Focus on the Valencia Fluorine Days: 3rd International Symposium on Organofluorine Compounds in Biomedical, Materials and Agricultural Sciences, May 20–24, 2012, Valencia (Spain)

Preparation of AlkylMagnesium Reagents from Alkenes through Hydroboration and Boron–Magnesium Exchange

Urea Activation of $\alpha$-Nitro-diazoesters: An Organocatalytic Approach to N–H Insertion Reactions

Valencia Technology Park at night
Dear readers,

I am writing while the 2012 Olympic Games in London are heading towards the end. We are witnessing a fantastic event, although for me it is a bit of a struggle to watch the Games on the BBC, because I am supporting Italy and 90% of the time is dedicated to the GB team. Fair enough. I wonder whether academic chemists should also compete in some kind of Chemistry Olympic Games every four years or so. I am not talking about the existing Chemistry Olympiads for students; this would be for professional academic chemists, possibly open to chemists in industry, although I suspect they would be too busy to join in. It would be a lot of fun, I think! Who would win the gold medal of Synthetic Organic Chemistry? And what about the Lab-based Organic Chemistry competition? And that for the Best Bioactive Compound? Some of the big names may not even qualify for the semi-finals. I am not sure whether and how this could be actually done, but definitely it would be much more fun than the REF-Assessment or other evaluation platforms meant to measure the quality of our work. Not to mention the thrill of it all! If anybody has an idea, please let me know – we could ask Thieme Chemistry to organize the first Chemistry Olympic Games in Stuttgart. No doubts about the logo: it would be five round-bottomed flasks...

It may not be Olympic but this issue of SYNFORM is very interesting too! The first SYNSTORY is focused on a new methodology developed by Professor B. Breit (Germany) for preparing Grignard Reagents via boron-magnesium exchange. The second article reports on the α-amination of a phenylglycine synthon prepared from α-nitrodiazoesters (Prof. A. E. Mattson, USA). Last but not least, this issue is closed with a report on the recent “Valencia Fluorine Days” Symposium, which gathered together a large number of fluorine chemists in the beautiful city in the south-east of Spain.

Enjoy your reading!

Matteo Zanda

Editor of SYNFORM

SYNSTORIES

Preparation of Alkylmagnesium Reagents from Alkenes through Hydroboration and Boron–Magnesium Exchange ................. A87

Urea Activation of α-Nitrodiazoesters: An Organocatalytic Approach to N–H Insertion Reactions .................................. A91

Focus on the Valencia Fluorine Days: 3rd International Symposium on Organofluorine Compounds in Biomedical, Materials and Agricultural Sciences, May 20–24, 2012, Valencia (Spain) ........................................ A93

COMING SOON ............................................... A95

CONTACT

If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it
The direct synthesis of organomagnesium reagents by insertion of magnesium metal into the C–X bond of alkyl halides (Grignard reaction) is one of the most popular and used reactions in organic chemistry. However, despite its usefulness, nearly every synthetic chemist has experienced its drawbacks, consisting of a certain degree of capriciousness and the presence of a number of side reactions, particularly with sterically hindered or functionalized compounds.

During the last few years, the research group of Bernhard Breit from the Institut für Organische Chemie und Biochemie at the University of Freiburg (Germany) has developed stereospecific SN’- and SN-type reactions of organomagnesium compounds catalyzed either by copper or zinc salts (Scheme 1). These methods have proved to be valuable synthetic alternatives for enolate alkylation chemistry to access tertiary and quaternary stereogenic carbons in a stereospecific and reliable fashion.

“The application of these methods in total synthesis (Scheme 2) challenged us with the preparation of highly functionalized alkyl Grignard reagents which proved cumbersome in some cases due to side reaction such as homocoupling,” said Professor Breit.

“This made us wonder whether there are alternatives for alkyl Grignard generation,” he continued. “We were inspired by the beautiful work of Professor Paul Knochel, who has developed an efficient method for the preparation of dialkyl-zinc reagents from the corresponding trialkylboranes through a boron–zinc exchange reaction.” Since the corresponding boranes are readily available through anti-Markovnikov hydroboration of alkenes, which occurs with known and reliable regio- and stereoselectivity, this could also be a very valuable synthetic step towards alkylmagnesium reagents, provided that a corresponding boron–magnesium exchange...
reaction is possible. Professor Breit explained that a former PhD student, Christian Rein (now at BASF), searched the literature for previous work on this matter and found an important early contribution from Murahashi et al. They explored the use of a C5-diGrignard reagent to effect a boron–magnesium exchange starting from trialkylboranes,” said Professor Breit. “However, the method suffers from three major limitations: First, it is limited to the generation of primary alkyl Grignard reagents starting from mono-substituted alkenes, since steric hindrance inhibits the boron–magnesium exchange reaction. Second, the method is restricted to the use of trialkylboranes. Third, the use of the more stable alkylboronic esters obtained through rhodium-catalyzed hydroboration would be highly desirable,” he finished.

This was the starting point of the diploma work and finally PhD thesis of Markus Reichle. “Markus started by looking at the corresponding C4-diGrignard reagent,” explained Professor Breit. “We speculated that formation of the five-membered spiroboronates would be faster, hence accelerating the boron–magnesium exchange reaction.” This indeed proved to be the case. Furthermore, he was then able to apply, for the first time, the more stable alkylboronic esters derived from

**Scheme 2 Application of functionalized Grignard reagents in total synthesis projects completed by the Breit group**
metal-catalyzed hydroboration of alkenes with pinacolborane to generate both primary alkyl and secondary alkyl organomagnesium reagents (Scheme 3). The boron–magnesium exchange was monitored by $^{11}$BNMR and in all cases high yields of the corresponding Grignard reagents were obtained,” remarked Professor Breit. Functional groups such as silyl ethers and tert-butyl esters were tolerated. Professor Breit concluded, “The resulting Grignard reagents could be applied in a wide range of alkylations, 1,2-additions as well as iron-, copper- and palladium-catalyzed cross-coupling reactions. Now, the method is under exploration in total synthesis projects going on in my group.”

**Scheme 3** Alkyl-Grignard reagents from alkenes through hydroboration and B-Mg-exchange reaction

Matteo Zanda

**REFERENCES**


About the authors

Bernhard Breit studied chemistry at the University of Kaiserslautern (Germany) where he obtained his doctorate in 1993 with Professor Manfred Regitz. After postdoctoral training with Professor Barry Trost at Stanford University (USA), he worked in Marburg (Germany) with Professor R. W. Hoffmann to obtain his habilitation in 1998. In 1999 he was appointed as an Associate Professor at the University of Heidelberg (Germany). Since 2001 he has been a Full Professor of Organic Chemistry at the Albert-Ludwigs-Universität Freiburg i. Brsg. His current research interests focus on the development of new concepts and methodology for organic synthesis, including organometallic reagents and homogeneous catalysis.

Markus Reichle was born in Weingarten (Germany) in 1982. He studied chemistry in Freiburg (Germany) and at Stanford University (USA), where he gained his first experience in research by working on palladium-catalyzed asymmetric allylic alkylation in the group of Professor Barry Trost. He then obtained his diploma at the Albert-Ludwigs-Universität Freiburg in 2008 in the group of Professor Bernhard Breit, where he continued his research on developing the boron-magnesium exchange to obtain his PhD in 2012.
α-Aryl-glycine derivatives are important α-amino acids present in a number of natural and biologically active molecules. Recently, the group of Professor Anita E. Mattson from The Ohio State University (Columbus, Ohio, USA) devised a new synthetic strategy for accessing α-aryl-glycines, based on the use of α-nitrodiazo esters as building blocks. Despite limited accounts on the chemistry of α-nitrodiazo compounds, these nitrocarbene precursors have interesting reactivity and have been shown to undergo cyclopropanation reactions as well as O–H insertion reactions under transition-metal catalysis. “To the best of our knowledge, non-covalent organocatalysts have not been previously explored to activate α-nitrodiazo esters,” said Professor Mattson. “Our desire to develop complementary reactions to those typically catalyzed by metals led us to the use of hydrogen bond donor ureas and thioureas in N–H insertion chemistry,” she continued.

Professor Mattson explained that Sonia So, a third-year graduate student, began initial studies with the synthesis of α-nitrodiazo ester 1, which was easily accessed following a literature procedure. “The nitrodiazo esters were stable, easy to work with, and synthesized on a 10 gram scale, although any diazo compound should be handled with care,” Professor Mattson explained.

“With the nitrodiazo compound in hand, our initial experiments began by heating the reaction mixtures with aniline to 80 °C,” she continued. “We proposed that N–H insertion into aniline could lead to nitro ester 3.” Professor Mattson explained how the consumption of the starting diazo compound had been observed by 1H NMR spectroscopy, but they had difficulty isolating the product. “We found that some of the products were slightly unstable to silica, so a short silica gel or basic alumina column helped in isolating the products in good yield,” she said. “We were finally able to isolate compound 4 along with compound 5 and determined the structure following NMR and mass spectrometry studies. We deduced that initial N–H insertion into aniline formed ester 3; however, extrusion of NO2 then allowed for a second molecule of aniline to add forming α-amino-α-aryl ester 4.” She went on to explain how, under optimized reaction conditions, they were able to minimize the formation of compound 5. Extension of this chemistry to include three-component coupling reactions allowed for selective insertion into 4-fluoroaniline in the presence of aniline.

“A short catalyst screen determined that boronate urea 2a was the most active catalyst while boronate urea 2b, containing pinacol ligands, was much less active, perhaps due to issues of solubility,” said Professor Mattson. Thiourea 2c, a catalyst generally more active than urea 2d, was found to give poorer yields of the desired product, most likely due to decomposition of the catalyst.

“The elusive nitrocarbene intermediate has yet to be observed and we are currently investigating the possibility of the formation of a hydrogen bond donor stabilized nitrocarbene,” continued Professor Mattson.

“This initial report introduces a new area of hydrogen bond donor catalyzed reactions, breaking from traditional activation of carbonyls or nitroalkenes. Chiral catalysts are currently being investigated to afford three-component coupling products in an enantioselective fashion. Further extension of this chemistry could include dipolar cycloadditions as well as C–H activation reactions,” she concluded.
Reactions performed using 10 equiv of online at a concentration of 1 M (for experimental details see Supporting Information of the original publication).

\(^a\) Isolated yield.

\(^b\) An average of \(k_{\text{obs}}\) determined at multiple catalyst loadings (see Supporting Information of the original publication).

**About the authors**

From left: Prof. A. E. Mattson, S. S. So
More than 145 scientists from 15 countries contributed to the recent “Valencia Fluorine Days” symposium, held in sunny Valencia (Spain) on from May 20–24, 2012, with nine plenary lectures, 41 invited lectures and 56 posters reflecting the progress in different fields and topics of organofluorine chemistry.

The aim of the symposium was to provide an overview of current directions in all research areas of fluorine chemistry and it actually provided a unique opportunity to contribute to discussions on the most recent developments in fluorine chemistry, including biomedical applications, materials and nano science, agrochemistry, PET imaging and more. The meeting saw significant participation by companies, such as Syngenta, Ely Lilly, Janssen and many more.

“Valencia Fluorine Days’ forms part of an initiative by Professor Manfred Schlosser and Professor Renzo Ruzziconi, who first considered the idea and then organized the first ‘Fluorine Days’ symposium, held in Perugia in 2001,” explained the chief organizer, Professor Santos Fustero from the University of Valencia. “Taking the ‘Perugia Fluorine Days’ as a model, Professor Schlosser, together with Professors K.-H. Altmann, P. Maienfisch, and K. Müller organized the ‘Fluorine in the Life Sciences’ symposium in Bürgenstock (July 6–9) in 2003. In July 2010, R. Ruzziconi and M. Schlosser organized the second ‘Perugia Fluorine Days’ (July 11–15), which I attended as a participant. Both prompted me to organize ‘Valencia Fluorine Days’ and finally I accepted.”

The final result was spectacular and the ‘Fluorine Days’ meeting, which was superbly organized in Valencia, holds promise to become a classic event in fluorine chemistry. “Professor Tamejiro Hiyama and Professor Koichi Mikami took up the idea, and they have announced the first Fluorine Days symposium ‘TokyoTech Fluorine Days’ to be held for the first time in a non-European country in April 2013,” said Professor Fustero. The next European ‘Fluorine Days’ will be organized in Bordeaux (France) in 2014.
Group picture with Professor S. Fustero (third from left) and Professor K. Mikami (center)
Effects in Palladium-Catalyzed Enantioselective C(sp^3)–H Functionalization is available from SYNFORM.

In the next issues:

SYNSTORIES

- Chiral Monodentate Phosphines and Carboxylic Acids: Cooperative Effects in Palladium-Catalyzed Enantioselective C(sp^3)–H Functionalization

P137, Poster Presented at the ISACS-7 Conference, Edinburgh (UK), June 12–15, 2012 (Focus on a poster presented at an international conference)

- B(OCH_2CF_3)-Mediated Amidation and Transamidation Reactions

P48, Poster Presented at the ISACS-7 Conference, Edinburgh (UK), June 12–15, 2012 (Focus on a poster presented at an international conference)

FURTHER HIGHLIGHTS

SYNTHESIS

Special Topic on “Aziridines and Azetidines/Small Rings” in issue 18/2012

SYNLETT

Account on: The Application of Bis(trifluoroacetoxyl)iodo)benzene (PIFA) in the Synthesis of Nitrogen-Containing Heterocycles (by E. Dominguez, I. Tellitu)

SYNFACTS

Synfact of the Month in category “Synthesis of Natural Products and Potential Drugs”: Synthesis of (--)-Teucvidin

CONTACT

Matteo Zanda,
NRP Chair in Medical Technologies
Institute of Medical Sciences
University of Aberdeen
Foresterhill, Aberdeen, AB25 2ZD, UK
and C.N.R. – Istituto di Chimica del Riconoscimento Molecolare, Via Mancinelli, 7, 20131 Milano, Italy,
e-mail: Synform@chem.polimi.it, fax: +39 02 23993080

Editor
Matteo Zanda, NRP Chair in Medical Technologies, Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK and C.N.R. – Istituto di Chimica del Riconoscimento Molecolare, Via Mancinelli, 7, 20131 Milano, Italy
Editorial Assistant: Alison M. Sage
synform@chem.polimi.it, phone: +39 02 23993080

Editorial Office
- Managing Editor: Susanne Haak, susanne.haak@thieme.de, phone: +49 711 8931 786
- Scientific Editor: Selena Boothroyd, selena.boothroyd@thieme.de
- Scientific Editor: Stefanie Baumann, stefanie.baumann@thieme.de, phone: +49 711 8931 776
- Assistant Scientific Editor: Michael Binanzer, michael.binanzer@thieme.de, phone: +49 711 8931 768
- Senior Production Editor: Thomas Loop, thomas.loop@thieme.de, phone: +49 711 8931 778
- Production Editor: Helene Deufel, helene.deufel@thieme.de, phone: +49 711 8931 929
- Production Editor: Thorsten Schön, thorsten.schoen@thieme.de, phone: +49 711 8931 781
- Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
- Marketing Manager: Julia Stützner, julia.stutzner@thieme.de, phone: +49 711 8931 771
- Postal Address: SYNTHESES/SYNLETT/SYNFACTS, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, phone: +49 711 8931 744, fax: +49 711 8931 777
- Homepage: www.thieme-chemistry.com

Publication Information
SYNTHESES will be published 12 times in 2012 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESSES, SYNLETT and SYNFACTS.

Publication Policy
Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

Ordering Information for Print Subscriptions to SYNTHESSES, SYNLETT and SYNFACTS
The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
To order: customerservice@thieme.com or use the Web site facilities at www.thieme-chemistry.com, phone: +1 212 760 8888
Order toll-free within the USA: +1 800 782 3488
Fax: +1 212 947 1112
Airfreight and mailing in the USA by Publications Expediters Inc., 300 Meacham Ave., Elmont NY 11003. Periodicals postage paid at Jamaica NY 11431.
Europe, Africa, Asia, and Australia: Thieme Publishers Stuttgart, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.
To order: customerservice@thieme.de or use the Web site facilities at www.thieme-chemistry.com, phone: +49 711 8931 421; Fax: +49 711 8931 410
Current list prices are available through www.thieme-chemistry.com.

Online Access via Thieme-connect
The online versions of SYNTHESSES, SYNLETT and SYNFACTS are available through Thieme-connect (www.thieme-connect.com/products) where you may also register for free trial accounts. For information on multi-site licenses and pricing for corporate customers as well as backfiles please contact our regional offices:
The Americas: esales@thieme.com, phone: +1 212 584 4695
Europe, Africa, Asia, and Australia: products@thieme.de, phone: +49 711 8931 407

Manuscript Submission to SYNTHESSES and SYNLETT
Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at www.thieme-chemistry.com. Use of the Word template helps to speed up the refereeing and production process.

Copyright
This publication, including all individual contributions and illustrations published therein, is legally protected by copyright for the duration of the copyright period. Any use, exploitation or commercialization outside the narrow limits set by copyright legislation, without the publisher’s consent, is illegal and liable to criminal prosecution. This applies translating, copying and reproduction in printed or electronic media forms (databases, online network systems, Internet, broadcasting, telecasting, CD-ROM, hard disk storage, microcopy edition, photomechanical and other reproduction methods) as well as making the material accessible to users of such media (e.g., as online or offline backfiles).

Copyright Permission for Users in the USA
Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Georg Thieme Verlag KG Stuttgart – New York for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of US$ 25.00 per copy of each article is paid directly to CCC, 22 Rosewood Drive, Danvers, MA 01923, USA, 0341-0501/02.