β-Chlorovinyl Ketones to (Thio)chromenones: A Substrate- Controlled Mechanistic Dichotomy

Highlighted article by H. Y. Kim, E. Song, K. Oh

Stereochemistry and conformation of chlorovinyl ketones for the (E)-isomer
Dear Readers,

Happy 10th Anniversary SYNFORM!!!

It seems like yesterday, but actually the first issue of SYNFORM was published exactly ten years ago, in May 2007. That pilot issue – opened by an Inside Story interview on cannabinoids chemistry and pharmacology to Dr. Vincenzo Di Marzo (CNR, Italy) by the former Director General of the Italian Medicines Agency (AIFA), Dr. Luca Pani – was preceded by months of careful editorial planning for defining all the main features of the new journalistic-style supplement of the Thieme Chemistry journals.

After ten years, nearly 500 published articles and 1500 pages, SYNFORM has certainly evolved and has a more sophisticated cover and look, but its spirit is younger than ever and its aim, as set in that first Editorial – 10 years ago – is still exactly the same: “SYNFORM aims at complementing the information provided by the Thieme Chemistry journals. SYNFORM will serve the international chemistry community by publishing timely information about new scientific advances in organic chemistry and related fields of research. In addition, SYNFORM will inform you about facts and people from the world of chemical sciences – all this in a stimulating and thought-provoking manner.”

We will duly celebrate the 10th Anniversary with an interview with... myself! It will be published in the forthcoming June issue (online in May). For the moment, let’s kick-start the celebrations with four new articles of undisputed scientific quality. The opening story covers a novel approach to (thio) chromenones from β-chlorovinyl ketones developed by K. Oh (South Korea). The runner-up is a SYNTHESIS Highlight describing a method developed by M. Reggelin (Germany) for preparing oxathiazin-S,O-acetals through a carbenoid route. The third literature-coverage article details a novel strategy recently published by I. Coldham (UK) for achieving highly enantioselective tandem metalation–substitutions in α-position to chiral nitriles. The closing article is a Young Career Focus interview with the 2016 Thieme Chemistry Journals Award winner L. Pilarsky (Sweden).

As always, enjoy your reading!

Matteo Zanda
Chromenones and thiochromenones are widely represented among natural products and their synthetic derivatives typically display a wide array of biological activities. The growing interest in the pharmaceutical properties of (thio)chromenones has spurred the development of novel synthetic methods to (thio)chromenone derivatives. The typical synthetic approaches to chromenones rely on the intramolecular condensation of 3-hydroxy 1,3-diones and the intermolecular conjugate addition of 3-hydroxy chalcones under oxidation conditions (Scheme 1, A). In contrast, the synthetic approaches to (thio)chromenones are limited to a handful of Ni-catalyzed and Pd-catalyzed reactions of thio-substituted substrates. With the aim of developing a facile and efficient synthesis of (thio)chromenones without using elaborated substrates or expensive reagents, the group of Professor Kyungsoo Oh at Chung-Ang University (Seoul, South Korea) proposed a reaction sequence of Friedel–Crafts acylation of alkynes and intramolecular cyclization of in situ generated β-chlorovinyl ketones.
“The Friedel–Crafts acylation of alkynes can result in the formation of stereoisomeric β-chlorovinyl ketones. Our previous studies suggested that the stereoselectivities for reactions involving alkyl- and aryl-substituted alkynes is substrate-dictated (Scheme 1, B),” explained Professor Oh. He continued: “Thus, the use of alkyl alkynes can lead to the kinetically favored (Z)-β-chlorovinyl ketones and the thermodynamically favored (E)-β-chlorovinyl ketones. While the (E)/(Z)-selectivity of reactions utilizing alkyl alkynes could be controlled by the reaction temperature and the amount of AlCl₃, the aryl alkynes exclusively produced (Z)-β-chlorovinyl ketones regardless of the reaction conditions used. The reaction pathways of such distinctive stereochemistry of β-chlorovinyl ketones has been the focal point in the synthesis of (thio)chromenones.”

The stereochemistry of β-chlorovinyl ketones afforded mechanistic insights into the formation of (thio)chromenones. Professor Oh explained that utilizing the methoxy- and thiomethoxy-substituted aryl acid chlorides, the Friedel–Crafts acylation of aryl alkynes led to the formation of (Z)-β-chlorovinyl ketones with an intact (thio)methoxy group (Scheme 1, C). In contrast, the formation of (E)-β-chlorovinyl ketones with a hydroxy (or thiol) group was observed from alkyl alkynes. “The most probable conformation of (Z)-β-chlorovinyl ketones with an intact (thio)methoxy group would initiate a conjugate addition reaction in the presence of a Lewis acid, such as AlCl₃, through the activation of the carbonyl group,” remarked Professor Oh. After the demethylation of the oxonium (or thionium) ion and elimination of chloride, the (thio)chromenones were obtained. For (E)-β-chlorovinyl ketones with a hydroxy (or thiol) group, the most probable conformation would prefer the intramolecularily H-bonded conformation. Thus, the use of base was required to break the H-bonding network. “To this end, instead of employing strong bases, we turned to the use of KOT-Bu and a mild base, Et₃N, to prompt a mild α-vinyl enolization of (E)-β-chlorovinyl ketones to allenes that in turn undergo a rapid cyclization to (thio)chromenones,” said Professor Oh, continuing: “This mild in situ allene formation avoids the functional group compatibility issues present under strongly basic conditions. The substrate scope of the current method was broadly applicable to aryl and alkyl alkynes with suitably substituted acid chlorides, providing a facile one-pot access to pharmaceutically important heterocycles, (thio)chromenones (Figure 1).”

Professor Oh concluded: “From our studies on the divergent reaction pathway of stereoisomeric β-chlorovinyl ketones, we were strongly reminded of the stereochemical and conformational significance of compounds involved in the subsequent reaction pathways.”

![Substrate scope](image)

Figure 1
About the authors

**Eunsun Song** was born in Daejeon (South Korea). She received her B.S. in chemistry from the Chungnam National University (South Korea) in 2015, and then joined the Professor Kyungsoo Oh’s group at the College of Pharmacy, Chung-Ang University (South Korea). For her Master’s degree, Eunsun is currently working on the synthesis of heterocyclic compounds with a strong emphasis on furan synthesis. Her research interests encompass synthetic methodology, catalysis, and medicinal chemistry.

**Hun Young Kim** was born in Seoul (South Korea). She attended the Ewha Woman’s University (South Korea) and received her B.S. in chemistry in 1997. Continuing her research training at Ewha, she obtained her M.S. degree in 1999 under the guidance of Professors B. T. Ahn and M. Y. Lee. After five years at the Samsung R&D Center in Suwon (South Korea) as a research chemist, she moved to the University of Pennsylvania (USA) in 2003 for her doctoral studies. While at Penn, she worked on the stereoselective synthesis of cyclopropyl derivatives under the guidance of Professor Patrick J. Walsh. In late 2008, she joined the Department of Chemistry & Chemical Biology at Indiana University–Purdue University Indianapolis (IUPUI, USA) as a research scientist in collaboration with Professor Kyungsoo Oh. In 2014, she was appointed as an Assistant Professor in the College of Pharmacy at Chung-Ang University (South Korea). Her current research interest lies in the field of asymmetric catalysis with strong focus on the development of conceptually new asymmetric strategies.

**Kyungsoo Oh** was born in Inchon (South Korea). After early education in Korea and Japan, he read chemistry at Queen Mary College, University of London (UK), obtaining a B.Sc. (First Class) in 1999. Under the auspices of AstraZeneca he studied for his Ph.D. in the laboratory of Professor Philip J. Parsons at the University of Sussex (UK). While at Sussex, he worked on the silicon-mediated fragmentation and the total synthesis of rapamycin, an immunosuppressant drug. At the end of 2002, he joined the laboratory of Professor Jeffrey D. Winkler as a postdoctoral fellow at the University of Pennsylvania (USA). At Penn, he investigated the Diels–Alder reactions of electron-rich dienes and the synthesis of neokauluamine, a dimeric manzamine. In 2005, he was appointed as an Assistant Professor at the Indiana University–Purdue University Indianapolis (IUPUI, USA) and promoted to Associate Professor with tenure in 2011. After a brief sabbatical of seven months at Imperial College London (UK), he was appointed Associate Professor in the College of Pharmacy at Chung-Ang University (South Korea) in 2014. In 2015, he attained the Science Research Center (SRC), a key national research laboratory, in the College of Pharmacy at Chung-Ang University, focusing on cancer metastasis research. His current research interest is centered on the development of novel synthetic strategies for pharmaceutically important chemical entities, in particular anticancer agents.
3-Oxo-[1,3λ^{6},4]-oxathiazines: A Novel Class of Heterocyclic S,O-Acetals

*Synthesis* 2017, 49, 403–408

About 30 years ago, during his Ph.D. work, in an attempt to prepare enantiomerically pure sulfonimidoylfluorides, Professor Michael Reggelin of the Technische Universität Darmstadt (Germany) serendipitously synthesized the first cyclic sulfonimidates 1 and epi-1 (Scheme 1).

Since that initial discovery, both S-epimeric compounds and derivatives thereof have proven to be valuable starting materials for the synthesis of enantiomerically pure sulfoximines in general and 2-alkenyl sulfoximines in particular. These latter compounds are of special importance, because their preparation via imination of allylic sulfoxides is severely hampered by the racemizing [2,3]-sigmatropic rearrangement (Mislow rearrangement) they tend to undergo,” explained Professor Reggelin. He continued: “Moreover, we found that titanated 2-alkenylsulfoximines can be γ-hydroxyalkylated with exceptional diastereoselectivity and the resulting products were found to be valuable intermediates for the synthesis of highly substituted polyheterocyclic ring systems like 2 (Scheme 1). Up to this point everything worked out very well but the removal of the sulfonimidoyl auxiliary turned out...
to be a nightmare! The α-carbon in 2 is in a neopentyl position rendering nucleophilic substitutions impossible (even after electrophilic activation of the sulfoximine). The carbon can be deprotonated, but with the exception of a deuteron no electrophile reacts there. Only reductions with strong reducing agents like aluminum amalgam, Raney nickel or samarium(II) iodide successfully removed the sulfur yielding angular methyliated compounds. Obviously this chemistry was rather limited and the group therefore made efforts to find desulfurations with concomitant production of a useful functional group. One successful solution delivering an angular vinyl group is indicated in Scheme 1. Reaction of the deprotonated α-position with a methylene source prepared the system to undergo a β-elimination to the desired olefin 4.

“At the same time we thought about possibilities to involve the auxiliary itself in its own removal!,” remarked Professor Reggelin. Instead, the group changed their interests from stoichiometric to catalytic applications of sulfoximines. “However, this also changed because of the newly aroused interest of the chemical industry in this neglected functional group,” explained Professor Reggelin.

“The sulfoximines themselves became objects of interest and not the compounds prepared with their assistance.” Professor Reggelin concluded: “Due to the recent industrial interest in this area, we think that sulfoximine chemistry will experience a renaissance, as will be the case for the even more ‘exotic’ chiral sulfur(VI) derivatives like sulfonimidamides or sulfoximides. A strong hint that this is likely to happen is the enormous activity in the field (at the moment the 2013 article of Lücking has been cited 72 times!) even from groups other than the ‘usual suspects’ (C. Bolm and M. Harmata to name only two of the latter).”

REFERENCES

Michael Reggelin was born in Elbingerode/Harz (Germany) in 1960. He received his undergraduate education at the universities of Giessen and Göttingen (Germany) and graduated from the University of Kiel (Germany), receiving his Ph.D. with Professor D. Hoppe in 1989. After postdoctoral work at the Technical University of Munich (Germany) with Professor H. Kessler, he completed his Habilitation in 1997 at the University of Frankfurt (Germany) in Professor Griesinger’s group. In 1998, he was appointed C3 Professor at the University of Mainz (Germany) and since 2001 he holds his current position as C4 Professor of Chemistry at the TU Darmstadt (Germany). Professor Reggelin’s research interests are: (a) development of new stereoasymmetric reactions, asymmetric allyl transfer reactions, asymmetric catalysis with helically chiral ligands, and development of sulfoximine-based chiral ligands; (b) NMR spectroscopy in anisotropic media, development of new polymeric chiral alignment media; and (c) development of new materials for organic electronics applications.

Jochen Kühl was born in Münster (Germany) in 1972. He studied chemistry at the Westfälische Wilhelms Universität in Münster (Germany), then joined the group of Professor E.-U. Würthwein working on his diploma thesis. He received his diploma degree in 2001 after which he moved to TU Darmstadt (Germany) where he received his Ph.D. under the supervision of Professor M. Reggelin in 2008. Currently, he is working as a project manager, responsible for the supervision of the reconstruction of the chemical department buildings at the TU Darmstadt (Germany).
Carbanion chemistry is extremely important in synthesis, since carbanions act as nucleophiles for efficient carbon–carbon bond formation. Arguably the most-used type of carbanion is an enolate, and enolate alkylation and the aldol reaction play a key role in many synthetic endeavors. As the anion in enolates is delocalized, they adopt a planar structure. Therefore, any stereocenter that was present alpha to the carbonyl is lost on formation of the enolate and it is necessary to use a chiral auxiliary, a chiral electrophile, or a chiral catalyst that is associated with the transition state to induce asymmetry in the resulting alkylated product.

The similarity of nitriles to carbonyls has led the scientific community to consider their reactivity to be related. Indeed, deprotonation of a nitrile to form a carbanion using a base such as LDA provides a carbanion where the lithium ion resides on the nitrogen atom in a dimeric structure.1 Such a ketenimine, like an enolate, reacts with alkyl halides and carbonyl compounds through the carbon atom thereby leading to C-alkylated products. Therefore, it might be expected that starting from an alpha chiral nitrile the reaction would give, after deprotonation, an achiral metalated intermediate and hence racemic products. Indeed, this is typically the case,2

Scheme 1 Deprotonation of chiral nitrile 1

![Scheme 1 Deprotonation of chiral nitrile 1](image)
and the Coldham group at the University of Sheffield (UK) has found that treating the chiral nitrile 1 with LDA followed by addition of electrophiles gives racemic products, such as 2a–f (Scheme 1a). However, by using the magnesium base TMPMgCl, the products were formed with high enantioselectivity (Scheme 1b).

Professor Coldham explained: “Deprotonation alpha to a nitrile with a magnesium base is likely to lead to a metalated intermediate in which the magnesium ion is attached, at least initially, to the carbon rather than the nitrogen atom.” This then provides a chiral metalated intermediate from which it is possible to obtain enantiomERICally enriched products. The intermediate organomagnesium compound is not particularly configurationally stable and we found that the half-life for enantiomerization is only about three minutes in Et₂O at about –104 °C. However, this is sufficient to allow rapid quench either in situ or after a few seconds without significant loss of enantiopurity in many cases.” A plot for the loss of enantiomeric excess (at –104 °C, quenching with cyclobutanone and assuming 100% at time zero) is shown in Figure 1. This illustrates that the racemization occurs at low temperature within several minutes. “However, the quench can be conducted without the need for the electrophile to be present in situ to give enantiomerically enriched products,” continued Professor Coldham. The electrophilic quench was found to occur with overall retention of configuration, as determined for ketone 2d by recrystallization to high enantiopurity (er = 99:1 by chiral stationary phase HPLC) and single crystal X-ray analysis.

The reaction was followed by in situ IR spectroscopy (ReactIR) and this demonstrated that at least two equivalents of TMPMgCl were required for full metalation. “The structure of the magnesiated intermediate was studied computationally and DFT calculations suggested that there are two magnesium ions involved, one attached to the carbon atom and one on the nitrogen atom,” said Professor Coldham. He continued: “The lowest energy form has the nitrile in an axial location and the carbonyl oxygen chelated with the magnesium attached to the alpha carbon atom. However, rotation of the carbonyl group is likely to be very slow at low temperatures so the rotamer without chelation was also modelled. Although this was higher in energy, it presumably also exists in solution. It is likely that the two rotamers have different rates of enantiomerization but both can lead to enantiomerically enriched products.”

Professor Coldham concluded: “This study provides useful insight into the intermediates involved in metalations of nitriles. A magnesiated intermediate does not necessarily lose its configuration immediately on forming, as occurs with enolates, and this methodology could be valuable for the preparation of enantiomerically enriched products starting from chiral nitriles. The combination of experiment and calculations gives us real insight into the molecular basis for the effects we see, giving us confidence that we understand why our approach works the way it does, boding well for its future applicability.”

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Iain Coldham received his PhD from the University of Cambridge (UK). After postdoctoral research in Austin, Texas (USA), he joined the faculty at the University of Exeter (UK) in 1991. He was a visiting Professor at the University of Miami (USA) in 2001. He moved to the University of Sheffield (UK) in 2003 and was promoted to Professor in 2008. His research is centered on chiral organometallic chemistry and cascade reactions involving dipolar cycloadditions.

Anthony J. H. M. Meijer received his PhD from the University of Nijmegen (Netherlands). After postdoctoral research at Wayne State University, Detroit, MI (USA) and University College London (UK), he was appointed as a lecturer in Theoretical Chemistry at the University of Sheffield (UK) in 2003, where he is currently a Reader. His research centers on the study of reactions and reactivity using theoretical methods.

Arghya Sadhukhan received his PhD from the CSIR-Central Salt & Marine Chemicals Research Institute (CSIR-CSMCR, India) in 2013. He then moved to the KTH-Royal Institute of Technology (Sweden) for six months. In 2014, he moved to Sheffield (UK) to join the Coldham research group as a Marie Curie Research Fellow. We acknowledge funding from the European Union (award PIIF-GA-2013-625471).

Melanie Hobbs received her PhD from the University of Sheffield (UK) in 2013 and we acknowledge funding from the EPSRC. Her research focused on the enantioselective synthesis of substituted nitrile-containing compounds. Currently she is training to be a secondary school chemistry teacher.
INTERVIEW

SYNFORM What is the focus of your current research?

Dr. L. T. Pilarski My group is interested in the discovery and development of new synthetic methods based on catalytic C–H functionalization, the reactivity of (hetero)aryne intermediates and that of organo-main-group compounds. Each of these can offer great flexibility in synthesis; we seek to combine them in interesting new ways that benefit organic synthesis.

SYNFORM When did you get interested in synthesis?

Dr. L. T. Pilarski I gravitated towards synthesis though a combination of influences. I was lucky to have excellent lecturers during my undergraduate degree at the University of Bristol, several of whom managed to impress upon me the synergy that exists between logic and creativity in synthesis. Moreover, my Masters project (supervised by Professor Booker-Milburn), PhD research (supervised by Professor Robin Bedford) and postdoc work (supervised Professor Kálmán Szabó at Stockholm University) were flexible and curiosity-driven, which I greatly enjoyed.

Despite its central role in science,1 I think that synthesis shares many similarities with engineering. Synthetic chemists are, ultimately, in the construction business. I like the idea of making molecules that might previously not have existed anywhere in the Universe except a person’s imagination.

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

Dr. L. T. Pilarski Organic synthesis was responsible in the twentieth century for some of humanity’s greatest achievements, many of which contributed to improving life expectancy and quality far beyond what could previously have
been anticipated. Twenty-first century science will be more complex and sophisticated, but I think organic synthesis will remain at the heart of things; our health and influence on the environment, for example, will always depend on the ability to understand and manipulate molecules.

I think it is important to emphasize the enormously positive influence of curiosity-driven research. History shows that the most important scientific advances, including in synthesis, have come to us that way. For this reason I am heartened every time the Nobel Prize in Chemistry is awarded for fundamental and curiosity-driven work related to synthesis, as it was just a few months ago (to Jean-Pierre Sauvage, Sir J. Fraser Stoddart and Bernard Feringa for their work on the synthesis of molecular machines).

**SYNFORM** Your research group is active in the area of catalytic C–H functionalization and the reactivity of (hetero)aryne intermediates. Could you tell us more about your research and its aims?

**Dr. L. T. Pilarski** Organic synthesis is fraught with compromises: atom- and step-economies, functional group tolerance, purification costs – and many other complications. We are interested in uniting three powerful approaches to address these challenges: catalytic C–H activation, (hetero)aryne chemistry and organo-main-group reactivity. The selective substitution of a C–H bond is one of the most direct ways of building up molecular complexity in organic molecules. It can not only expedite a synthetic route but also make previously impossible transformations available, or even easy. (Hetero)arynes are unusually versatile intermediates for producing functionalized aromatics; they can form two bonds selectively at the same time to an almost bizarrely broad range of elements/functional groups, and often under mild conditions. Organo-main-group compounds can also be very versatile. We believe some of their properties can be harnessed to afford unusual modes of selectivity in C–H activation and (hetero)aryne chemistry. One of our goals is to bring together these three areas of synthesis, for example by using them to create flexible molecular building blocks in which multiple functional groups can be converted selectively.

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

**Dr. L. T. Pilarski** I hope my group’s most important achievements lie in the future. My group has published work which we are very proud of, for example protocols that offer previously unavailable functional group tolerance (Scheme 1). We showed that it is possible to leverage the immense versatility of aryl boronates and that of fluoride-activated aryne precursors for their mutual derivatization. Through selective, catalytic C–H borylation, we were able to generate precursors 1, in which the reactivity of B(pin) or the aryne triple bond may be accessed selectively (Scheme 1a). Thus, it is possible to generate a wide range of more complex aryne precursors (3) or use aryne reactivity to generate new, previously inaccessible aryl boronates (4). The latter, for example, allows the facile introduction of heteroatoms to the aryne boronate backbone, for which there were very few methods prior to this work (and even those were limited). We were also pleasantly surprised to discover that under appropriately chosen conditions, fluoride sources may be used to activate the boronate or the aryne component of precursors 1 and their derivatives.

Our Ru-catalyzed C–H functionalizations of heteroarenes are also tolerant in unusual ways. For example, our indole and pyrrole C–H arylation conditions preserve aryl bromides and even aryl iodides, which would typically be cleaved or consumed but which can serve as handles for further manipulation (Scheme 1b). We also reported a Ru-catalyzed C–H silylation of heteroarenes that requires no protecting groups for alkyl or aryl amine substituents, and demonstrates for the first time that undirected C–H silylation is possible under Ru catalysis (Scheme 1c). Additionally, we found that electron-rich Ru centers are able to cleave the indole C4–H bond, which was previously the exclusive province of strongly electrophilic metals. We hope to build on these discoveries, of course.
Scheme 1 Our work on functional-group-tolerant (hetero)arene transformations enabled by catalytic C–H activation, the strained triple bond of arynes and/or organo-main-group elements

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SYNFORM issue 2017/06 is available from May 16, 2017

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