SYNSTORIES

1,4-Dicarbonyl Compounds via Pd(II)-Catalyzed Carbonylation of C(sp³)–H Bonds

An Efficient Organocatalytic Method for Constructing Biaryls through Aromatic C–H Activation

SYNTHESIS/SYNLETT Advisory Board Focus: Professor Thomas Wirth (Cardiff University, UK)

CONTACT

Your opinion about SYNFORM is welcome, please correspond if you like: marketing@thieme-chemistry.com
Dear readers,

This issue of SYNFORM is very much focused on a process which has long been considered a sort of “Holy Grail” in organic synthesis: the functionalization of C–H bonds. Although in my opinion a C–H bond cannot be considered (yet) as a standard functional group amenable of being smoothly synthetically modified, such as a hydroxyl, a carbonyl, and so on; undoubtedly there is impressive progress in the area and a number of rather efficient and user-friendly methodologies are emerging to achieve activation of C–H bonds, as emphasized by Professor Thomas Wirth (UK) in the Advisory Board Focus interview. In the first SYNSTORY, Professor Z.-J. Shi (P. R. of China) explains how his group was able to develop an outstanding organocatalytic, metal-free (with some caveat, as explained by Professor Shi) reaction for achieving aromatic C–H activation for the synthesis of biarylic compounds. In the second SYNSTORY, Professor J.-Q. Yu (USA) describes his recent discovery of a process for preparing 1,4-dicarbonyl compounds through a novel Pd(II)-mediated carbonylation of aliphatic C–H bonds which takes place at an amazingly low pressure of CO (1 atm). Undoubtedly this is exciting progress towards making a C–H bond just another functional group that organic chemists can routinely use for their syntheses.

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM

SYNFORM, 2011/03
Published online: 16.02.2011, DOI: 10.1055/s-0030-1259585
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The direct functionalization of C–H bonds has drawn much attention from chemists since the beginning of the 20th century. Following the blossoming of transition-metal-catalyzed cross-coupling reactions, direct C–H functionalization began to flourish too, becoming progressively more significant in both academic and industrial processes. One of the most active groups worldwide in this area is led by Professor Zhang-Jie Shi from Peking University (Beijing, P. R. of China) who recently reported a novel methodology for achieving the formation of biaryls exploiting the potential of organocatalytic direct C–H transformation. “We are devoting ourselves to the cross-coupling of aromatic C–H bonds with functionalized arenes in an efficient, atom-economic and waste-free manner and different strategies are being approached in our lab,” confirmed Professor Shi.

“Obviously, the replacement of transition-metal catalysts by organocatalysts is a wonderful way to diminish the environmental burden of such a synthetic route,” explained Professor Shi. “As described in our paper, the construction of biaryl compounds was achieved in an efficient organic compound-mediated process. Although we observed such an interesting result quite a long time ago,” continued Professor Shi, “this ‘unbelievable’ observation still shocked us.” In order to understand the nature of such a metal-free process, Professor Shi and his coworkers did everything they could to examine the process in a conclusive manner: 1) they performed the reactions by using highly pure reagents, reagents from different commercial sources, and new glassware and even in different laboratories; 2) they carried out ICP-MS experiments for a quantitative analysis of metal contaminants, and kinetic experiments both with and without additional transition metals; 3) they undertook mechanistic studies to support the radical pathway. Professor Shi revealed that at first sight he said “Unbelievable”, but now with all the supporting data in hand he is pretty much sure about the conclusions described in the Nature Chemistry paper. “When we face unusual and doubtful results, we always try our best to clarify them and have the responsibility to share it with our colleagues” said Professor Shi.

“Without the requirements for expensive transition-metal catalysts and the worry of costly subsequent procedures for removing toxic heavy-metal impurities and their residual presence in the final products, our reported processes are quite synthetically useful, especially from an industrial chemistry standpoint, regardless of whether transformations like these are or are not transition-metal-free” said Professor Shi, in agreement with the comments in Professor Leadbeater’s article in the same issue of Nature Chemistry. “Although a radical mechanism was proposed, the exact pathways are still unknown. Undoubtedly, this process provides a new thinking to approach direct C–H transformation and other C–C bond formations. Notably, almost at the same time, two other groups (Hayashi and Lei) also reported similar observations,” concluded Professor Shi.

Matteo Zanda
About the authors

Zhang-Jie Shi was born in Anhui (P. R. of China) in 1974. He obtained his BSc at the East China Normal University in 1996 and his PhD at the Shanghai Institute of Organic Chemistry (SIOC), CAS (P. R. of China), supervised by Professor Shengming Ma in 2001. After his postdoctoral studies at Harvard University (USA) with G. L. Verdine and at The University of Chicago (USA) with C. He, he joined the College of Chemistry and Molecular Engineering (CCME) of Peking University in 2004, where he was promoted to Full Professor in 2008. In 2009, he received the National Science Fund for Distinguished Young Scholars of NSFC Award.

Chang-Liang Sun, Hu Li, Da-Gang Yu, Miao Yu, Xiao Zhou, Xing-Yu Lu, Kun Huang, and Bi-Jie Li work at the Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Molecular Engineering at Peking University.

Shu-Fang Zheng works at the Department of Chemistry and Materials Science, Sichuan Normal University in Chengdu, Sichuan (P. R. of China).
Carbonylation of organic compounds has been extensively investigated in both academic and industrial settings since it utilizes carbon monoxide (CO) as a carbon-atom source for the formation of a new carbon-carbon (C–C) bond with concomitant introduction of a highly oxidized functional group. Recently, the group of Professor Jin-Quan Yu from The Scripps Research Institute (La Jolla, California, USA) has achieved the first example of Pd(II)-catalyzed carbonylation of sp³ C–H bonds under 1 atm CO. The process is particularly impressive because it takes place at 1 atm of CO pressure, and holds remarkable promise of finding important applications and of inspiring further discoveries in the area of metal-catalyzed carbonylation reactions.

“Following amide-directed cleavage of sp³ C–H bonds and insertion of CO into the resulting cyclopalladated intermediate,” said Professor Yu, “intramolecular C–N reductive elimination gave the corresponding succinimides, which could be readily converted into 1,2-dicarboxylic acids or butanedioic acids that are widely found in potent biologically active natural products, such as herquiline.” According to Professor Yu, the three unique features of this catalytic reaction are: 1) the use of a polyfluorinated arylamide directing group that greatly accelerates the rate of Pd(II)-catalyzed sp³ C–H cleavage; 2) a newly developed catalytic system which utilizes a TEMPO/AgOAc oxidant mixture to reoxidize Pd(0) to Pd(II); and 3) that carbonylation of β-C–H bonds reported in this work provides a novel disconnection for the synthesis of 1,4-dicarbonyl compounds, which are broadly useful synthons for organic synthesis. “Currently, studies to carry out this transformation using simple carboxylic acid substrates and to develop enantioselective variants for substrates containing gem-dimethyl or cyclopropyl groups are being pursued in our laboratory,” concluded Professor Yu.
Masayuki Wasa earned his BSc degree with Highest Honors from Brandeis University (USA) in 2006. He is currently pursuing his PhD at The Scripps Research Institute, where he is a Bristol-Myers Squibb Fellow. His research in the laboratory of Professor Jin-Quan Yu focuses on the development of new methods to functionalize unactivated sp³ C–H bonds using transition-metal catalysis.

Jin-Quan Yu received his BSc in Chemistry from East China Normal University (P. R. of China) and his MSc from the Guangzhou Institute of Chemistry (P. R. of China). In 2000, he obtained his PhD at the University of Cambridge (UK) with Professor J. B. Spencer. Following time as a Junior Research Fellow at Cambridge, he joined the laboratory of Professor E. J. Corey at Harvard University (USA) as a Postdoctoral Fellow. He then began his independent career at Cambridge (2003–2004) before moving to Brandeis University (2004–2007), and finally to The Scripps Research Institute where he is currently Professor of Chemistry. His group studies transition-metal-catalyzed C–H activation reactions.
SYNTHESIS/SYNLETT Advisory Board Focus: Professor Thomas Wirth (Cardiff University, UK)

Background and Purpose. 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 issue, we present Professor Thomas Wirth, Cardiff University (UK).

INTERVIEW

SYNFORM | Professor Wirth, what are your main current research interests?

T. Wirth | Oxidations: hypervalent iodine chemistry; Stereoselective synthesis: the development of chiral electrophilic reagents based on selenium and iodine for alkene functionalization; Microreactor technology: access to unusual reaction conditions enabling new chemistry.

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

T. Wirth | The development of simple and easily accessible, enantiomERICLY pure electrophiles for highly efficient stoichiometric and catalytic stereoselective conversions of alkenes.

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

T. Wirth | Various efforts are being made in finding efficient ways of activating carbon–hydrogen bonds. This allows for the direct conversion of saturated hydrocarbons into valuable products needed as basic chemicals or synthetic intermediates. Some recent examples also demonstrate the power of such methodologies in complex syntheses.

SYNFORM | Do you have hobbies, besides chemistry?

T. Wirth | Yes: skiing, cycling, and performing house and garden improvements.

BIOGRAPHICAL SKETCH

Thomas Wirth obtained his Diploma (1989) from the University of Bonn (Germany), and his PhD (1992) on the use of 2-vinylindoles in synthesis from the Technical University of Berlin (Germany) with Professor Siegfried Blechert. After a postdoctoral stay (1993) working on memory of chirality with Professor Kaoru Fuji at Kyoto University (Japan) as a JSPS fellow, he started his independent research at the University of Basel (Switzerland). In the group of Professor Bernd Giese he obtained his habilitation on stereoselective oxidation reactions (1999) supported by various scholarships, before taking up his current position at Cardiff University in 2000. He was invited as a visiting professor to a number of places including the University of Toronto (Canada, 1999), Chuo University in Tokyo (Japan, 2000), Osaka University (Japan, 2004) and Osaka Prefecture University (Japan, 2008) and was awarded the Werner-Prize from the New Swiss Chemical Society in 2000. Thomas Wirth is the author of ~130 publications and has written/editied five books. He was an Associate Editor of SYNLETT from 2003 until 2010. For further information see: http://www.cf.ac.uk/chemy/contactsandpeople/academic-staff/wirth-thomas-overview_new.html.

Matteo Zanda
Ni-Catalyzed Reduction of Inert C–O Bonds
(Focus on an article from the current literature)