

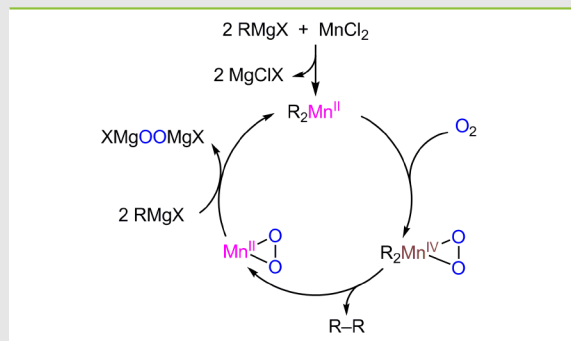
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2009/04

SYNSTORIES

■ **Manganese-Catalyzed Cross-Coupling Reaction between Aryl Grignard Reagents and Alkenyl Halides**



■ **A Diels–Alder Approach to Benzannulated [5,6]-Spiroketal**

■ **Radical Catalysis of Kumada Cross-Coupling Reactions Using Functionalized Grignard Reagents**

CONTACT +++++

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Dear readers,

for the first time this editorial is, to a large extent, autobiographical. In fact, I would like to share with you my excitement for a big change that is going to happen in my life and career: I accepted the NRP (Northern

Research Partnership) Chair in Medical Technologies at the University of Aberdeen, Scotland (UK), and I will soon move to the Highlands with my family. My research group will be based mainly at the Institute of Medical Sciences (IMS, <http://www.abdn.ac.uk/ims>), which opened in 1996 and currently is home to ca. 130 principal investigators leading important biomedical research in a variety of fields. The University of Aberdeen, and particularly the College of Life Sciences and Medicine, recently decided to integrate organic chemistry into the research activities of the IMS, with an emphasis on medicinal chemistry. Furthermore, it was decided to potentiate the chemical research in support of the Biomedical Imaging Center (<http://www.abdn.ac.uk/ims/imaging>), within the frame of the NRP (<http://www.northscotland-research.ac.uk>). I feel lucky for having been chosen to address these exciting scientific challenges, even though I heard that the weather in the Highlands is not as good as in Italy... Despite the presumably bad Scottish weather, I am by no means planning to give up my editorial activity for **SYNFORM** that will continue exactly as it used to be. This is further demonstrated by the three new **SYNSTORIES** featured in this issue of **SYNFORM**, which highlights the exciting discoveries recently reported by the groups of C. D. Bray (UK), G. Cahiez (France) and P. Knochel (Germany).

Enjoy your reading!!!

Matteo Zanda

Editor of SYNFORM

CONTACT ++++

If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it

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A Diels–Alder Approach to Benzannulated [5,6]-Spiroketal

Synlett 2008, 2500–2502; *Synfacts* 2008, 1259 (Synfact of the Month)

■ Spiroketal are found in a huge range of natural products. The simplest examples are found as insect pheromones, with each enantiomer being gender-specific. They are also building blocks in a number of incredibly complex compounds such as spongistatin and okadaic acid. Significant work has been carried out by a number of research groups looking into the synthesis of molecules, where the spiroketal moiety is invariably formed via an acid-catalyzed spirocyclization of a suitable keto-diol precursor or its equivalent.

The hetero-Diels–Alder reaction between *exo*-enol ethers such as 2-methylenetetrahydrofuran and enals/enones, for example acrolein, was first described as early as 1954¹ and, although there have been notable applications of this method being employed in the syntheses by Ireland² and later by Rizzacasa,³ it remains relatively little used.

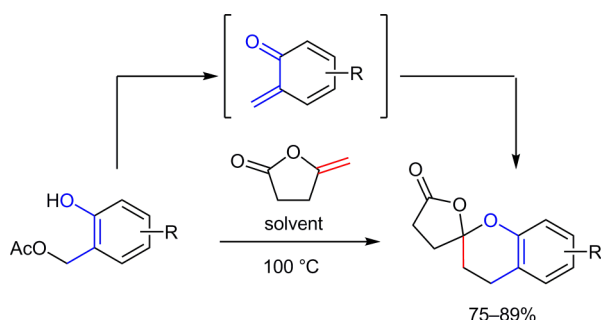
Recently, Dr. Christopher D. Bray from the Queen Mary University of London (UK) reported a novel application of the hetero-Diels–Alder reaction for the synthesis of benzannulated [5,6]-spiroketals from the thermal reaction of 2-hydroxybenzylacetates with γ -methylene- γ -butyrolactone.

According to Dr. Bray, the hetero-Diels–Alder approach offers a number of advantages over the spirocyclization strategy. “Firstly,” he said, “it is more convergent since two halves of the eventual spirocyclic ring system are brought together and two new C–C bonds are formed in one single step.” In contrast, the spirocyclization method requires pre-assembly of

the carbon skeleton which is often lengthy, followed by the formation of the two spiroketal C–O bonds, usually in a subsequent step. “Secondly,” he continued, “whilst spirocyclization is under thermodynamic control, leading in general to products which are doubly anomeric, the hetero-Diels–Alder reaction is under kinetic control which can lead to a completely different ratio of the various possible diastereomeric products.”

Dr. Bray explained that the two disadvantages of the hetero-Diels–Alder method are 1) that the reactions with simple enals/enones are relatively slow, often requiring several days for the cycloadditions to go to completion and 2) that simple *exo*-enol ethers are rather unstable with respect to isomerization to the corresponding *endo*-isomers. “*ortho*-Quinone methides were known to be highly reactive enone partners due to their propensity to rearomatize and so it was thought that, if they were employed as the enone 4π partner, the reactions would be much more facile,” he said. “In an earlier publication,⁴ we had shown that simple *exo*-enol ethers, i.e. those which isomerize readily, could be used in hetero-Diels–Alder reactions with *ortho*-quinone methides to give benzannulated spiroketals. The latter species had been generated under base-induced conditions from 2-hydroxybenzylacetate. However, we wondered if the same *ortho*-quinone methide could be generated under thermal conditions via extrusion of acetic acid, as originally described by Baldwin using these substrates, and whether spiroketals would still be generated if we used an *exo*-enol ether that would not readily isomerize.”

As reported, Dr. Bray simply heated 2-hydroxybenzylacetate with γ -methylene- γ -butyrolactone as the solvent. “The reaction worked the first time it was attempted and gave the desired benzannulated spiroketal in 84% yield. A range of other *ortho*-quinone methide precursors were employed in the reaction. Those could be readily accessed from the corresponding salicyl alcohols, many of which are commercially available.” A variety of different substituents could be placed on the aromatic ring with very little effect on the yield of the spirocycle formed. “Most notably,” explained Dr. Bray, “electron-withdrawing substituents were tolerated. This is important since spirocyclization routes to benzannulated spiroketals



R = H, 4-Me, 4-OAc, 4-CO₂Me, 4-Cl, 5-Me, etc.

can be problematic when the alcohol is a phenol bearing an electron-withdrawing group, since the nucleophilicity of the oxygen is greatly diminished when compared to an aliphatic alcohol. This can open the way for other eliminative reaction pathways to occur. Overall, this method provides a rapid and experimentally simple entry to benzannulated spiroketals,” concluded Dr. Bray. Work in the Bray laboratories is ongoing to further explore the scope of these and related reactions as well as their potential synthetic and biological applications. ■

Matteo Zanda



Dr. C. D. Bray

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- (3) M. El Sous, D. Ganame, P. A. Tregloan, M. A. Rizzacasa *Org. Lett.* **2004**, *6*, 3001.
- (4) C. D. Bray *Org. Biomol. Chem.* **2008**, *6*, 2815.

INFORMATION + + + +

How many resources do you need to get the full picture?

Labels on puzzle pieces include: Synthetic Path, Formulations (e.g., 'tabl. 5 mg, 10 mg, 20 mg, 40 mg'), References (e.g., 'US 4 444 784 (Merck)'), and various chemical structures and names (e.g., Simvastatin, Ranbaxo, Lipovon).

**Just one –
Pharmaceutical Substances!**

Syntheses – Patents – Applications

Manganese-Catalyzed Cross-Coupling Reaction between Aryl Grignard Reagents and Alkenyl Halides

Org. Lett. **2008**, *10*, 5255–5256; *Synfacts* **2009**, 189 (Synfact of the Month)

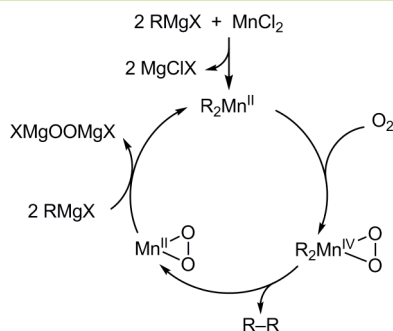
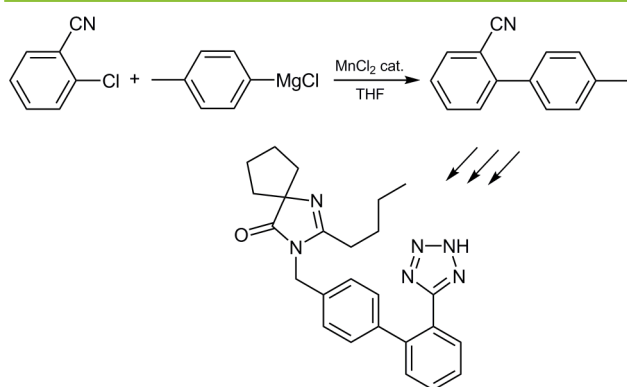
In these last years, sustainable development has led organic chemists to search for less expensive and more eco-friendly reactions. As an example, in the field of transition-metal-catalyzed cross-coupling reactions, a very important effort was made to replace palladium or nickel by iron. Manganese is also an interesting candidate (*Chem. Rev.* **2009**, *109*, 1434). A very efficient manganese-catalyzed aryl–aryl coupling was described some years ago (*Synthesis* **1999**, 2138). It is applied for on industrial scale for the production of an intermediate used in the synthesis of Irbesartan®, an antihypertensive drug from Sanofi Aventis.

However, until now the scope of application of manganese-catalyzed coupling reactions was limited to a few classes of activated organic halides. Recently, Dr. Gérard Cahiez, Director of Research at the CNRS (Paris, France), and coworkers showed that with manganese the reductive elimination step is

clearly more difficult to achieve than with palladium or nickel (*J. Am. Chem. Soc.* **2007**, *129*, 13788). In case of the aryl–aryl coupling it only occurs if manganese is oxidized [Mn(II) → Mn(IV)].

Now, the group of Dr. Cahiez has reported the first example of coupling with nonactivated organic halides. “We believe this new piece of research is important,” said Dr. Cahiez, “because it shows that reductive elimination slowly takes place between 20–50 °C. It is very promising and we hope that in the future it will be possible to develop more manganese-catalyzed cross-coupling reactions as an alternative to the classical palladium or nickel procedure.”

Matteo Zanda



About the authors



Dr. G. Cahiez

Gérard Cahiez received his PhD in 1973 at the University Pierre and Marie Curie (Paris VI) under the supervision of Professor Jean François Normant on the carbocupration of terminal alkynes (vinyl copper reagents). Then, he joined the CNRS. After a post-doctoral year in the Roussel Uclaf Laboratories (now Sanofi Aventis) on the chemistry of steroids, he returned to the

University Pierre and Marie Curie and, in 1980, he was promoted Director of Research at the CNRS. Then, he moved to the Ecole Supérieure de Chimie Organique et Minérale (ESCOM, Cergy-Pontoise) in 1993. From 1993–2008 he was Director of Research at the CNRS and Professor of Chemistry at ESCOM. Since 2000 until recently he was also Director of the UMR 8123, a joint research unit CNRS-University of Cergy-Pontoise–ESCOM. In June 2009 he will be moving to the University of Paris 13, as Director of Research at the CNRS, to constitute a new research team on organometallic

chemistry. The research developed since 1973 dealt with the use of organometallic reagents in organic synthesis and especially with the development of the chemistry of organomanganese reagents. His current interest is still focused on organo-manganese chemistry but more generally on the search for new highly selective organometallic reactions, in particular Mn-, Co-, and Fe-catalyzed cross-coupling reactions, involving no toxic and expensive metal or additive.



Dr. O. Gager

Olivier Gager was born in Versailles (France) in 1978. In 2002, he graduated from the Ecole Supérieure de Chimie Organique et Minérale (ESCOM, Master's degree in Chemistry and Chemical Engineering) and the University of Cergy-Pontoise (Master's degree in organic chemistry). He received his PhD degree in 2005 from the University of Cergy-Pontoise under the supervision of Dr. G. Cahiez. His research focused on the

stereoselective iron-catalyzed coupling reaction between Grignard reagents and enol phosphates. Currently, he is a researcher for R&D projects in the group of Dr. G. Cahiez.

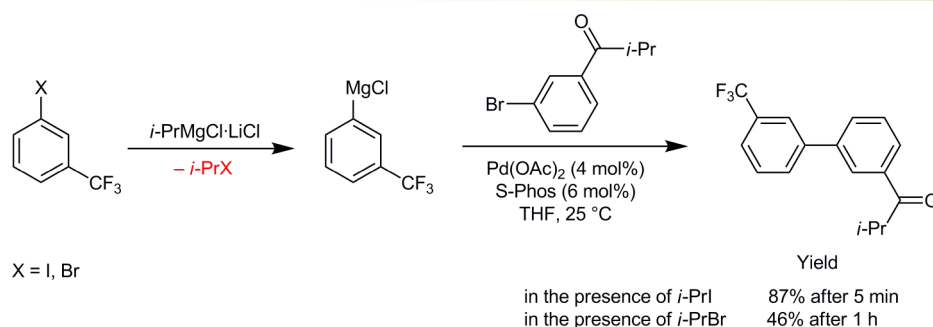


Dr. F. Lecomte

Fabien Lecomte was born in Chateauroux (France) in 1978. He graduated from the Ecole Nationale Supérieure de Chimie Montpellier (ENSCM) in 2001. Then, he received his PhD degree in 2005 from the University of Cergy-Pontoise under the guidance of Dr. G. Cahiez. His research focused on the mechanism and applications of manganese-catalyzed cross-coupling reactions between Grignard reagents and aryl or vinyl halides. After two years of postdoctoral studies in the laboratory of Professor S. Hanessian at the University of Montréal (Canada) on total synthesis of natural compounds, he joined UCB-Celltech (Slough, UK) as a research scientist in medicinal chemistry.

Radical Catalysis of Kumada Cross-Coupling Reactions Using Functionalized Grignard Reagents

Angew. Chem. Int. Ed. **2009**, *48*, 205–209



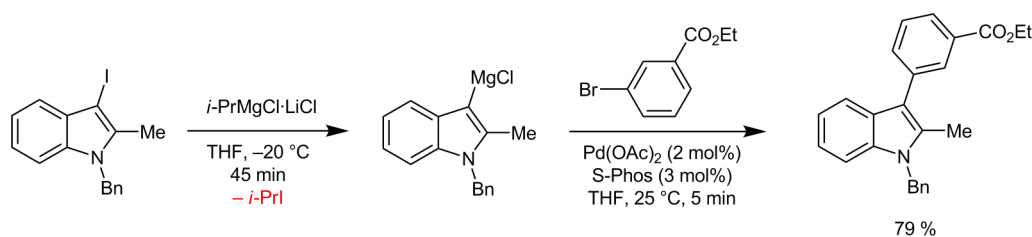
■ The synthesis of complex molecular frameworks using economically and environmentally sustainable methodologies is becoming an absolute research priority in organic chemistry. The Kumada cross-coupling allows a direct Pd-catalyzed carbon–carbon bond formation between unsaturated halides and organomagnesium reagents (without further transmetalations) and is therefore a highly atom-economical cross-coupling reaction. Recently, the group of Professor Paul Knochel from the Ludwig Maximilians University Munich (Germany) described a novel strategy that makes it possible to perform a Kumada cross-coupling via radical catalysis at room temperature, using short reaction times and inexpensive reagents like aryl bromides, including functionalized ones, in the presence of an alkyl iodide.

“In recent years,” said Professor Knochel, “our group has developed several methods for the preparation of functionalized Grignard reagents. A wide range of polyfunctional organomagnesium compounds has become available through halogen–magnesium exchange reactions (*Angew. Chem. Int. Ed.* **2003**, *42*, 4302), directed metalations using magnesium amides

(*Angew. Chem. Int. Ed.* **2006**, *45*, 2958), or the direct magnesium insertion into aryl halides in the presence of LiCl (*Angew. Chem. Int. Ed.* **2008**, *47*, 6802). In most instances, however,” he continued, “these Grignard reagents could not be used directly in transition-metal-catalyzed cross-coupling reactions due to their instability at the temperatures required for the coupling reactions and were, therefore, transmetalated to the corresponding zinc reagents prior to the cross-coupling reaction.”

Inspired by the work of Buchwald, who demonstrated the feasibility of the cross-coupling of aryl iodides with functionalized arylmagnesium reagents by using an appropriate phosphine ligand at low temperatures (–20 to –65 °C; R. Martin, S. L. Buchwald *J. Am. Chem. Soc.* **2007**, *129*, 3844), Professor Knochel and his coworkers envisioned that this methodology could be useful for their own research and presumably extended to readily available aryl bromides.

“During our own studies,” confirmed Professor Knochel, “we observed a remarkable rate acceleration of these Kumada couplings, when the arylmagnesium reagent was prepared by



I/Mg exchange using *i*-PrMgCl·LiCl. This unexpected effect was finally attributed to the presence of *i*-PrI obtained as side product during the I/Mg exchange. Mixing a Grignard reagent, prepared by insertion or Br/Mg exchange, with *i*-PrI or a range of other alkyl iodides led to similar rate enhancements." According to Professor Knochel, this *i*-PrI-accelerated Kumada cross-coupling allows a rapid reaction (25 °C, average reaction time: 5 min) of a wide range of functionalized aryl- and heteroarylmagnesium reagents with aryl bromides, it avoids

transmetalation of readily available Grignard reagents to zinc or boron intermediates, and it leads to a more atom-economical Kumada cross-coupling reaction. "We assume these reactions proceed via a radical pathway. Currently," concluded Professor Knochel, "we are studying the effect of alkyl iodides in other palladium-catalyzed coupling reactions." ■

Matteo Zanda

About the authors



Prof. P. Knochel

Paul Knochel was born in 1955 in Strasbourg (France). He did his undergraduate studies at the University of Strasbourg (France) and his PhD at the ETH Zürich (Switzerland) with Professor D. Seebach. He spent four years at the CNRS at the University Pierre and Marie Curie in Paris (France) with Prof. J.-F. Normant and one year of post-doctoral studies at Princeton University (USA) in the laboratory of Prof.

M. F. Semmelhack. In 1987, he accepted a position as Assistant Professor at the University of Michigan at Ann Arbor (USA). In 1991, he became Full Professor at this University, and in 1992 he moved to the Philipps University of Marburg (Germany) as C4-Professor in Organic Chemistry. In 1999, he moved to the Chemistry Department of the Ludwig Maximilians University in Munich (Germany). His research interests include the development of novel organometallic reagents and methods for use in organic synthesis, asymmetric catalysis and natural product synthesis.



Dr. G. Manolikakes

Georg Manolikakes was born in Ebersberg (Germany) in 1979. After studies at the Ludwig Maximilians University Munich (Germany) and the University of Oxford (UK), he obtained his diploma in 2005. He carried out his PhD studies under the supervision of Professor P. Knochel at the Ludwig Maximilians University Munich between 2005–2009. He is currently a postdoctoral research assistant with Professor P. Baran at The Scripps Research Institute (USA), supported by a DAAD fellowship.

COMING SOON ► ► COMING SOON ► ►

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In the next issues:

SYNSTORIES ■ ■ ■ ■ ■

■ Structure of Reactive Intermediates of Organocatalysis

(Focus on an article from the current literature)

■ Organocatalytic Asymmetric Alkylation of Aldehydes by S_N1 -Type Reaction of Alcohols

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: The Chemistry of Deprotonated α -Aminonitriles

(by T. Opatz)

SYNLETT

Cluster on "Bifunctional Catalysis" in issue 10/2009

SYNFACTS

Synfact of the Month in category "Organo- and Biocatalysis": Fluorinated Designer Organocatalyst

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