Synform SYNTHESIS Highlight

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

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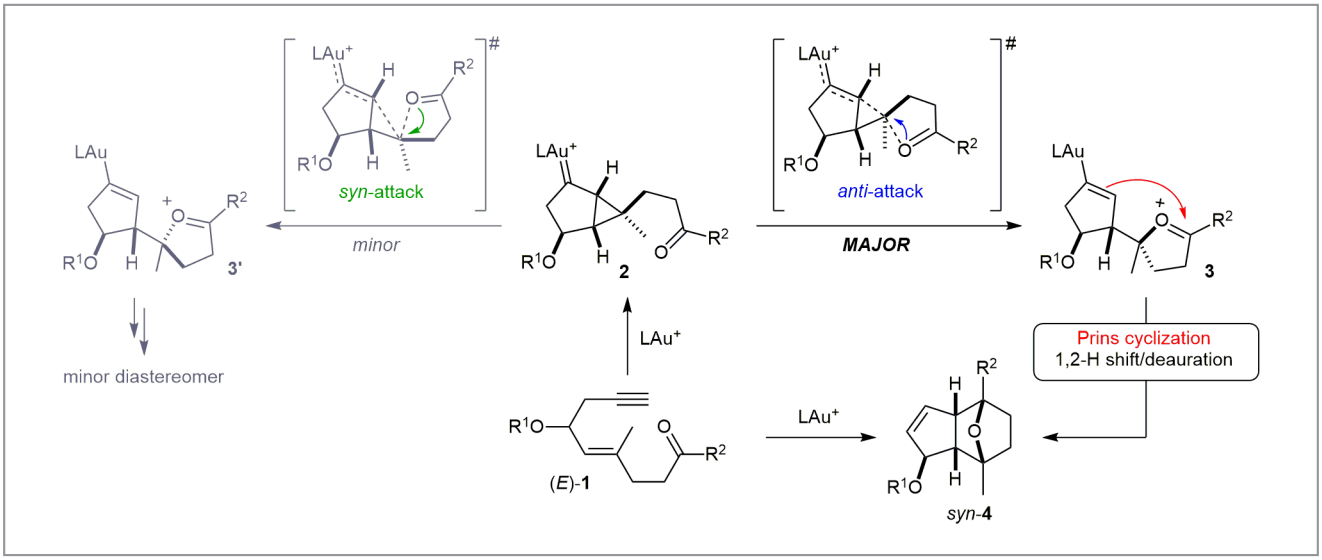
The activation of alkynes towards nucleophilic addition employing gold salts and complexes has become a powerful and versatile tool for the construction of C–C and C–heteroatom bonds. In particular, the reaction of alkynes with alkenes has been studied extensively, and the intramolecular reactions of 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



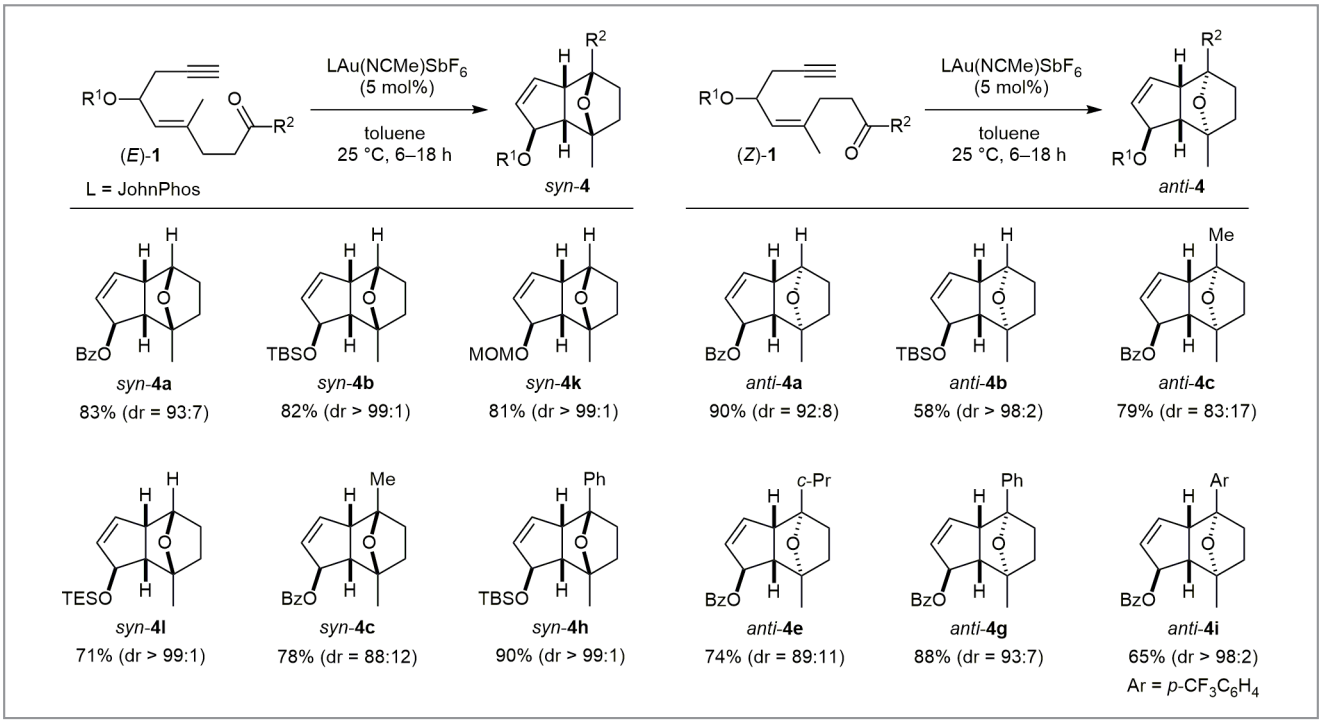
Scheme 1 Mechanism of the formal [2+2+2] cycloaddition of oxo-1,5-enynes, supported by DFT calculations

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



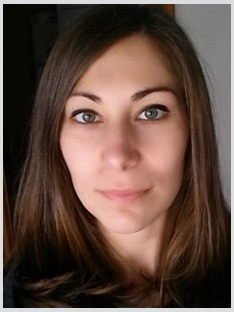
Scheme 2 Selected scope of the formal [2+2+2] cycloaddition of oxo-1,5-enynes

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

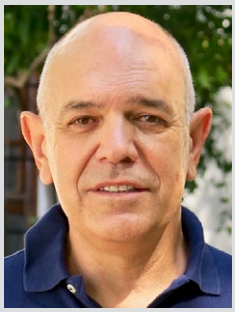
Pilar Calleja was born in Barcelona (Spain) in 1988. She completed her B.Sc. (2011) at the University of Barcelona (Spain). In 2012, she received the Master of Synthesis and Catalysis Extraordinary Award at the Rovira i Virgili University (Tarragona, Spain). Since 2012 she has been carrying out her Ph.D. 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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