

SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2010/06

SYNSTORIES ■ ■ ■ ■

■ **Stereoselective Addition of Grignard Reagents to New P-Chirogenic N-Phosphinoylimines**



■ **First Catalytic Enantioselective Dieckmann-Type Annulation**

■ **SYNTHESIS/SYNLETT**
Advisory Board Focus: Professor Carmen Nájera (University of Alicante, Spain)

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Dear readers,

This issue of **SYNFORM** presents a new feature: the “Advisory Board Focus” which is a portrait of the 25 Advisory Board Members of **SYNTHESIS** and **SYNLETT**. The protagonists provide their biographical sketch, and answer several questions about themselves and their professional views and achievements. This first Focus article features Professor Carmen Nájera from the University of Alicante (Spain), an inspiring example of successful women in chemistry.

The issue is completed by two **SYNSTORY** articles, the first one covering the enantioselective Dieckmann-type annulation reaction recently developed by Dr. C. G. Frost and his group (UK), and the second one highlighting a novel class of phosphorus-based auxiliaries for the addition of nucleophiles to imines, developed by Professor F. Colobert and co-workers (France).

Enjoy your reading!

Matteo Zanda

Editor of SYNFORM

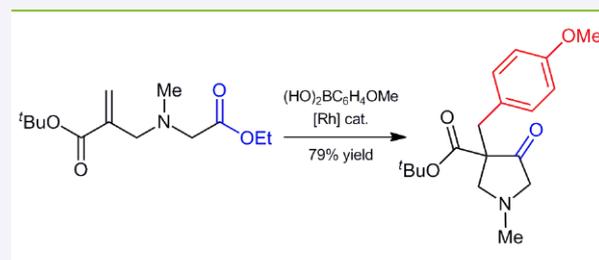
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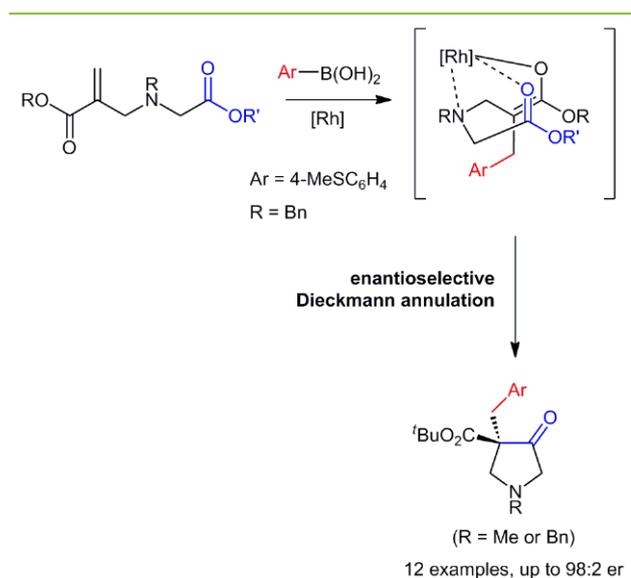
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First Catalytic Enantioselective Dieckmann-Type Annulation

Angew. Chem. Int. Ed. **2010**, *49*, 1825–1829

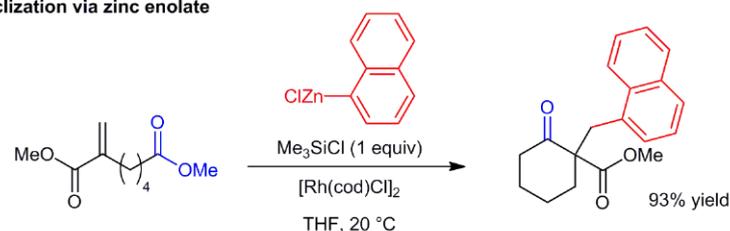
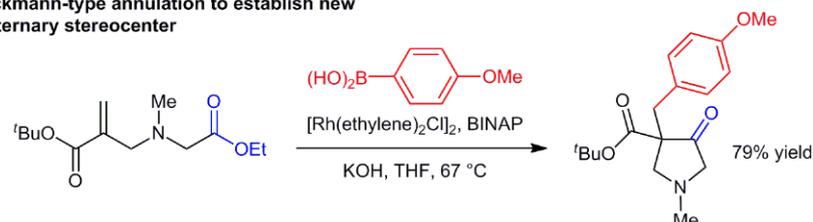
■ The enantioselective synthesis of heterocycles with quaternary stereogenic centers by two consecutive catalytic C–C bond-forming processes is very demanding. Recently, the group of Dr. Christopher G. Frost from the University of Bath (UK) described the first example of a catalytic enantioselective Dieckmann-type annulation to form pyrrolidines with quaternary stereogenic centers (up to 98:2 er).



According to Dr. Frost, the principal challenge in this domino catalytic asymmetric process was that the enantioselectivity is determined at the acylation step and not, as is common in enantioselective conjugate additions, at the insertion step. “The background for this work came from our previous studies on the asymmetric arylation of activated alkenes via enantioselective protonation,” confirmed Dr. Frost. “Along with the groups of Darses, Genêt and Reetz, we had published a novel catalytic enantioselective synthesis of α -amino esters and succinic esters via a tandem 1,4-addition–enantioselective protonation,” he continued. “As part of this study we were investigating the role of the pendant carbonyl functionality in stabilizing the transition state leading to high enantioselectivi-

ty, and to our initial surprise we observed low yields of the Dieckmann-type annulation (with low enantioselectivity) along with the usual protonation product.” Despite several months of work Dr. Frost and his coworkers were not able to optimize this reaction to afford the Dieckmann annulation as the major product with arylboronic acids. However, the use of highly reactive arylzinc halides as the organometallic donors did increase the efficiency of the tandem process. “The transformation led to the facile preparation of substituted cyclopentanones and cyclohexanones containing quaternary carbon centers under mild conditions and in high yields from acyclic precursors,” explained Dr. Frost (see Scheme on the next page). The products were racemic due to the rapid transmetalation of the arylzinc reagents to afford the zinc enolate.²

“At this time, Jonathan Hargrave was in the final year of his PhD studies working on rhodium-catalyzed conjugate additions when we had the idea to include a coordination site within the substrate,” said Dr. Frost. “It was hoped that a hemilabile functional group would stabilize a reactive intermediate in a suitable conformation for cyclization,” he continued. “Our first attempts at this with an oxygen (or *N*-Boc) linker were unsuccessful. We identified the elimination product as the only product in quantitative yield. On reflection,” said Dr. Frost, “this was not unexpected. Darses and Genêt had reported an elimination pathway in their elegant studies on the rhodium-catalyzed reaction of unactivated Baylis–Hillman adducts with arylboronic acids.”³ In a last throw of the dice, the researchers decided to subtly change the electronic nature of the linker (to a *N*-Me group) in the hope of reducing the formation of elimination product. “We were delighted to see the NMR and discover that the reaction had gone according to plan and the Dieckmann-annulation product was isolated in high yield. By this stage, Jonathan should have been writing up as the funding for his PhD had finished. However, his dedication and enthusiasm for the project led him to carry on and explore the enantioselective process,” said Dr. Frost. “As the majority of researchers in asymmetric catalysis will appreciate, it can be very challenging and time-consuming optimizing a new catalytic, asymmetric reaction, especially when all the compounds you make are novel and

**Rapid cyclization via zinc enolate****Competitive elimination with boronic acids****Dieckmann-type annulation to establish new quaternary stereocenter**

there are no existing protocols for determining enantioselectivities,” he continued. “We were very fortunate in this case. The first attempt at carrying out an enantioselective reaction resulted in close to 90% ee. It turned out that BINAP analogues afforded the best results in our reaction. We did test a large number of ligands and in the majority of cases DIFLUORPHOS (developed by Genêt for asymmetric hydrogenations) gave excellent enantioselectivities. At this stage,” said Dr. Frost, “Jonathan was joined by Joe Allen, a second-year PhD student, to establish the scope of the reaction. Joe tested the *N*-benzyl substrates and got the all-important crystalline product to establish the absolute configuration of the products (X-ray crystal structure carried out by Gabriele Kociok-Köhn).” An interesting observation made by the authors is that enantiopure diene ligands afforded complete conversion to elimination product even with the *N*-Me linker. “Our mechanistic rationale for these observations is shown in the paper. We believe this novel method of catalytic acylation is of significant potential

utility in enantioselective synthesis and further applications are anticipated in the future,” concluded Dr. Frost. ■

Matteo Zanda

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- T. Gendrineau, N. Demoulin, L. Navarre, J.-P. Genêt, S. Darses *Chem. Eur. J.* **2009**, *15*, 4710.

About the authors*Dr. J. D. Hargrave*

Jonathan D. Hargrave received his MChem(Hons) degree from the University of Bath in 2004. In 2008 he was awarded a PhD in organic chemistry with a thesis entitled 'Applications of rhodium-catalysed 1,4-addition reactions in organic synthesis' under the direction of Dr. Christopher G. Frost. He currently occupies a research position within the pharmaceutical company Sterix, focusing on the development of anti-cancer drug targets.

*J. C. Allen*

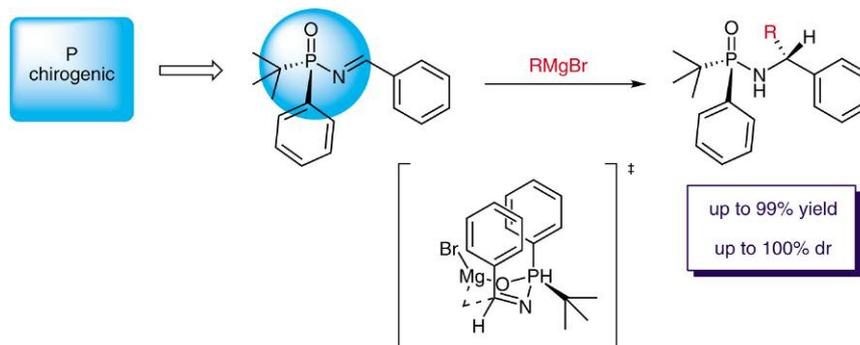
Joseph C. Allen received his MChem(Hons) degree from the University of Leicester (UK) in 2006. He is currently undertaking his PhD with Dr. Christopher G. Frost at the University Of Bath exploring tandem processes triggered by rhodium-catalyzed conjugate addition reactions.

*Dr. C. G. Frost*

Christopher G. Frost completed his BSc(Hons) and PhD (with Jonathan M. J. Williams) at the University of Loughborough (UK). After a postdoctoral fellowship with Professor Philip D. Magnus at the University of Texas at Austin (USA), he joined the Chemistry Department at the University of Bath and in 2007 was promoted to Reader in Organic Chemistry. His interests are in the application of transition-metal catalysis to organic synthesis, collecting fine wine and playing the saxophone.

Stereoselective Addition of Grignard Reagents to New P-Chirogenic *N*-Phosphinoylimines

Chem. Commun. **2010**, *46*, 2139–2141



■ Stereoselective addition of nucleophiles to imines is an efficient method for the synthesis of chiral amines. In particular, imines with electron-withdrawing groups on the nitrogen atom such as *N*-sulfonyl-, *N*-sulfinyl-, and *N*-acylimines have been used extensively in the last decades because of their superior electrophilicity. On the other hand, *N*-phosphinoylimines have emerged more recently as good electrophiles in many reactions. However, despite the extensive use of *P,P*-diaryl- or *P,P*-diethoxy-*N*-phosphinoylimines, only rare examples concerning the introduction of the chirality on the phosphorus atom can be found in the literature (for a recent publication see: M. Benamer, S. Turcaud, J. Royer *Tetrahedron Lett.* **2010**, *51*, 645). Recently, the group of Professor Françoise Colobert, in collaboration with Dr. Alain Wagner, from the University of Strasbourg (France), described a novel strategy to achieve a stereoselective addition of Grignard reagents to *N*-phosphinoylimines, based on the use of the stereogenic *P-tert*-butyl-*P*-phenyl-phosphinoyl auxiliary. The method holds considerable promise for further applications with many more nucleophilic reagents.

“We chose the addition of Grignard reagents to evaluate the degree of asymmetric induction issued from the stereogenic phosphorus atom,” said Professor Colobert. “This method afforded *P*-chirogenic *N*-phosphinoylamines in excellent yields and moderate to excellent diastereomeric ratios.”

“Our preliminary results were quite encouraging, suggesting that this new class of compounds deserves to be further explored especially in the relatively new concept of chirality

transfer from *P*-chirogenic species,” she added. “The equilibrium between reactivity and stability, together with the presence of a stereogenic phosphorus close to the reacting center, makes phosphinoylimines suitable candidates for many synthetic transformations.”

Indeed, this original class of stereogenic inductors could offer an interesting alternative to the widely used *N*-sulfinyl-imines and the methodology disclosed by Professor Colobert opens new perspectives in the synthesis of interesting intermediates such as phosphinoylamines that could be considered as Lewis bases, or chiral amines which are fundamental building blocks in organic synthesis and omnipresent compounds in biology. ■

Matteo Zanda



I. Notar Francesco



Prof. F. Colobert

SYNTHESIS/SYNLETT Advisory Board Focus: Professor Carmen Nájera (University of Alicante, Spain)

■ **Background and Purpose.** From this issue on, *SYNFORM* will from time to time portrait *SYNTHESIS/SYNLETT* Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. In this first *SYNSTORY* with a *SYNTHESIS/SYNLETT Advisory Board Focus*, we present Professor Carmen Nájera from the University of Alicante in Spain.

BIOGRAPHICAL SKETCH



Prof. C. Nájera

Carmen Nájera obtained her BSc at the University of Saragossa (Spain) in 1973 and her PhD at the University of Oviedo (Spain) with J. Barluenga and M. Yus in 1979. She performed postdoctoral work at the ETH Zurich (Switzerland) with D. Seebach, at the Dyson Perrins Laboratory (Oxford, UK) with J. E. Baldwin FRS, at Harvard University (USA) with E. J. Corey, and at Uppsala University (Sweden)

with J.-E. Bäckvall. She was promoted to Associate Professor in 1985 at the University of Oviedo and to Full Professor in 1993 at the University of Alicante. She has held visiting Professorships at the University of Arizona in Tucson (USA), Universidad Nacional del Sur in Bahía Blanca (Argentina), Louis Pasteur University in Strasbourg (France), and Ecole Nationale Supérieure de Chimie de Paris (France). She is co-author of more than 250 papers and 35 reviews and has supervised the work of 26 PhD students. Carmen Nájera is a member of the advisory board of *Synthesis*, *Synlett*, *European Journal of Organic Chemistry*, and *Letters in Organic Chemistry*. She was awarded the “2006 Janssen Cilag Organic Chemistry Prize” from the Spanish Royal Society of Chemistry and the “2006 Rosalind Franklin International Lectureship” from the British Royal Society of Chemistry. She is the co-founder of a new chemical company MEDALCHEMY, S. L. as a spin-off of the University of Alicante.

INTERVIEW

SYNFORM | Professor Nájera, which are your main current research interests?

C. Nájera | Asymmetric metal- and organocatalyzed reactions, palladium-catalyzed carbon–carbon bond-forming reactions, and gold-catalyzed hydroamination reactions.

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

C. Nájera | The use of oxime-derived palladacycles as catalysts, see for example *Synthesis* **2004**, 1713–1718 and *Chem. Rec.* **2006**, 6, 117–132, because they are an excellent source of very reactive palladium nanoparticles in aqueous and organic media.

SYNFORM | Can you mention a recent discovery in the area of organic chemistry that you consider to be particularly important?

C. Nájera | Iron-catalyzed oxidations, see for example *Science* **2010**, 327, 566–571.

SYNFORM | Do you have hobbies, besides chemistry?

C. Nájera | Hiking, reading, cinema, music, and meeting friends.

SYNFORM | What is the main goal in your scientific career?

C. Nájera | To find industrially applicable synthetic procedures. ■

Matteo Zanda



COMING SOON ►► COMING SOON ►►

SYNFORM 2010/07 is available from June 22, 2010

In the next issues:

SYNSTORIES ■ ■ ■ ■ ■

■ Enantioselective Ring Opening of Epoxides by Fluoride Anion

(Focus on an article from the current literature)

■ Three-Component Reaction Using the Bestmann–Ohira Reagent

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: Chiral Phosphoric Acids as Versatile Catalysts for Enantioselective Transformations

(by M. Terada)

SYNLETT

Account on: Large Molecules – Small Energies: Challenges for Contemporary Quantum Chemistry

(by S. Grimme)

SYNFACTS

Synfact of the Month in category “Synthesis of Materials and Unnatural Products”: [Radialene Synthesis](#)

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
Synform@chem.polimi.it
Fax: +39 02 23993080

Editorial Office

- Managing Editor: Susanne Haak,
susanne.haak@thieme.de, phone: +49 711 8931 786
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thorsten.schoen@thieme.de, phone: +49 711 8931 781
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sabine.heller@thieme.de, phone: +49 711 8931 744
- Marketing: Thomas Krimmer,
thomas.krimmer@thieme.de, phone: +49 711 8931 772
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