

The ISHC Bulletin

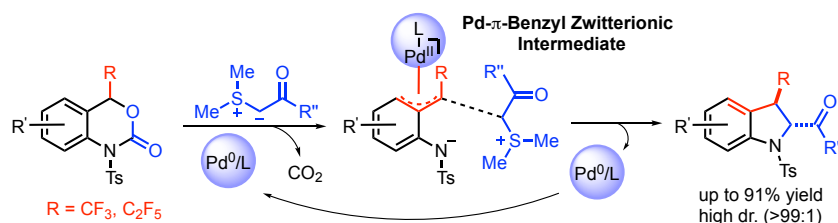
Recent Publications of ISHC Members

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Highly Diastereoselective Synthesis of Trifluoromethyl Indolines by Interceptive Benzylic Decarboxylative Cycloaddition of Nonvinyl, Trifluoromethyl Benzoxazinanones with Sulfur Ylides under Palladium Catalysis

Nagender Punna, Pulakesh Das, Véronique Gouverneur, Norio Shibata
Org. Lett. **2018**, *20*, 1526–1529.

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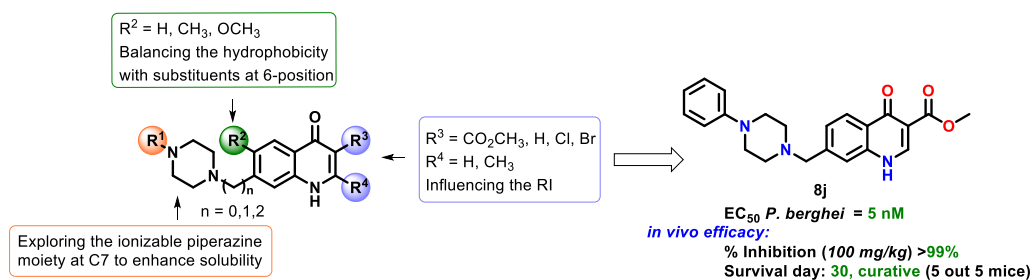


Abstract: A highly diastereoselective synthesis of trifluoromethyl-substituted indolines under palladium catalysis is disclosed. The reaction proceeds by interceptive decarboxylative benzylic cycloaddition (IDBC) of nonvinyl, trifluoromethyl benzoxazinanones with sulfur ylides. The palladium- π -benzyl zwitterionic intermediates are suggested for this transformation, and this would be the first example of an IDBC reaction.

Design and Synthesis of Orally Bioavailable Piperazine Substituted 4(1*H*)-Quinolones with Potent Antimalarial Activity: Structure–Activity and Structure–Property Relationship Studies

Raghupathi Neelarapu, Jordany R. Maignan, Cynthia L. Lichorowic, Andrii Monastyrskiy, Tina S. Mutka, Alexis N. LaCrue, Lynn D. Blake, Debora Casandra, Sherwin Mashkouri, Jeremy N. Burrows, Paul A. Willis, Dennis E. Kyle, Roman Manetsch
J. Med. Chem. **2018**, *61*, 1450–1473.

DOI: 10.1021/acs.jmedchem.7b00738



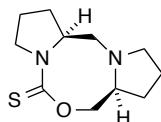
Abstract: Malaria deaths have been decreasing over the last 10–15 years, with global mortality rates having fallen by 47% since 2000. While the World Health Organization (WHO) recommends the use of artemisinin-based combination therapies (ACTs) to combat malaria, the emergence of artemisinin resistant strains underscores the need to develop new antimalarial drugs. Recent in vivo efficacy improvements of the historical antimalarial ICI 56,780 have been reported, however, with the poor solubility and rapid development of resistance, this compound requires further optimization. A series of piperazine-containing 4(1*H*)-quinolones with greatly enhanced solubility were developed utilizing structure-activity relationship (SAR) and structure-property relationship (SPR) studies. Furthermore, promising compounds were chosen for an in vivo scouting assay to narrow selection for testing against a more accurate in vivo Thompson test. Finally, two piperazine-containing 4(1*H*)-quinolones were curative in the conventional Thompson test and also displayed in vivo activity against the liver stages of the parasite.

Octahydro-1*H*,5*H*,7*H*-dipyrrolo[1,2-*c*:1',2'-*f*][1,3,6]oxadiazocine-5-thione

R. Alan Aitken and Karamat Ali

Molbank **2018**, 2018, M993, 1–5.

DOI: 10.3390/M993



¹H, ¹³C NMR, HRMS

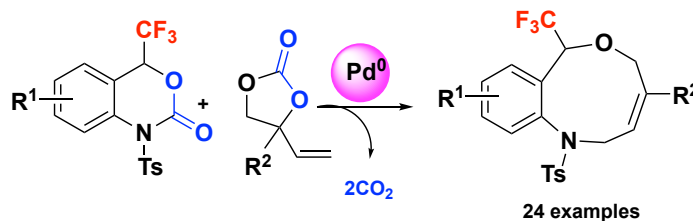
Abstract: A minor byproduct in the reaction of (*S*)-prolinol with thiophosgene in the presence of triethylamine is identified as a novel tricyclic dipyrrolidino-1,3,6-oxadiazocane-2-thione, the first example of such a ring system, and a representative of the uncommon, but useful 1,3,6-oxadiazocanes. A mechanism is proposed for its formation.

Access to Benzo-fused Nine-membered Heterocyclic Alkenes with a Trifluoromethyl Carbinol Moiety *via* a Double Decarboxylative Formal Ring-expansion Process under Palladium Catalysis

Pulakesh Das, Satoshi Gondo, Punna Nagender, Hiroto Uno, Etsuko Tokunaga, Norio Shibata

Chem. Sci. **2018**, 9, 3276–3281.

DOI: 10.1039/C7SC05447E



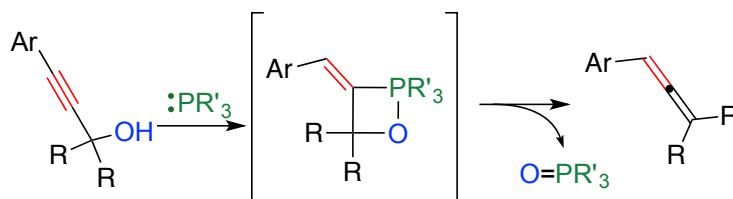
Abstract: Direct access to pharmaceutically attractive benzo-fused nine-membered heterocyclic alkenes **3** with a trifluoromethyl carbinol moiety was achieved *via* a palladium-catalyzed double-decarboxylative formal ring-expansion process from six-membered trifluoromethyl benzo[*d*][1,3]oxazinones to nine-membered trifluoromethyl benzo[*c*][1,5]oxazonines in the presence of vinyl ethylene carbonates. Generation of a Pd- π -allyl zwitterionic intermediate was proposed in the catalytic cycle. The trifluoromethyl group in the benzoxazinones plays an important role throughout the transformation. Diastereoselective chemical transformations of products were also demonstrated.

A Direct Synthesis of Trisubstituted Allenes from Propargyl Alcohols *via* Oxaphosphetane Intermediates

Kento Iwai, Soichi Yokoyama, Haruyasu Asahara, Nagatoshi Nishiwaki

Bull. Chem. Soc. Jpn. **2018**, 91, 337–342.

DOI: 10.1246/bcsj.20170372



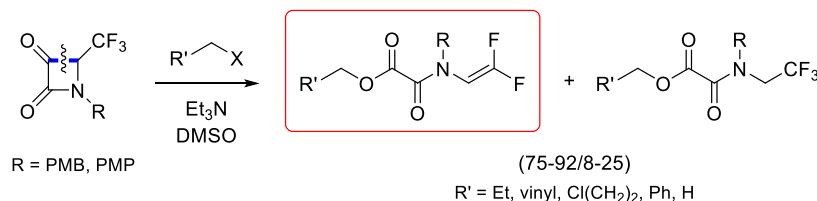
Abstract: A direct synthetic method for trisubstituted allenes from propargyl alcohol is provided; the synthesis proceeds *via* an oxaphosphetane intermediate. Functional groups such as formyl and pyridyl exhibited a degree of tolerance during reaction without any protection. The alcohol dimethylated at the propargyl position afforded two structural isomers, allene and 1,3-diene. The product ratio was considerably influenced by the solvent. Allene was predominantly obtained when the reaction was conducted in cyclohexane, and the ratio was inverted by changing the solvent to dichloromethane. The prepared (2-pyridyl)allene served as a substrate for the copper(I) catalyzed cyclization reaction to afford 3,3-dimethylindorizine-2-one.

Formation of Fluorinated Amido Esters through Unexpected C3–C4 Bond Fission in 4-Trifluoromethyl-3-oxo-β-lactams

Hang Dao Thi, Hannelore Goossens, Dietmar Hertsen, Valerie Otte, Tuyen Van Nguyen, Veronique Van Speybroeck and Matthias D'hooghe

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DOI: 10.1002/asia.201701636



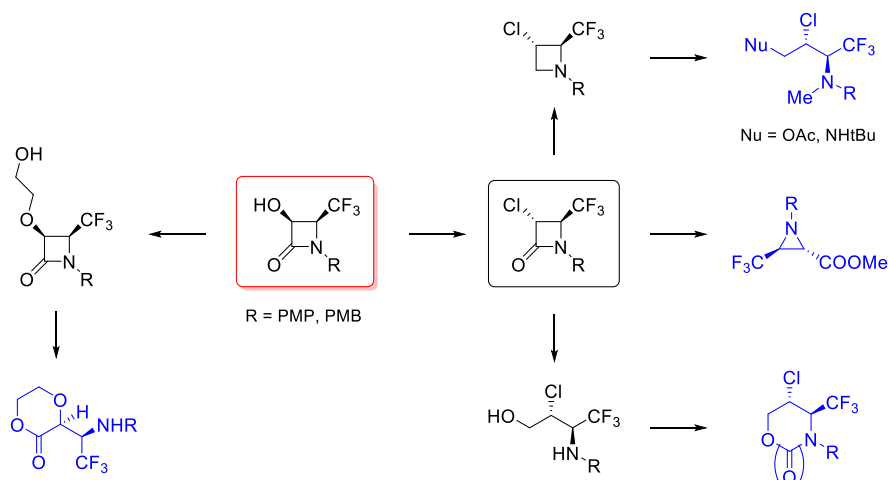
Abstract: 4-Trifluoromethyl-3-oxo-β-lactams were unexpectedly transformed into 2-[(2,2-difluorovinyl)amino]-2-oxoacetates as major products, accompanied by minor amounts of 2-oxo-2-[(2,2,2-trifluoroethyl)amino]acetates, upon treatment with alkyl halides and triethylamine in DMSO. This peculiar C3–C4 bond fission reactivity was investigated in-depth, from both an experimental and a computational point of view, in order to shed light on the underlying reaction mechanism.

Use of 3-Hydroxy-4-(trifluoromethyl)azetid-2-ones as Building Blocks for the Preparation of Trifluoromethyl-Containing Amino-propanes, 1,3-Oxazinan-2-ones, Aziridines, and 1,4-Dioxan-2-ones

Hang Dao Thi, Giang Le Nhat Thuy, Saron Catak, Veronique Van Speybroeck, Tuyen Van Nguyen, Matthias D'hooghe

Synthesis **2018**, *50*, 1439–1456.

DOI: 10.1055/s-0036-1591537



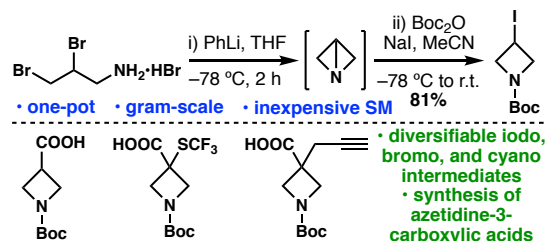
Abstract: 3-Hydroxy-4-(trifluoromethyl)azetid-2-ones were synthesized from the corresponding 3-benzyloxy-β-lactams and successfully transformed into new 3-chloro-4-(trifluoromethyl)azetid-2-one building blocks. The latter chlorides were shown to be eligible precursors for the construction of CF₃-containing aminopropanes, 1,3-oxazinanones, 1,3-oxazinan-2-ones and aziridines. In addition, 3-hydroxy-4-(trifluoromethyl)azetid-2-ones proved to be interesting substrates for the synthesis of novel 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones via intramolecular cyclization of 3-(2-hydroxyethoxy)-β-lactam intermediates.

An Improved, Gram-scale Synthesis of Protected 3-Haloazetidines: Rapid Diversified Synthesis of Azetidine-3-carboxylic Acids

Youngran Ji, Lukasz Wojtas, Justin M. Lopchuk

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Abstract: Azetidines are increasingly important heterocycles found in a variety of natural products and pharmaceutical compounds. Protected 3-haloazetidines, widely used and versatile building blocks in medicinal chemistry, have been prepared in a one-pot, gram-scale strain-release reaction of 1-azabicyclo[1.1.0]butane from commercially available starting materials. These intermediates were subsequently used to prepare a series of high value azetidine-3-carboxylic acid derivatives including the first reported synthesis of 1-(*tert*-butoxy-carbonyl)-3-((trifluoromethyl)thio)azetidine-3-carboxylic acid.