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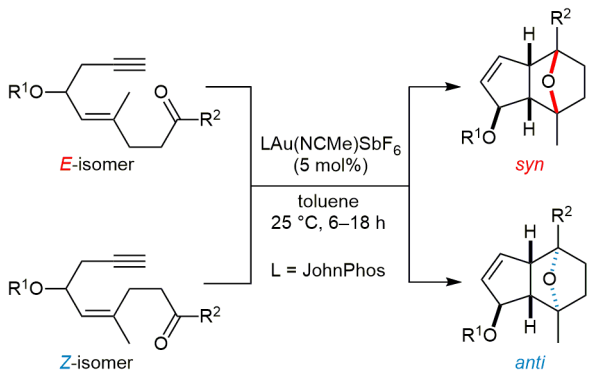
2017/01

Diastereoselective Gold(I)-Catalyzed [2+2+2] Cycloaddition of Oxo-1,5-Enynes

Highlighted article by P. Calleja, M. E. Muratore, T. Jiménez, A. M. Echavarren



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Dear Readers,

I would like to open this first issue of 2017 on a personal note, taking advantage of the privilege of being Editor of SYNFORM for remembering Professor Pierfrancesco Bravo, who passed away in November 2016 at the age of 82. Professor Bravo was an organofluorine chemist who spent most of his scientific career at the Italian National Research Council in Milan first, and then at Politecnico, always in Milan. Some of you – among the 'less young' chemists – may remember his work on fluorinated sulfoxides, which was still ongoing when I joined his group in 1993. I will always be grateful to him for being my PhD supervisor and then for generously helping me out through my first career phase. When Professor Bravo retired, I took over his group for a few years, before moving to Scotland. He was an honest and generous man, and a passionate researcher and teacher who will always be remembered dearly by the many students and co-workers he trained in his group.

This issue and the new year of SYNFORM opens in a glittering way with an article on a novel gold(I)-catalyzed [2+2+2] cycloaddition reported by A. Echavarren (Spain) and continues under similarly noble auspices with a palladium-catalyzed arylation of aliphatic aldehydes developed by G. Li (P. R. of China). The third contribution is all about copper and tin, but believe me – the oxidative fluorination leading to aryl fluorides developed by J. Murphy (USA) is no less precious than the previous two. The final story doesn't involve any noble metal, but the AZADO reagents developed and used by Y. Iwabuchi (Japan) to prepare 1,3-cycloalkadienes from cycloalkenes are definitely very valuable!!

Enjoy your reading!

In this issue

SYNTHESIS Highlight
Diastereoselective Gold(I)-Catalyzed [2+2+2] Cycloaddition of Oxo-1,5-Enynes A3

Literature Coverage
Catalytic C–H Arylation of Aliphatic Aldehydes Enabled by a Transient Ligand A7

Literature Coverage
Copper-Mediated Oxidative Fluorination of Aryl Stannanes with Fluoride A10

Literature Coverage
Synthesis of 1,3-Cycloalkadienes from Cycloalkenes: Unprecedented Reactivity of Oxoammonium Salts A13

Coming soon A17

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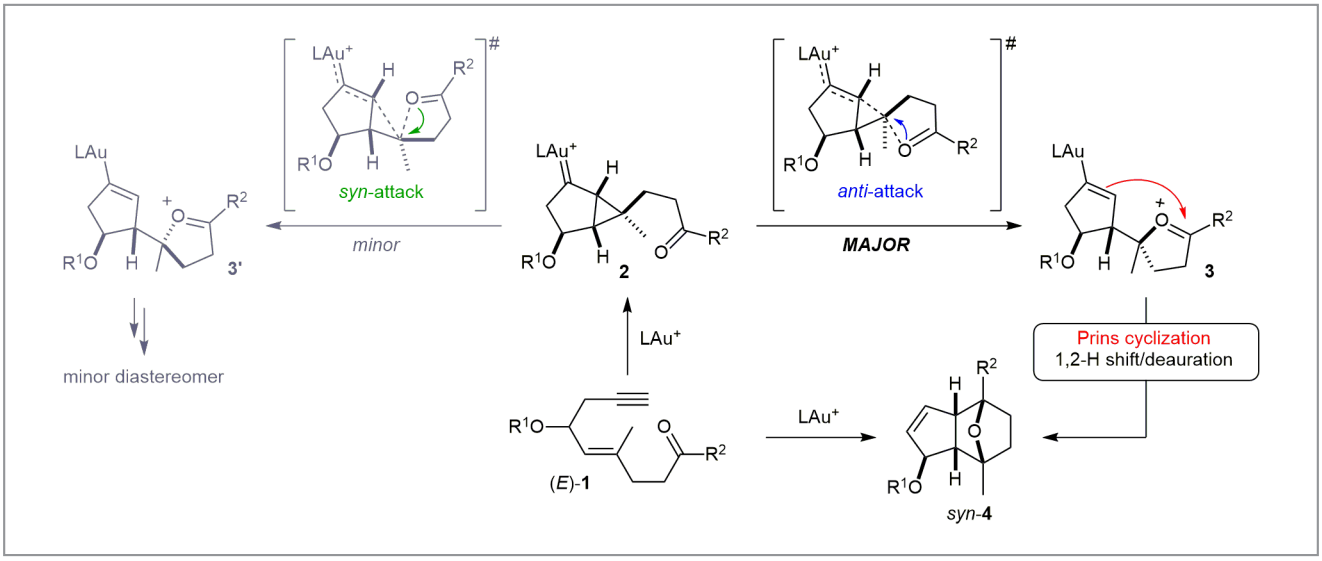
Diastereoselective Gold(I)-Catalyzed [2+2+2] Cycloaddition of Oxo-1,5-Enynes

Synthesis **2016**, *48*, 3183–3198

The activation of alkynes towards nucleophilic addition employing gold salts and complexes has become a powerful and versatile tool for the construction of C–C and C–heteroatom bonds. In particular, the reaction of alkynes with alkenes has been studied extensively, and the intramolecular reactions of 1,n-enynes has led to the development of novel methods and strategies to construct new rings and complex polycycles. In this context, the group of Professor Antonio Echavarren at the Institute of Chemical Research of Catalonia (ICIQ), Barcelona Institute of Science and Technology (Spain) recently reported the application of this strategy to a formal [2+2+2] cycloaddition of oxoenynes, and the preparation of decahydro-4,8-epoxyazulene scaffolds.[1] "This novel approach provided an expedient entry into the total synthesis of naturally occurring sesquiterpenoids such as (+)-orientalol F[2] and (–)-englerin A,[3]" said Professor Echavarren. He continued: "Other natural products, including isovelerenol and bakkenolide III featuring an octahydro-1*H*-indene core, may be obtained from suitably functionalized oxo-1,5-enynes."

"Although the formal [2+2+2] cycloaddition of oxo-1,6-enynes and oxo-1,7-allenenes[4] developed in our group proved to proceed with exquisite diastereoselectivity (single diastereomer in most cases), the preliminary results obtained for oxo-1,5-enynes[5] demonstrated that the control of the diastereoselectivity would be more challenging with these substrates," explained Professor Echavarren. "Therefore, we focused our attention on studying the reactivity of O-protected homopropargylic and allylic oxo-1,5-enynes, since these substrates provided two advantages: 1) the protected alcohol could later be easily derivatized; 2) by controlling the configuration of the stereogenic center (protected secondary alcohol), one should be able to control the final configuration of the obtained polycycles."

Professor Echavarren emphasized that similar oxatricyclic compounds showed potential as herbicides and may be prepared, from furan derivatives and maleic anhydride, via an initial Diels–Alder cycloaddition followed by a lengthy synthetic sequence.[6] "This approach suffers several drawbacks such as the limited availability of substituted furans, the formation of only one diastereomer (no opportunity to prepare the complementary diastereomer via this strategy) and the large number of steps to obtain the hexahydro-4,7-epoxyindene framework," said Professor Echavarren. He continued: "Our strategy implements a series of improvements: 1) an overall



Scheme 1 Mechanism of the formal [2+2+2] cycloaddition of oxo-1,5-enynes, supported by DFT calculations

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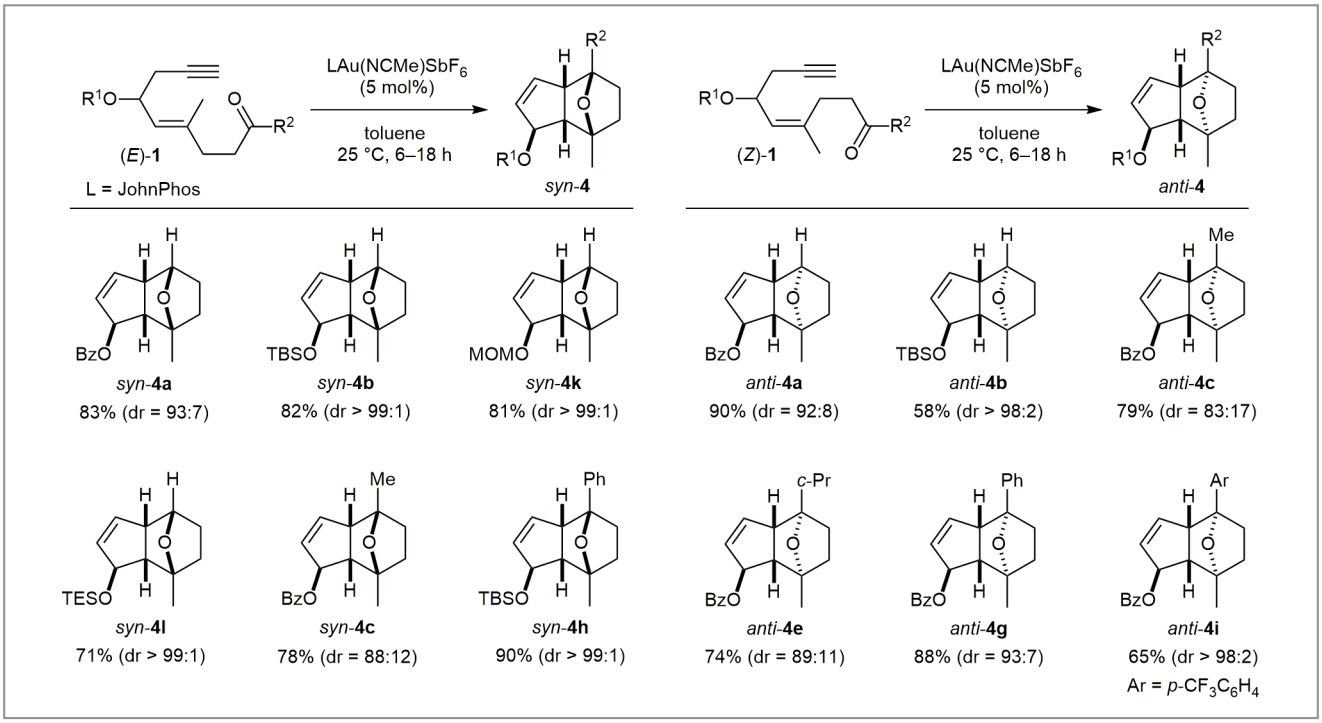
shorter synthetic sequence to the final oxatricycles; 2) a late-stage derivatization (introduction of R^2) that allows us to make a library of derivatives in an expedient manner; 3) control of the relative configuration of the final oxatricycles by selecting the geometry of the olefin precursor."

The proof of concept for this formal cycloaddition was demonstrated by treatment of model oxo-1,5-enyne (*Z*)-**1a** (R^1 = Bz, R^2 = H) with [JohnPhosAu(NCMe)]SbF_6 in dichloromethane at room temperature. Although the desired tricycle *anti*-**4a** was formed in moderate yield, partial decomposition of the substrate, presumably through elimination of benzoic acid, was observed to a significant extent. Professor Echavarren said: "Our extensive screening of conditions allowed us to find that this undesired elimination could be almost completely suppressed by carrying out the reaction in toluene instead of chlorinated solvents and at higher dilution. We found that carrying out this transformation in anhydrous solvent and under an inert atmosphere was beneficial and the product was formed more cleanly under these conditions."

Professor Echavarren explained: "Our theoretical study of the mechanism of this transformation confirmed our proposed mechanistic picture via a step-wise process (Scheme 1): 1) The reaction first proceeds through the cycloisomerization of the 1,5-enyne in an *endo* fashion, forming an intermediate that is best represented as a cyclopropyl gold-carbene (endocyclic). According to our calculations and in agreement with observations, this step is fully diastereoselective. 2) Two competitive pathways arising from the preferred face for the nucleophilic attack of the carbonyl group are then involved and can explain the lack of complete stereoselectivity. Hence, the *anti*-attack of the carbonyl onto the cyclopropyl moiety is kinetically more favored than the corresponding attack of the carbonyl from the opposite face (*syn* to the breaking cyclopropane C–C bond) on a highly distorted cyclopropyl gold-carbene (that can be depicted as a gold-stabilized homoallylic carbocation). The lack of stereoselectivity in some of our examples can be attributed to these competitive processes and, presumably, to a lower difference of energy between the two corresponding transition states. 3) Subsequent Prins-type cyclization (only one possible mode of cyclization in each scenario) followed by hydride shift and deauration lead to the observed diastereomeric oxatricycles."

Professor Echavarren continued: "On our model system and more generally with *Z*-configured oxoenynes, the reaction proceeded with high to excellent diastereoselectivity, whereas with *E*-configured oxoenynes, the stereoselectivity strongly depended on the size of the substituent at the carbonyl. However, a large protecting group (R^1) such as TBS on the



Scheme 2 Selected scope of the formal [2+2+2] cycloaddition of oxo-1,5-enynes

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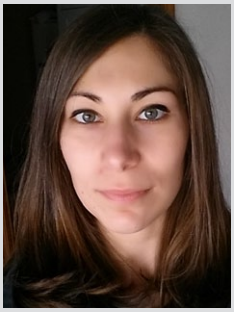
alcohol seemed to override this effect and allowed the formation of oxatricycles with consistently high diastereoselectivity (Scheme 2)."

Although these oxatricycles are not direct derivatives of natural products, they constitute intriguing one-carbon-lower analogues of the polycyclic skeleton of the aforementioned orientalol/englerin family of sesquiterpenoids. For this reason, the group is currently evaluating their biological properties.

"Future developments will aim at exploring the reactivity of other functionalized oxoenynes as well as developing asymmetric alternatives, either on enantioenriched substrates or employing a chiral catalyst for the reaction of achiral substrates," concluded Professor Echavarren.

About the authors



P. Calleja

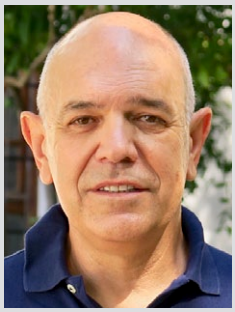
Pilar Calleja was born in Barcelona (Spain) in 1988. She completed her B.Sc. (2011) at the University of Barcelona (Spain). In 2012, she received the Master of Synthesis and Catalysis Extraordinary Award at the Rovira i Virgili University (Tarragona, Spain). Since 2012 she has been carrying out her Ph.D. studies with a FPU fellowship at the Institute of Chemical Research of Catalonia (ICIQ) under the supervision of Professor Antonio M. Echavarren. Her research focuses on the synthesis of natural products and polyaromatic compounds employing gold catalysis.

Dr. M. E. Muratore

Michael E. Muratore was born in Grasse (France) in 1983. He first studied at the University of Nice-Sophia Antipolis (France) and obtained his B.Sc. in 2004, then continued his undergraduate studies at the École Nationale Supérieure de Chimie de Montpellier (ENSCM, France) where he obtained his M.Sc. in 2007. After completing his Ph.D. under the supervision of Professor Darren J. Dixon at the University of Oxford (UK) in 2011, he spent 18 months in the research group of Professor Magnus Rueping at RWTH Aachen University (Germany) as a postdoctoral research assistant. From March 2013 to July 2016, he was an ICIQ-IPMP postdoctoral fellow in the group of Professor Antonio M. Echavarren, where he developed new methodologies employing gold catalysis and worked on the total syntheses of natural products ranging from a norsesquiterpenoid to indole alkaloids.

Dr. T. Jiménez

Tania Jiménez was born in La Línea de la Concepción (Cádiz, Spain) in 1984. She studied chemistry at University of Granada (Spain) and she received her B.Sc. in 2007. The same year, she joined the group of Dr. Juan Manuel Cuerva Carvajal to carry out her graduate work on the development of new applications of titanocene(III) chemistry, C-radical reduction, and bioinspired synthesis of terpenic skeletons. After completing her Ph.D. in 2013 in Granada, she joined the research group of Professor Antonio M. Echavarren at ICIQ (Tarragona, Spain) as a postdoctoral research associate working on the synthesis of biologically active natural products and the development of new catalytic transformations employing gold catalysis. In early 2015 she moved to Antwerp University (Belgium) as a postdoctoral fellow in the group of Professor Bert Maes. Later in the same year, she received a Marie Skłodowska-Curie grant and moved to Göteborg University (Sweden) where she is currently working in the group of Professor Morten Grøtli on the synthesis, biological evaluation, and structural optimization of derivatives of natural compounds.



Prof. A. M. Echavarren

Antonio M. Echavarren received his Ph.D. at the Universidad Autónoma de Madrid (UAM, Spain) in1982 with Professor Francisco Fariña. After a postdoctoral stay in Boston College (USA) with Professor T. Ross Kelly, he joined the UAM as an Assistant Professor. Following a two-year period as a NATO-fellow with Professor John K. Stille in Fort Collins (Colorado State University, USA), he joined the CSIC (Institute of Organic Chemistry) in

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Madrid (Spain). In 1992 he returned to the UAM as a Professor of Organic Chemistry and in 2004 he moved to Tarragona (Spain) as a Group Leader at the Institute of Chemical Research of Catalonia (ICIQ). He has been Liebig Lecturer (Organic Division, German Chemical Society, 2006), Abbot Lecturer in Organic Chemistry (University of Illinois at Urbana-Champaign, USA, 2009), Schulich Visiting Professor (Technion, Haifa, Israel, 2011), Sir Robert Robinson Distinguished Lecturer (University of Liverpool, UK, 2011), and Novartis Lecturer in Organic Chemistry (Massachusetts Institute of Technology, USA, 2015). In 2012 he was awarded a European Research Council Advanced Grant and in 2014 he was the President of the 49th EUCHEM Conference on Stereochemistry (Bürgenstock Conference). Professor Echavarren is a member of the International Advisory Boards of *Organic & Biomolecular Chemistry*, *Chemical Society Reviews*, *Advanced Synthesis and Catalysis*, and *Organic Letters*, member of the Editorial Boards of *ChemCatChem and Chemistry – A European Journal*, and Associate Editor of *Chemical Communications*. He is a Fellow of the Royal Society of Chemistry. He received the 2004 Janssen-Cylag Award in Organic Chemistry and the 2010 Gold Medal from the Royal Spanish Chemical Society. In 2015 he received an Arthur C. Cope Scholar Award from the American Chemical Society.

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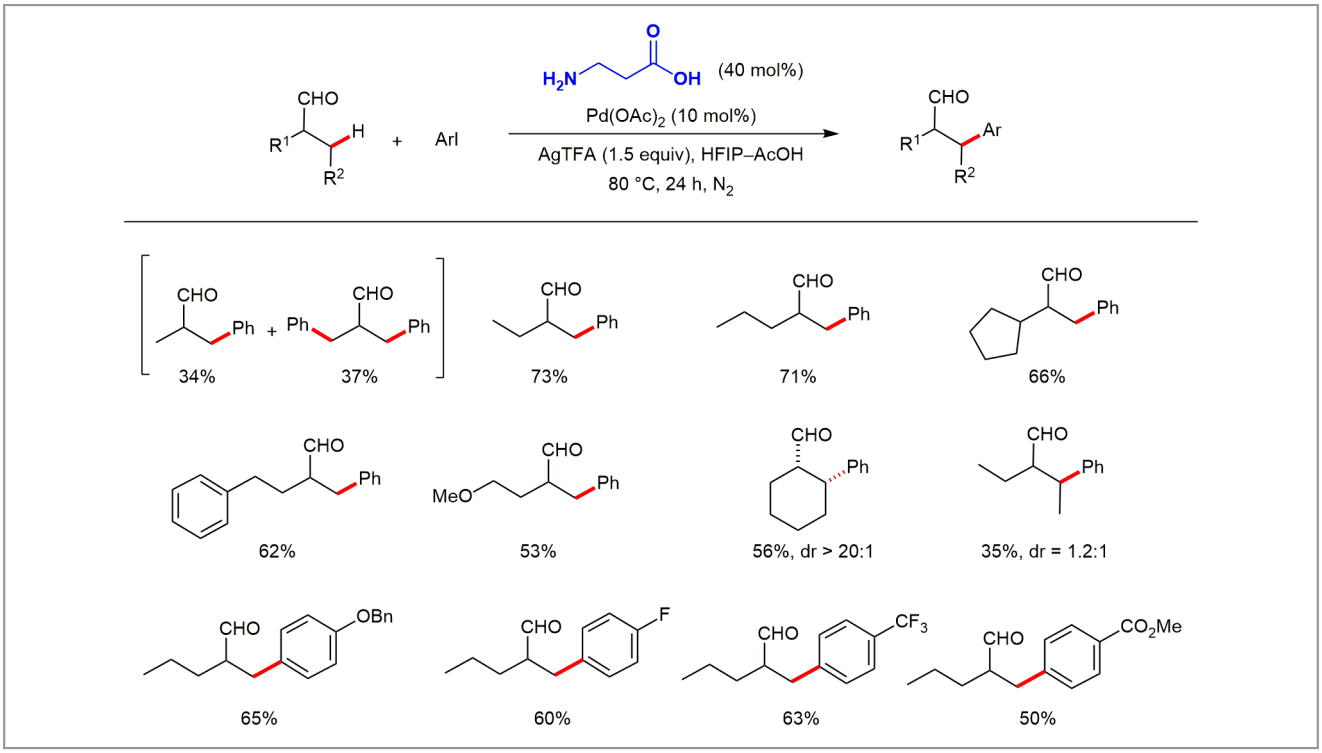
Catalytic C–H Arylation of Aliphatic Aldehydes Enabled by a Transient Ligand

J. Am. Chem. Soc. **2016**, *138*, 12775–12778

In recent years, significant progress on transition-metal-catalyzed site-selective C–H bond activation has been achieved by introducing directing groups on substrates.[1] However, this method has inherent limitations: the process of construction of the original substrates and removal of the directing groups diminishes the efficiency and/or compatibility of the reactions. Therefore, there is a demand for developing a process without installing a directing group. The groups of Professor Guigen Li from Nanjing University (P. R. of China) and Professor Haibo Ge from Indiana University–Purdue University Indianapolis (IUPUI, USA) are aiming to design a specific catalyst as a transient directing group that can bind reversibly to the substrate and the metal center. Professor Ge said: "Some previous literature indicates that the reversible imine linkage was effective in Rh- or Pd-catalyzed selective C–H bond functionalization reactions.[2] Very recently, our group reported the direct palladium-catalyzed γ-arylation of primary alkylamines with glyoxylic acid as a transient directing group.[3]"

He continued: "However, the direct β-functionalization of aliphatic aldehydes has not yet been discovered. Based on our previous results, we believe that the arylation of unactivated β-C–H bonds of aliphatic aldehydes is feasible using metal catalysts by employing appropriate amine compounds as transient directing groups."

After extensive investigations, 3-aminopropanoic acid was proven to be the most suitable transient directing group in the process of Pd-catalyzed arylation of unactivated β-C–H bonds of aliphatic aldehydes. "As expected, this reaction exhibited excellent functional group compatibility and site-selectivity. In the process, functionalization of the unactivated β-C–H bonds of methyl groups was favored over the β-methylene, γ- or δ-methyl C–H bonds," said Professor Ge. He continued:



Scheme 1 Selected substrate scope of palladium-catalyzed direct β-arylation of aliphatic aldehydes

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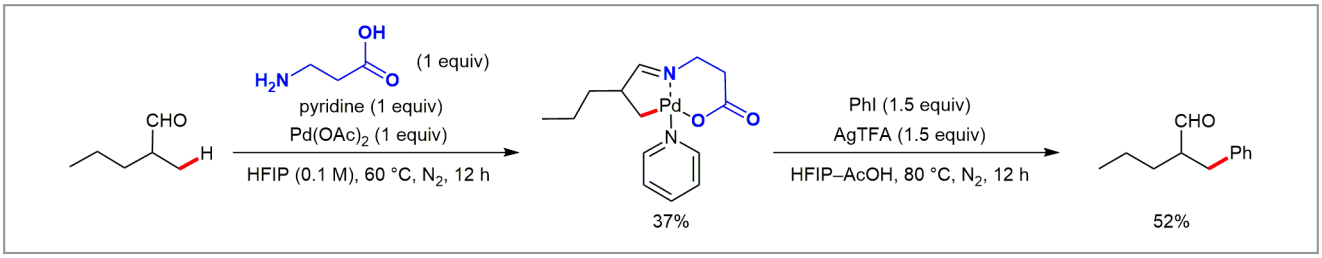

Scheme 2 Synthesis of the [5,6]-bicyclic palladium complex and the subsequent arylation reaction

"Moreover, unactivated secondary sp^3 carbons could also be functionalized (Scheme 1). More importantly, β-arylation of *n*-pentanal could also be accomplished in this catalytic cycle by using 3-amino-3-methylbutanoic acid as the transient directing group. Furthermore, the control experiments indicated that dehydrogenation of aliphatic aldehydes was not involved in this process and a [5,6]-bicyclic palladium complex might be the intermediate in the catalytic cycle. After a multitude of attempts, the [5,6]-bicyclic palladium complex was finally isolated by employing pyridine as an auxiliary ligand, and the desired arylated product was also captured from the reaction of palladium intermediate with iodobenzene successfully (Scheme 2)."

Professor Ge concluded: "We hope that further detailed mechanistic studies of this reaction will provide us more insights in developing novel transient directing groups to extend both the substrate and reaction scopes."

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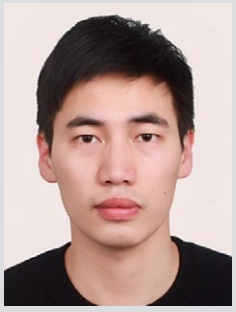

Dr. K. Yang

Ke Yang was born in Jiangsu Province (P. R. of China). He completed his B.S. and M.S. degrees at Jiangsu Normal University (P. R. of China). Next, he received his Ph.D. from Nanjing University (P. R. of China) under the supervision of Professor Yan Zhang. In 2014, he became a postdoctoral fellow at Nanjing University with Professor Guigen Li. In 2015, he joined the group of Professor Haibo Ge at IUPUI (USA). His research interests involve novel transition-metal-catalyzed C–H bond functionalization reactions.

Q. Li

Qun Li was born in Hubei Province (P. R. of China) and received his B.S. degree from Wuhan University of Technology (P. R. of China) in 2012. In 2013, he became a graduate student under the supervision of Professor Guigen Li at Nanjing University (P. R. of China). His main research interest is transition-metal-catalyzed methodologies.

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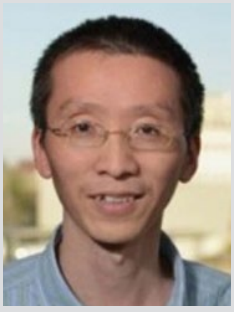
Dr. Y. Liu

Yongbing Liu was born in 1984 in Hengyang (P. R. of China). In 2008, he received his bachelor's degree from Xiangtan University (P. R. of China). After obtaining his M.S. degree in organic chemistry from the same university in 2011, he moved to the Institute of Chemistry, Chinese Academy of Sciences (Beijing, P. R. of China) where he worked on the development of new strategies for borane-catalyzed hydrogenation under the guidance of Professor Haifeng Du. He finished his Ph.D. studies in 2014 and then joined the Ge group as a postdoctoral researcher in November 2014. He is currently studying novel organic transformations based on transition-metal-catalyzed C–H activation.

Prof. G. Li

Guigen Li was born in 1962 in Jiangsu (P. R. of China). He received his B.S. in 1984 at Jiangsu Normal University (P. R. of China) and M.S. in 1987 at Nankai University (P. R. of China) under the direction of the late Professor Zhenheng Gao. After he graduated from Nankai, he was immediately recruited as a faculty member at Nanjing University (P. R. of China) in July 1987 where he worked for three years. He came to the USA in 1990 and received his Ph.D. in 1995 at the University of Arizona (USA) with Professor Victor J. Hruby, and conducted his postdoctoral research on the asymmetric catalytic aminohydroxylation reaction (AA) at the Scripps Research Institute (USA) with Professor K. Barry Sharpless until summer 1997. He joined Texas Tech University (USA) in August 1997 as an Assistant Professor and was promoted to Associate Professor in 2002 and to Full Professor in 2006. Currently, he holds an adjunct Professorship and Director position at the Institute of Chemistry & BioMedical Sciences (ICBMS) at Nanjing University (P. R. of China) and is an innovation team member at Shanghai Institute of Organic Chemistry (SIOC, P. R. of China). So far, he has trained over 40 graduates and 60 undergraduates in his research and achieved over 270 publications (H-index 45). His research interests are on establishing new synthetic concepts/technologies, new reagents (chiral and achiral), new methodologies and related mechanisms. He is also interested in bioorganic and medicinal chemistry.



Prof. H. Ge

Haibo Ge was born in Yancheng, Jiangsu (P. R. of China). He received his Ph.D. in medicinal chemistry from The University of Kansas (Lawrence, USA) in 2006 with Professor Gunda Georg. He then moved to The Scripps Research Institute (La Jolla, USA) for his postdoctoral studies with Professor Dale Boger. In 2009, he began his independent academic career at the Department of Chemistry and Chemical Biology at Indiana University–Purdue University Indianapolis (IUPUI, USA). Research in his group is mainly focused on the development of novel methods towards carbon–carbon and carbon–heteroatom bond formation through transition-metal-catalyzed C–H functionalization. Additionally, his group is working on the synthesis and structure–activity relationship studies of anticancer and antibacterial agents.

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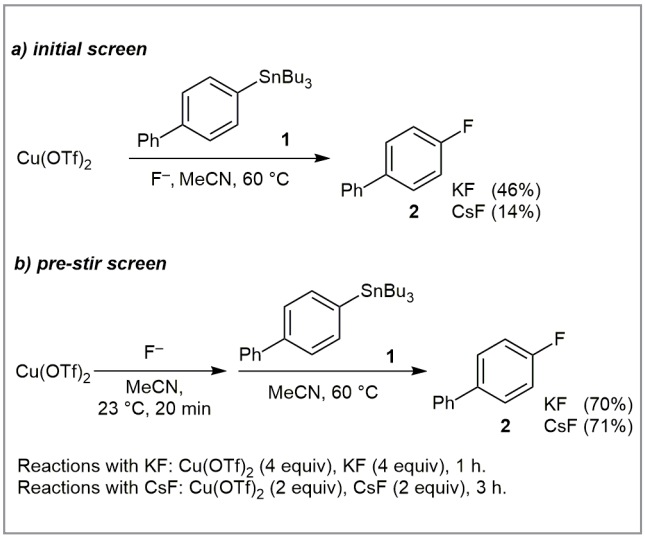
Copper-Mediated Oxidative Fluorination of Aryl Stannanes with Fluoride

Org. Lett. **2016**, *18*, 4522–4525

The importance of fluorinated organic molecules in applications such as pharmaceuticals, agrochemicals, new materials and imaging agents for positron-emission tomography (PET) has become well understood within the scientific community. While carbon–fluorine bond construction is a challenging chemical transformation that, until recently, was limited to simple substrates that could tolerate harsh conditions, a remarkable number of novel synthetic methodologies for C–F bond construction has been reported in the past decade.[1–3] Notable improvements in aryl fluoride bond formation have involved the use of transition metals to facilitate this transformation.[4–6] While these methods have considerably improved the accessibility of fluorinated arenes, many of them require the use of electrophilic fluorinating sources (e.g., Selectfluor, *N*-fluoropyridinium salts) which are not useful for applications in PET, a powerful noninvasive imaging technique that can provide information about molecular targets *in vivo*. The positron-emitting radioisotope fluorine-18 (^{18}F) is generated as nucleophilic fluoride and thus fluorination methods using electrophilic fluorine sources are not broadly useful for PET molecular imaging applications.



Scheme 1 Effects of pre-stir towards oxidative fluorination of aryl stannanes (Yields were determined by ^{19}F NMR spectroscopy with 1-fluoro-3-nitrobenzene as an internal standard.)

The group of Professor Jennifer Murphy at the University of California Los Angeles (UCLA, USA) was interested in expanding the methods available for ^{18}F-radiofluorination towards applications in PET and this led them to investigate oxidative fluorination chemistry. "Oxidative fluorination transformations, which utilize a nucleophilic fluoride source and an external oxidant, are conceptually challenging due to the fact that fluorine is the most oxidizing element known. Such oxidative fluorination transformations have been reported, yet they require the synthesis of complex starting materials, use of directing groups, long reaction times or a large excess of transition metal,[7–11]" said Professor Murphy, who explained: "Our group sought to develop a mild, relatively quick, oxidative fluorination reaction using nucleophilic fluoride and synthetically accessible starting materials. Aryl stannanes are highly stable and can be readily obtained with a wide range of complex functionality, attracting our attention to their use over other starting materials. In addition, reports confirming reductive elimination of high-valent Cu(III) species initiated our interest in evaluating this transition metal to facilitate C–F bond formation with nucleophilic fluoride."

Copper-based methods for C–F bond formation are known[11,12] and mechanistic studies suggest that copper plays a dual role of transition-metal mediator for aryl–F coupling as well as the oxidant to access a Cu(III) intermediate, requiring excess copper reagent. "In agreement with the proposed dual role of copper, our initial experiments screening the fluorination of aryl stannanes required upwards of four equivalents of copper to obtain moderate yields, which dramatically dropped off when less than two equivalents were used," said Professor Murphy. She continued: "We hypothesized that initial formation of a Cu(II)(OTf)(F) complex might facilitate the transmetalation more efficiently and tested this hypothesis by pre-stirring the fluoride source and copper(II) triflate before adding the stannane to the reaction mixture. Gratifyingly, this stepwise protocol resulted in significant improvement in yield of the aryl fluoride, 70% compared to 46% obtained from single addition (Scheme 1). Of note, these effects were more apparent with CsF as the fluoride source, which enabled the reaction to proceed with only two equivalents of copper(II) triflate."

In their evaluation of solvent effects on the reaction, the authors of this study found that the presence of acetonitrile

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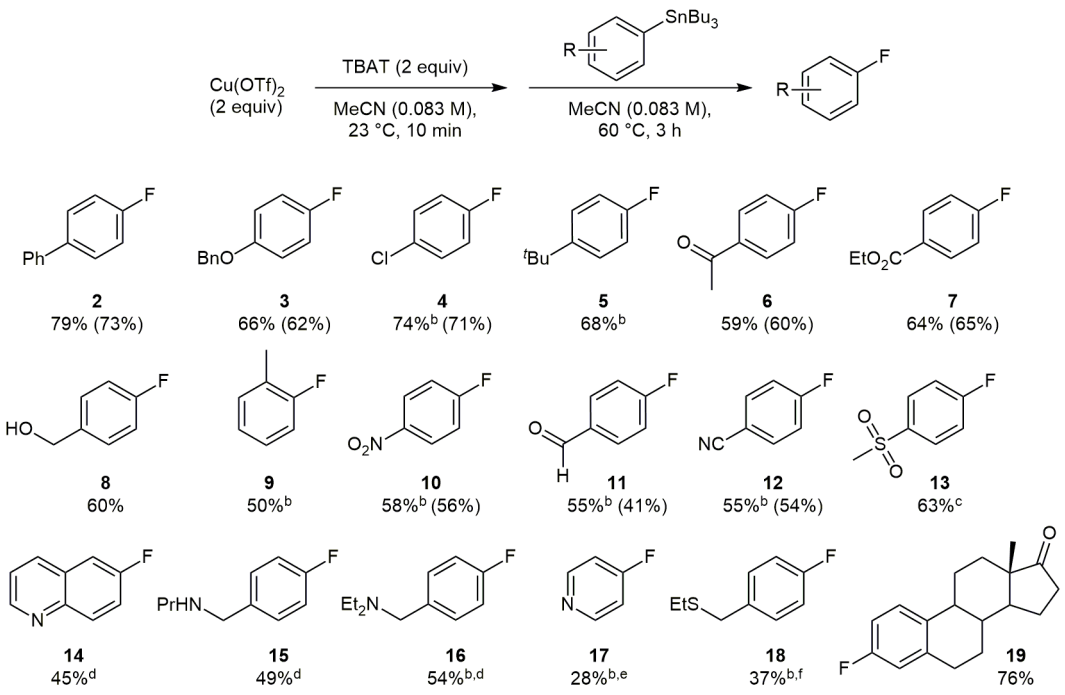

[a] Isolated yields are reported unless noted otherwise. Yields using CsF (2 equiv) as fluoride source are reported in parentheses and determined by ^{19}F NMR.
[b] Yields were determined by ^{19}F NMR spectroscopy with 1-fluoro-3-nitrobenzene as an internal standard added after the reaction. Pre-stir was conducted at 60 °C.
[c] Stirred for 5 h.
[d] $Cu(OTf)_2$ (4 equiv).
[e] 80 °C, 3 h.
[f] $Cu(OTf)_2$ (3 equiv), TBAT (3 equiv).

Scheme 2 Oxidative fluorination of aryl stannanes with $Cu(OTf)_2$ and TBAT.[a]

was required for efficient fluorination to proceed. The use of various other solvents provided no detectable fluorinated products; however, when these solvents were spiked with as little as 10% acetonitrile, the fluorination proceeded in moderate to good yields. Professor Murphy remarked: "We hypothesize that acetonitrile plays a key role as a ligand for copper, perhaps to stabilize the copper center to promote rapid transmetalation and to support reductive elimination of the arylcopper(III) intermediate. Further evaluation of fluoride sources revealed tetrabutylammonium triphenyldifluorosilicate (TBAT) gave the highest yields while, in the context of alkali metal fluoride sources, CsF gave comparable yields."

This reaction demonstrates broad compatibility and a large functional group tolerance (Scheme 2). Common functionality including esters, nitriles, aldehydes, ketones, ethers, sulfones and alcohols survive the reaction conditions and provide the corresponding arylfluorides in good yields (Scheme 2). Notably, arenes bearing protic groups or nucleophilic moieties, such as amines or thioethers, also participated in fluorination in modest yields. Professor Murphy concluded: "Given the versatility of this method, we expect other oxidative fluorination methods such as this one to become more prevalent amongst the broad chemistry community. Translation of this methodology into ^{18}F-radiofluorination for applications in PET is currently being investigated in our laboratory."

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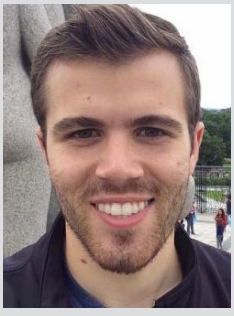
Prof. J. M. Murphy

Jennifer M. Murphy received her B.S. degree in chemistry (cum laude) from Santa Clara University in Northern California (USA). In 2010, she obtained her Ph.D. working under the direction of Professor Michael E. Jung at UCLA (USA). She then became a Scholar in Oncologic Molecular Imaging (SOMI) postdoctoral fellow in the Ahmanson Translational Imaging Division at the David Geffen School of Medicine at UCLA. In 2012, Jennifer joined Professor Tobias Ritter's research laboratory as a visiting scholar at Harvard University (USA). In 2013, she was appointed as Assistant Professor in the Department of Molecular and Medical Pharmacology at the Crump Institute for Molecular Imaging at UCLA. Her lab resides in the California NanoSystems Institute building and she is also a member of the Jonsson Comprehensive Cancer Center at UCLA.



R. Gamache

Raymond Gamache was born in Burlington, VT (USA) and raised in King George, VA (USA). In 2013, he received his B.S. degree in chemistry from Christopher Newport University (CNU, USA). At CNU he worked under the supervision of Professor Jeffrey Carney researching the synthesis of heterocycles using the Hosami–Sakurai reaction. Raymond also participated in several internships at the Naval Research Laboratories with Dr. Mike Roland where he studied the physical attributes of polyurea rubber. After graduating from CNU, Raymond began his Ph.D. studies in organic chemistry at the University of California Los Angeles (UCLA, USA). In 2014, Raymond joined Professor Jennifer Murphy's laboratory where his research involves the development of new fluorination methods, rapid bioorthogonal reactions and approaches for [^{18}F]-radiolabeling of proteins for molecular imaging applications.

Dr. C. Waldmann

Christopher Waldmann was born in Tübingen (Germany) and received his M.S. in chemistry from the University of Cologne (Germany) in 2009. At the same university, he performed undergraduate research with Professor Hans-Günther Schmalz. He obtained his Ph.D. in organic synthesis and radiochemistry working with Professor Günter Haufe as well as Professor Klaus Kopka at the University of Münster (Germany) in 2013. He then moved to Los Angeles and worked under the mentorship of Professor Jennifer Murphy as a postdoctoral scholar in the Crump Institute for Molecular Imaging at UCLA (USA). In 2016, Christopher joined the laboratory of Professor Saman Sadeghi as a postdoctoral scholar. His research interests include the synthesis and radiolabeling of small organic molecules as imaging probes for positron emission tomography (PET).

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Synform | Literature Coverage

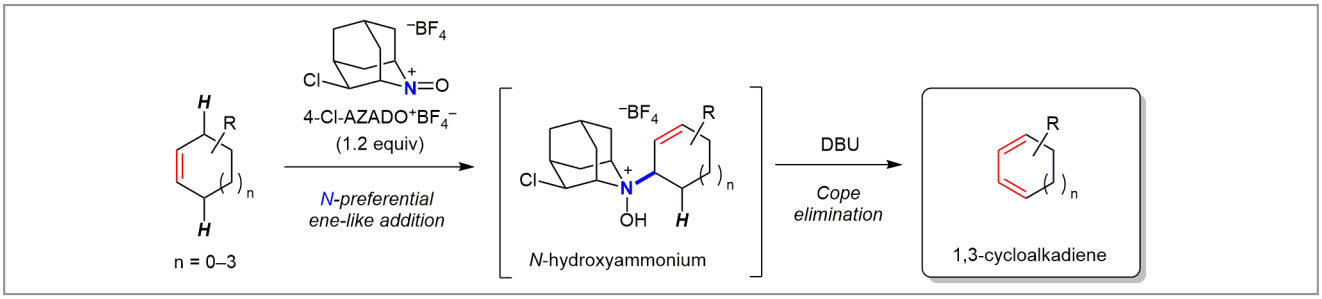
Synthesis of 1,3-Cycloalkadienes from Cycloalkenes: Unprecedented Reactivity of Oxoammonium Salts

Angew. Chem. Int. Ed. **2016**, *55*, 13189–13194

Cyclic 1,3-dienes or 1,3-cycloalkadienes are important chemicals that have a variety of synthetic applications in organic chemistry, but their preparation – particularly in the case of highly functionalized 1,3-cycloalkadienes – can be challenging, thus affecting the availability of these molecules as building blocks. A convenient one-pot synthesis of 1,3-cycloalkadienes via a regioselective dehydrogenation of the corresponding cycloalkenes has been developed recently by the group of Professor Yoshiharu Iwabuchi from Tohoku University (Japan). Professor Iwabuchi said: "The novel synthetic method stemmed from a serendipitous discovery during our attempt to expand the synthetic scope of oxoammonium salts. After extensive investigations, we realized that this dehydrogenation involves unprecedented reactivity of oxoammonium salts with cycloalkenes: an azaadamantane-type oxoammonium salt reacts with a cycloalkene to form a key *N*-hydroxyammonium intermediate via an N-preferential ene-like addition (Scheme 1)." Professor Iwabuchi revealed that PhD student Shota Nagasawa discovered the novel reactivity of the azaadamantane-type oxoammonium salt, and designed and conducted all the experiments covered in their paper as well as co-authoring it with Professor Yusuke Sasano and Professor Yoshiharu Iwabuchi.

Professor Iwabuchi continued: "Our investigation on the development and synthetic use of azaadamantane-*N*-oxyl (AZADO)-related compounds began in 2002 when I took over a laboratory from my mentor, Professor Emeritus Kunio Ogasawara at Tohoku University." The Ogasawara group had been preparing for publication of the seminal work entitled 'The Chiral Modification of Adamantane'.[1] "By learning the unique synthetic approach which employs an annulation of bicyclo[3.3.1]nonane skeleton to adamantane, inspiration dawned on the possible use of AZADO and its derivatives as a less-hindered congener of TEMPO that would mediate or catalyze oxidation of organic substrates," Professor Iwabuchi recalled. He continued: "The catalytic activity and the substrate applicability exhibited by AZADOs in alcohol oxidation were far beyond our expectation.[2] The discovery of the ultra-highly active catalyst spurred us to develop a commercial synthesis of AZADO. After productive collaboration with Nissan Chemical Industry, Ltd., a kilogram-scale synthesis process was established and AZADO (AZADOL®) is now widely distributed by several vendors.[3] The large-scale synthetic route to AZADO allowed us to enjoy the fertile chemistry of AZADO and related compounds: the less-hindered active site offers ultra-high activity and tunable redox potential. Either introducing electronegative substituents onto the azaadamantane skeleton[4] or coupling with different counter-anions significantly expanded the synthetic scope of the method.[5]"

Recently, the group's interests have expanded into reactions of AZADOs and related oxoammonium salts with alkenes. The reaction of oxoammonium salts with alkenes was first reported in 2006 by Bobbitt and co-workers: a TEMPO-derived oxoammonium salt (Bobbitt's salt) was found to react with trisubstituted alkenes selectively to give alkoxyamines.[6] "This new reaction, featuring the O-preferential ene-like addition of oxoammonium ion onto alkene, opened a new avenue for oxidation of alkenes, however, the substrate scope was limited to trisubstituted alkenes," said Professor Iwabuchi. "We envisioned that an electronically tunable AZADO-derived



Scheme 1 Dehydrogenation of cycloalkenes using an azaadamantane-type oxoammonium salt

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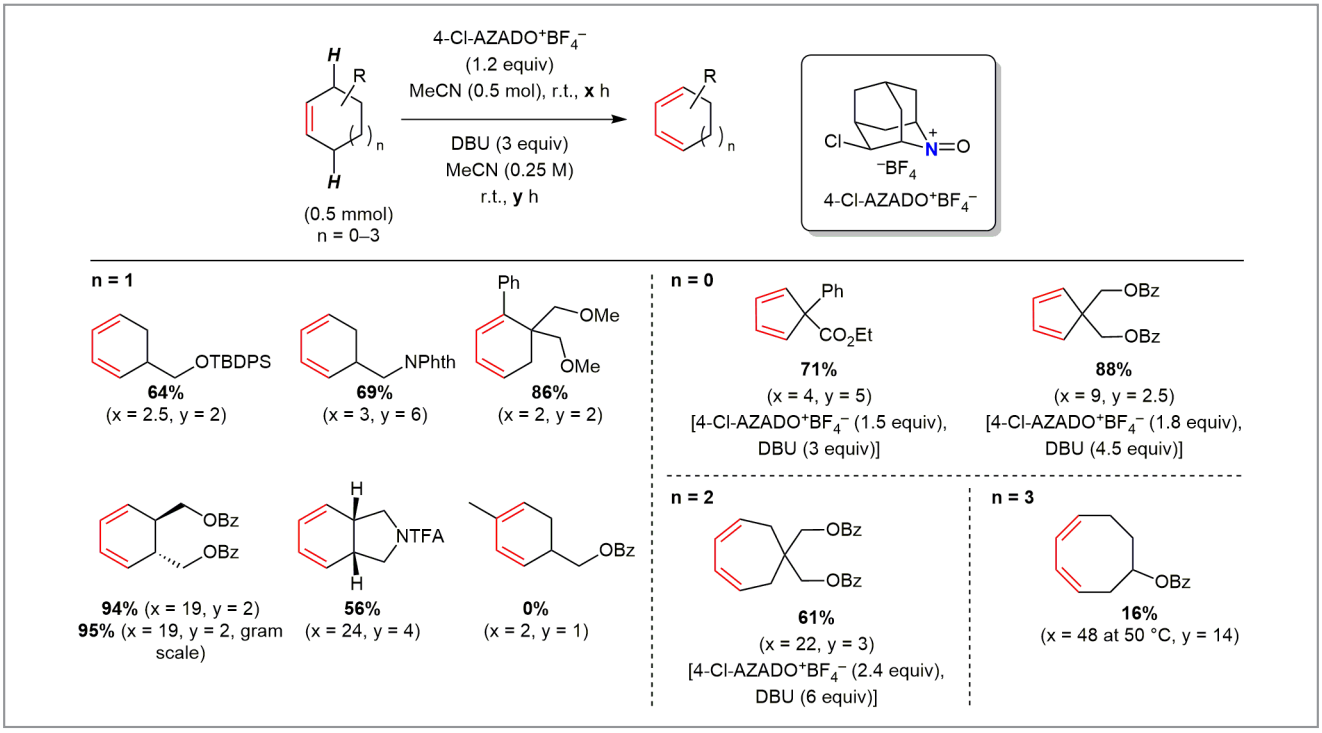
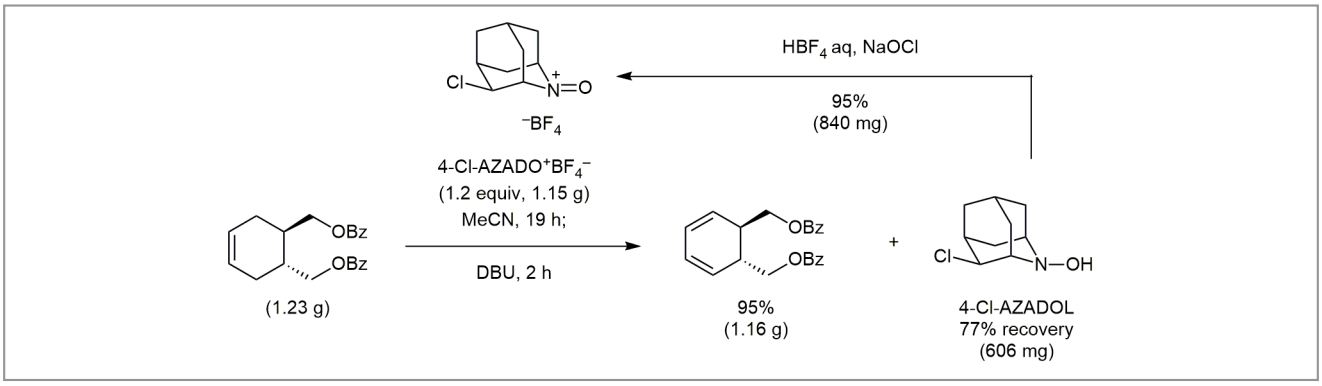
oxoammonium ion would acquire an enhanced electrophilic nature that would enable its attack onto disubstituted alkenes to give the corresponding adducts. The resulting story is described in detail in our *Angewandte* paper."

The selected scope of this reaction is shown in Scheme 2. "The most outstanding point of this reaction should be the complete regioselectivity in the dehydrogenation step," said Professor Iwabuchi. Dibromination–dehydrobromination sequence, which is a well-known method to synthesize cycloalka-1,3-dienes from cycloalkenes, often gives a regioisomeric mixture of cycloalka-1,3-dienes depending on structures of the substrates. In contrast, the Iwabuchi group's method gives cycloalka-1,3-dienes as a single isomer.

Professor Iwabuchi said: "A scalable synthesis of the key reagent 4-Cl-AZADO$^+$BF$_4^-$ has been developed on the basis of the kilogram-scale synthesis of AZADO. It should be stressed that 4-Cl-AZADO$^+$BF$_4^-$ can be recyclable: the corresponding hydroxylamine (4-chloro-2-azaadamantane-2-ol: 4-Cl-AZADOL) was recovered after the dehydrogenation and was converted into 4-Cl-AZADO$^+$BF$_4^-$ quantitatively (Scheme 3)."



Scheme 2 Substrate scope (selected)



Scheme 3 Large-scale experiment and regeneration of 4-Cl-AZADO$^+$BF$_4^-$

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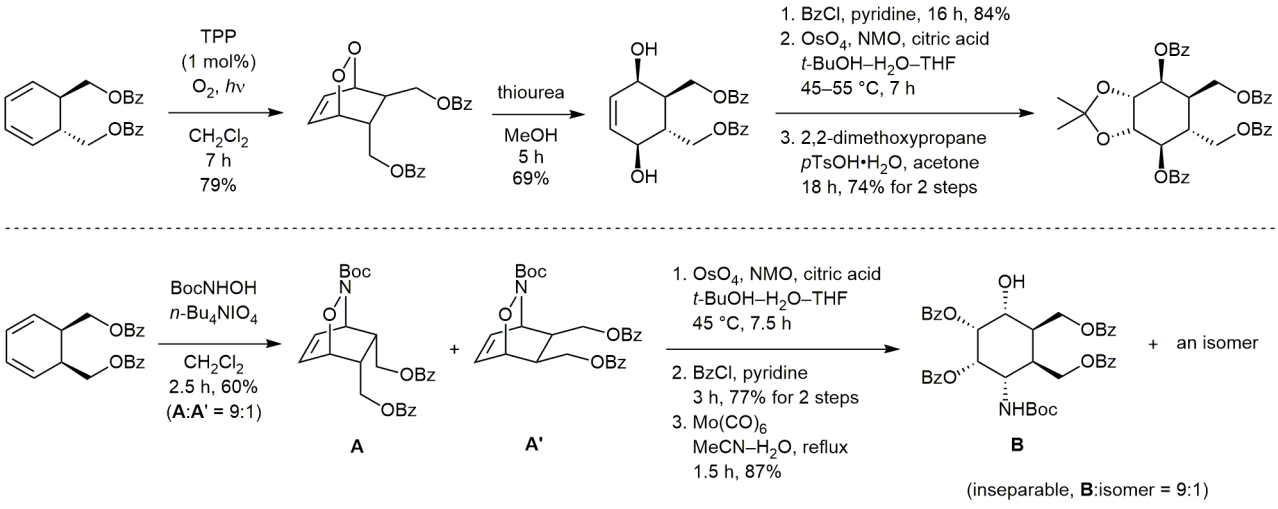

Scheme 4 Functionalization of the obtained 1,3-cyclohexadienes

Professor Iwabuchi remarked: "We demonstrated the synthetic use of the 1,3-cyclohexadiene products by the synthesis of carbasugar derivatives (Scheme 4). Since our method has a potential to afford various 1,3-cycloalkadienes (including unprecedented ones), various carbasugar derivatives could be synthesized."

Concerning future prospects and developments of this work, Professor Iwabuchi said: "In this paper, we reported the novel reactivity of oxoammonium species and the preliminary results of its applicability. Based on this finding, improvement of the efficiency (which includes the development of catalytic conditions) and expansion of the scope to other alkene substrates would be possible and are under way in our lab.

Furthermore, 4-Cl-AZADO$^{+}BF_4^{-}$, the key reagent in this reaction, is readily prepared in multigram scale and shows improved reactivity compared with previously developed oxoammonium salts," said Professor Iwabuchi. He concluded: "We believe that a sufficient supply of this oxoammonium salt should allow the research community to develop new reactions based on this chemistry, without the risk of missing opportunities because of difficulties connected with the availability of these compounds. Commercialization of 4-Cl-AZADO$^{+}BF_4^{-}$ is currently being discussed."

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Shota Nagasawa was born in Yamagata (Japan) in 1989. He studied at the Department of Pharmaceutical Sciences, Tohoku University (Japan), where he obtained his B.S. degree in 2012, and his M.S. degree in 2014 under the supervision of Professor Yoshiharu Iwabuchi. He is currently a Ph.D. candidate in the Iwabuchi group. His research interest is the development of novel reactions which has interesting reaction mechanism and makes the synthesis of complex molecules easy.

Prof. Y. Sasano

Yusuke Sasano was born in Sagamihara (Japan) in 1986. He studied at the Department of Pharmaceutical Sciences, Tohoku University (Japan), where he obtained his B.S. degree in 2008 and his Ph.D. in 2014 under the supervision of Professor Yoshiharu Iwabuchi. He was appointed as a Research Instructor in the Iwabuchi group in 2012, and has been an Assistant Professor in the same group since 2014. He worked as a Research Associate in Professor Ryan A. Shenvi's group at The Scripps Research Institute (USA) in 2014–2015. His current research interest is the development of selective oxidation methods.

Prof. Y. Iwabuchi

Yoshiharu Iwabuchi was born in Yamagata (Japan) in 1963. He studied at the Department of Pharmaceutical Sciences, Tohoku University (Japan), where he obtained his B.S. in 1986, and his Ph.D. in the laboratory of Professor Seiichi Takano under the guidance of Dr. Kunio Ogasawara in 1991. After a year of postdoctoral work with Professor K. C. Nicolaou in The Scripps Research Institute (USA), he joined the group of Dr. Ikuo Fujii at Protein Engineering Research Institute (Japan). In 1997 he was appointed Associate Professor in Professor Susumi Hatakeyama's group at Nagasaki University (Japan). In 2002 he returned to Tohoku University as a Full Professor. His research interests include the development of organocatalysts, asymmetric synthesis, and natural product synthesis.

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