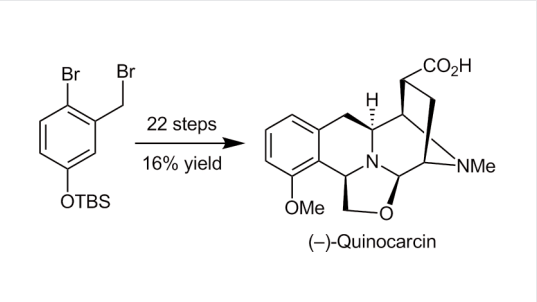
# SYNFORM

*People, Trends and Views in Synthetic Organic Chemistry*

2008 / 09

## SYNSTORIES

- Stereoselective Synthesis of β-L-Rhamnopyranosides
- Total Synthesis of (–)-Quinocarcin




- Pd(II)-Catalyzed Cross-Coupling of $sp^3$ C–H Bonds with $sp^2$ and $sp^3$ Boronic Acids Using Air as the Oxidant
- Nickel-Catalyzed Cross-Coupling of Aryl Methyl Ethers with Aryl Boronic Esters

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Thieme Chemistry

## Dear readers,

The season of conferences is moving into top gear, and the agenda of ***SYNFORM*** is becoming quite crowded. Indeed, in the forthcoming issues we will report on several top events of the year 2008, such as the 236th ACS Conference that was recently held in Philadelphia (in the next issue of ***SYNFORM***), and the looming 2nd EuCheMS Chemistry Congress in Turin.

Although there are no conference reports in this issue, we cover some of the most exciting achievements in the area of organic synthesis, published in the current literature. Two out of four come from Japan, and specifically from the lab of Dr. Yukishige Ito, who revealed a stereoselective entry to β-L-rhamnopyranosides, and from the group of Professor Naoto Chatani and Dr. Mamoru Tobisu, who discovered how to use anisole derivatives as substrates for the Suzuki–Miyaura cross-coupling.

Europe is represented by the group of Dr. Jieping Zhu (France), who developed an elegant and effective total synthesis of the alkaloid (–)-quinocarcin. Since the issue would not be complete without America, the fourth ***SYNSTORY*** article is focused on another innovative cross-coupling reaction, recently reported by the group of Professor Jin-Quan Yu (USA).

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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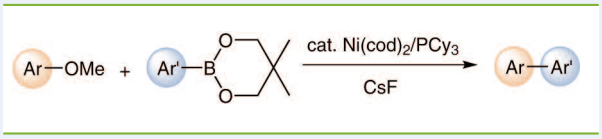


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NEWS AND VIEWS NEWS AND VIEWS NEWS AND VIEWS

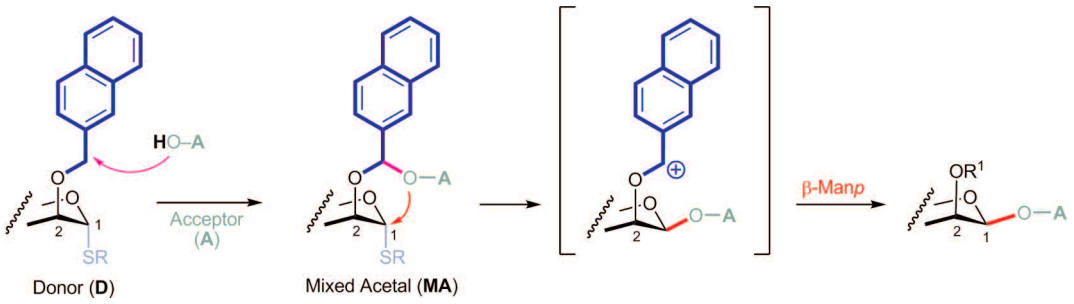
# Stereoselective Synthesis of β-L-Rhamnopyranosides

*J. Am. Chem. Soc.* **2008**, *130*, 6330–6331

The glycosylation reaction is an important synthetic process particularly because of the remarkable biological significance of complex oligosaccharides and glycoconjugates. However, stereoselective glycosylation is still a challenging endeavor. Indeed, one of the most serious problems in synthetic carbohydrate chemistry is the stereoselective synthesis of 1,2-*cis* glycosides. A number of strategies toward 1,2-*cis* glycoside formation have been explored. Among them, approaches based on intramolecular aglycon delivery (IAD)[1] are especially promising, because they are expected to occur with the exclusive formation of 1,2-*cis* glycosides. "The concept of IAD was first proposed by Baressi and Hindsgaul in 1991 who employed isopropylidene mixed acetal as a tether for β-mannopyranosylation," explained Dr. Yukishige Ito from The Institute of Physical and Chemical Research of RIKEN, Wako (Japan). "Subsequent work by Stork and co-workers explored the use of silaketal for similar purposes." Following these pioneering reports, newer versions of IAD have been developed using various types of tethers.

"Our original approach[2] took advantage of the special reactivity of *p*-methoxybenzyl (PMB) ether," explained Dr. Ito. "The formation of mixed acetal upon oxidative activation with DDQ, followed by subsequent activation of the thioglycosidic linkage initiated the rearrangement of an aglycon from the *p*-methoxybenzylidene acetal moiety to give the desired β-mannopyranoside. The practicality of this method has also been shown to be applicable to the synthesis of various complex oligosaccharides," continued Dr. Ito, "which has proven to be a powerful tool for glycoscience.[3]" Since the 2-naphthylmethyl (NAP) group is similar to PMB in that it can be removed with DDQ, it was expected that IAD using a 2-*O*-NAP-protected donor should be possible. "In fact," said Dr. Akihiro Ishiwata, a co-author of the paper, "NAP-assisted IAD turned out to be highly versatile, giving various types of 1,2-*cis* glycosides, such as β-mannopyrano-, β-arabinofurano-, and α-glucopyranosides, in high yield.[4]"

In this context, Dr. Ito and co-workers have recently developed the stereoselective formation of 1,2-*cis*-β-L-rhamnopyranoside (β-L-Rha*p*). β-L-Rha*p* is an important constituent of bacterial polysaccharides which provide a plentiful source of antigenic material and principal antigenic determination of the parent microorganism. "Although the difficulty of stereoselective synthesis of β-L-Rha*p* derives from the structural feature similar to β-D-mannoside, which has a 1,2-*cis*-equatorial glycosidic bond and cannot be controlled by the anomeric effect," said Dr. Ito, "the formation of β-L-Rha*p* is much more difficult because of the 6-deoxy functionality. The state-of-the-art of this report," he continued, "is that various attempts using structurally modified donors and synthetic strategies have been done; however, the stereoselectivity of the rhamnosylation seemed not to be enough and also was dependent on the structure of the aglycon (acceptor)." "We focused on generally applicable β-L-rhamnopyranosylation to synthesize various substructures of bacterial polysaccharide, which are (1→3)-β-L-Rha*p* that are linked to Glc$^{O\text{-}4}$, Glc$^{O\text{-}3}$, Man$^{O\text{-}2}$, Rha$^{O\text{-}4}$, and GlcNAc$^{O\text{-}4}$," said the other co-author Dr. Yong Joo




***Scheme 1*** *NAP-IAD for 1,2-cis glycosylation*

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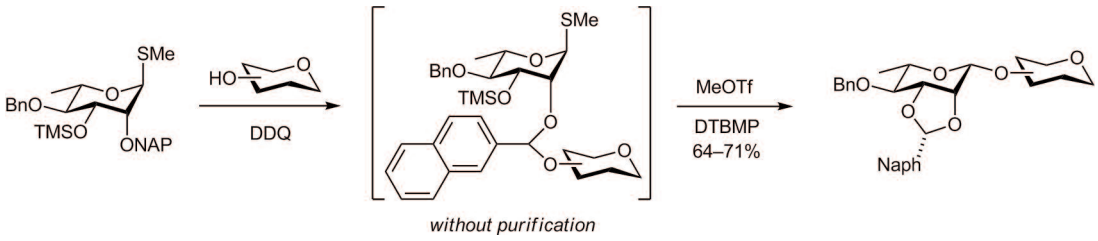


***Scheme 2*** *NAP-IAD for β-rhamnosylation*

Lee, "and using our NAP ether-mediated IAD, the only breakthrough so far, the stereoselective construction of β-L-Rha*p* linkages, was achieved to give the single isomer (Scheme 2)." The total stereoselective synthesis of a trisaccharide, α-L-Rha*p*-(1→3)-β-L-Rha*p*-(1→4)-Glc*p* from *S. natans*, was successfully accomplished through regioselective reductive ring opening of a naphthylidene acetal of the resultant disaccharide followed by subsequent α-L-rhamnopyranosylation.

"We have successfully developed a new methodology to make β-L-Rha*p* linkages and we suggested that one of most unified strategies to obtain β-L-rhamnopyranosylation, as well as other 1,2-*cis* glycosides, should be through NAP ether-mediated IAD," concluded Dr. Ito. "We will demonstrate the synthesis of important glycans which include β-L-Rha*p* linkages so far, to study the biological significance of complex oligosaccharides and glycoconjugates."

**Matteo Zanda**

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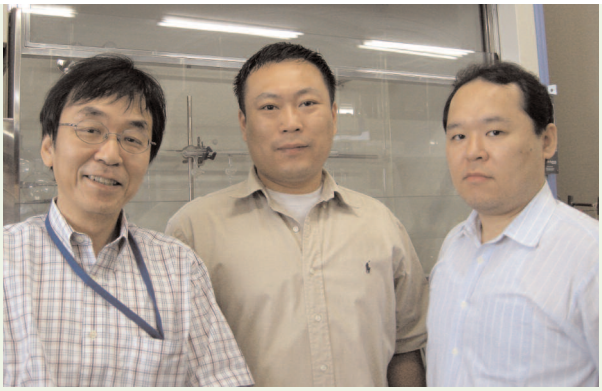
(b) I. Cumpstey *Carbohydr. Res.* **2008**, *343*, 1553.
(2) Y. Ito, T. Ogawa *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765.
(3) Y. Ito, S. Hagihara, I. Matsuo, K. Totani *Curr. Opin. Struct. Biol.* **2005**, *15*, 481.
(4) A. Ishiwata, Y. Munemura, Y. Ito *Eur. J. Org. Chem.* **2008**, 4250.



*From left: Dr. Y. Ito, Dr. Y. J. Lee, Dr. A. Ishiwata*

### About the corresponding author

**Dr. Yukishige Ito**, Chief Scientist and Director of Synthetic Cellular Chemistry Laboratory, Advanced Research Institute, RIKEN (The Institute of Physical and Chemical Research) (Japan), was born in Hyogo (Japan) in 1954. He graduated from the Faculty of Pharmaceutical Sciences, The University of Tokyo, in 1977, and obtained his PhD in 1982 from the same university. After two years of postdoctoral training at the Department of Chemistry, Massachusetts Institute of Technology in Cambridge (USA), he returned to Japan as a research scientist at RIKEN, where he started his career in carbohydrate chemistry. He spent two years from 1991 as a visiting scientist at Cytel Corp. and Scripps Research Institute in San Diego (USA). He was promoted to senior scientist in 1996 and to chief scientist in 1998. Since then, he has been the director of his own research group. His research focuses on the synthesis and functional analysis of glycoprotein-related compounds and the development of methodologies for efficient and selective synthesis of glycoconjugates.

### About the coauthors

**Dr. Yong Joo Lee**, Foreign Postdoctoral Researcher, Advanced Research Institute, RIKEN (The Institute of Physical and Chemical Research) (Japan). **Dr. Akihiro Ishiwata**, Senior Research Scientist, Advanced Research Institute, RIKEN (The Institute of Physical and Chemical Research) (Japan).

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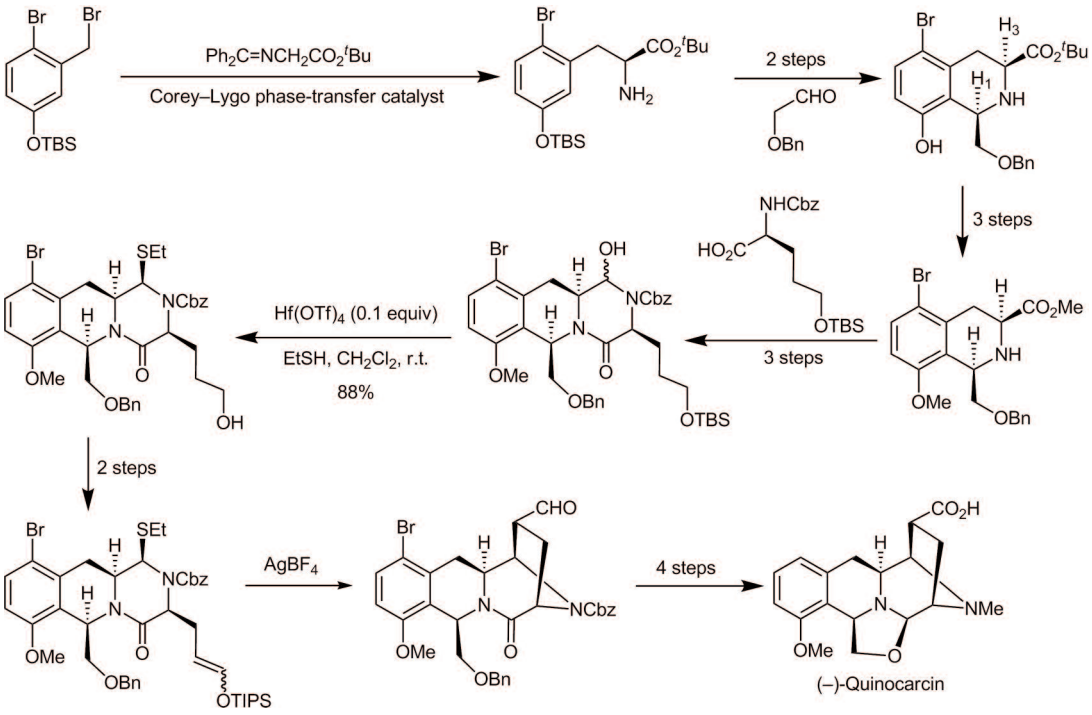
# Total Synthesis of (–)-Quinocarcin

J. Am. Chem. Soc. **2008**, *130*, 7148–7152

■ Quinocarcin belongs to the family of complex tetrahydroisoquinoline natural products that include naphthyridinomycins, saframycins, renieramycins, and ecteinascidins. These compact polyheterocycles display potent antitumor and antimicrobial activities. Indeed, ecteinascidin 743 (Et 743, Yondelis®) has recently received authorizations from the European Medicines Agency (EMEA) for the treatment of advanced soft-tissue sarcoma.

(–)-Quinocarcin is a pentacyclic tetrahydroisoquinoline alkaloid that was isolated by Takahashi and Tomita in 1983 from the culture broth of *Streptomyces melunovinuceus*. It exhibited potent antitumor activities against a variety of tumor cell lines and its citrate salt (KW2152) had been in clinic trials in Japan. The antiproliferative effect of (–)-quinocarcin was partly accounted for by its ability to inhibit RNA and/or DNA synthesis. However, it has been suggested that (–)-quinocarcin exerted its cytotoxic activity through the expression of multiple mechanisms, including the mediation of oxidative damage to DNA via the reduction of molecular oxygen to superoxide. The fascinating molecular architecture and important biological profile of quinocarcin have attracted significant attention from the synthetic community, culminating in one racemic and three asymmetric syntheses of (–)-quinocarcine in the span of twenty years.

Recently, Drs. Yan-Chao Wu, Mélanie Liron and Jieping Zhu from the Institut de Chimie des Substances Naturelles of CNRS, Gif-sur-Yvette (France) have developed an efficient asymmetric total synthesis of (–)-quinocarcin in a longest linear sequence of 22 steps starting from cheap and commercially available starting materials. "Our synthesis is convergent, modular and features 16% overall yield," explained Dr. Zhu. "Moreover, it has other distinctive features, namely: 1) an efficient synthesis of 2-bromo-5-methoxy phenylalanine by catalytic enantioselective alkylation of a glycine template in the presence of the Corey–Lygo phase-transfer catalyst; 2) temporary protection of the aromatic ring with a Br atom to direct the regiochemistry of the Pictet-Spengler reaction; and 3) $Hf(OTf)_4$-catalyzed transformation of a hemiaminal func-

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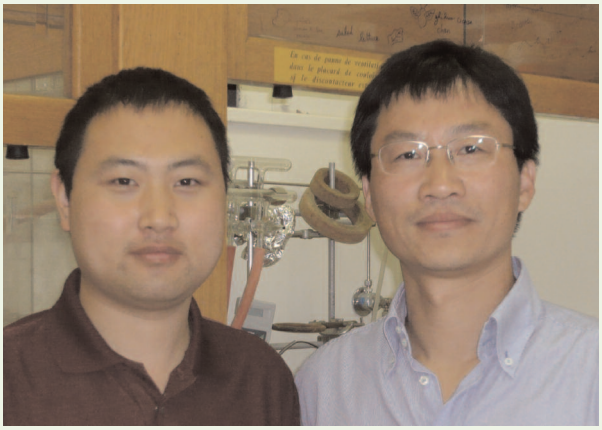
tion to aminothioether, which acted remarkably well as a latent iminium species for the Mannich-type cyclization." From the practical point of view, the one-pot partial reduction of lactam to aminal followed by direct oxazolidine formation was also remarkably effective, as it reduced the previous three-step sequence involving the production of an aminonitrile intermediate to a single operation. "We believe," said Dr. Zhu, "that it is one of the most efficient and stereocontrolled total syntheses of (–)-quinocarcine known to date."

Dr. Jieping Zhu's research group has been interested in tetrahydroisoquinoline alkaloids for some time and has developed three different strategies for the total syntheses of ecteinascidin 743, ecteinascidin 597, and cribrostatin 4. "It is expected that the strategy developed for (–)-quinocarcine would be applicable to other members of this family, such as tetrazomine, lemonomycin, and bioxalomycins. In addition," concluded Dr. Zhu, "we believe that the $Hf(OTf)_4$-catalyzed transformation of hemiaminal to aminothioether developed in the course of this study should find other applications in organic synthesis."

*Matteo Zanda*



*From left: Dr. Y.-C. Wu, Dr. J. Zhu*

*Dr. M. Liron*

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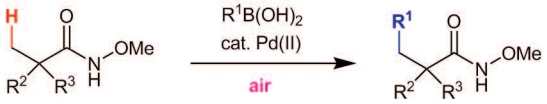
# Pd(II)-Catalyzed Cross-Coupling of sp³ C–H Bonds with sp² and sp³ Boronic Acids Using Air as the Oxidant

*J. Am. Chem. Soc.* **2008**, *130*, 7190–7191

Mild and selective activation of tetrahedral C–H bonds still represents a challenging endeavor in modern organic synthesis, and research in this particular area is very active and competitive. One important step forward was reported recently, by the research group of Associate Professor Jin-Quan Yu from The Scripps Research Institute in La Jolla (California, USA). Professor Yu and co-workers discovered that the $sp^3$ C–H bond in the β-position with respect to a methoxy hydroxamate function can be activated in the presence of a Pd(II) catalyst and the resulting Pd(II)-alkyl intermediate undergoes cross-coupling reaction with both $sp^2$- and $sp^3$-boronic acids. This new C–H activation/C–C coupling reaction exploits air as the oxidant, instead of Ag(I) or Cu(II) salts previously used by the same group, thus representing a truly "green" and environmentally benign process.




"Since our first discovery of C–H activation/C–C coupling reagents with organotin and organoboron reagents in 2006," explained Professor Yu, "we have focused on improving the versatility and practicality of this catalytic reaction. This paper overcomes three main limitations that existed in our C–H activation/C–C coupling reaction."

"First, the rate of C–H activation, especially when $sp^3$ C–H bonds are involved, is slow. Increasing the rate of the C–H activation step is crucial for raising the turnover frequency and numbers. The CONHOMe is by far the most effective functional group in directing Pd insertion into $sp^3$ C–H bonds. Second," continued Professor Yu, "functional groups assisting site-selective C–H activation are either not synthetically useful or limited in scope in terms of coupling partners. CONHOMe has been used as an ester surrogate in synthesis. Finally, the previously used metal oxidants [Cu(II), Ag(I)] for this reaction are too expensive. The use of air as the oxidant will be the ultimate solution." Concerning the future research perspectives, Professor Yu said that "the discovery of using a synthetically useful CONHOMe group to promote C–H activation significantly improves the practicality of C–H activation/C–C coupling reactions by overcoming the above-mentioned three limitations. We are currently modifying the conditions to reduce the pressure of air from 20 atm to 1 atm," he continued, "thereby making it more convenient for process chemistry on large scale. Furthermore, we are developing an enantioselective version of this reaction to provide a versatile approach to construct chiral quaternary carbon centers," he concluded.

*Matteo Zanda*

## About the authors

**Jin-Quan Yu** studied chemistry at East China Normal University (P. R. of China) from 1982–1987, during which time he completed his thesis work under the supervision of Professor L. X. Dai and B. Q. Wu at the Shanghai Institute of Organic Chemistry (P. R. of China). He obtained his MSc degree under the supervision of Professor S. D. Xiao at Guangzhou Institute of Chemistry (P. R. of China) in 1990. He then went to Cambridge University (UK) in 1994 and obtained his PhD in 2000 under the supervision of Dr. J. B. Spencer. He was a Junior Research Fellow in St. John's College from 1999–2003, during which time he spent 15 months in Professor E. J. Corey's laboratory as a postdoctoral fellow. In 2003 he was awarded a Royal Society University Research Fellowship to start his independent work on oxazoline-directed asymmetric C–H activation in Cambridge. He joined the faculty of Brandeis University (USA) in 2004 as an Assistant Professor and moved to The Scripps Research Institute in 2007 as an Associate Professor where his research group is engaged in the development of catalytic C–H activation reactions.

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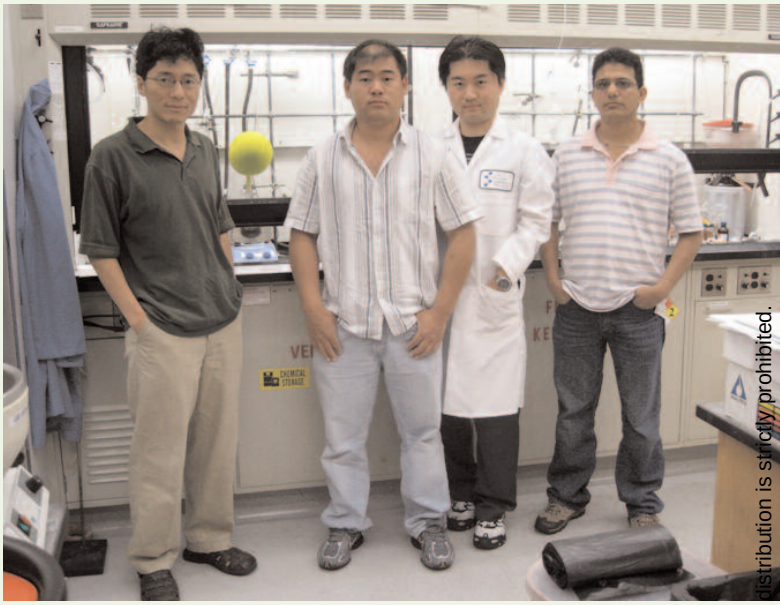
**Donghui Wang** was born in Heilongjiang (P. R. of China). He obtained his BSc degree from Lanzhou University (P. R. of China) in 2000. After working as a research assistant at the Shanghai Institute of Organic Chemistry, he went to Brandeis University for graduate studies in 2004 and obtained an MSc degree. He is currently a graduate student at The Scripps Research Institute, working under the supervision of Professor J.-Q. Yu. His research interests include transition-metal-catalyzed reactions and organic syntheses.

**Masayuki Wasa** was born in Osaka (Japan). He graduated with highest honor from Brandeis University, with a BS in chemistry in 2006. He is currently pursuing his PhD at The Scripps Research Institute under the supervision of Professor J.-Q. Yu. His research interests include catalytic reactions and organic synthesis.

**Ramesh Giri** was born in Chitwan (Nepal). He graduated with distinction from Tribhuvan University (Nepal) with an MSc in organic chemistry in 2000 under the supervision of Professor S. M. Tuladhar. He went to Cambridge University for graduate studies where he received his MPhil in bio-organic chemistry in 2003 under the guidance of Dr. J. B. Spencer. He is currently pursuing his PhD at The Scripps Research Institute under the supervision of Professor J.-Q. Yu. His research is focused on transition-metal-catalyzed reactions and development of synthetic methodologies.



*From left: Prof. J.-Q. Yu, D. Wang, M. Wasa, R. Giri*

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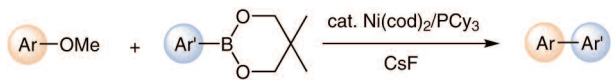
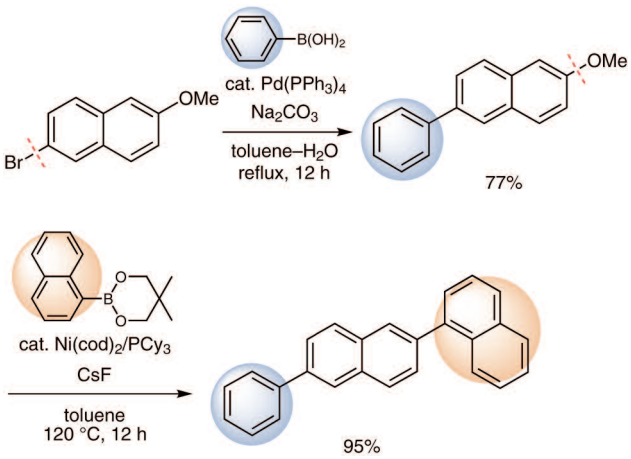
# Nickel-Catalyzed Cross-Coupling of Aryl Methyl Ethers with Aryl Boronic Esters

*Angew. Chem. Int. Ed.* **2008**, *47*, 4866–4869

The Suzuki–Miyaura reaction is recognized as an indispensable tool for organic chemists, allowing for the building of complex molecules via the palladium- or nickel-catalyzed cross-coupling of organoboron compounds with electrophiles. Although this reaction has seen explosive advancement since it was first discovered in 1979, the choice in terms of electrophilic coupling partner remains essentially limited to organic halides and sulfonates. If anisole derivatives could be used in place of aryl halides for the Suzuki–Miyaura coupling, this would significantly expand the utility of the methodology. The C–OMe bond in anisoles, however, is inactive for most organic transformations. Recently a group of researchers from the Osaka University (Japan) has established the first catalytic system that cross-couples aryl methyl ethers with organoboronic esters.




"We began this research project with a high degree of optimism," said Professor Naoto Chatani, "focusing on the development of a Suzuki–Miyaura-type reaction using anisole derivatives, based on the pioneering works of Wenkert (*J. Am. Chem. Soc.* **1979**, *101*, 2246; *J. Org. Chem.* **1984**, *49*, 4894) and Dankwardt (*Angew. Chem. Int. Ed.* **2004**, *43*, 2428), who demonstrated the feasibility of the cross-coupling of anisole derivatives with Grignard reagents. Thus, we initially employed a $Ni(cod)_2/PCy_3$ catalyst system, which is effective for the cross-coupling of anisoles with Grignard reagents. As expected, optimizing the substituent on the boron atom," continued Professor Chatani, "as well as solvent, base, and temperature, led to the formation of the cross-coupled product in 93% isolated yield when 2-methoxynaphthalene and phenylboronic ester were used as substrates." With respect to the boronic ester component, the scope of this cross-coupling proved to be quite broad. "Functional groups that cannot be used in the previously reported cross-coupling with Grignard reagents," confirmed Professor Chatani, "including ketones and esters, are tolerated by our reaction. On the other hand, we were surprised to find that no cross-coupling products could be obtained using simple anisoles." Indeed, subsequent studies revealed that the applicable substrates are limited to aryl methyl ethers on fused aromatic systems, such as naphthalene and phenanthrene, and to anisoles containing electron-withdrawing groups. "Fortunately," said Professor Chatani, "we chose 2-methoxynaphthalene as a test substrate for the initial optimization study, because it led to the discovery of this new cross-coupling reaction. Although the process has limitations, this discovery establishes anisole derivatives as potential electrophiles for cross-coupling processes. Currently, we are studying the reaction mechanism, which seems to be quite different from cross-coupling using Grignard reagents," concluded Professor Chatani, "and we are also working toward the development of a more versatile catalyst system and its application to oligoarene synthesis (a preliminary result is shown below)."




According to Professor Paul Knochel, an expert in organometallic chemistry and an Editor of **SYNTHESIS** from the Ludwig-Maximilians-Universität Munich (Germany), "This nickel-catalyzed cross-coupling of aryl methyl ethers using aryl boronic esters extends further the scope of modern cross-

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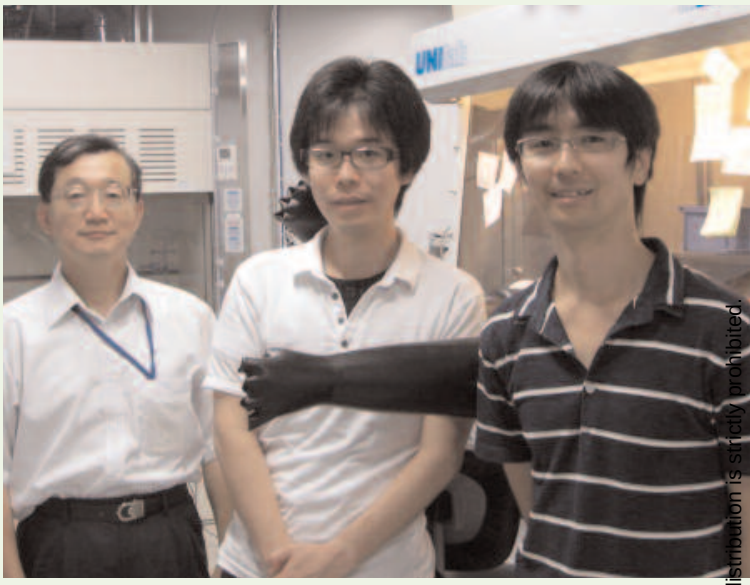
coupling methodology. M. Tobisu and N. Chatani have found a simple, convenient catalytic system. The reaction," concluded Professor Knochel, "is compatible with many functional groups and opens new perspectives for the synthesis of complex aromatic and heterocyclic rings."

Matteo Zanda



From left: Prof. N. Chatani, Dr. T. Shimasaki, Dr. M. Tobisu

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- **Direct and Stereospecific Synthesis of Allenes via Reduction of Propargylic Alcohols with $Cp_2Zr(H)Cl$**
  *(Focus on an article from the current literature)*
- **Conference Report**
  *(Focus on the American Chemical Society 236th National Meeting, Philadelphia, USA, August 17–21, 2008)*

## FURTHER HIGHLIGHTS

**SYNTHESIS**
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**SYNLETT**
**Account on: Synthetic Methods for Multiply Substituted Butadiene-Containing Building Blocks**
*(by Z. Xi, W.-X. Zhang)*

**SYNFACTS**
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