SYNSTORIES

- Metal-Free Photochemical Aromatic Perfluoroalkylation of α-Cyano Arylacettes

- Synthesis of Tetrahydropyran- or Tetrahydrofuran-Containing Macrolides by Palladium-Catalyzed Alkoxy carbonylative Macrolactonizations

- Young Career Focus: Dr. Stellios Arseniyadis (ESPCI ParisTech, Paris, France)

- Thieme Chemistry Journals Editorial Board Meeting 2014

CONTACT

Your opinion about SYNFORM is welcome, please correspond if you like:
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Dear Readers,

I have already anticipated in the previous Editorial that important and exciting changes are looming for SYNFORM, but let me tell you something more about that. The most exciting change is that SYNFORM will become SYNFORM 2.0, which means that SYNSTORIES and other articles will be published eFirst as soon as possible. This also implies that the SYNFORM website will be updated much more frequently (at least once a week) and will become central to SYNFORM. The current pdf version will continue to be published monthly but it will no longer be the main publication channel for SYNFORM. Importantly, SYNFORM will dedicate more space and attention to Thieme Chemistry authors: in fact, articles published in SYNLETT and SYNTHESIS will be regularly selected for News and SYNSTORY articles in order to further increase both impact and dissemination of the important research that appears in our journals. SYNFORM will also start publishing new types of articles, such as focus articles on academic and research institutes (by the way, if you are interested in having your institute featured in a SYNFORM article please drop me an email!), on major award winners and commentaries of variable nature. Furthermore, SYNFORM will strengthen its links with social media, where Thieme Chemistry is already present and widely followed. Last but not least, if these changes are appreciated by our readership, the number of SYNFORM articles and therefore the publication frequency would increase accordingly. I truly believe this is all very exciting and I am looking forward to the new SYNFORM 2.0! Let’s have a glimpse at the new articles published in this exciting new issue of SYNFORM now. The first article is a thorough report on the recent breakthrough achieved by P. Melchiorre (Spain) with the photochemical aromatic perfluoroalkylation of α-Cyano Arylacettes. Synthesis of Tetrahydropyran- or Tetrahydrofuran-Containing Macrolides by Palladium-Catalyzed Alkoxy carbonylative Macrolactonizations.

SYNSTORIES

Metal-Free Photochemical Aromatic Perfluoroalkylation of α-Cyano Arylacettes

SYNLETT

Synthesis of Tetrahydropyran- or Tetrahydrofuran-Containing Macrolides by Palladium-Catalyzed Alkoxy carbonylative Macrolactonizations

Young Career Focus: Dr. Stellios Arseniyadis (ESPCI ParisTech, Paris, France)

Thieme Chemistry Journals Editorial Board Meeting 2014

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM
Metal-Free Photochemical Aromatic Perfluoroalkylation of α-Cyano Arylacacetates


The group of Professor Paolo Melchiorre at the Institute of Chemical Research of Catalonia (ICIQ), Tarragona (Spain), has recently developed an operationally simple strategy for the direct aromatic perfluoroalkylation and trifluoromethylation of α-cyano arylacetates. The method is synthetically attractive because it provides a very mild way to directly install a perfluoroalkyl fragment into aromatic compounds. It is well known that fluorne-containing functional groups can profoundly alter the intrinsic properties of organic compounds. For this reason, the incorporation of perfluoroalkyl groups into aromatic compounds is a chemical strategy often exploited in medicinal chemistry to modulate the biological activity and metabolic fate of drug candidates. This justifies the profuse efforts made by the synthetic community to develop effective perfluoroalkylation methods. Modern technologies generally rely upon the use of expensive metals, or harsh conditions. Professor Melchiorre said: “Our metal-free approach requires very mild conditions in order to proceed, since it occurs at ambient temperature and under illumination by a readily available compact fluorescent light (CFL) bulb. What is needed is to simply mix an α-cyano arylacetate 2 with the desired perfluoroalkyl iodide 1 in the presence of tetramethyl guanidine (TMG), an organic base, and then shine light over the reaction vessel!”

He continued: “Besides the potential synthetic merits of our methodology (selected examples of its broad scope are reported in Scheme 1), the aspect we are more intrigued with is that we can use the energy of visible light to drive a synthetically appealing transformation. The reactivity behind our perfluoroalkylation strategy is well known, since it capitalizes upon the strongly electrophilic nature of the perfluoroalkyl radicals, which are eager to react with arenes through the classical homolytic aromatic substitution (HAS) pathway (A. Studer Angew. Chem. Int. Ed. 2012, 51, 8950).” The interesting aspect here, as evidenced by Professor Melchiorre, is that open-shell reactive species can be photo-generated under mild conditions, instead of using the generally required harsh reaction conditions, which include high temperatures and the use of stoichiometric radical initiators and/or metals. Professor Melchiorre next revealed how the photochemical strategy for generating open-shell reactive species from perfluoroalkyl iodides was conceived. He said: “The study was conducted by two very talented Italian PhD students of mine, Giulia Bergonzini and Manuel Nappi. In our laboratory, we recently discovered that the photochemical activity of in situ formed electron-donor–acceptor (EDA) complexes, molecular aggregations which occur in the ground state upon interaction of organic substrates (R. S. Mulliken J. Phys. Chem. 1952, 56, 801; R. Foster J. Phys. Chem. 1980, 84, 2135), can serve to photo-generate open-shell reactive species at ambient temperature. Specifically,” he continued, “we developed a photochemical stereoselective intermolecular α-alkylation of aldehydes (E. Arceo, I. D. Jurberg, A. Álvarez-Fernández, P. Melchiorre Nature Chem. 2013, 5, 750; highlighted in Synfacts 2013, 9, 1229).” According to Professor Melchiorre, the success of this asymmetric, metal-free process relied upon the formation of photon-absorbing chiral EDA complexes, arising from the association of a transiently generated chiral electron-rich enamine I with alkyl bromides with a high electron affinity. Visible-light irradiation of the colored EDA complex induced an electron transfer to occur, allowing easy access to radical species.

Expanding upon this precedent, the researchers envisioned the possibility of using donor substrates other than enamines I to form photo-active EDA complexes (Scheme 2). In fact, given the electronic similarities with I, in situ generated enolates of type II were considered as suitable donors. Perfluoroalkyl iodides 1 were selected as potential electron-accepting substrates for facilitating EDA association in the ground state. Professor Melchiorre explained: “The feasibility of our plan was tested in the reaction of ethyl α-cyano phenylacetate (2a) with perfluorohexyl iodide (1a) under irradiation by a 23 W CFL lamp. The reaction was conducted in the presence of TMG so as to favor the formation of the corresponding enolate.” He continued: “We recognized the formation of the EDA as critical to reaction development, since visible-light irradiation might induce an electron transfer to occur, giving the anionic contact radical pair.”

Professor...
Melchiorre explained that the presence of iodide as a suitable
leaving group within the radical anion partner triggers a rapid
fragmentation event, productively rendering the iodide anion
along with the desired open-shell species, including the per-
fluoroalkyl radical \( V \). “In analogy to our alkylation of aldehydes,” he said, “we anticipated the formation of the \( \alpha \)-car-

Scheme 1 Metal-free photochemical aromatic perfluoroalkylation of \( \alpha \)-cyano arylacetates

Scheme 2 Rational plan or serendipity?
bonyl perfluoroalkylated adduct 4 to be favored, by means of a radical–radical combination or a radical trap by the enolate. It was a real surprise when Giulia came to my office claiming that the arene-perfluoroalkylation product 3 (para/ortho formed in a 2:1 ratio) was generated instead. This was really a serendipitous and unanticipated observation, but such unexpected results are what any scientist is really looking for! (If you can fully anticipate the reactivity, then probably it might not be such an interesting/novel chemistry.)

Professor Melchiorre continued: “My co-workers were able to further refine and optimize the reaction conditions, to make this photochemical perfluoroalkylation a potentially useful synthetic method.” A control experiment, carried out by performing the reaction in the dark, did not provide any reactivity, testifying to the photochemical nature of the transformation. “The efforts by Manuel have been crucial to better understanding the reaction mechanism,” acknowledged Professor Melchiorre. In particular, a quantum yield (Φ) of 3.8 was determined (λ = 400 nm), suggesting a radical chain mechanism as the main reaction pathway. The team proposes a homolytic aromatic substitution HAS mechanism (Scheme 3) which is initiated by the photochemical activity of the EDA complex of type III, formed upon aggregation of the enolate-type compound II with perfluoroalkyl iodides. “A visible-light-driven electron transfer leads to the formation of radical species RF·, which then reacts with the arene within the enolate II to form the new C–C bond,” explained Professor Melchiorre. The mesomeric effect of the anionic substituent in II facilitates the C–C bond formation leading to the cyclohexadienyl radical VI. A single-electron-transfer (SET) mechanism is proposed by the authors as the propagation step of the radical chain.

Professor Melchiorre said: “Both of my young co-workers did an outstanding job and it was extremely rewarding for me to see their constant positive attitudes and to share with them the excitement of understanding this unanticipated photochemical reactivity. We believe that our results corroborate the idea that the photochemistry of EDA complexes, formed upon aggregation of organic substrates in the ground state, may provide a general reactivity framework for the design of unprecedented photochemical transformations, expanding the way chemists think about making organic molecules.” For example, this study establishes the possibility for enolates to work as suitable donors in EDA formation, and the group is actively pursuing the possibility of using this reactivity to design an enantioselective photochemical reaction. “Our strategy differs from but complements the approach of photoredox catalysis (Science 2014, 343, 10.1126/science.1239176; Science 2008, 322, 77), a fast developing area of modern chemical research,” said Professor Melchiorre. “On this basis, our findings have the potential to immediately impact the organic chemistry community, particularly when considering the universal need for more sustainable and environmentally responsible chemical processes.”

One may wonder why a research group, traditionally involved in the field of classical polar reactivity applying organocatalytic strategies, has become interested in photochemistry and radical reactivity. Professor Melchiorre revealed: “Our motivations come from the notion that the use of light excitation to bring a molecule from its ground state to

**Scheme 3** The proposed radical chain mechanism
an electronically excited state can open new dimensions in chemistry. This is because excited states can react in different ways, both qualitatively and quantitatively, compared with the ground state, which can provide unexplored possibilities for developing processes driven by light that cannot be realized using thermal activation.” He concluded: “Of course this idea is as old as the venerable field of photochemistry, since reactions driven by light have been observed as long as chemistry has been studied. It is also very suggestive to us (the perfluoroalkylation team is composed by three Italians) that Giacomo Ciamician, an Italian chemist who is considered one of the fathers of organic photochemistry, recognized more than a century ago the potential of using the energy of sunlight to do chemistry in a fully environmentally respectful way (Science 1912, 36, 385).”

**About the authors**

**Paolo Melchiorre** was born in Camerino (Italy) in 1973. He was educated at the Alma Mater Studiorum-University of Bologna (Italy), where he graduated in 1999. He received his Ph.D. in chemistry in 2003 from the same university, working in the area of asymmetric catalysis, under the direction of Professor Achille Umani-Ronchi and the supervision of Professor Pier Giorgio Cozzi. In 2002, he spent a research period working with Professor Karl Anker Jørgensen at the “Center for Catalysis”, Århus University (Denmark), where his studies centered on asymmetric organocatalysis. In October 2007 he took a permanent position as an Assistant Professor at Bologna University. In September 2009 Paolo joined the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona (Spain) as an ICREA (Catalan Institution of Research and Advanced Studies) Professor and ICIQ Senior Group Leader.

Paolo has received the “G. Ciamician” Medal, awarded by the Italian Chemical Society (2007), the Thieme Chemistry Journal Award (2009), and a JSPS Fellowship under the FY2013 Program for Research in Japan. He was also nominated Liebig Lecturer 2008 by the Organic Division of the German Chemical Society. Paolo has been recently awarded an ERC Starting Grant to carry out the 5-year project “ORGA-NAUT: Exploring Chemical Reactivity with Organocatalysis”, funded by the European Research Council. His research interests include the discovery and mechanistic elucidation of new asymmetric organocatalytic and photochemical processes that address unsolved problems in synthetic methodology.

**Giulia Bergonzini** was born in Modena (Italy) in 1985. She received her B.Sc. and M.Sc. degrees from the Alma Mater Studiorum-University of Bologna in 2007 and 2009, respectively. She then moved to Spain where she carried out her Ph.D. studies under the supervision of Professor Paolo Melchiorre at the ICIQ. In 2012 she joined the group of Professor Corey R. J. Stephenson at Boston University (USA) for a period of six months. In October 2013 she received her Ph.D. from the University Rovira i Virgili (Spain) and she is now a postdoctoral researcher at the Department of Chemistry and Molecular Biology at the University of Gothenburg (Sweden) working in the fields of photoredox catalysis and natural product synthesis.

**Manuel Nappi** was born in Torino (Italy) in 1986. He was educated at the University of Torino, where he received his B.Sc. and M.Sc. degrees in 2008 and 2010, respectively. He received the Best Master Thesis in Advanced Chemical Methodologies Award in the Faculty of Mathematical, Physical and Natural Sciences, awarded by the University of Torino. In 2010 he joined the group of Professor Paolo Melchiorre for his Ph.D. studies where he is currently working in the fields of organocatalysis and photoredox chemistry. In 2012 he joined the group of Professor David W. C. MacMillan at Princeton University (USA) for a period of six months. His research interests include the development of new asymmetric organocatalytic and photochemical processes as well as mechanistic understanding of novel transformations.
Synthesis of Tetrahydropyran- or Tetrahydrofuran-Containing Macrolides by Palladium-Catalyzed Alkoxy carbonylative Macrolactonizations


Tetrahydropyran (THP)- and tetrahydrofuran (THF)-containing bridged macrolactones are distinctive structural motifs of many important biologically active natural products. A variety of synthetic strategies have been developed to prepare such structural motifs and related natural products. The commonly used strategies involve macrolactonization of seco-acid precursors, which are already equipped with the THP or THF ring. These seco-acids require multiple synthetic steps to prepare. Moreover, macrolactonization of seco-acids generally requires a large excess amount of reagents to activate the carboxylic acid and/or alcohol functional groups, and the reaction conditions to promote the cyclization can be very
harsh. Therefore, catalytic cascade processes to build both the THP or THF ring and the macrolactone ring in one transformation became an appealing target to Professor Mingji Dai at Purdue University Department of Chemistry (West Lafayette, IN, USA) and some of his students.

“The potent biological activity of THP- and THF-containing bridged macrolactones and their potential as lead compounds for drug discovery prompted us to develop an efficient method to streamline the synthesis of these complex natural products and related molecular libraries,” said Professor Dai. Inspired by the Semmelhack reaction, Professor Dai and two of his graduate students, Yu Bai and Dexter C. Davis, have developed a palladium-catalyzed alkoxycarbonylative macrolactonization to synthesize various THP- and THF-containing bridged macrolactones in one step from relatively simple alkenediols. “The reaction is amenable to form macrolactones of different ring size (11- to 23-membered rings),” said Professor Dai. “Furthermore, the reaction conditions are very mild and tolerate a variety of functional groups, including ketals and internal double bonds.” Even more importantly, this palladium-catalyzed alkoxycarbonylative macrolactonization was able to provide synthetically challenging tertiary macrolactones. “While tertiary macrolactones are frequently found in many important natural products, macrolactonization involving the OH group of a tertiary alcohol persists as a challenging synthetic problem and has barely been studied,” remarked Professor Dai. “It was a big surprise for us that our reaction proceeded very smoothly to form the THP- and THF-containing tertiary macrolactones,” he added. Overall, the reaction requires only a catalytic amount of palladium catalyst. As emphasized by Professor Dai, no carboxylic acid synthesis is required, nor is further activation.

“Active acyl palladium species are generated and trapped in situ,” he confirmed. The effectiveness of this new synthetic method was demonstrated in the synthesis of 9-demethyl-neopeltolide, a potent anticancer compound.

Professor Dai revealed that although good to excellent diastereoselectivity was obtained in most of the cases investigated, several products, which lack the quaternary carbon center in the THP ring, were obtained in poor diastereoselectivity. “While our current mechanistic study supports a Wacker-type trans-oxypalladation step, which is similar to the Semmelhack process, there are still many unanswered questions about the detailed mechanism of this reaction and the controlling factors of the observed diastereoselectivity. Answering these questions will provide insights to guide new reaction and reactivity development,” concluded Professor Dai.
Young Career Focus: Dr. Stellios Arseniyadis (ESPCI ParisTech, Paris, France)

Background and Purpose. SYNFORM will from time to time meet young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This SYNSTORY with a Young Career Focus presents Dr. Stellios Arseniyadis (ESPCI ParisTech, Paris, France).

INTERVIEW

SYNFORM | What is the focus of your current research activity?

Dr. Stellios Arseniyadis | There are three main research topics running in the group. The first one concerns the development of new synthetic tools in the field of asymmetric organic and organometallic catalysis and their application to the synthesis of natural products, the second one focuses on innovative DNA-hybrid asymmetric catalysis and the third one combines acoustics and microfluidics to devise new drug-delivery devices.

SYNFORM | When did you get interested in synthesis?

Dr. Stellios Arseniyadis | That’s a really interesting question. I think I started being fascinated by synthetic organic chemistry when I was an undergraduate student at the Université d’Orsay owing to Professors such as Henri Kagan, André Lubineau and Olivier Kahn. But most of all, I think I was fortunate to interact with some truly inspiring people starting with my dad, who’s probably one of the most passionate chemists I’ve ever met, but also Dr. Mioskowski, Professor Spivey and Professor Nicolaou, who shaped the chemist I am today.

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

Dr. Stellios Arseniyadis | Synthetic organic chemistry is a fascinating art that has definitely shaped science by impacting a variety of fields from materials science to physics, biology and medicine. It is a discipline that requires creativity, scientific knowledge and persistence and is as such genuinely formative and attractive. The development of innovative synthetic tools that take into consideration environmental constraints is clearly becoming a necessity and will have a deep impact on society. I just hope funding agencies will continue to support academic projects even if they do not target specific applications in the short term.

BIOGRAphICAL SKETCH

Stellios Arseniyadis was born in Athens (Greece) in 1975 and studied chemistry at the Université d’Orsay, Paris XI (Magistère de Physico-chimie Moléculaire) and at the Université René Descartes, Paris V (DEA de Chimie et de Physico-chimie des Composés d’Intérêt Biologique). After graduating in 1999, he joined the group of Dr. Charles Mioskowski at the Université Louis Pasteur in Strasbourg where he began his training as a synthetic chemist working on the development of new chiral acylating agents for the kinetic resolution of amines. After completing his PhD, he joined the Research & Innovation Team at Rhodia Chirex (Boston, USA) for 18 months of compulsory civil service, during which time he worked on various palladium- and copper-catalyzed aryl-bond-formation processes in collaboration with Professor Stephen L. Buchwald at MIT (MA, USA). In 2003, he did a first postdoc in Professor Alan C. Spivey's group at Imperial College (London, UK) to work in the field of asymmetric organocatalysis before moving back to the USA to join Professor K. C. Nicolaou’s group at The Scripps Research Institute (La Jolla, USA). There, he was involved in the synthesis of new epothilone B analogues and in the total synthesis of vannusatal B. Finally, in 2005, he was appointed a permanent CNRS position in Professor Janine Cossy’s group at ESPCI ParisTech (Paris, France) where his research interest encompasses various areas of chemistry, including asymmetric catalysis, natural product synthesis, organometallic chemistry, and sustainable chemistry.
Your research group is active in the area of total synthesis and development of new synthetic methodology. Could you tell us more about your research and its aims?

Dr. Stellios Arseniyadis | The group is particularly interested in uncovering new reactivity trends and applying them to the synthesis of structurally appealing natural products of significant pharmacological value. In this context, we have developed a number of new synthetic tools in the fields of organo- and metallo catalysis, asymmetric synthesis and bio-catalysis. For example, we recently developed a highly enantioselective organocatalytic transfer hydrogenation reaction involving β-azole-containing α,β-unsaturated aldehydes, which was used as a key step in the synthesis of myxothiazole Z and ulapualide A, both possessing interesting anti-tumor activities. The team has also been involved in the field of olefin cross-metathesis, developing various processes that were used to access a number of natural products including melithiazoles A, C, G and H and cystothiazoles A and F, which exhibit potent antifungal activities. Finally, the concomitant development of an enantioselective pentenylation reaction and a one-pot hydrosilylation/RCM/protodesilylation of dienynes allowed us to complete the total synthesis of (-)-pironetin, which was found to display plant-growth-regulatory as well as immunosuppressive activities.

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

Dr. Stellios Arseniyadis | Honestly, I have the feeling that I have learnt more than I have achieved, so hopefully my most important contribution to science is still to come. If I had to pick, though, I would probably choose the development of our enantioselective acylating agent for the kinetic resolution of amines, a project which was started during my thesis and that is still ongoing in the group. Another favorite is the implementation of the palladium-catalyzed asymmetric allylic alkylation reaction to cyclic dienol carbonates, which allows...
straightforward and highly enantioselective access to a wide variety of chiral heterocyclic scaffolds, including butenolides, butyrolactones and furanones, all bearing an all-carbon quaternary stereogenic center. Finally, I am also particularly fond of our DNA-based asymmetric catalysis project, which is turning out to be very exciting. Indeed, the predictable nature of nucleic acid hybridization offers a simple and cutting-edge platform to program assemblies with specific functions. Puzzlingly, many hurdles still prevent full exploitation of the power of DNA in asymmetric catalysis; however, we aim to bring DNA to everyone’s bench.
The Editors of SYNTHESIS, SYNLETT, SYNFACS and SYNFORM, and the Thieme Chemistry team met on June 20th and 21st in the beautiful town of Saint-Émilion, in the southwest of France. It was obviously a pure coincidence that Saint-Émilion is renowned worldwide for its excellent wine production: the Editors, in fact, selected Saint-Émilion as the meeting locale only because of its peaceful countryside and the beauty of the landscape.

Inspired by the peaceful and relaxing atmosphere, the Editorial Boards and the Thieme Chemistry team gave life to one of the most productive meetings ever. A number of exciting editorial novelties were approved, some of them specifically concerning SYNFORM, which is going to become “eFirst”: within a few months, in fact, SYNFORM articles will begin to be published individually online on Thieme Chemistry’s new SYNFORM website (https://www.thieme.de/en/thieme-chemistry/journals-synform-54850.htm), as soon as they are ready. Furthermore, SYNFORM will be further enriched by News Articles covering the most exciting papers published in SYNLETT and SYNTHESIS, thus giving additional visibility and impact to Thieme Chemistry authors. The traditional downloadable monthly pdf format will continue to be published, but our readership is advised to connect frequently to our website in order to read the newest individual SYNFORM articles “as soon as published”!

Concerning SYNLETT and SYNTHESIS, let me just mention that a new, very appealing layout will be launched in January 2015, and it’s not the only exciting news on Thieme Chemistry’s journals. Make sure that you check the new website at https://www.thieme-chemistry.com frequently to find out how our journals are evolving and developing.

Below you will find the group picture that was taken on the top of the Dune of Pyla. The friendly atmosphere and smiling faces you will clearly detect in the picture were facilitated exclusively by the fantastic scenery, and have absolutely nothing to do with the different Chateau wines produced in the region. In fact, the Thieme Chemistry Editors remained entirely focused on their professional duties throughout the meeting; there was no room at all for any liquid distraction. It’s a tough life for Editors…
SYNFORM 2014/10
is available from September 17, 2014

In the next issues:

SYNSTORIES

- An Insight of Silver-Catalyzed Hydroazidation for the Thriving Synthesis of Vinyl Azides
  (Focus on an article from the current literature)

- CpRu-Catalyzed Carbene Insertions into Epoxides: 1,4-Dioxene Synthesis via S,1-like Chemistry with Retention of Configuration
  (Focus on an article from the current literature)

- Gold-Catalyzed Intermolecular C–S Bond Formation: Efficient Synthesis of α-Substituted Vinyl Sulfones
  (Focus on an article from the current literature)

FURTHER HIGHLIGHTS

SYNTHESIS
Review on: Advancements in Catalytic Asymmetric Intermolecular Ene-Type Reactions
(by X. Feng)

SYNLETT
Account on: Alkynyl Silyl Sulfides as Versatile Thioketene Equivalents
(by C. Spanka, E. Schaumann)

SYNFACS
Synfact of the Month in category “Organo- and Biocatalysis”: Catalytic Enantioselective [2+2] Intermolecular Photocycloaddition

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