

## The ISHC Bulletin

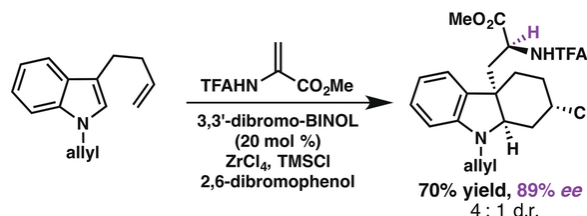
### Recent Publications of ISHC Members

Issue 2; June 1, 2016

#### Synthesis of Enantioenriched Indolines by a Conjugate Addition/Asymmetric Protonation/Aza-Prins Cascade Reaction

Blake E. Daniels, Jane Ni, Sarah E. Reisman  
*Angew. Chem. Int. Ed.* **2016**, *55*, 3398–3402.

DOI: 10.1002/anie.201510972

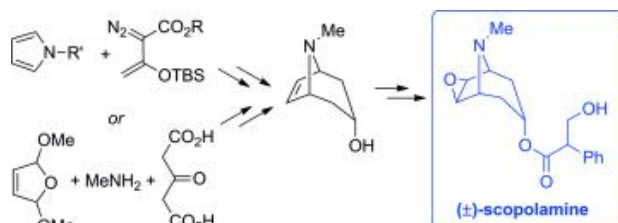


**Abstract:** A conjugate addition/asymmetric protonation/aza-Prins cascade reaction has been developed for the enantioselective synthesis of fused polycyclic indolines. A catalyst system generated from  $ZrCl_4$  and 3,3'-dibromo-BINOL enables the synthesis of a range of polycyclic indolines in good yields and with high enantioselectivity. A key finding is the use of TMSCl and 2,6-dibromophenol as a stoichiometric source of HCl to facilitate catalyst turnover. This transformation is the first in which a  $ZrCl_4$ :BINOL complex serves as a chiral Lewis-acid-assisted Brønsted acid.

#### Total Synthesis of (±)-Scopolamine: Challenges of the Tropane Ring

Pierre-Antoine Nocquet and Till Opatz  
*Eur. J. Org. Chem.* **2016**, 1156–1164.

DOI: 10.1002/ejoc.201501430

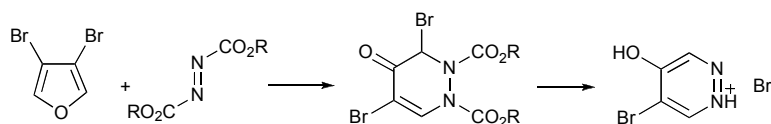


**Abstract:** Scopolamine was synthesized using 6,7-dehydrotropine as a key intermediate. Rhodium-catalyzed [4 + 3] cycloaddition chemistry and a modified Robinson–Schöpf reaction were each independently evaluated for their utility in constructing the tropane core. Both synthetic approaches gave comparable overall yields.

#### Novel Reaction of 3,4-Dibromofuran with Azo Diesters to Give Tetrahydropyridazinones

Kati M. Aitken, R. Alan Aitken, Alexandra M. Z. Slawin  
*RSC Adv.* **2016**, *6*, 22969–22972.

DOI: 10.1039/c6ra02735k

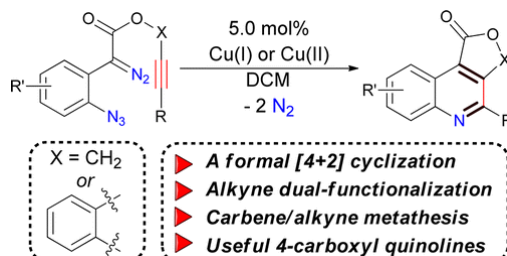


**Abstract:** Cycloaddition of 3,4-dibromofuran with azo diesters proceeds by a Diels–Alder reaction followed by a novel rearrangement to give 3,5-dibromotetrahydropyridazin-4-ones. Variable-temperature NMR spectroscopy shows four separate conformations at low temperature attributed to restricted rotation about the carbamate functions. The ethyl compound decomposes upon storage with loss of the carbamate groups and aromatisation to give a simple bromohydroxypyridazinium salt.

## Dual-Functionalization of Alkynes via Copper-Catalyzed Carbene/Alkyne Metathesis: A Direct Access to the 4-Carboxyl Quinolines

Ruwei Yao, Guangwei Rong, Bin Yan, Lihua Qiu, Xinfang Xu  
*ACS Catal.* **2016**, *6*, 1024–1027.

DOI: 10.1021/acscatal.5b02648

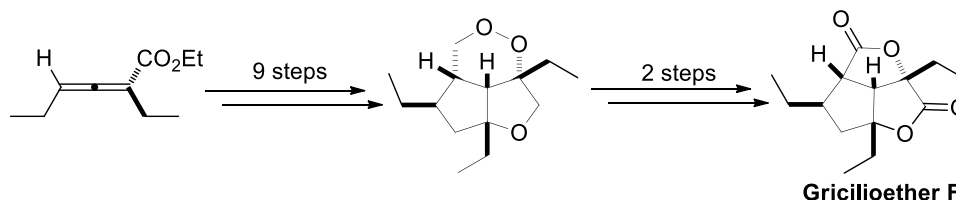


**Abstract:** A copper-catalyzed novel carbene/alkyne metathesis cascade reaction with alkyne-tethered diazo compounds is described. The whole transformation features a dual-functionalization of alkyne to install one C–N and one C–C bond on each carbon with azide and diazo groups, respectively, in one reaction, which represents a practical synthetic alternative to the multisubstituted 4-carboxyl quinoline derivatives and with most of them in high to excellent yields.

## Total Synthesis of (±)-Gracilioether F

Xin-Yue Shen, Xiao-Shui Peng, Henry N. C. Wong  
*Org. Lett.* **2016**, *18*, 1032–1035.

DOI: 10.1021/acs.orglett.6b00161

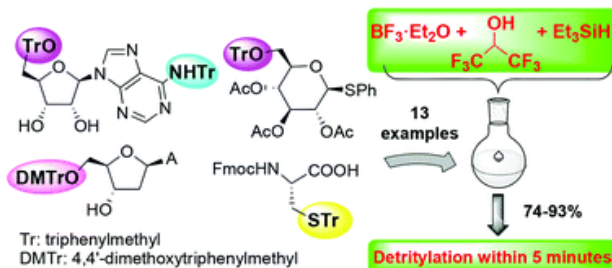


**Abstract:** Total synthesis of (±)-gracilioether F was achieved via a pivotal reductive cleavage of 1,2-dioxane from allenic ester in 11 steps. The key 1,2-dioxane species, derived from singlet oxygen and a diene, could be used as a common precursor for a stereo-controlled formation of the crucial 1,4-diol through a reductive cleavage.

## A Three-Component Reagent System for Rapid and Mild Removal of *O*-, *N*- and *S*-Trityl Protecting Groups

Máté Kicsák, Miklós Bege, Ilona Bereczki, Magdolna Csávás, Mihály Herczeg, Zoltán Kupihár, Lajos Kovács, Anikó Borbás, Pál Herczegh  
*Org. Biomol. Chem.* **2016**, *14*, 3190–3192.

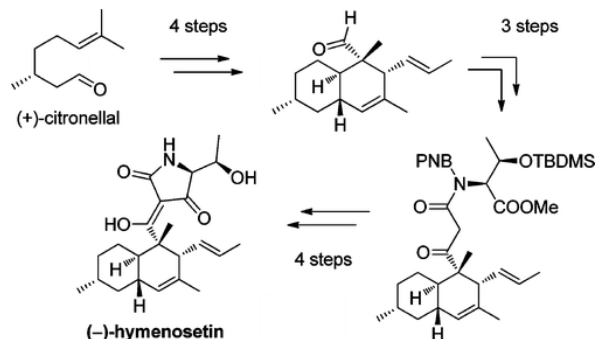
DOI: 10.1039/C6OB00067C



**Abstract:** A new reagent system consisting of a Lewis acid such as BF<sub>3</sub>·Et<sub>2</sub>O or Cu(OTf)<sub>2</sub>, the mild protic acid hexafluoroisopropanol and the reducing quenching agent triethylsilane was elaborated for *O*-, *N*- and *S*-detritylation of nucleoside, carbohydrate and amino acid derivatives. The method is compatible with acetyl, silyl, acetal and Fmoc groups.

## Total Synthesis of (–)-Hymenostetin

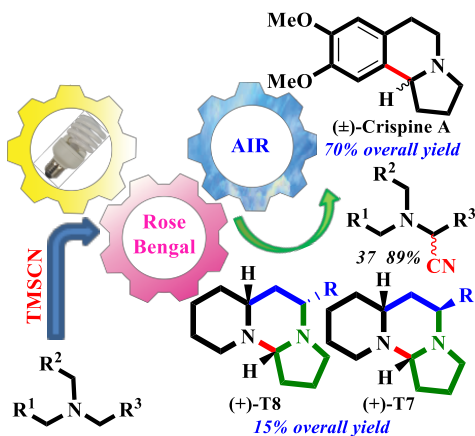
Ulrich Kauh, Lars Andernach, Stefan Weck, Louis P. Sandjo, Stefan Jacob, Eckhard Thines, Till Opatz  
*J. Org. Chem.* **2016**, *81*, 215–228. DOI: 10.1021/acs.joc.5b02526



**Abstract:** The 3-decalinoyltetramic acid (–)-hymenostetin and its *N*-methyl analogue were prepared in 11 and 8 steps, respectively, from (+)-citronellal using an intramolecular Diels–Alder reaction as the key step. This method represents the first example for the synthesis of a 3-decalinoyltetramic acid with a free NH moiety. The stereochemistry of the title compound, an unnatural diastereomer, and of a decalin building block was studied in detail using circular dichroism spectroscopy in the IR and UV/VIS frequency range. This allowed to determine the absolute configuration of the natural product and to plan the synthetic route.

## A Highly Active System for the Metal-Free Aerobic Photocyanation of Tertiary Amines with Visible Light: Application to the Synthesis of Tetraopnerines and Crispine A

Julio Cesar Orejarena Pacheco, Alexander Lipp, Alexander M. Nauth, Fabian Acke, Jule-Philipp Dietz, Till Opatz  
*Chem. Eur. J.* **2016**, *22*, 5409–5415. DOI: 10.1002/chem.201504845



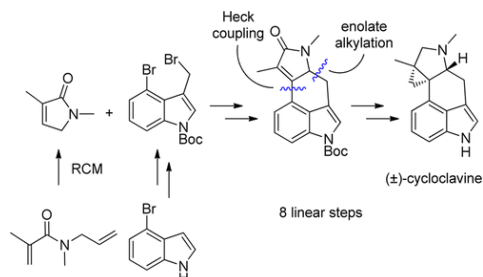
**Abstract:** A highly efficient metal-free catalytic system for the aerobic photocyanation of tertiary amines with visible light is reported. The use of air as terminal oxidant offers an improved safety profile compared with pure oxygen, the used compact fluorescent lamp (CFL) light sources are highly economical, and no halogenated solvents are required. This system not only proves to be effective for a wide variety of trialkylamines, pharmaceuticals, and alkaloids but remarkably also allows the lowest catalyst loading (0.00001 mol% or 0.1 ppm) ever reported for an organic dye. Bruylants reactions and C-alkylation/decyanations were performed on the obtained  $\alpha$ -aminonitriles to demonstrate the postfunctionalization of complex molecules. The catalytic system is furthermore applied in the short and effective syntheses of the alkaloids (±)-crispine A and the tetraopnerines T7 and T8.

## A Modular Formal Total Synthesis of (±)-Cycloclavine

Natalie Netz and Till Opatz

*J. Org. Chem.* **2016**, *81*,1723–1730.

DOI: 10.1021/acs.joc.5b02815



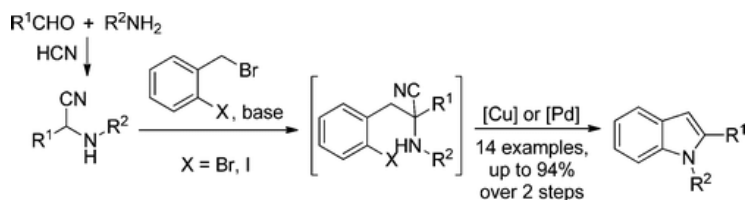
**Abstract:** Cycloclavine is a clavine-type *Ergot* alkaloid noteworthy for its unique pentacyclic skeleton featuring a 3-azabicyclo[3.1.0]hexane substructure. A short convergent route to the racemic alkaloid is described which comprises only eight linear steps and requires only four chromatographic purifications. The two key building blocks can be prepared in high yield from commercially available starting materials. Two consecutive coupling reactions, namely a selective alkylation of a dienolate and a Heck reaction, are the key steps of the reaction sequence

## Synthesis of 1,2-Disubstituted Indoles from $\alpha$ -Aminonitriles and 2-Halobenzyl Halides

Anne-Karin Bachon and Till Opatz

*J. Org. Chem.* **2016**, *81*,1858–1869.

DOI: 10.1021/acs.joc.5b02659



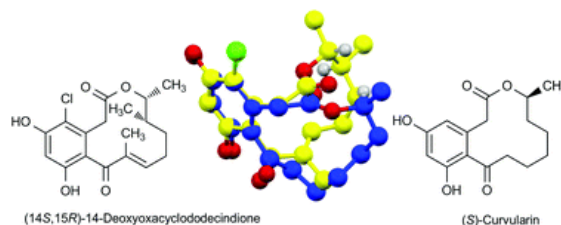
**Abstract:** The  $\alpha$ -alkylation of deprotonated Strecker products derived from primary amines and aromatic aldehydes with 2-halobenzyl halides furnishes intermediates that can be cyclized to 1,2-disubstituted indoles in moderate to high yields (up to 94% over two steps) by microwave-assisted copper- or palladium-catalyzed intramolecular cross-coupling.

## A Surprising Switch in Absolute Configuration of Anti-Inflammatory Macrolactones

Johannes Tauber, Markus Rohr, Thorsten Walter, Dieter Schollmeyer, Karin Rahn-Hotze, Gerhard Erkel, Till Opatz

*Org. Biomol. Chem.* **2016**, *14*, 3695–3698.

DOI: 10.1039/C6OB00430J



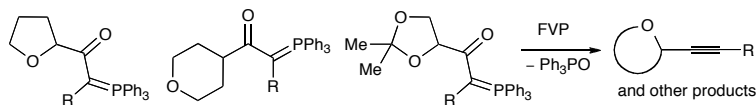
**Abstract:** Oxacyclododecindione-type macrolactones exhibit highly potent anti-inflammatory activities even at nanomolar concentration. After the determination of the relative configuration of the stereocenters at C14 and C15 by total synthesis of 4-dechloro-14-deoxyoxacyclododecindione and 14-deoxyoxacyclododecindione, the absolute configuration has now been assigned by X-ray crystallography. Surprisingly, the absolute configuration is (14*S*,15*R*) which differs for C15 from that of the well-known derivatives of (*S*)-curvularin. The biological activities of both enantiomers of 14-deoxyoxacyclododecindione, obtained by racemic synthesis and optical resolution, were investigated and the ring conformation of the natural product was compared to that of (*S*)-curvularin and (*R*)-dehydrocurvularin.

## Synthesis, Structure and Pyrolysis of Stabilised Phosponium Ylides Containing Saturated Oxygen Heterocycles

R. Alan Aitken, Nazira Karodia, Hollie B. McCarron, Cécile Rouxel, Nina Sahabo, Alexandra M. Z. Slawin

*Org. Biomol. Chem.* **2016**, *14*, 1794-1804.

DOI: 10.1039/c5ob02467f



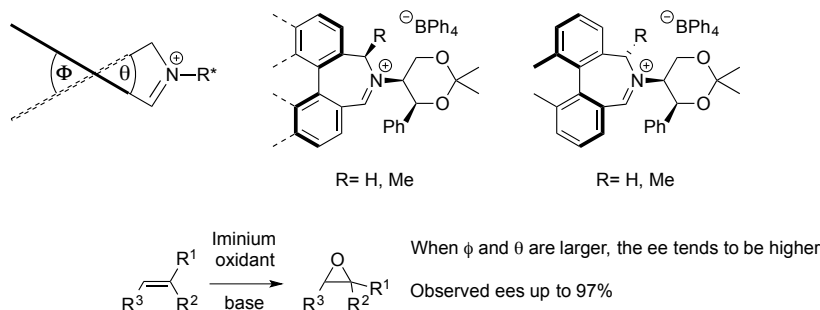
**Abstract:** A range of twelve stabilised phosphonium ylides containing tetrahydrofuran, tetrahydropyran or 2,2-dimethyl-1,3-dioxolane rings have been prepared and fully characterised, including one X-ray structure determination of each type. The X-ray structures confirm the P=C and C=O functions to be *syn* and all the compounds undergo thermal extrusion of Ph<sub>3</sub>PO to give the corresponding alkynes. In some cases there is also competing loss of Ph<sub>3</sub>P to give different carbene-derived products and evidence has been obtained for the generation of 2-phenyloxete in this way. Raising the pyrolysis temperature leads in several cases to new secondary reactions of the alkyne products involving a sequence of alkyne to vinylidene isomerisation, intramolecular CH insertion, and retro Diels Alder reaction.

## New Biphenyl Iminium Salt Catalysts for Highly Enantioselective Asymmetric Epoxidation: Role of Additional Substitution and Dihedral Angle

Philip C. Bulman Page, Christopher J. Bartlett, Yohan Chan, Steven M. Allin, Michael J. McKenzie, Jérôme Lacour, Garth A. Jones

*Org. Biomol. Chem.* **2016**, *14*, 4220-4232.

DOI: 10.1039/c6ob00542j



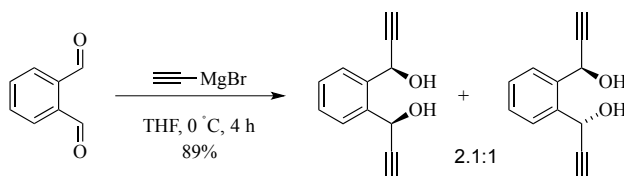
**Abstract:** New biaryl iminium salt catalysts for enantioselective alkene epoxidation containing additional substitution in the heterocyclic ring are reported. The effects upon conformation and enantioselectivity of this additional substitution, and the influence of dihedral angle in these systems, has been investigated using a synthetic approach supported by density functional theory. Enantioselectivities of up to 97% ee were observed.

## Convenient Access to *meso* Benzylic Bisalkynes

Philip C. Bulman Page, G. Richard Stephenson, James Harvey, Annie-Claude Gaumont, Carole Alayrac, Alexandra M. Z. Slawin

*Synlett* **2016**, *27*, 961-964.

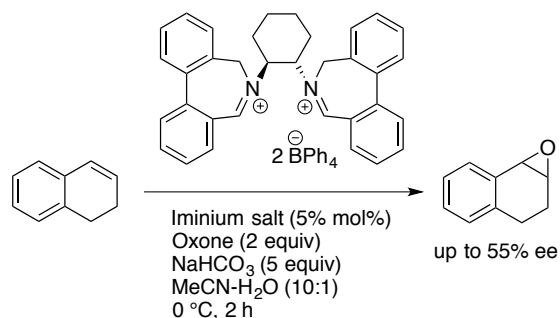
DOI: 10.1055/s-0035-1561318



**Abstract:** *meso*-Bisalkynes and alkenes have potential as substrates for desymmetrization processes. The preparation of several *meso*-bis(1'-hydroxy-2'-propynyl)benzenes and their derivatives from phthalaldehydes using inexpensive and readily available reagents is described.

## Preparation of C<sub>2</sub>-Symmetric Biaryl Bisiminium Salts and Their Use as Organocatalysts for Asymmetric Epoxidation

Philip C. Bulman Page, Mohamed M. Farah, Benjamin R. Buckley, Yohan Chan, A. John Blacker  
*Synlett* **2016**, 27, 126–130. DOI: 10.1055/s-0035-1560540

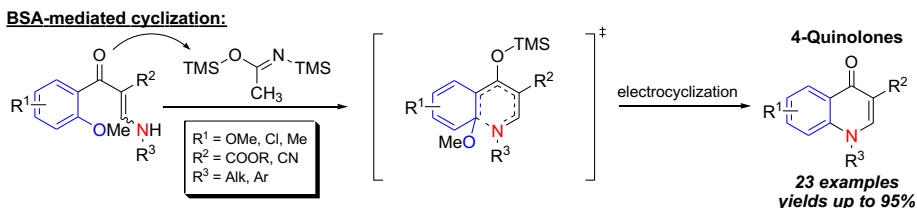


**Abstract:** Two C<sub>2</sub>-symmetric bisiminium salt species containing biphenylazepinium units and derived from two chiral diamines were prepared and tested as organocatalysts for asymmetric epoxidation.

## Synthesis of 4-Quinolones: *N,O*-Bis(trimethylsilyl)acetamide-Mediated Cyclization with Cleavage of Aromatic C–O Bond

Ondřej Piša and Stanislav Rádl  
*Eur. J. Org. Chem.* **2016**, 2336–2350.

DOI: 10.1002/ejoc.201600178



**Abstract:** The synthesis of 1,4-dihydro-4-oxoquinoline derivatives (4-quinolones) based on a BSA [*N,O*-bis(trimethylsilyl)acetamide]-mediated cyclization of substituted 1-(2-methoxyphenyl)-3-(alkyl/arylamino)prop-2-en-1-ones is described. The reaction belongs to a rare set of cyclizations in which a methoxy group serves as the leaving group. Reaction takes place by the action of silylating agent under mild conditions and provides high yields of pure products following simple aqueous work-up. The versatility of the approach is exemplified by a wide range of 1-alkyl/aryl 3-carboxylates and 3-nitriles that have been prepared. A crucial advantage of this approach is the facile availability of starting methoxy compounds enabling new synthetic possibilities as well as improved cost efficiency.