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Short Abstracts of Interesting Recent Publications of Swiss Origin

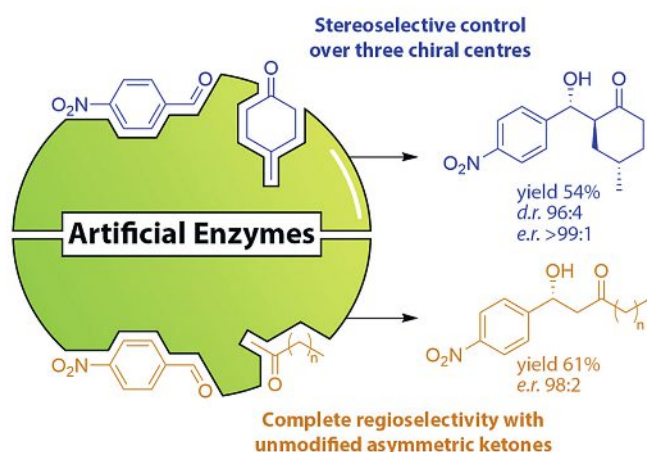
Engineered Artificial Carboligases Facilitate Regioselective Preparation of Enantioenriched Aldol Adducts

D. S. Macdonald, X. Garrabou, C. Klaus, R. Verež, T. Mori, and D. Hilvert,* *J. Am. Chem. Soc.* **2020**, *142*, 10250–10254.
Eidgenössische Technische Hochschule Zürich

Controlling the regio- and stereoselectivity of aldol additions is generally challenging with small-molecule catalysts, particularly with unmodified ketones. Enzymes offer a promising alternative, thanks to their inherent chirality and precise substrate recognition, but the engineering of natural aldolases is still far from meeting synthetic demands. The authors reengineered an artificial aldolase RA95.5-8F *via* single active site mutations. They discovered that two sets of variants, F112I/L/V and I133F, efficiently catalyzed additions of cyclic and linear ketones, respectively, to aldehydes with complete regioselectivity and control of up to three stereocenters. Broadening the substrate scope proved much easier with these artificial enzymes than in previous attempts with natural aldolases. These biocatalysts are an important addition to the toolbox of synthetic chemist for the regio- and stereocontrolled construction of C–C bonds.

Authors' comments:

“Designer enzymes have made great strides in recent years and we were excited to learn how easy it is to expand their substrate scope through a few mutations.”



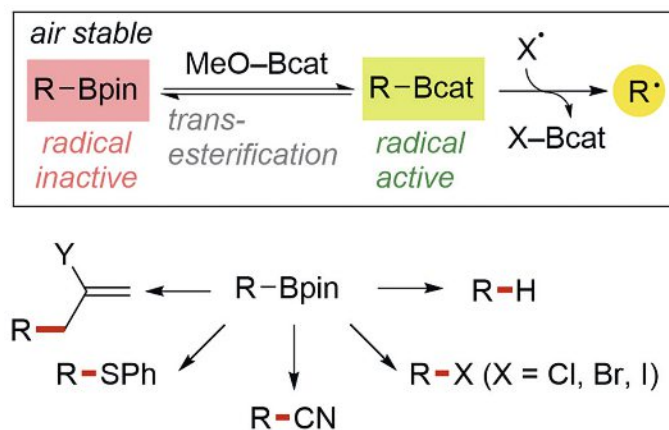
A General Approach to Deboronative Radical Chain Reaction with Pinacol Alkylboronic Esters

E. André-Joyaux, A. Kuzovlev, N. D. C. Tappin, and P. Renaud,* *Angew. Chem. Int. Ed.* **2020**, *59*, 13859–13864.
University of Bern

Nucleohomolytic substitution at boron is one of the most common ways to generate carbon-centered radicals. However, organoboron radical precursors are limited to air-sensitive compounds, and the stable, well-developed pinacol alkylboronates (R–Bpin) are radical-inactive. Herein, the authors report powerful one-pot deboronative radical chain reactions employing R–Bpin as precursors. This process involves the *in situ* conversion of R–Bpin into radical-active catechol alkylboronates (R–Bcat) by boron-transesterification with a substoichiometric amount of catechol methyl borate. The obtained R–Bcat reagents were engaged in a variety of radical reactions including halogenation, sulfanylation, alkylation, cyanation and protodeboronation. This work combining radical reactions with the rich chemistry of boronic esters will open new perspectives in synthetic chemistry.

Authors' comments:

“Adding radical reactivity to the amazing reaction toolbox of the popular and user friendly pinacol alkylboronic esters was a long-standing goal. The solution was so simple: transesterification!”



TiCl₃-Mediated Synthesis of 2,3,3-Trisubstituted Indolenines: Total Synthesis of (+)-1,2-Dehydroaspidospermidine, (+)-Condyfoline and (-)-Tubifoline

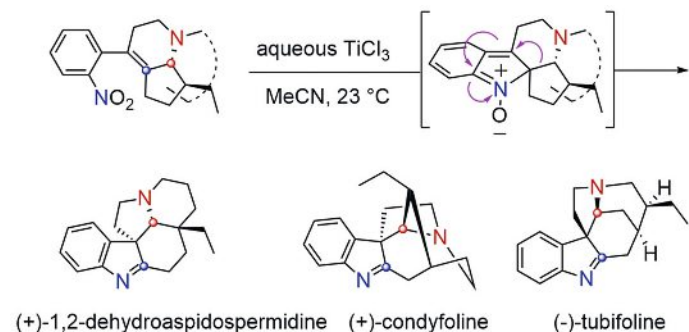
B. Delayre, C. Piemontesi, Q. Wang, and J. Zhu,* *Angew. Chem. Int. Ed.* **2020**, *59*, 13990–13997.

Ecole Polytechnique Fédérale de Lausanne

Monoterpene indole alkaloids (MIA) account for more than 3000 compounds distinguished by no less than 42 different skeletons. Of these, members of the akuammicine class possessing a 2,3,3-trisubstituted indolenine core are formed in nature from 19*E*-geissoschizine through a formal 1,2-alkyl shift. In this work, the TiCl₃-mediated reductive cyclization of 2-nitrostyrene derivatives was applied to the concise total synthesis of three MIAs, (+)-1,2-dehydroaspidospermidine, (+)-condyfoline and (-)-tubifoline. The key cyclization proceeded smoothly with highly functionalized substrates under mild conditions suitable for application at a late-stage of the synthesis. As supported by DFT calculations, this transformation was proposed to proceed through a concerted 1,5-sigmatropic rearrangement rather than a classic stepwise retro-Mannich/transannular Mannich reaction sequence. This method should be applicable to the synthesis of a broad range of other 2,3,3-trisubstituted indolenine alkaloids.

Authors' comments:

“By accomplishing the total synthesis of the three skeletally different natural products, we illustrate that the structural complexity and diversity of the natural products not only provide a test ground for the methodology development, but also are excellent probes for understanding the reaction mechanism.”



Enantioselective Hydroxylation of Benzylic C(sp³)-H Bonds by an Artificial Iron Hydroxylase Based on the Biotin–Streptavidin Technology

J. Serrano-Plana, C. Rumo, J. G. Rebelein, R. L. Peterson, M. Barnett, and T. R. Ward,* *J. Am. Chem. Soc.* **2020**, *142*, 10617–10623.

University of Basel

The selective functionalization of inert C–H bonds is a major challenge in synthetic chemistry. In contrast to homogeneous catalysts, which typically require directing groups, enzymes possess tailored active sites that lead to exquisite selectivity in C–H functionalization reactions. In this context, artificial metalloenzymes have attracted increasing interest in the past years as they combine features reminiscent of both enzymes and homogeneous catalysts. The authors report on a new artificial iron hydroxylase that enables enantioselective hydroxylation of benzylic C(sp³)-H bonds using H₂O₂ as oxidant. Substrates including alkylbenzenes, indane and tetralin were oxidized to the corresponding benzylic alcohols, with up to > 98% ee for (*R*)-tetralol. Additionally, they developed an enzymatic cascade with glucose oxidase, enabling the *in situ* generation of H₂O₂ from glucose using O₂ as the oxidant.

Authors' comments:

“After finishing this project, we 3D-printed a model of the artificial hydroxylase and used some confinement time to hand-paint it (see graphical abstract).”

