

## Catalytic Asymmetric Addition of Grignard Reagents to Alkenyl-Substituted Aromatic N-Heterocycles

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Functionalized chiral heteroarenes are common structural motifs in numerous bioactive products, pharmaceuticals, and agrochemicals. Out of the top 200 drugs by worldwide sales in 2013, more than 70 are chiral and contain heteroaromatic motifs. Currently the vast majority of chiral pharmaceuticals are produced as single enantiomers, but the syntheses often rely on non-catalytic stoichiometric methods and the use of chiral separation techniques. The difficulties in preparing these molecules as single enantiomers persist because of a lack of sufficient catalytic enantioselective transformations. Thus, efficient catalytic synthesis of pharmaceutically important chiral heteroarenes is a core objective of modern chemistry.

The group of Professor Syuzanna Harutyunyan at the Stratingh Institute for Chemistry, University of Groningen (The Netherlands) investigated the hypothesis that catalytic asymmetric C–C bond formation using conjugate addition of organometallics to conjugated alkenyl-heteroarenes would be a straightforward approach for constructing single enantiomers of chiral heteroarenes.

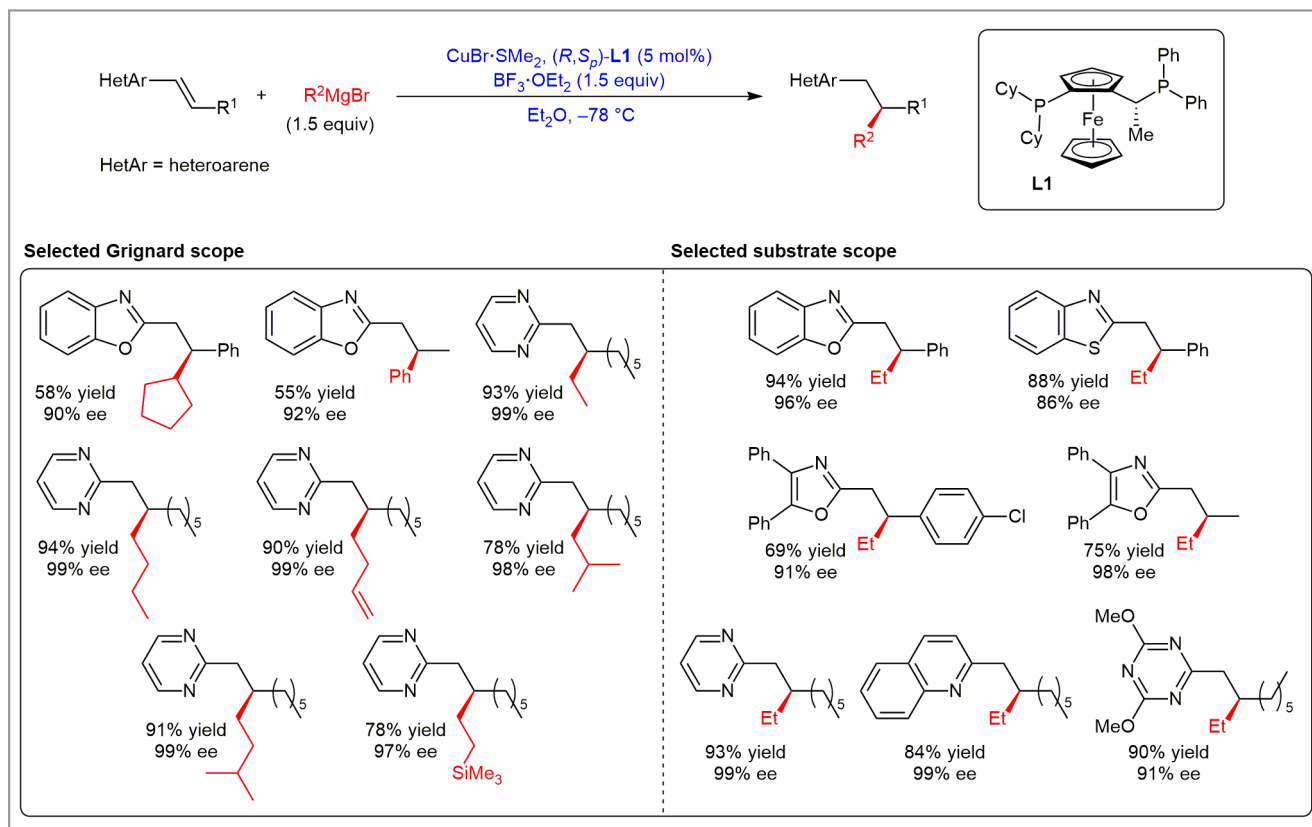
However, although numerous efficient methods exist for conjugate alkylations, arylations, alkynylations and allylations of common Michael acceptors (e.g. enones, enals or enoates), according to Professor Harutyunyan the only known examples of additions to  $\beta$ -substituted alkenyl-heteroarenes were reported by Lam et al. (*J. Org. Chem.* **2014**, *79*, 831) and were restricted to arylations using organoboron reagents, in combination with rhodium catalysis. Professor Harutyunyan explained: “The lack of methodologies for nucleophilic additions to  $\beta$ -substituted alkenyl-heteroarenes is the result of the intrinsically lower reactivity of these molecules compared to common Michael acceptors. In fact, the activation provided by the heteroarene moiety of the former is weaker than that provided by the electron-withdrawing groups present in the latter.”

For several years the group's research focused on using highly reactive and readily available Grignard reagents in Cu(I)-catalyzed C–C bond forming reactions. Thus, the Harutyunyan group surmised that the high reactivity of Grignard reagents could be beneficial when considering the low reactivity of alkenyl-heteroarenes, and that chiral copper catalysis will provide the required selectivity. “The initial results obtained by postdoctoral researcher Ravindra Jumde were

not promising,” said Professor Harutyunyan. “He did not observe any product formation at different temperature ranges and decided to use more reactive organolithiums instead of Grignard reagents. Once again, the reaction outcome was unsuccessful, side products were formed and starting material was left.”

To overcome the reactivity issues associated with alkenyl-heteroarenes, Professor Harutyunyan and co-workers decided to investigate the Lewis acid ( $\text{BF}_3 \cdot \text{OEt}_2$ ) activation of the substrates in combination with Grignard reagents. The main question was the compatibility of Grignard reagents with  $\text{BF}_3 \cdot \text{OEt}_2$ . Professor Harutyunyan said: “From our previous studies on Grignard addition to acyl silanes we were aware that for a short time at low temperature these two reagents are compatible. The Lewis acid was used in our previous research to avoid the reduction of ketones, which is an important side reaction. We were extremely pleased to see the conjugate addition product for the first time when using the Lewis acid/Grignard reagent/Cu/phosphine reaction system applied to alkenyl-heteroarenes.” At this point PhD student Francesco Lanza and, later, bachelor's student Marieke Veenstra joined the project. The team was capable of achieving alkylation of unreactive alkenyl-heteroarenes to the corresponding chiral N-containing aromatic heterocycles. Professor Harutyunyan revealed that after months of optimization studies they developed a methodology: an operationally simple, chemoselective and highly enantioselective conjugate addition reaction that utilizes readily available and cost-efficient reagents and catalysts. “As is evident from the experimental data, the stereoselectivities are extremely high, reaching 99% in many cases,” said Professor Harutyunyan. “Remarkably, a variety of heterocyclic motifs can be employed in this reaction successfully and the system also tolerates various types of Grignard reagents, including linear, branched, functionalized as well as aryl analogues.”

Professor Harutyunyan remarked: “The key to this success was our ability to combine several critical elements: 1) enhancing the reactivity of alkenyl-heteroarenes via Lewis acid activation, 2) harnessing the high reactivity of readily available and atom-efficient Grignard reagents, and 3) using a chiral copper complex as the catalytically active structure. Furthermore, our experiments on catalyst loading and recovery,



**Scheme 1** Copper-catalyzed addition of Grignard reagents to alkenyl-heteroarenes: selected Grignard reagents and heteroarene-substrate scope

also on preparative scale, demonstrate that the method is very promising for large-scale applications.” She continued: “What is also remarkable is that this reaction system tolerates various solvents such as toluene, dichloromethane, ether and MTBE, as well as different chiral ligands, which can be used in combination with copper catalysis. This flexibility of both solvent and chiral ligand is quite important for further applications. The current drawback of the method – which we still need to address – is the low temperature (–78 to –50 °C) required for compatibility of Grignard reagents and Lewis acid.”

Following this initial discovery, the group now aims to take it to the next level and develop methylations as well as to generate quaternary stereocenters. Professor Harutyunyan concluded: “These are real challenges for such unreactive substrates that we have to address in the near future. Also from the mechanistic point of view, we suspect that the reaction follows a common pathway established for Cu(I)-catalyzed additions of organometallics. However, the role of Lewis acid, besides the activation of heteroarene substrates, is not clear yet and remains to be investigated.”

Matthew Farnish

## About the authors



Prof. S. R. Harutyunyan

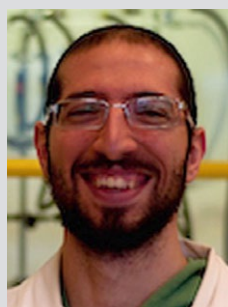
**Syuzanna R. Harutyunyan** received her Master's degree in chemistry from Yerevan State University (Armenia). In 1999 she moved to Moscow (Russia) to undertake PhD studies under the supervision of Professor Yuri N. Belokon. During her PhD, Syuzanna developed new strategies for enantioselective synthesis of amino acids under phase-transfer conditions. In 2002 she spent several months as a visiting scientist in Warsaw (Poland), working with Professor Karol Grela on developing highly reactive alternatives to the well-known Grubbs catalysts. In 2003 Syuzanna joined the research group of Professor Ben L. Feringa at the University of Groningen (The Netherlands) as a post-doctoral research fellow and worked in asymmetric catalysis. In 2007 she joined the Process & Development department at Janssen Pharmaceutica (Belgium). Her research focused on the development of new RCM metathesis catalysts for application in the industrial-scale synthesis of a new anti-HCV drug. In 2010 Syuzanna was appointed as a tenure-track Assistant Professor at the University of Groningen and subsequently started her independent research career. In 2013 Syuzanna was tenured and promoted to Associate Professor at the University of Groningen. Her research activities include organic synthesis, organometallic reactions, catalysis, autocatalysis and enantioselective transformations.



Dr. R. P. Jumde

**Ravindra P. Jumde** was born and raised in the small town of Achalpur in the Maharashtra region of India. He obtained his MSc in 2005 from S.G.B. Amravati University (MS, India). He worked as a project assistant at National Chemical Laboratory, Pune (India) from 2006 to 2008. In January 2009 he won a 'Galileo Galilei PhD fellowship' at University of Pisa (Italy), where he worked in the group of Professor Dario Pini and Dr. Alessandro Mandoli on 'supported chiral ligands and organocatalysts for enantioselective transformations.' After obtaining his PhD in January 2012, he won a post-doctoral grant from ISTM-CNR (Italy) to work in the same group on 'the development of novel catalytic asymmetric reactions' (intramolecular cyclization), and 'study of asymmetric transformations in flow, micro and mini flow devices.' In September 2013 he moved to Milan (Italy)

at ISTM-CNR to work with Dr. Claudio Evangelisti on the preparation of metal nanoparticles by MVS technique and their use in different metal-catalyzed reactions in continuous flow. Since January 2015 he has been working at the University of Groningen (The Netherlands) in the group of Professor Syuzanna R. Harutyunyan. His main scientific interests are asymmetric catalysis, new reaction methodology development, and mechanistic investigations.



F. Lanza

**Francesco Lanza** was born in Messina (Italy) in 1987. In 2010 he received his B.S. degree from the Università degli Studi di Messina. In the same year he moved to Bologna (Italy) to attend the Master's course in chemistry at the Alma Mater Studiorum – Università di Bologna where he obtained his M.S. degree in chemistry under the supervision of Professor Marco Lombardo in 2012. Since 2013 he has been working at the University of Groningen (The Netherlands) in Professor Syuzanna R. Harutyunyan's research group. He is currently working on copper-catalyzed addition of organometallic reagent to heteroaromatic frameworks.



M. J. Veenstra

**Marieke J. Veenstra** was born and raised in Kropswolde in the province of Groningen (The Netherlands). She obtained her B.Sc. in chemistry from the University of Groningen in 2015. During her Bachelor's project she worked in the group of Professor Syuzanna R. Harutyunyan on copper-catalyzed asymmetric addition to alkenyl-substituted aromatic N-heterocycles.