total of 79 steps with a 41 step longest linear sequence.

Comment: Retrosynthetically, bryostatin 7 was broken into three fragments (**A**, **B**, and **D**). **A** and **B** were used for a matched aldol reaction followed by Hg-mediated cyclization. Further manipulations yielded **C**. Fragment **D** (prepared in 22 steps) underwent a Julia–Lythgoe olefination with **C** to complete the unification of all fragments. A DCC-mediated macrocyclization was used to close the lactone.

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