

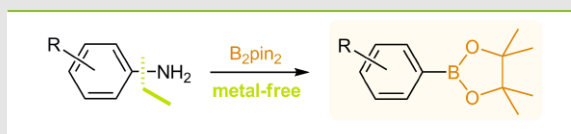
# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2010/05

## SYNSTORIES ■ ■ ■ ■

■ **Direct Conversion of Arylamines to Pinacol Boronates**



■ **Palladium-Catalyzed Intermolecular Addition of Formamides to Alkynes**

■ **Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides**

### CONTACT ++++

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Dear readers,

Very few of us will disagree on the fact that there is still a great need for more environmentally and economically sustainable, more efficient synthetic methods that can be used to produce the organic molecules which are essential components of drugs, materials, agrochemicals, and all the organic-chemistry-based items which are heavily used by our society. This issue of **SYNFORM** presents three important and novel reactions which definitely contribute to the advancement of organic synthesis in the direction outlined above. The first **SYNSTORY** describes a strategy developed by the group of Yasushi Tsuji (Japan) for the preparation of  $\alpha,\beta$ -unsaturated amides from alkynes and formamides via palladium catalysis. In the second **SYNSTORY**, Jianbo Wang (P. R. of China) elaborates on his recent metal-free conversion of arylamines into pinacol boronates, which are heavily used in Suzuki–Miyaura-type chemistry. Finally, Daniel J. Weix (USA) provides an insight into his novel reductive cross-coupling reaction of aryl halides with alkyl halides, which occurs without the need of generating intermediate organometallic species.

Enjoy your reading!

**Matteo Zanda**

Editor of **SYNFORM**

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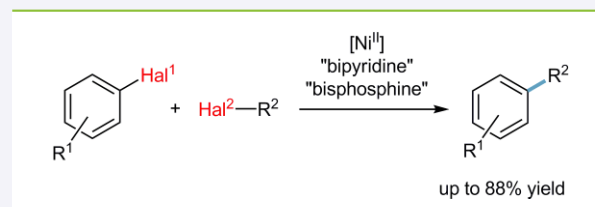
## IN THIS ISSUE

### SYNSTORIES ■ ■ ■ ■

**Palladium-Catalyzed Intermolecular Addition of Formamides to Alkynes** ..... A41

**Direct Conversion of Arylamines to Pinacol Boronates** ..... A43

**Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides** ..... A45

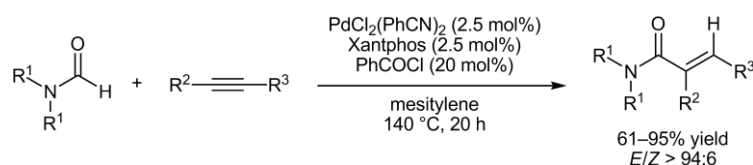


**COMING SOON** ..... A47

NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

## Palladium-Catalyzed Intermolecular Addition of Formamides to Alkynes

*J. Am. Chem. Soc.* **2010**, *132*, 2094–2098



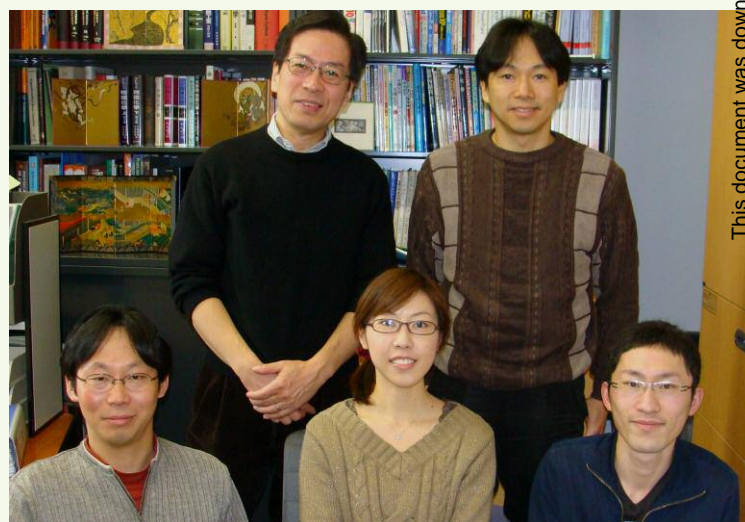
■ The addition of formamides to unsaturated compounds is a synthetically important process since an amide functionality can be introduced with high atom-efficiency. More than twenty years ago, Professor Yasushi Tsuji, now at Kyoto University (Japan), described the first example of the addition of formamides to alkenes (Y. Tsuji, S. Yoshii, T. Ohsumi, T. Kondo, Y. Watanabe *J. Organomet. Chem.* **1987**, *331*, 379). However, the reaction conditions were very harsh and carbon monoxide pressure was indispensable to prevent catalyst decomposition. To date, the addition of formamides to alkenes has not been reported to be particularly efficient, in spite of many efforts following its original discovery. The first addition of formamides to alkynes was reported as an intramolecular reaction (Y. Kobayashi, H. Kamisaki, K. Yanada, R. Yanada, Y. Takemoto *Tetrahedron Lett.* **2005**, *46*, 7549). In 2009, the first *intermolecular* addition of formamides to alkynes was reported by Nakao and Hiyama to occur in the presence of the Ni(0)-AlMe<sub>3</sub> catalyst system (Y. Nakao, H. Idei, K. S. Kanyiva, T. Hiyama *J. Am. Chem. Soc.* **2009**, *131*, 5070). “This publication prompted us to report our independent studies on palladium-catalyzed intermolecular addition of formamides to alkynes,” said Professor Tsuji.

“Our methodology differs in many respects from the Ni(0)/AlMe<sub>3</sub>-catalyzed process: (1) *terminal* alkynes were successfully utilized and afforded adducts for the first time; (2) carbonyl functionalities susceptible to AlMe<sub>3</sub> could be tolerated; (3) adducts with diarylacetylenes did not undergo *E/Z* isomerization. The transition-metal-catalyzed addition reaction is expected to be very important and should allow many different highly efficient transformations to be carried out,” explained Professor Tsuji.

“All the authors belong to my laboratory at Kyoto University,” said Professor Tsuji. “Miss Katafuchi did all the experiments in the paper. Assistant Professor Fujihara gave her a lot of advice, and Associate Professor Terao and Mr. Iwai added a great conceptual contribution. Miss Katafuchi is definitely one of the best students I have ever seen,” he concluded. ■

Matteo Zanda

### About the authors



In the back row, from left: Prof. Y. Tsuji, Prof. J. Terao  
 In the front row, from left: Prof. T. Fujihara, Y. Katafuchi, T. Iwai

>>

**Yasushi Tsuji** was born in Osaka-fu, Japan in 1953. He received his Bachelor's (1976) and Master's (1978) degrees and his Doctor of Engineering (1981) from Kyoto University under the supervision of Professor Yoshinobu Takegami. He was appointed as a Research Associate at the Faculty of Engineering, Kyoto University in 1981. He spent the year 1986 to 1987 as a postdoctoral fellow at Northwestern University (USA) with Professor Tobin J. Marks. He was an Associate Professor at the Faculty of Engineering, Gifu University (Japan) from 1989 to 1998, then at the Institute for Molecular Science from April to September in 1998. He was promoted to a Full Professor at the Catalysis Research Center, Hokkaido University (Japan) in 1998. In 2006, he moved back to Kyoto and has been a Full Professor at the Faculty of Engineering, Kyoto University since then. He received the Chemical Society of Japan Award for Creative Work in 2002. He has been interested in the development of new catalysis by transition-metal complexes.

**Yuko Katafuchi** was born in Hong Kong (1985) and raised in New Jersey (USA) (1989–1995) and Kanagawa (Japan) (from 1995 onwards). She received her Bachelor of Engineering degree in 2008 and Master of Engineering degree in 2010 from Kyoto University under the supervision of Professor Yasushi Tsuji. She is currently a researcher at Sumitomo Chemical Co., Ltd.

**Tomohiro Iwai** was born in Gunma (Japan) in 1984. He received his Bachelor's (2006) and Master's (2008) of Science degrees from Hokkaido University (Japan) under the supervision of Professor Yasushi Tsuji and Professor Takanori Suzuki. In 2008 he joined Professor Yasushi Tsuji's research group and he is currently a PhD student in the Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University. He works as a JSPS Research Fellow and his current research interest is organometallic chemistry.

**Jun Terao** was born in Osaka (Japan) in 1970. He received his PhD degree from Osaka University under the guidance of Professor N. Sonoda and Professor N. Kambe in 1999. After working as a postdoctoral fellow at Hokkaido University with Professor T. Takahashi, he joined the Department of Applied Chemistry, Graduate School of Engineering, Osaka University, as an Assistant Professor. From 2002 to 2003, he worked at the University of Oxford (UK) with Professor H. L. Anderson as a postdoctoral fellow. He was promoted to Associate Professor in 2008 in the Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University. He received the Thieme Chemistry Journal Award in 2005. His current research interests are organic synthesis, organo-metallic chemistry, supramolecular chemistry and molecular electronics.

**Tetsuaki Fujihara** was born in Shiga (Japan) in 1973. He received his BSc from Shizuoka University (Japan) in 1996. He moved to Hokkaido University (Japan), where he pursued his M.Sc. (1998). He received his PhD in 2001 from Hokkaido University under the supervision of Professors Yoichi Sasaki and Taira Imamura. Subsequently, he conducted postdoctoral research with Professor Koji Tanaka at the Institute for Molecular Science (Japan). In 2004, he joined Professor Yasushi Tsuji's group at the Catalysis Research Center, Hokkaido University as a postdoctoral fellow. He was appointed an Assistant Professor at Kyoto University in 2006. His research interests are related to the synthesis of nano-scale molecular catalysts as well as the development of novel organic transformations catalyzed by transition-metal complexes.

## Direct Conversion of Arylamines into Pinacol Boronates

*Angew. Chem. Int. Ed.* **2010**, *49*, 1846–1849

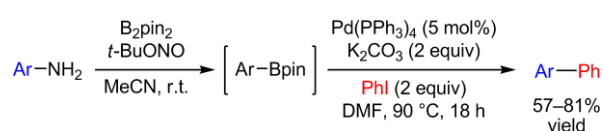
■ Arylboronic acids or arylboronates are important synthetic building blocks which are extensively used in Suzuki–Miyaura cross-coupling reactions. This has created an increasing demand for various boronic acids and esters from both academia and industry. In general, boronic acids are prepared by the reaction of aryl Grignard or aryllithium reagents with trialkyl borates followed by hydrolytic workup. This traditional approach, although still widely practiced, suffers from obvious drawbacks such as rigorously anhydrous conditions and narrow functional group compatibility. Palladium-catalyzed cross-coupling of aryl bromides or iodides with the pinacol ester of diboronic acid is another important approach to these compounds. More recently, great efforts have been concentrated on the transition-metal-catalyzed direct borylation of aromatic C–H bonds.

All of these approaches require some kind of metal in the transformation, either as catalysts or as stoichiometric reagents. Recently, Professor Wang and coworkers at Peking University (P. R. of China) have developed a metal-free approach by directly converting arylamines into pinacol boronates at room temperature. This novel transformation follows a Sandmeyer-type reaction sequence: the arylamine is first converted into the corresponding diazonium ion by reaction with *tert*-butyl nitrite, and then the diazonium ion further reacts with the diboron reagent  $B_2pin_2$  to deliver the final product.



“This new methodology has several advantages,” explained Professor Wang. “First, compared with traditional methods which use aryl halides, arylamines are inexpensive and largely available starting materials. In fact, they are readily made from arenes through nitration and subsequent reduction. Thus, this method provides the possibility of reducing the cost for the preparation of this class of compounds. Second,” continued Professor Wang, “it is metal-free, thus avoiding possible contamination of the boron products by metals, which is very

important for industrial applications. The use of metals may indeed cause environmental problems for large-scale production, as well as difficulties in the purification of the products. Third, the reaction conditions are mild, as the reactions can be carried out in the air at room temperature, while traditional methods require anhydrous conditions and low temperature. Fourth, the boronate products from this reaction can be used in the subsequent palladium-catalyzed coupling reaction without isolation. This avoids the tedious column-chromatographic separation of unstable boronate compounds.”



Serendipity plays a vital role in many scientific discoveries. When asked where this extraordinary idea came from, “it arose by chance”, was the answer given by Fanyang Mo, one of the co-authors. “When I was working on another project, I needed to convert an aromatic amino group into pinacol boronate. The standard procedure for converting arylamines into arylboronic acids or -boronates would need two steps, namely a Sandmeyer reaction to convert the amino group into a halogen group, followed by use of a Grignard reagent or a palladium-catalyzed borylation,” he continued. “Although the two-step procedure is highly reliable, the combination of these reactions in the conversion of arylamines into arylboronates is usually not very efficient because of the generally low-yielding and tedious separation procedures required. This led us to wonder if there was a way to skip the halogenation step and to convert the amine directly into the boronate.”

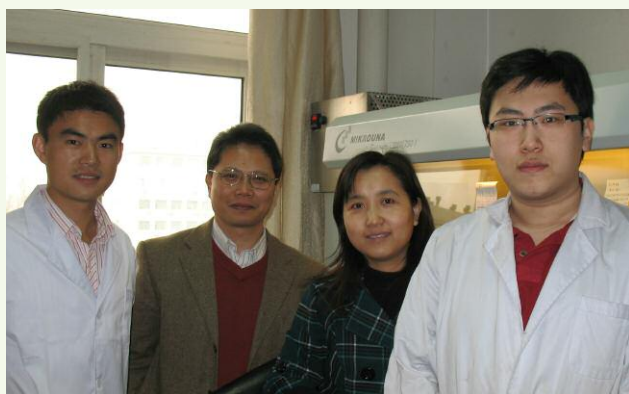
“As we know, the Sandmeyer reaction is a classic reaction that replaces an aromatic amino group with halogen as well as other groups such as hydrogen, hydroxy, cyano and azido groups,” said Professor Wang. “Diazonium ions are the common intermediates in these synthetically very useful transformations. In view of the diversity of transformations through diazonium ions, we conceived that it might be possible to replace an aromatic amino group with a boron group under Sandmeyer reaction conditions. We tried this reaction and it was indeed the case,” added Professor Wang.

Concerning future research prospects, Professor Wang said that “the discovery of direct conversion of arylamines into arylboronates provides an alternative method to synthesize

this type of important compound. Moreover, it opens the possibility to further develop new synthetic methods based on the diazonium ion,” he concluded. ■

Matteo Zanda

### About the authors



From left: F. Mo, Prof. J. Wang, Dr. Y. Zhang, D. Qiu

**Fanyang Mo** was born in Liaoning Province of China in 1982. He received his BSc and MSc degrees from Beijing Institute of Technology (P. R. of China) in 2004 and 2006 under the supervision of Professor Zhiming Zhou. He is currently a PhD student in the College of Chemistry and Molecular Engineering, Peking University, under the supervision of Professor Jianbo Wang. His research interests include synthetic applications of diazo compounds in stereoselective synthesis, as well as aromatic C–H and C–N bond activation and functionalization.

**Yubo Jiang** was born in Anhui province of China in 1975. He obtained his BSc from Huaibei Coal Industry Teachers College and MSc from Tongji University (P. R. of China). He is now a PhD student at Tongji University. He spent one year (2009) as visiting student in Professor Jianbo Wang's laboratory.

**Di Qiu** was born in Tianjin (P. R. of China). He is now an undergraduate student at Peking University. He joined Professor Jianbo Wang's lab in 2009. He expects to pursue his PhD studies in the same research group.

**Yan Zhang** obtained her BSc degree in 1997 and PhD in 2002 from Lanzhou University (P. R. of China). She continued her research as a postdoctoral associate at Hong Kong University of Science and Technology (P. R. of China), University of Innsbruck (Austria) & Leibniz Institute of Surface Modification (IOM) e. V. (Germany), University of Missouri-St. Louis (USA), and Auburn University (USA). She began her academic career at Peking University in 2008 in Professor Jianbo Wang's group. Her research focuses on the application of transition-metal complexes of N-heterocyclic carbenes and the synthesis of small biological compounds.

**Jianbo Wang** received his BSc degree from Nanjing University of Science and Technology (P. R. of China) in 1983 and his PhD from Hokkaido University (Japan) in 1990. He was a postdoctoral associate at the University of Geneva (Switzerland) from 1990 to 1993, and at the University of Wisconsin-Madison (USA) from 1993 to 1995. He began his independent academic career at Peking University in 1995. His research interests are focused on catalytic metal-carbene transformations.

## Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides

*J. Am. Chem. Soc.* **2010**, *132*, 920–921; *Synfacts* **2010**, 457 (Synfact of the Month)

■ In spite of the remarkable progress made in organic synthesis, there is still a great need for novel environmentally and economically sustainable, user-friendly methods, that can be used to produce organic molecules in an efficient and straightforward manner. One such method was discovered recently by the group of Professor Daniel J. Weix at the University of Rochester, NY (USA). The new reaction allows for the synthesis of functionalized alkylated aromatic compounds in one pot from the corresponding aryl and alkyl iodides/bromides, and does not require the pre-generation of organometallic reagents.

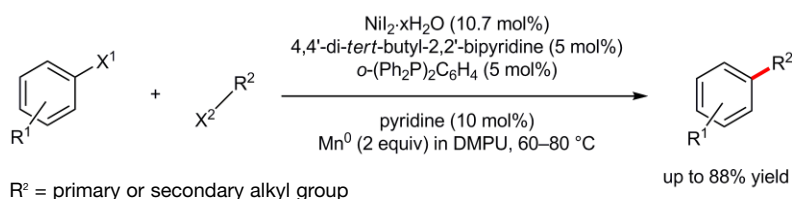
“Cross-coupling reactions have changed the way molecules are made,” said Professor Weix, “but I think many researchers have had the experience that the synthesis of the appropriate organometallic precursor requires more time and care than the cross-coupling reaction it is being made for! And while stunning advances in the synthesis of organometallic reagents have made more functionalized organometallic reagents accessible, these procedures still require time and special care (often cryogenic temperatures).” According to Professor Weix, these problems are multiplied whenever a researcher wants to make many analogues, such as is common during the drug discovery process or in any other situation where a molecule is being designed for a function. “Because so many organometallic reagents are derived from organic halides, and transition metals can easily insert into carbon–halogen bonds under very mild conditions, the cross-coupling of two organic halides is obviously an attractive solution,” he said. “Yet the question then becomes one of selectivity – selectivity for cross-coupling over competitive homocoupling and selectivity for coupling over potential side reactions, like  $\beta$ -hydride elimination.”

According to Professor Weix, the availability of starting materials is one big advantage of using organic halides in

place of pre-formed organometallic reagents. “Even when considering organoboronic acids, the most widely commercially available organometallic reagents, there are only about 3000 commercially available,” he said. “Compare this to organic iodides, the least available of the organic halides, where there are about 84000 commercially available. (Search of commercially available derivatives with MW < 500, Scifinder Scholar 2009) When one considers bromides, the number available improves to about 650000! To top it all off, the reagents are generally very stable – filtration through a small amount of basic alumina is sufficient to clean up even the oldest samples.”

The overall process is reductive, so a terminal reductant is required (zinc, magnesium, manganese, etc.), but from the start Professor Weix and his coworkers wanted to develop a process that did not proceed by the in situ generation of an organometallic reagent followed by a traditional cross-coupling mechanism. “While methods of this type could be envisioned to solve many of the problems listed above,” he said, “we thought that, ultimately, this mechanism would be limiting and a focus of our research is to explore less-well-studied mechanisms that have the potential for new modes of reactivity.”

Professor Weix and the coauthors of the paper chose to focus on the coupling of an aryl halide with an unactivated alkyl halide because they thought the inherent differences between  $sp^3$ - and  $sp^2$ -hybridized organic halides would allow them to develop a general, cross-selective process, and because the products remain a challenge for traditional methods. “We also set out looking for multimetallic catalysis as a potential solution to this problem, which led us to our reported catalytic system that contains two different ligands, a bipyridine and a bisphosphine,” he said. “While we have yet to discern how the bisphosphine’s presence increases the yield of the



reactions, we were able to gather some evidence that organomanganese reagents are not intermediates in the cross-coupling reaction.” According to Professor Weix, the strongest piece of evidence is the reasonable yield obtained when an organic reductant [tetrakis(dimethylamino)ethylene, TDAE] is used in place of manganese. “While we are continuing to explore the potential and mechanism of the reaction,” he confirmed, “our initial results demonstrate its promise with high functional-group compatibility, a simple procedure (set up on bench-top, all reagents air- and moisture-stable, reaction changes color when complete), and generally good yields. The ability to use an unprotected alcohol, the tolerance for common nitrogen protecting groups (Boc, Cbz), and the lack of cross-reactivity with a boronic acid ester should be particularly helpful in synthesis.”

Professor Weix explained that several groups actually developed protocols for the in situ generation and cross-coupling of organometallic reagents concurrent with their work (Gosmini,<sup>1</sup> Jacobi von Wangelin,<sup>2</sup> Lipshutz<sup>3</sup>) that, collectively, are a really nice advance over previous one-pot organometallic reagent synthesis/cross-coupling sequences and certainly raised the bar for their own work.

“While we have not yet investigated the mechanism of our nickel-catalyzed process, it is very likely similar to one of two proposed for the electrochemical nickel-catalyzed homocoupling of aryl halides.<sup>4</sup> In fact, there was an isolated report of the electrochemical coupling of an unactivated alkyl bromide with an aryl iodide in low yield back in 1996 – an important precedent.<sup>5</sup> Concurrent with our work, Durandetti and co-workers<sup>6</sup> had found that nickel and a manganese reductant could cross-couple allyl acetate or benzyl chloride with an sp<sup>2</sup>-hybridized organic halide in the context of a domino reaction,” concluded Professor Weix. ■

Matteo Zanda



Prof. D. J. Weix



D. A. Everson



R. Shrestha

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## SYNFORM 2010/06 is available from May 20, 2010

In the next issues:

### SYNSTORIES ■ ■ ■ ■ ■

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

■ **Catalytic Enantioselective Dieckmann-Type Annulation**  
(*Focus on an article from the current literature*)

■ **Stereoselective Addition of Grignard Reagents to New  
P-Chirogenic N-Phosphinoylimines**  
(*Focus on an article from the current literature*)

### FURTHER HIGHLIGHTS + + + +

#### SYNTHESIS

**Special Issue dedicated to Rolf Huisgen on the occasion of  
his 90th birthday in issue 12/2010**

#### SYNLETT

**Account on: Asymmetric Friedel–Crafts Alkylation of Indoles:  
The Control of Enantio- and Regioselectivity**  
(*by M. Zeng, S.-L. You*)

#### SYNFACTS

**Synfact of the Month in category “Polymer-Supported  
Synthesis”: Graphene-Coated Cobalt Nanoparticles Supported  
Palladium Catalyst**

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