A Stoichiometric Haloform Coupling for Ester Synthesis with Secondary Alcohols

Highlighted article by A. C. Rowett, S. G. Sweeting, D. M. Heard, A. J. J. Lennox

- Stoichiometric ROH
- Selective ester formation
- Primary and secondary ROH
- Complex esters formed directly
Dear Readers,

In this September issue of Synform we welcome a new Editorial Board Member: Prof. Dr. Tanja Gulder (Saarland University, Germany) who joined the Editorial Board of SYNLETT with effect of July 2024. Tanja has been interviewed by Synform about her scientific interests, her feelings about becoming a Thieme Chemistry Editorial Board Member, as well as her extra-lab interests. A warm welcome to Tanja!!

The first Literature Coverage article focuses on a novel version of an evergreen classic of organic chemistry: the haloform reaction, the scope of which has been expanded by the group of A. J. J. Lennox (UK) to include a stoichiometric coupling-type reaction with secondary alcohols to give directly the corresponding esters. The next article is a Young Career Focus interview with one of the most recent Thieme Chemistry Journals Awardees, B. Schmidt (Germany), who talks with us about his scientific and extra-lab interests. The issue is wrapped up by another Literature Coverage article, highlighting a novel enantioselective synthesis of α-tertiary ethynylamines and related tandem sequence to provide also azacycles, as reported in Nat. Chem. by the group of J. Zhou (P. R. of China).

Enjoy your reading!

Matteo Zanda
Editorial Board Focus: Prof. Dr. Tanja Gulder (Saarland University, Germany)

**Background and Purpose.** From time to time, SYNFORM portraits Thieme Chemistry Editorial Board or Editorial Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. This Editorial Board Focus presents Prof. Dr. Tanja Gulder (Saarland University, Germany) who joined the Editorial Board of SYNLETT with effect of July 2024.

**Interview**

**SYNFORM** What fascinates you most about organic chemistry and synthesis?

Prof. Dr. T. Gulder The creativity and complexity of building structurally complex molecules from simple substances is not just a scientific pursuit for me but a passion. The ability to design and construct molecules with specific, often complex structures with a particular function is like solving a complex puzzle, and this challenge is what drives my enthusiasm for organic chemistry and synthesis.

**SYNFORM** What do you think about the modern role and prospects of organic chemistry?

Prof. Dr. T. Gulder Organic chemistry, despite its long history, remains a field of endless discovery and innovation. It creates new tools that push the pharmaceutical, agrochemical, and material industries, impacting other scientific disciplines and everyone’s lives. This significant impact comes with great responsibilities. One of the main aims of modern organic synthesis is to rethink chemical feedstocks, processes, and products concerning environmental safety and sustainability. This makes organic chemistry a perpetually exciting and rewarding science area, offering endless exploration opportunities and a promising future.

**SYNFORM** Please comment on your role as a member of the Editorial Board of SYNLETT.

Prof. Dr. T. Gulder As I am new on the SYNLETT Editorial Board, I am still figuring out my specific role. Besides the daily business of handling manuscripts, I started to develop on the first thematic issue for the journal, which may be devoted to enzymes in organic reactions, an emerging field in organic synthesis.
SYNFORM Finally, on a personal note, what do you do in your free time?

Prof. Dr. T. Gulder In my free time, I like to read books, do gardening, and cook together with my family. My most favorite thing is to spend time with my daughter and my husband outside.

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A Stoichiometric Haloform Coupling for Ester Synthesis with Secondary Alcohols

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The haloform reaction, first reported in 1822 by Georges Simon Serullas, is a staple of undergraduate organic chemistry courses taught in universities. It takes methyl ketones to carboxylic acids through the triple α-halogenation of the methyl group to form a good nucleofuge, which is replaced by hydroxide (Scheme 1A). This reaction has been widely applied in the pharmaceutical and fragrance industries. It has since evolved to form methyl or ethyl esters when the reaction is performed in methanol or ethanol, respectively (Scheme 1B). “Undergraduate textbooks tell you this is all that is possible,” said Dr. Alastair Lennox (University of Bristol, UK), who—together with his group—wondered why it was not possible to use more complicated and extravagant alcohols to make more interesting esters. “We conducted an in-depth literature search on whether it had been done before,” said Dr. Lennox, continuing: “When my PhD student, Bert [Albert Rowett, first author of the title paper], came back to me to tell me it had not been done, I told him to go back and look again as I could not believe there was nothing on it. As well as finding no examples of complicated alcohols, we also found that secondary alcohols had hardly been attempted; we found one example of the use of isopropanol. Hence, based on these surprisingly limited publications, we were inspired to explore whether it was possible to derive conditions with one equivalent of a complex primary or secondary alcohol (Scheme 1C).”

When the authors first started exploring this reaction, they realised that carboxylic acid would competitively form very readily and the alcohol nucleophile would oxidise, removing it from the reaction and providing the opportunity for other esters to form. Dr. Lennox explained: “We explored many different combinations of halogenating reagents and bases, and eventually found that I₂ with DBU was especially proficient and facilitated 1 equivalent of our model primary alcohol to be used in the reaction (Scheme 2). This is because it was possible to dry these reagents well, which avoids the formation of carboxylic acid, and also slow the rate of alcohol oxidation down relative to the desired iodination of the methyl ketone.”

However, when applying these optimised conditions to secondary alcohols, the yield decreased significantly. “To understand why this occurred and how to adapt our conditions, we turned to kinetic studies and modelling,” remarked Dr. Lennox. He continued: “Through this, we discovered that the iodination steps were under equilibrium, which became apparent with secondary alcohols because the final substitution

Scheme 1 The haloform reaction forms carboxylic acids and esters with solvent-level primary alcohol from methyl ketones. This work presents the synthesis of new complex esters using stoichiometric primary and secondary alcohols.

Scheme 2 The haloform reaction conducted with 1 equivalent of a primary alcohol, selected examples.
step is slower: the deiodination of the triiodo species started to compete with the substitution step that forms the ester (Scheme 3). This insight enabled a very simple solution, which was to increase the concentration of DBU•I₂ to increase the concentration of reactive triiodo species through Le Chatelier’s principle, and therefore improve the rate of substitution for secondary alcohols. This change facilitated a range of complex secondary alcohols to be used in the reaction.” Dr. Lennox concluded: “We now wonder how we could further change the reaction to work with different nucleophiles, increasing the available chemical space of this discovery.”

Scheme 3 Mechanistic studies led to the development of conditions for secondary alcohols
About the authors

Albert C. Rowett studied chemistry at the University of Bristol, UK (MSci, 2018). He then joined the EPSRC Centre for Doctoral Training (CDT) in Catalysis (University of Bath, University of Bristol and Cardiff University, UK), returning to Bristol to complete his PhD research under the supervision of Dr. Alastair Lennox. His research focused on (electro)halogenation reactions and, in particular, the development of the novel haloform coupling methodology discussed here.

Stephen G. Sweeting received his MSci Chemistry degree from the University of Bristol (UK) in 2021. He is now pursuing his PhD under the supervision of Dr. Alastair Lennox, also at the University of Bristol. His main area of study focuses on understanding fluorination reactions involving hydrogen fluoride complexes, as well as developing new electrochemical methodologies to achieve selective fluorinations.

David M. Heard studied at the University of Sheffield, UK (MChem, 2014) and completed a PhD in chemical synthesis at the University of Bristol, UK (2019), researching the structural elucidation and total synthesis of maleidride natural products with Prof. Chris Willis. David completed postdoctoral studies with Dr. Alastair Lennox (University of Bristol) on electrosynthetic methods and reactor technology, and with Prof. Dennis Hall (University of Alberta, Canada) investigating photoredox catalysis in organoboron chemistry. David now works in process development in the pharmaceutical industry.

Alastair J. J. Lennox attained his PhD from the University of Bristol, UK (Prof. Guy Lloyd-Jones) and did postdoctoral studies in Rostock, Germany (Prof. Matthias Beller) as an Alexander von Humboldt Fellow and at the University of Wisconsin, Madison, USA (Prof. Shannon Stahl). In 2018, Alastair returned to the University of Bristol as a Royal Society University Research Fellow to start his independent research programme. He was promoted to Associate Professor of Chemistry in 2022. His group are interested in the development of novel synthetic organic methods with sustainability and mechanism as themes that strongly underpin their approach to this. Specific interests include the exploration of electrochemistry as a tool for performing selective redox transformations, and also in the development of fluorination reactions and fluorinated building blocks.
Young Career Focus: Dr. Bernd M. Schmidt (Heinrich Heine Universität, Germany)

**Background and Purpose.** SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Bernd M. Schmidt (Heinrich Heine Universität, Germany).

**INTERVIEW**

**SYNFORM** Which field of organic chemistry are you interested in the most and why?

**Dr. B. M. Schmidt** I am particularly interested in supramolecular chemistry within the field of organic chemistry. In our research group, we leverage self-assembly to develop novel compounds and materials, spanning from individual molecules to intricate assemblies. Our aim is to explore the interdisciplinary applications of supramolecular structures in materials chemistry, photochemistry, macromolecular chemistry, and biochemistry.

**SYNFORM** Following that, what is the focus of your current research activity?

**Dr. B. M. Schmidt** My research group deals with various aspects of supramolecular chemistry (Figure 1), such as porous imine-based organic compounds containing fluorinated motifs, which we were able to establish with a series of publications. This is complemented by our pioneering work in the field of mechanoresponsive macromolecular supramolecular systems for releasing guests from aqueous solutions, as well as supramolecular building blocks that react to visible light. We combine the possibilities of organic synthesis chemistry with the self-organisation of complex molecular structures and molecular recognition in solution and in the solid state.

In the beginning of 2024, we published our work on multifold post-modification of macrocycles and cages by isocyanate-induced azadefluorination cyclisation. For this project, we designed suitable building blocks using organic chemistry knowledge, self-assembled them using dynamic-covalent imine chemistry, and transformed the supramolecular structures into (non-dynamic) covalent compounds by reduction with sodium borohydride. Reactive isocyanates can be used to introduce functional groups into the cages...
and macrocycles, leading to rigid and chemically stable molecules that can undergo further reactions. It is a dream to use concepts like this, combining the strength of supramolecular chemistry, the one-step self-assembly of complex structures, with the power of organic chemistry to make further precise modifications thereof.

**SYNFORM** What do you think about the modern role and prospects of organic chemistry?

**Dr. B. M. Schmidt** Organic chemistry provides the foundation for understanding the structure, reactivity, and synthesis of organic molecules, which are essential building blocks in supramolecular systems. Supramolecular chemists can then design and construct a wide range of molecular architectures with tailored properties and functions. In terms of prospects, organic chemistry continues to play a vital role in driving innovation and advancing scientific knowledge, extending over various fields, particularly within the dynamic and rapidly evolving field of supramolecular chemistry.

**SYNFORM** Which difficulties are there for young upcoming chemists in your field? Do you have any tips?

**Dr. B. M. Schmidt** The status of junior researchers in Germany, particularly in the phase before obtaining a lifetime professorship, is currently varied and often not aligned with their responsibilities in this important qualification phase. In contrast to counterparts abroad, who often have clearly defined roles (e.g., assistant professor) with specified rights and duties, Germany lacks nationwide uniform standards. Even when standards are proposed by funding organisations, such as for Emmy Noether research groups, implementation might vary. As a result, individuals frequently need to advocate for their rights in order to carry out their work effectively.

I co-authored a recent discussion paper on this topic in German [link].

**SYNFORM** What is your most important scientific achievement to date and why?

**Dr. B. M. Schmidt** My most significant achievement lies in the dedicated effort I’ve invested in nurturing and guiding the next generation of scientists. I take pride in training and preparing them for the challenges they may encounter in their future roles, regardless of the specific positions they choose to pursue. I am very grateful to see how they surpass themselves and find success.

The most important scientific achievement is always the next big project or paper for me, I do not like looking back.

**SYNFORM** Could you tell us something about yourself outside the lab, such as your hobbies or extra-work interests?

**Dr. B. M. Schmidt** I am an absolutely crazy foodie, and I love cooking (and eating), exploring things, restaurants, and everything. I also got into wine during the pandemic, so there’s a whole new field to explore for me, too. I even interned in a restaurant before studying chemistry because I was wondering if I should become a chef.

![Figure 1](image)

**Figure 1** Current areas of research in the Schmidt group: fluorinated materials, photoswitchable supramolecular assemblies, and ultrasound-induced mechanochemistry in complex systems.
Optically active amines and azacycles are widely present in drugs, bioactive compounds and agrochemicals. The synthesis of chiral α-tertiary amines and related azacycles in sufficient structural diversity is important for drug development, but constitutes a long-term challenge confronting organic chemists. "Enantioenriched α-tertiary propargylamines featuring an α-ethynyl substituent are valuable platform molecules, because their sp C–H bonds and carbon–carbon triple bonds..."
permit versatile diversifying reactions,” said Professor Jian Zhou [East China Normal University (ECNU), P. R. of China], adding: “Nevertheless, their facile access is undeveloped in terms of enantioselectivity, substrate scope and synthetic efficiency, as compared with internal propargylamines.”

According to Professor Zhou, asymmetric Cu(I)-catalysed propargylic amination (ACPA) is a promising strategy to access enantioenriched ethynylamines, following the seminal independent work of Maarseveen, Nishibayashi and colleagues. However, despite previous enlightening studies, there remains much to explore (Scheme 1a). This is because only substrates leading to Cu–allenylidene intermediates with both an aryl and an oxygen-containing moiety could give satisfactory results, while aliphatic compounds and, especially, simple ketone-derived propargylic alcohol derivatives still represent problematic substrates. Moreover, the modular combination of ACPA into tandem sequences for diverse synthesis of azacycles remains an untrodden path.

“As the prochiral carbon in the Cu–allenylidene intermediate is further away from the ligand sphere, how to achieve excellent remote enantiofacial control is the key to success,” said Professor Zhou. He continued: “With our experience in asymmetric CuAAC reactions realized by PYBOX ligands featuring a bulky C4 shielding group, along with the fact that both reactions are proposed to involve di-copper catalysis, we wondered whether these C4-modified PYBOX ligands were effective for ACPA of challenging substrates.” Professor Zhou further stated: “Initial trials using PYBOX ligands with a single C4 shielding group all failed, thus prompting us to exploit sterically more confined PYBOX ligands by installing relaying groups on the 5-position of both oxazoline rings, to form a sterically constrained microenvironment to relay stereochemical information from the ligand chirality through steric interactions (Scheme 1b).”

Indeed, sterically confined PYBOX ligands with both C4 shielding group and relaying groups can achieve excellent...
remote enantiofacial discrimination of the Cu–allenylidenes, thus allowing the highly enantioselective ACPA of aliphatic and alkyl aryl ketone-derived propargylic carbonates with a variety of primary and secondary amines (Scheme 1c). “The ACPA-based tandem sequences were also established as a new strategy to synthesize various chiral azacycles, such as dihydropropyrroles, tetrahydropropyrroles, dihydroquinines, or tetrahydroquinines with an aza-quaternary stereocenter (Figure 1a),” said Professor Zhou, adding: “The value of the thus-obtained chiral α-tertiary α-ethylnylamines was demonstrated by various transformations and the enantioselective total synthesis of a selective multi-target β-secretase inhibitor (Figure 1b).” A collaboration with Prof. Xin Wang on theoretical calculations revealed that both the C4 bulky benzyloxy group and the phenyl relaying group on the oxazoline ring are responsible for the high enantioselectivity (Figure 1c). Professor Zhou explained: “With the combination of C4 benzyloxy and the phenyl relaying group, a more sterically confined chiral pocket should be formed, which enhances the favorable π–π stacking interactions and also the unfavorable repulsion interaction, thus resulting in a higher free energy gap of 2.6 kcal/mol.”

Professor Zhou emphasized that the working model of sterically confined PYBOX ligands could also be extended to the asymmetric propargylic substitution of α-CF₃ propargylic carbonate with O- and C-centered nucleophiles. “This work provides a flexible solution to develop asymmetric propargylic substitutions involving metal–allenylidene intermediates,” said Professor Zhou. He concluded: “Since the pioneering work of Nishibayashi, Hidai, Uemura and co-workers, a variety of primary and secondary amines (Scheme 1c). “The ACPA-based tandem sequences were also established as a new strategy to synthesize various chiral azacycles, such as dihydropropyrroles, tetrahydropropyrroles, dihydroquinines, or tetrahydroquinines with an aza-quaternary stereocenter (Figure 1a),” said Professor Zhou, adding: “The value of the thus-obtained chiral α-tertiary α-ethylnylamines was demonstrated by various transformations and the enantioselective total synthesis of a selective multi-target β-secretase inhibitor (Figure 1b).” A collaboration with Prof. Xin Wang on theoretical calculations revealed that both the C4 bulky benzyloxy group and the phenyl relaying group on the oxazoline ring are responsible for the high enantioselectivity (Figure 1c). Professor Zhou explained: “With the combination of C4 benzyloxy and the phenyl relaying group, a more sterically confined chiral pocket should be formed, which enhances the favorable π–π stacking interactions and also the unfavorable repulsion interaction, thus resulting in a higher free energy gap of 2.6 kcal/mol.”

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REFERENCES

Yi Gong received his Master’s degree from the Guizhou University (P. R. of China) in 2018. Then he moved to East China Normal University (P. R. of China) to pursue his Ph.D. in the group of Jian Zhou. He received his Ph.D. in 2023. Currently, he is a postdoctoral fellow with Prof. Jian Zhou. His work revolves around the catalytic asymmetric synthesis of fully substituted carbon stereocenters.

Daliang Tang received his Master’s degree from Yangzhou University (P. R. of China) in 2017. He then worked for Wuxi AppTec for four years and in 2021, he moved to East China Normal University (P. R. of China) to pursue his Ph.D. in the group of Jian Zhou. His work revolves around the catalytic asymmetric synthesis of the fully substituted carbon stereocenters and synthesis of novel chiral Pybox ligands.

Hui Luo was born in Jiangxi province, P. R. of China. He obtained his bachelor’s degree in chemistry in 2021 from Yichun University (P. R. of China). Since 2021, he has been studying for a master’s degree in East China Normal University (P. R. of China) under the supervision of Professor Feng Zhou in the group of Professor Jian Zhou. Now he works in Shanghai Yuanhua Pharmaceutical Technology Co., Ltd.

Zhi-Peng Zhao obtained his bachelor’s degree from the China West Normal University (P. R of China) in 2020. He then pursued his master’s degree in the group of Prof. Jian Zhou at East China Normal University (P. R of China), where he worked on organic synthesis methods. He received his master’s degree in 2023.

Feng Zhou was born in 1987 in Shandong province, P. R. of China. After obtaining his bachelor’s degree in 2009 from Sichuan Normal University (P. R of China), he joined Professor Jian Zhou’s group at East China Normal University (P. R of China) and obtained his PhD in 2014. Subsequently, he embarked on his academic career at East China Normal University and has been a professor there since 2021. His research interest centers on the catalytic asymmetric construction of tetrasubstituted stereogenic centers and the utilization of CO₂.

Xin Wang obtained his PhD in 2002 from Sichuan University (P. R. of China). After spending two years working as a postdoctoral fellow with Professor Yuansheng Jiang and Professor Shuhua Li at Nanjing University (P. R. of China), he joined Sichuan University in 2004. He has been a professor at Sichuan University since 2014. His current research interests include molecular design and simulation of materials and theoretical study of organocatalytic reaction mechanism.

Jian Zhou obtained his PhD in 2004 from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China), under the guidance of Professor Yong Tang. After spending one year working as a postdoctoral fellow with Professor Shū Kobayashi at the University of Tokyo (Japan), and three years with Professor Benjamin List at Max-Planck-Institut für Kohlenforschung (Germany), he joined the Shanghai Key Laboratory of Green Chemistry and Chemical Processes at East China Normal University (P. R. of China) as a professor from the end of 2008. His group focuses on the development of new chiral catalysts and new catalytic asymmetric reactions allowing the catalytic, economical and enantioselective construction of tetrasubstituted stereogenic carbon centers.
Coming soon

**Literature Coverage**

**Phase-Transfer Catalysts Shift the Pathway to Transmetalation in Biphasic Suzuki–Miyaura Cross-Couplings**

**Literature Coverage**

**Copper-Catalysed Perarylation of Cyclopentadienes: Synthesis of Hexaarylcyclopentadienes**

**Literature Coverage**

**Radical-Mediated α-tert-Alkylation of Aldehydes by Consecutive 1,4- and 1,3-(Benzo)thiazoly Migration**

Further highlights

**Synthesis** Review: **1,2-trans-Diaminocyclohexane (DACH) in Asymmetric Catalysis: Nearing Fifty Years of Faithful Service and Counting** (by S. Hanessian)

**Synlett** Account: **Acetal Substitution Reactions: Stereo-electronic Effects, Conformational Analysis, Reactivity vs Selectivity, and Neighboring-Group Participation** (by K. A. Woerpel and co-workers)

**Synfacts** Synfact of the Month in category “Innovative Drug Discovery and Development”: **Discovery and Development of CNS-Penetrant IRAK4 Inhibitors**