Copper-Catalyzed Highly Enantioselective Cyclopent-annulation of Indoles with Donor–Acceptor Cyclopropanes

Cobalt-Catalyzed ortho-Alkylation of Aromatic Imines with Primary and Secondary Alkyl Halides

Copper-Catalyzed Annulation of Amidines for Quinazoline Synthesis

Young Career Focus: Professor Liang Deng (Shanghai Institute of Organic Chemistry, P. R. of China)
Dear readers,

This issue of SYNFORM is entirely dedicated to groundbreaking research coming from Asia, and predominantly from P. R. of China. We didn't do it on purpose, but it's a very good opportunity for emphasizing the outstanding progress made by Asian researchers. Until 10 years ago, Asian research was mostly identified with Japan but nowadays countries like P. R. of China, Singapore, South Korea and India, just to mention a few, have become research giants and give a major contribution to the scientific progress worldwide. Browsing the highest impact journals one can see a very significant and constantly increasing number of contributions originated by research institutions in these Asian countries. The outstanding quality of the work presented in the three SYNSTORIES and the Young Career Profile of this issue is a further clear indicator of the strength of Asian chemistry. The first SYNSTORY deals with a new process for forming indole-fused cyclopentane rings published by Professor Y. Tang (P. R. of China). The second SYNSTORY covers a methodology reported by Professor N. Yoshikai (Singapore) which allows the efficient formation of ortho-substituted acetophenones carrying a cycloalkyl ring. The third SYNSTORY reports on a copper-catalyzed quinazoline-forming reaction developed by the group of Professor Q. Zhang (P. R. of China). Finally, another contribution from P. R. of China, where Professor L. Deng explains his research work and plans in a Young Career Profile. Great chemistry from a great continent!

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM
There is an increasing urgency to access the complex structural framework of bioactive natural substances through efficient, environmentally and economically sustainable synthetic protocols. In this context, C2,C3-fused indoline frameworks are quite common in a large number of naturally occurring compounds and biologically active molecules, and therefore represent important synthetic targets. Their asymmetric and concise construction has been the pursuit of organic chemists for a long time, and several efficient methods have been developed. However, much less attention has been paid to the construction of cyclopenta-fused indolines, also a key structure in many natural products such as kopsane, vindolinine, and dasyrachine. A general and enantioselective catalytic method to synthesize this skeleton is still highly in demand. Recently, based on the ring-opening and annulation reactions of donor-acceptor cyclopropanes, the research group led by Professor Yong Tang from the Shanghai Institute of Organic Chemistry (P. R. of China) has accomplished several asymmetric transformations by virtue of Ni(II) or Cu(II) catalysis in combination with sidearm-modified chiral bisoxazoline (BOX) ligands. Professor Tang said: “These successes piqued our great interest to attempt the asymmetric [3+2] annulation of indoles with donor–acceptor (D–A) cyclopropanes, which feature a rapid assembly of the multicyclic indoline skeletons in a cascade fashion and the basis of readily available indole and cyclopropane substrates.” The first example of [3+2] annulation of indoles with cyclopropanes was introduced by Kerr in 1997 (*Tetrahedron Lett.* 1997, 38, 5949), followed by many extensions and applications. However, according to Professor Tang, 16 years later, an enantioselective version of this reaction remains elusive, even though it could be an attractive approach for synthesizing optically active cyclopenta-fused indolines and has already shown its potential in total synthesis.

“Though we initially failed to obtain turnover with typical tridentate ligands such as Ph-DBFOX and -PyBOX in combination with Cu(OTf)2, we achieved a promising level of enantioselectivity with benzyl-modified Inda-BOX ligand L1,” said Professor Tang. “Through an extensive ligand screening we were pleased to find out that the introduction of two tert-butyl groups at the 3,5-positions of the pendant phenyl group (L2) was very effective to elevate both the diastereo- and enantiomeric excesses. For more details, please refer to the publication in *J. Am. Chem. Soc.* 2013, 135, 7851–7854.”

**Scheme 1** Sidearm group effect on the stereoselectivity
enantioselectivity. This finding is similar to our recent observation in the Cu(I)/BOX-catalyzed cyclopropanation reaction of alkenes in which the BOX ligands that contain two aryl sidearm groups adopted a cage-like conformation and afforded much better enantioselectivities than the ligands without this sidearm modification. In fact, a cage-like conformation was also found in the X-ray crystal structure of L2/CuBr2, with the two pendant aryl groups bending over the copper center. This structural information is in accord with the significant enantioselectivity change from L1 to L2, resulting from the substitution variation at the phenyl group.

Professor Tang said: “To our delight, the reaction worked well with a variety of indoles and cyclopropanes,” (Scheme 2, a). For instance: (a) [3,3,3,0]-tetracyclic indolines containing two quaternary bridging carbons and three consecutive stereocenters were accessible by using 2,3-disubstituted indoles; b) for less reactive cyclopropanes (slow racemization), the reaction proceeded with a concurrent kinetic resolution of the cyclopropanes, and both the [3+2]-annulation products and the recovered cyclopropanes were obtained in high yields and high enantioselectivities; (c) indoles without a C3-substituent normally underwent a C3-Friedel–Crafts alkylation reaction but did so with high enantioselectivity.

Encouraged by the excellent results with 2,3-disubstituted indoles, the researchers designed a synthetic route based on the cyclopentannulation of pyrroloindole for the synthesis of the tetracyclic core of borreverine (Scheme 2, b). “To our great pleasure, the reaction proceeded very quickly and could even be carried out at −40 °C,” said Professor Tang. “Furthermore, only a single diastereoisomer was observed with 95% ee.” The success with the pyrroloindole-type substrates expanded the scope of the current reaction, and further extension to other fused indoles can be anticipated. Professor Tang concluded: “Synthetic applications aiming at the synthesis of natural products and an intramolecular version are currently ongoing in our laboratory.”

Scheme 2 Reaction scope and selected results
About the authors

Yong Tang received his BSc from Sichuan Normal University (P. R. of China) and his PhD from Shanghai Institute of Organic Chemistry (SIOC, P. R. of China), Chinese Academy of Sciences (CAS). He was a postdoctoral fellow with Professor Yian Shi at Colorado State University, Fort Collins (USA) and with Professor A. Kozikowski at Georgetown University (USA). He moved to Shanghai Institute of Organic Chemistry in 1999, where he was appointed as an Associate Professor, and promoted to Research Professor in 2000. His research interests include organometallic chemistry centering on olefin polymerization, ylide chemistry in organic synthesis, and asymmetric catalysis. He has received many honors and awards, including the State Natural Science Prize (2012) from The Ministry of Science and Technology of China and the Chinese Chemical Society Yao-Zeng Huang Award in Organometallic Chemistry (2012).

Zuowei Xie obtained his BSc from Hangzhou University (P. R. of China) in 1983, his MSc from SIOC, CAS in 1986, and his PhD in 1990, working in a special joint program between SIOC and Technische Universität Berlin (Germany). After serving as a Research Associate at the SIOC and as a Postdoctoral Fellow at the University of Southern California (Los Angeles, USA), he joined the Chemistry Department of The Chinese University of Hong Kong (P. R. of China) in 1995 as an Assistant Professor, where he is now a Choh-Ming Li Professor of Chemistry. He has received many honors and awards, including the State Natural Science Prize (2008) from The Ministry of Science and Technology of China, the Chinese Chemical Society Yao-Zeng Huang Award in Organometallic Chemistry (2010), and The Croucher Award (2003) from The Croucher Foundation (Hong Kong).

Saihu Liao was born in Taoyuan (P. R. of China). He received his BSc from Huazhong University of Science and Technology (P. R. of China) in 2005 and his MSc in 2007 under the guidance of Professor Yuefa Gong. In 2007, he moved to Mülheim in Germany and started his doctoral study with Professor Benjamin List at the Max-Planck Institute for Coal Research and obtained his PhD in 2011. He then returned to China and took his current position in Professor Tang’s group at the SIOC. His research interest concerns asymmetric catalysis and ylide chemistry.

Hu Xiong was born in Zhumadian (P. R. of China) in 1986. He received his BSc in chemistry from Zhengzhou University (P. R. of China) in 2009, and then joined the SIOC as a PhD candidate in 2009, working under the supervision of Professors Zuowei Xie and Yong Tang.

Hao Xu was born in Lu’an (P. R. of China) in 1986. He received his BSc in chemistry from Zhengzhou University (P. R. of China) in 2009. He is currently a fourth-year graduate student in Professor Yong Tang’s laboratory at the SIOC.
Methods for introducing an alkyl group on an aromatic ring are fundamental in organic synthesis. The groundbreaking work of the Murai group on ruthenium-catalyzed ortho-alkylation of aromatic ketones with olefins (Nature 1993, 366, 529) has opened completely new synthetic perspectives for regioselective aromatic alkylations that go beyond the conventional Friedel-Crafts chemistry. Subsequent studies with ruthenium catalysts, as well as rhodium and other transition-metal catalysts, have significantly expanded the scope of the 'directed olefin hydroarylation'. However, with a close look at the relevant literature, one can notice that, for various reasons, this chemistry is not generally suited for the introduction of secondary alkyl groups. Although an alternative ortho-alkylation strategy using alkyl halides as alkylating agents has emerged recently (Chem. Commun. 2010, 46, 4866; J. Am. Chem. Soc. 2013, 135, 5308 and references therein), this strategy has scarcely been practiced with secondary alkyl halides, presumably due to their low reactivity toward oxidative addition. Recently, the research group of Professor Naohiko Yoshikai at Nanyang Technological University (Singapore) developed a novel cobalt-based catalyst for ortho-alkylation of aromatic imines. Professor Yoshikai said: “With the background of ortho-alkylation reactions in mind, the new catalytic system we have developed is simply remarkable in that it allows the introduction of an unprecedentedly broad scope of primary and secondary alkyl groups, under mild conditions, using readily available alkyl chlorides and bromides.”

The present reaction is also notable in light of the recent progress of cross-coupling reactions of arylmetal reagents and alkyl halides, secondary alkyl halides in particular, using first-row transition-metal catalysts (e.g., iron, cobalt, nickel). “The new reaction we developed,” said Professor Yoshikai, “would serve as a good method complementary to such cross-coupling reactions, considering that arylmetal reagents bearing carbonyl functional groups at the ortho-position are not readily available. It is also interesting to note that optimum catalytic efficiency has been achieved with simple but far less popular (compared to IMes, IPr, etc.) N-heterocyclic carbene (NHC) ligands.”

**Scheme 1 The new ortho-alkylation reaction**

**Figure 1 Some of the products obtained with the new ortho-alkylation process**
“I have had a sketchy idea of the present reaction since we started our research program on cobalt-catalyzed ortho-C–H functionalization in late 2009, but did not imagine that my graduate student Ke Gao could eventually come up with a unique catalytic system with such a broad scope,” Professor Yoshikai acknowledged. “Although the detailed reaction mechanism is not clear yet, in retrospect, the success of the present cobalt catalysis may be ascribed to the unique ability of low-valent cobalt species to promote both one- and two-electron processes (i.e., single-electron transfer to alkyl halide and nitrogen-directed cyclometalation, respectively).

While further investigation is required to clarify the exact reaction mechanism, the experimental results with stereochemical probes imply that the reaction involves formation of an alkyl radical at some point in the catalytic cycle. With this implication, Professor Yoshikai believes that the development of stereoselective variants of the present alkylation reaction would be a clear and attractive option for further study. Professor Yoshikai remarked: “This could be achieved either by catalyst control (i.e., cobalt catalyst bearing a chiral NHC or other ligand) or substrate control (i.e., imine-bearing chiral N-substituent). We have already started to look into both of these possibilities and hope to report the results in due course.”

He continued: “At this moment, we do not have a particular target for the application of the present alkylation method. However, generally speaking, ortho-alkylation reactions of ours, and those of others, should have significant potential for applications in target-oriented synthesis, because alkylated benzenes are obviously as common as biaryl skeletons in pharmaceutically or otherwise useful small molecules.”

“For our reaction to have actual applications, further studies are necessary, for example, to expand the scope of directing groups, improve the functional group compatibility, and develop stereoselective variants, which represent major challenges not only in this particular alkylation reaction but also in cobalt-catalyzed C–H functionalization in general,” he concluded.
The development of methodologies to introduce nitrogen atoms into organic molecules is a crucial endeavor in chemical synthesis, owing to the ubiquity of C–N bond units in myriads of bioactive molecules, including alkaloid natural products and pharmaceuticals. In the last two decades, tremendous progress has been made in the field of metal-nitrene C–H insertion for the synthesis of nitrogen-containing products. However, the intermolecular amination of methyl C(sp3)–H bond through metal-nitrene intermediates in the more commonly used solvents, such as DMSO, DMF, N,N-dimethylacetamide (DMA), N-methylpyrrolidone (NMP) and N,N,N′,N′-tetramethylethane-1,2-diamine (TMEDA), remains a great challenge. Recently, Dr. Tao Xiong and Professor Qian Zhang from Northeast Normal University (Changchun, P. R. of China), developed a novel and efficient copper-catalyzed synthesis of quinazolines from amidines. Remarkably, for the first time the C–N bond formation proceeding through copper-nitrene species insertion into methyl C(sp3)–H bonds of DMSO, DMF, DMA, NMP and TMEDA is the key to the success of the methodology.

“Recently, with benzylic methyl sp3 carbon as the one-carbon synthon, Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bistetrafluoroborate) as oxidant, copper as catalyst, starting from N-(p-tolyl)amides, we accomplished the construction of benzoxazine derivatives via a dehydrogenative cross-coupling reaction between benzylic methyl C(sp3)–H and aromatic C(sp2)–H bonds, and subsequent intramolecular C–O bond formation (Angew. Chem. Int. Ed. 2011, 50, 7140), and also the construction of C–N bonds directly from C–H bonds (e.g., Chem. Commun. 2012, 48, 2246; Angew. Chem. Int. Ed. 2012, 51, 1244; J. Am. Chem. Soc. 2011, 133, 1694; Chem. Commun. 2010, 46, 6831). These works inspired us to seek a simple one-carbon synthon to construct new C–C bonds or C–heteroatom bonds,” said Professor Zhang. “DMSO is a widely used solvent and coordinates well with transition metals. The insertion of metal-nitrene species into various C–H bonds is a powerful strategy for the formation of C–N bonds. How about the methyl C(sp3)–H of DMSO? Indeed, after many investigations, we found that in the presence of a copper catalyst and an F+ oxidant, amidines can be used directly as nitrogen-centered radicals or nitrene nitrogen sources. The C–N bond was formed by the subsequently possible copper-nitrene insertion into methyl C(sp3)–H bonds of DMSO. Finally, in the presence of H+, tandem C–S bond cleavage and C–C bond formation provided the target quinazolines,” she continued.

“Quinazoline derivatives, which are widely distributed in natural products and synthetic pharmaceuticals, have been studied extensively for their biological and therapeutic activities. In contrast to most of the synthetic routes depending on the use of anilines bearing an ortho-functional group, the strategy of employing readily available ortho-unfunctionalized anilines (such as amidines, which were easily prepared by the reaction of commercially available anilines with nitriles in the presence of AlCl3 or NaH), is very attractive,” said Dr. Xiong. He continued: “To our delight, we found that other solvents..."
with similar methyl C(sp³)–H bonds adjacent to heteroatoms, such as DMF, DMA, NMP and TMEDA, in the presence of a copper catalyst and 1-fluoropyridinium tetrafluoroborate instead of Selectfluor, also afforded the desired quinazolines in moderate to good yields.

Mechanistic studies were also conducted on the reaction, showing that copper-nitrene insertion into C(sp³)–H bond of DMSO might be involved in the rate-limiting step. The possible nitrene species generated from amidine was trapped by DMSO to provide a sulfoximine compound along with the desired product, which showed that the in situ generated nitrene species could react with DMSO to form a quinazoline. Professor Zhang concluded: “The detailed mechanism of this annulation reaction remains to be elucidated and we are currently trying to utilize this strategy for the construction of various C–N bonds.”

About the authors

Tao Xiong was born in 1982 in ChongQing (P. R. of China). He received his PhD degree in 2011 from the Northeast Normal University (Changchun, P. R. of China) with Professor Qian Zhang. In 2012, he took up a position at Colorado State University (Fort Collins, USA) as Postdoctoral Fellow with Professor Yian Shi. His research focuses on transition-metal catalysis and asymmetric catalysis.

Qian Zhang received her BSc and MSc degrees (with Professor Q. Liu) in chemistry from Northeast Normal University (Changchun, P. R. of China). She obtained her PhD from Changchun Institute of Applied Chemistry, Chinese Academy of Sciences (P. R. of China) with Professor L.-X. Wang. She then began her independent career at Northeast Normal University in 2004, where she became a Full Professor in 2008. Her research focuses on the development of new synthetic methods in organic synthesis.
Young Career Focus: Professor Liang Deng (Shanghai Institute of Organic Chemistry, P. R. of China)

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 Professor Liang Deng, Shanghai Institute of Organic Chemistry, P. R. of China.

INTERVIEW

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

Prof. L. Deng | The focus of my current research is to establish the reactivity pattern of open-shell organo-iron and -cobalt compounds with the aim to develop new iron- and cobalt-mediated bond-cleavage and bond-forming transformations for organic synthesis. We construct targeted organometallic compounds by judicious design and selection of ligand set, perform systematic physical characterizations on the isolated compounds, and investigate the effect of spin state, coordination geometry and oxidation state on the reactivity of the organometallic compounds.

SYNFORM | When did you get interested in synthesis?

Prof. L. Deng | When I was a high school student, I had the opportunity to attend undergraduate chemistry courses. Through reading Stuart Warren’s book “Designing Organic Syntheses: The Synthon Approach” (Chinese Translation) and having done some basic organic synthesis experiments, I was fascinated by the logic of organic synthesis and the versatility of classical synthetic techniques. That started my interest in synthesis.

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

Prof. L. Deng | With people’s increasing concerns on the environmental and energy crisis, sustainable development has become a consensus for human beings. Keeping up with this theme, organic synthesis has made its great efforts to provide solutions to related problems. New organic materials, for example, bio-degradable polymers and organic optoelectronic materials, and new synthetic methods with high atom economy, emerged in recent years, are among the representative advances. Considering the central role of synthetic methods in organic synthesis and the success of catalysis with noble metals in developing new synthetic methods, I believe that the economical and environmentally benign feature of non-precious metals will make non-precious metal catalysis a promising feature in organic synthesis. To this

BIOGRAPHICAL SKETCH

Liang Deng is a CAS Hundred Talents Professor at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, P. R. of China. He was born in Hunan Province, China in 1980. As the son of a foundry worker, he developed his interest in chemistry during his teens while working in his family-owned workshop. He is a graduate of Peking University, P. R. of China (BS in Chemistry, 2002), and the Chinese University of Hong Kong, P. R. of China (PhD in Chemistry, 2006). His graduate research under the supervision of Professor Zuowei Xie led him to discoveries of supracarborane and metallocarboryne chemistry, with which he was awarded the Best Research Output Award by the University. He had his postdoc studies in the research group of Professor Zuowei Xie for a brief period in 2006 and the research group of Professor Richard H. Holm at Harvard University from 2007 to 2009. In Harvard, he worked on the biomimetic synthesis of iron-sulfur clusters of nitrogenase enzymes. In 2009, he started his independent research career at the Shanghai Institute of Organic Chemistry, and is now a Research Professor at the State Key Laboratory of Organometallic Chemistry there. His research focuses on synthetic organometallic chemistry emphasizing on reactive iron and cobalt complexes capable of activating small molecules and inert bonds. He has published ca. 30 research papers, and has been awarded the Hundred Talents Program of the Chinese Academy of Sciences (2010), the National Science Fund for Excellent Young Scholars (2012), and the Thieme Chemistry Journals Award (2013).
end, a deeper understanding on the organometallic chemistry of non-precious metals is the prerequisite.

SYNFORM | Your research group is active at the frontier of organic synthesis and organometallic chemistry. Could you tell us more about your research and its aims?

Prof. L. Deng | Iron and cobalt are typical non-precious metals and their metal complexes have gained more interest as pre-catalysts for organic synthesis than ever. Despite the fast development of iron and cobalt catalysis in recent years, fundamental processes of bond cleavage and bond forming on these metals’ coordination sphere have remained poorly understood. Aiming to build up a deep understanding on this point, we are currently investigating the structure-reactivity relationship of two types of reactive iron and cobalt complexes: open-shell σ-hydrocarbyl metal compounds and low-valent complexes. We found that N-heterocyclic carbenes are ideal ancillary ligands to stabilize open-shell σ-hydrocarbyl iron(II) compounds, such as iron alkyls, aryls, alkenyls, and alkynyls, and also low-valent iron and cobalt complexes, for example, three- and two-coordinated iron(I, 0) and cobalt(I, 0). The successful synthesis of these reactive metal compounds enables further investigations on their reactivity. We have revealed that the σ-hydrocarbyl iron(II) compounds can facilitate the cleavage of a series of carbon-halogen bonds via a single-electron-transfer pathway, and discovered that a zero-valent cobalt center can activate C(sp³)–H bonds via an oxidative addition mechanism. In addition to these findings, we also develop new iron- and cobalt-catalyzed organic transformations with well-defined iron and cobalt complexes as catalysts.

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

Prof. L. Deng | By examining the effect of the oxidation state of a cobalt center on its C–H activation reactivity, we have found that a cobalt(0) center can effectively activate C(sp³)–H bonds in an oxidative addition mechanism, which provides a solution to the open question as to how to achieve the oxidative addition of a C–H bond on cobalt (*Organometallics* 2012, 31, 7040). Furthermore, we achieved cobalt-mediated C–H bond silylation reactions by employing a sequential cobalt-mediated cyclometallation followed by a silylation protocol (Figure 1). The resulting silyl anion functionalized N-heterocyclic carbene–cobalt(II) compounds display very fast initial rates, high turnover numbers and selectivities in catalyzing the hydrosilylation of olefins that outperform those of classical cobalt-carbonyl catalysts (*Angew. Chem. Int. Ed.* 2013, DOI: 10.1002/anie.201304596). This study points out a new way for future catalyst design.

Figure 1 Synthetic approach for the silyl donor functionalized N-heterocyclic carbene–cobalt catalyst
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■ Direct Catalytic Cross-Coupling of Organolithium Compounds (Focus on an article from the current literature)

■ Total Synthesis of the Daphniphyllum Alkaloid Daphenylline (Focus on an article from the current literature)

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SYNFACTS

Synfact of the Month in category “Synthesis of Natural Products and Potential Drugs”: Synthesis of AMG 837

FURTHER HIGHLIGHTS

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, fax: +39 02 23993080

Editorial Office
Managing Editor: Susanne Haak, susanne.haak@thieme.de, phone: +49 711 8931 771
Scientific Editor: Selena Bootthoyd, selena.bootthoyd@thieme.de
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Production Editor: Thorsten Schin, thorsten.schin@thieme.de, phone: +49 711 8931 781
Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
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Postal Address: SYNFORM/ SYNFACTS, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany,
Homepage: www.thieme-chemistry.com

Publication Information
SYNFORM will be published 12 times in 2013 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for SYNTHESIS, SYNLETT and SYNFACTS.

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