

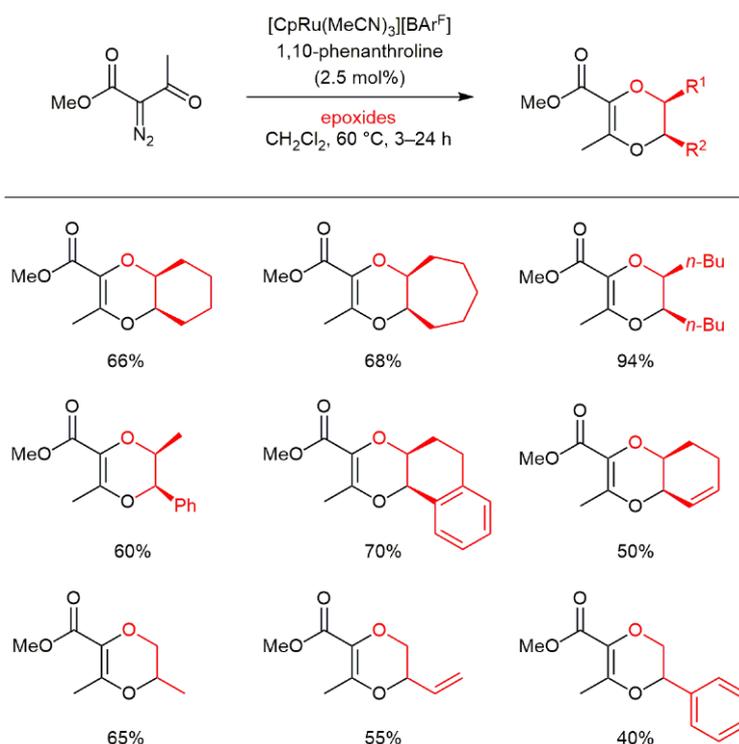
CpRu-Catalyzed Carbene Insertions into Epoxides: 1,4-Dioxene Synthesis via S_N1-like Chemistry with Retention of Configuration

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■ The group of Professor Jérôme Lacour at the University of Geneva (Switzerland) has recently reported a series of original transformations, using cyclic ethers as substrates, α -diazo- β -keto esters as reagents and rhodium/ruthenium catalysts for the diazo decomposition, that are best rationalized by the successive formation of metal carbenes and oxonium ylide intermediates. Professor Lacour explained that, interestingly, under the same reaction conditions, very different results are usually obtained under Rh(II) and Ru(II) catalysis. For instance, with THF, 16-membered macrocycles are obtained with Rh₂(OAc)₄ (*Angew. Chem. Int. Ed.* **2010**, *49*, 7253) while products of 1,3-C–H insertions result from combina-

tions of CpRu complexes and diimine ligands (*Angew. Chem. Int. Ed.* **2012**, *51*, 5847).

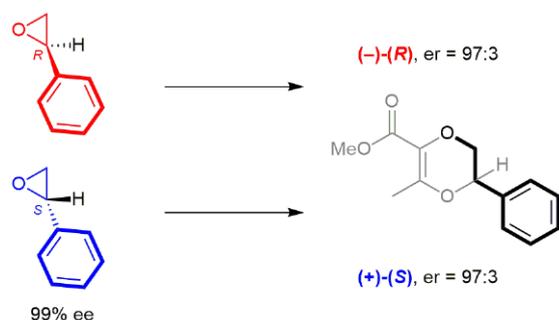
“As part of this program, it was then interesting to study the reactivity of α -diazo- β -keto ester reagents with the smallest cyclic ethers, the epoxides (oxiranes),” said Professor Lacour. “However, it was not clear whether remarkable results would occur this time.” Professor Lacour continued: “Epoxides are highly useful synthetic building blocks owing to their availability in well-defined stereochemical forms and their reactivity with a wide array of nucleophiles and acids leading to ring-opening reactions with often excellent levels of regioselectivity and/or stereoselectivity. Yet, as a rule,



Scheme 1

epoxides do not react with metal carbenes to afford synthetically useful oxonium ylide intermediates but undergo instead (less interesting) deoxygenation processes that transform them into alkenes.” Professor Lacour revealed that it was a surprise when Dr. Thierry Achard and graduate student Cecilia Tortoreto observed that the treatment the *cis*-stilbene oxide with methyl diazoacetylacetate in the presence of 1,10-phenanthroline and $[\text{CpRu}(\text{MeCN})_3][\text{BAR}_F]$ (2.5 mol% respectively) led to the clean formation of an original product of condensation of 1,4-dioxene type (Scheme 1). This first result was rapidly confirmed by a series of experiments with cyclic and acyclic symmetrical *cis*-epoxides. Satisfyingly, in all examples, 1,4-dioxene adducts were again obtained as single stereoisomers. Professor Lacour remarked: “All these experiments led to another surprise as, upon ^1H NMR and then later X-ray diffraction analyses, it became clear that the products were all of *cis*-configuration themselves. *syn*-Stereoselective openings of epoxides are known but they remain rare. It was thus a pleasure to have found another example.”

Furthermore, while working towards expanding the scope of the reaction to unsymmetrical *cis*-disubstituted and mono-substituted epoxides, it was found that ring-opening products were always obtained as single regioisomers as well, with the substitution reactions occurring at the activated carbon centers (benzylic, allylic or more substituted). Professor Lacour said: “The example with 2-vinylloxirane was particularly sweet as only the product of direct ring opening was obtained with no evidence of byproducts of [2,3]-sigmatropic reactions. Still, more globally and quite surprisingly, these latest experiments were advocating for a pathway occurring through an $\text{S}_{\text{N}}1$ -like mechanism; this preference being at first glance in contradiction with the highly stereoselective nature of transformation.”



Scheme 2

To shed some light on the process, a few unsymmetrical epoxides were used in enantiopure form by the researchers. For instance (Scheme 2), both *(R)*- and *(S)*-styrene oxides were tested and the corresponding products were obtained with an astonishing 97:3 enantiomeric ratio! Care was taken to determine the absolute configurations by X-ray diffraction analysis with the help of Dr. Laure Guénée and also by vibrational circular dichroism (VCD): both methods indicated *R*- and *S*-configurations for the corresponding 1,4-dioxenes and hence a retention of configuration! Professor Lacour mentioned: “It was important to perform the VCD study with a renowned expert, Prof. Thomas Bürgi, to ascertain the result of the solid-state analysis which had been performed without a heavy atom. VCD is a well-established spectroscopic method for the determination of absolute configurations. It is unfortunate that it is not used more often by synthetic chemists.”

Finally, thanks to computational studies, a mechanistic rationale coherent with the experimental information could be proposed. Professor Lacour continued: “Dr. Amalia Poblador-Bahamonde was able to define the ruthenium carbene species. She then showed that a nucleophilic attack of the epoxide occurs and a metal-bound oxonium ylide intermediate is formed. From there, promoted by strain and by the electrophilic activation, a carbocationic intermediate is produced which is very rapidly trapped by the keto group at proximity to form the cyclic 1,4-dioxene skeleton – and this with retention of the original configuration of the reacting carbon center.”

Professor Lacour concluded: “We have found a new reactivity for metal carbenes with epoxides owing to the combination of 1,10-phenanthroline and $[\text{CpRu}(\text{MeCN})_3][\text{BAR}_F]$ as catalyst. The protocol allows the formation of unprecedented 1,4-dioxene motifs as single regio- and stereoisomers. It relies on a strict *syn*-stereochemistry (retention of configuration, er up to 97:3) for the ring opening that behaves otherwise like an $\text{S}_{\text{N}}1$ -like transformation! Such unusual reactions are strokes of luck and those are the transformations that ‘make my day’!”

Matteo Zanda

About the authors



Dr. A. I. Poblador-Bahamonde

Thierry Achard studied at the University of Aix-Marseille, Faculté de St. Jérôme (France) and obtained his Master's degree in 1999. He received his PhD from both King's College London and Newcastle-upon-Tyne University (UK) in 2006. Then, he joined groups in Barcelona (Spain; Institute for Research in Biomedecine, 2006–2008), in Marseille (France; Ism2, 2009–2010) and in Geneva (Switzerland; 2011–2014) as a postdoctoral fellow. Since 2014, he is Chargé de Recherche (CNRS) at the Institut de Physique et Chimie des Matériaux de Strasbourg (UMR7504, équipe DMO) (France).

Cecilia Tortoreto studied at the University of Perugia (Italy) and received her MSc degree in 2009. Then, she moved to the chemical development department of GlaxoSmithKline research center in Verona (Italy) for a master graduate fellowship. She has been a PhD student at the University of Geneva since 2010.



Dr. A. I. Poblador-Bahamonde

Amalia I. Poblador-Bahamonde

received her PhD (2009) from Heriot-Watt University (UK). In 2010, she moved to Montpellier (France) as a postdoctoral fellow. In January 2013, she joined the Organic Chemistry Department of the University of Geneva as a lecturer. Her research interests lie in the use of computational chemistry to understand the structures and reactivity of transition-metal systems, particularly in organo-metallic chemistry.

Laure Guénée studied at the University of Paris XI, Orsay (France) and then obtained her PhD in crystallography from the University of Geneva (Switzerland) in 2002. After a postdoctoral stay at the Institut des Matériaux Jean Rouxel, Nantes (France), she returned to the University of Geneva in 2005. She is now collaboratrice scientifique in the Laboratoire de cristallographie.

Thomas Bürgi studied chemistry and obtained his PhD (1995) at the University of Berne (Switzerland). After a postdoctoral stay at MIT (USA), he did his habilitation at ETH Zürich (Switzerland). He became Assistant Professor at the University of Neuchâtel (Switzerland) in 2005 and Full Professor at the University of Heidelberg (Germany) in 2008. In 2010, he moved to the University of Geneva, where he is Professor of physical chemistry. His research focuses on chiral nanoparticles, plasmon-based metamaterials and in situ vibrational spectroscopy.

Jérôme Lacour was educated at the École Normale Supérieure (Ulm, Paris, France) and obtained in 1993 his PhD in chemistry at the University of Texas, Austin (USA). After postdoctoral studies at Harvard University (USA) in 1993–1994, he joined the Organic Chemistry Department of the University of Geneva in 1995. In 2001, he received the Sandoz Family Foundation professorship. Since 2004, he holds a Full Professor position in the department. Currently, his primary research interests are in asymmetric synthesis and catalysis using organic, physical organic, organometallic and coordination chemistry tools.