

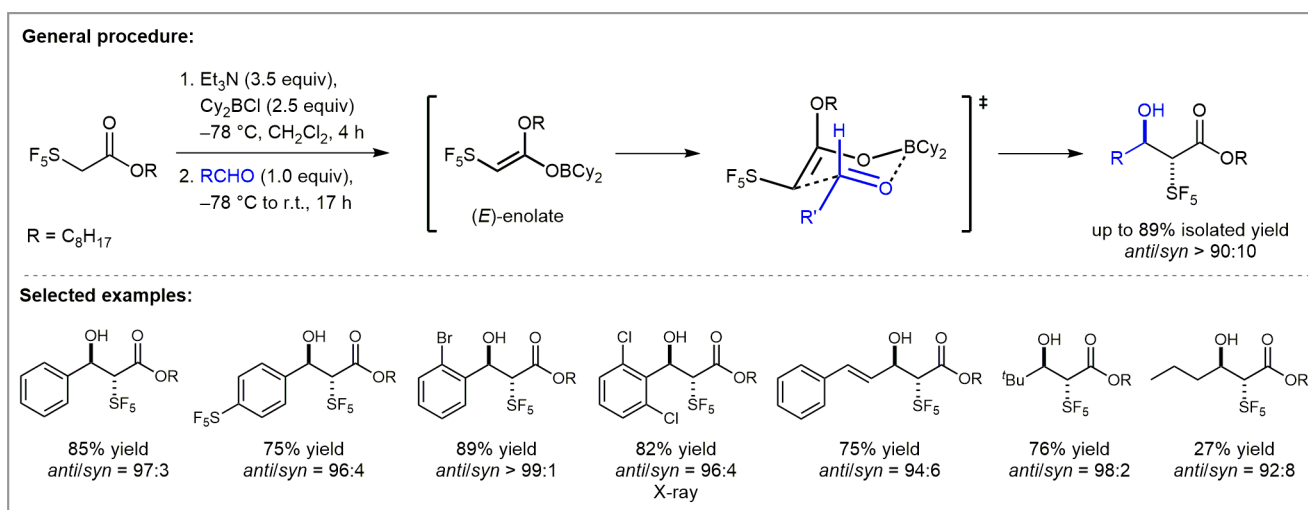
anti-Selective Aldol Reactions of SF₅-Acetic Acid Esters with Aldehydes Mediated by Dicyclohexylchloroborane

Org. Lett. 2016, 18, 1012–1015

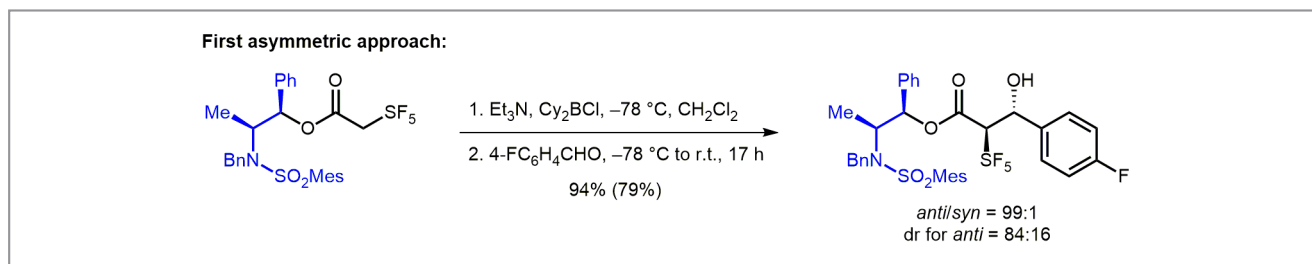
The aldol reaction is one of the most powerful and reliable C–C bond-forming processes in organic synthesis, and the resulting β -hydroxy carbonyl structural motif is present in many important natural and bioactive compounds. Even though this reaction has been known for more than 140 years, the fundamental studies by Wittig using preformed enolates made the reaction usable for the construction of more complex molecules. Progress in understanding the mechanism of these transformations led to the development of mild and highly selective reaction conditions useful for the construction of natural products such as polyketides and macrolides. In addition to Mukaiyama's silicon-based methodology, the boron-mediated variant has also been developed as one of the most powerful tools of modern aldol chemistry. Both silicon- and boron-Mukaiyama's aldol reactions involve highly diastereo- and enantioselective, and even catalytic, protocols.¹

The group of Professor Günter Haufe located at the University of Münster (Germany) is active in the development of new synthetic tools for the preparation of fluorinated compounds with the final aim of biomedical applications. Professor Haufe commented: "A couple of years ago we used intermediately formed ester enolates in Ireland–Claisen-type rearrangements to prepare α -fluoro- and α -trifluoromethyl carboxylic acid derivatives.² Now, in a fruitful cooperation with the

group of Professor Joseph S. Thrasher, Clemson University in South Carolina (USA), not only fluorinated carbon centers but also sulfur-containing groups [SF₅(CF₂)_n (n = 0–2)] are being investigated³ in order to achieve a better understanding of the intrinsic physicochemical properties of those groups." Among them, the fairly uncommon pentafluorosulfanyl (SF₅) group has gained much attention recently.⁴ The sheer size, comparable to that of a *tert*-butyl group, and the strong electron-withdrawing power are responsible for the strong steric and electronic effects exerted by the SF₅ group,⁵ making it a candidate for drug design studies, as well as an interesting functionality for agrochemicals and materials. "While the chemistry of aromatic SF₅ compounds has been improved significantly due to recent progress in large-scale preparation of these compounds," explained Professor Haufe, "the incorporation of the SF₅ group into aliphatic positions has lagged considerably behind. It is commonly achieved by the radical addition of SF₅Cl-type reagents to C–C multiple bonds. In this way, 2-(pentafluorosulfanyl)acetic acid became readily available recently⁶ and was identified as a convenient starting material. We have been able to successfully use it in the preparation of α -SF₅ carboxylic acid derivatives by Ireland–Claisen rearrangements of allylic SF₅ acetates," continued Professor Haufe, who added: "For the first time, intermediately formed SF₅-substituted



Scheme 1 Synthesis of α -SF₅- β -hydroxy esters by a boron-mediated aldol reaction via a Zimmerman–Traxler-like transition state



Scheme 2 Asymmetric approach of the boron-mediated aldol reaction

silicon enolates were established by low-temperature NMR spectroscopy.⁷ This observation led us to speculate whether enolates of alkyl SF₅ acetates might be useful in aldol reactions.

Professor Haufe told SYNFORM that the present work indeed profited from the power of the boron-mediated aldol reaction of (*E*)-enolates, formed highly selectively from alkyl SF₅ acetates to produce targeted aldols using dicyclohexylchloroborane/triethylamine. This system was previously used by Ramachandran for the enolization of α-trifluoromethyl carbonyl compounds.⁸ “Just like we hoped for, treatment of octyl SF₅ acetate with an excess of Cy₂BCl and Et₃N at -78 °C and subsequent addition of various aromatic and aliphatic aldehydes led to the formation of the *anti*-3-hydroxy-2-(pentafluorosulfanyl)alkyl esters almost exclusively,” remarked Professor Haufe. The *anti*-configuration of the hitherto unknown SF₅ aldols was established by X-ray structural analysis. Furthermore, the different conformations of *para*- and *ortho*-monosubstituted phenyl products on the one hand versus *ortho,ortho'*-disubstituted phenyl products on the other hand were elucidated by NMR spectroscopy and DFT calculations, again emphasizing the strong steric impact of the SF₅ group.

“Being aware of the stereochemical outcome of the reaction, we proposed a Zimmerman–Traxler-like transition state,” said Professor Haufe. “A strong interference of the SF₅ group with the rather bulky borane within the formed (*E*)-enolates might be the key for the high selectivity observed, but this is also creating the instability of these intermediates above -40 °C.”

As a result of the broad applicability, Professor Haufe and co-workers strived forward towards asymmetric approaches. “As a first success, a norephedrine-based auxiliary provided an *anti/syn*-selectivity of 99:1 and a *dr* of 84:16 for one of the *anti*-diastereomers while keeping a good level of conversion,” he said.

The usefulness of this type of aldol reaction has been shown independently by Carreira and co-workers in a practical synthesis of a number of six-membered nitrogen SF₅

heterocycles following a similar protocol, although the achieved stereochemistry was lost during subsequent transformations.⁹

Professor Thrasher explained: “I truly believe that only because of our collaborative effort have we been able to come up with as many exciting results as those in this review and our recent papers.³ Perhaps no single research group in the world would be able to meet all of the scientific goals that we set, especially at the beginning of our project, funded jointly by the U.S. National Science Foundation (NSF) and the German Deutsche Forschungsgemeinschaft (DFG). Only via cooperation could the complementary expertise of both groups guarantee the success of our project. Unfortunately for us, the U.S. NSF has archived their International Collaboration in Chemistry (ICC) Program from which we obtained part of the funding.”

Professor Haufe concluded: “We believe that, based on our and others’ results, aldol reactions will help to integrate SF₅ compounds into many fields of contemporary research. Application of alternative auxiliaries allowing milder deprotection conditions and catalytic approaches being under investigation will give rise to feasible asymmetric variants. Our preliminary results applying Mukaiyama’s silicon-based aldol chemistry proved the approach to the other stereochemical series.”

Matthias Haufe

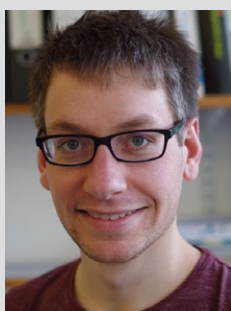
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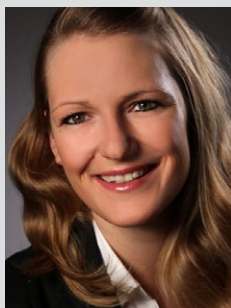
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About the authors



F. W. Frieze

Florian W. Frieze was born in Hamm (Germany) in 1990 and received his M.Sc. in chemistry from the University of Münster (Germany) under the supervision of Professor Günter Haufe. In 2016, he joined the group of Professor Armido Studer as a Ph.D. student. His future work will mainly focus on the development of new radical chain reactions.



Dr. A.-L. Dreier

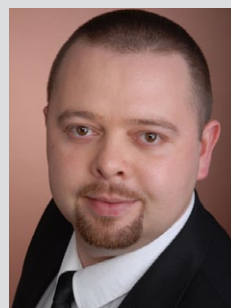
Anna-Lena Dreier was born in Münster (Germany) in 1986. After obtaining her Diploma degree in 2011, she worked on her Ph.D. thesis under the supervision of Professor Günter Haufe. She was mainly focused on the synthesis and characterization of new (pentafluorosulfanyl)-substituted compounds. After her graduation in 2015, she joined the German automotive supplier and tire manufacturer Continental.



Dr. A. F. Matsnev

Andrej V. Matsnev, a native Ukrainian, is a Research Scientist at Halocarbon Products Corporation and an Adjunct Assistant Professor at Clemson University (USA). He also serves as Vice-Chair Secretary of the American Chemical Society (ACS) Division of Fluorine Chemistry. In 2004, he obtained his Ph.D. from the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine in Kiev (IOCh NASU), where he worked under the supervision of Professor Lev M. Yagupolskii. In 2008, he joined the research group of Professor Norio Shibata at the Nagoya Institute of Technology (Japan). In 2010, he transferred

to the research group of Professor Joseph S. Thrasher at the University of Alabama (USA) and moved with the group to Clemson University (USA) in 2012.



Dr. C. G. Daniliuc

Constantin G. Daniliuc earned his Diploma degree from the University 'Al. I. Cuza' in Iasi (Romania) in 2002. As a recipient of an Erasmus Scholarship, he completed his Master thesis at the Technical University of Braunschweig (Germany) in collaboration with InnoChemTech Company (Germany). He received his Ph.D. from the same university in 2008 under the supervision of Professor W.-W. du Mont, and started there as a crystallographer in cooperation with Professors P. G. Jones and M. Tamm in 2009. Since 2012, he is Head of the Crystallographic Laboratory within the Organic Chemistry Institute, University of Münster (Germany).



Prof. J. S. Thrasher

Joseph S. Thrasher received his B.S. and Ph.D. degrees at Virginia Tech (USA) prior to carrying out postdoctoral research at the Freie Universität Berlin (Germany) with Professor Konrad Seppelt and at Clemson University (USA) with Professor Darryl DesMarteau. In 1984, he started his independent career at The University of Alabama (USA), where he served as Director of Graduate Studies (1995–2002) and Department Chair (2002–2007). In the fall of 2011, Dr. Thrasher returned to Clemson University to overlap with and follow Professor DesMarteau. He has served as Chair of the American Chemical Society (ACS) Division of Fluorine Chemistry (1994), co-chaired two ACS Winter Fluorine Conferences (1993 and 1995), and was lead organizer of the 19th International Symposium of Fluorine Chemistry (2009). Additionally, he became Regional Editor for the Americas for the *Journal of Fluorine Chemistry* in 2016.

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Prof. G. Haufe

Günter Haufe graduated from the University of Leipzig (Germany) with a Diploma degree in 1972 and a Dr. rer. nat. in 1975 both with Professor Manfred Mühlstädt. After basic military service he started his independent scientific career and did a Habilitation and *venia legendi* in Leipzig (1985). In 1986, he worked as a Research Fellow of Centre National de la Recherche Scientifique (CNRS) with André Laurent at the Université Lyon I (France), and as a visiting scientist with Jakko Paasivirta at the University of Jyväskylä (Finland). From 1988–1991 he was an Associate Professor (Docent) of Bioorganic Chemistry at the

University of Leipzig before he was appointed to his present position as a Professor of Organic Chemistry at the University of Münster (Germany). Guest professorships have led him to Lyon (France), Poznan (Poland), Rouen (France), Valencia (Spain), Nagoya (Japan) and to the University of Florida, Gainesville (USA) as a Paul Tarrant Visiting Professor. He was awarded with the 'Friedrich-Wöhler-Preis' in 1985 and elected as a member of the European Academy of Sciences in 2015. From 2008–2010 he served as a Chair of the group of German fluorine chemists within the German Chemical Society. He published a book on 'Alicyclic Chemistry' together with Gerhard Mann (1989) and edited a monograph 'Fluorine and Health' together with Alain Tressaud (2008). He was an Associate Editor of 'Advances in Fluorine Science' and is a Regional Editor of the *Journal of Fluorine Chemistry* since 2008.