

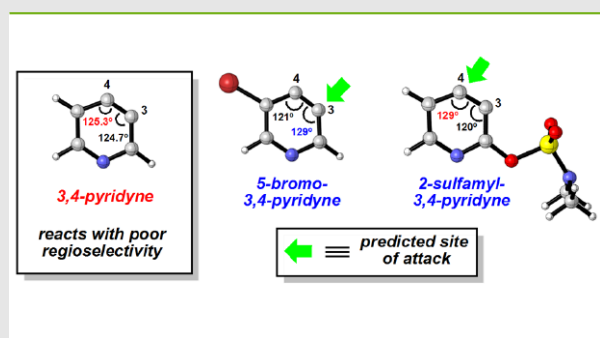
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2013/06

SYNSTORIES

■ **Regioselective Reactions of 3,4-Pyridynes Enabled by the Aryne Distortion Model**



■ **Cobalt-Catalyzed C4-Selective Direct Alkylation of Pyridines**

■ **Synthesis of Fluorenones via Quaternary Ammonium Salt Promoted Intramolecular Dehydrogenative Arylation of Aldehydes**

■ **Palladium(0)-Catalyzed Alkynylation of C(sp³)-H Bonds**

CONTACT ++++

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



Dear readers,

I am writing this editorial in the bar of a rather posh Hotel in Brussels, while enjoying a very good Belgian beer. What am I doing here? Well... you could easily guess... it's European Commission stuff. More precisely, EU project evaluations. I can't say more; it's confidential, you know. I can easily see what you are thinking now: I am here in this posh Hotel because I am taking advantage of European taxpayers' money. Well, that's not true... we get a lump sum from the European Commission, and we can save on that or rather waste it all in a posh Hotel like this one. I like this place, I see it as a reward and I try to make the most of these situations, which don't happen every day. It's a perfect situation for thinking and writing. Writing this editorial for example, right now there is classical music in the background – honestly I would prefer Michael Bublé in this situation... but that's still OK. So, let's try to remember why I am writing these things... oh yes, of course! It's **SYNFORM!** And it's a great issue of **SYNFORM**, by the way! The first **SYNSTORY** is about a new powerful method for achieving alkylation of pyridines on C-4, developed by Professor M. Kanai (Japan). Next, we have the conceptually innovative synthesis of xanthenes and fluorenones proposed by Professor F. Glorius (Germany). The third **SYNSTORY** leads us into the intriguing world of pyridynes (not pyridines!) that was recently explored by Professor N. K. Garg (USA). Finally, we jump into the hot-area of C(sp³)-H bond functionalizations under the expert guidance of Professor J.-Q. Yu (USA). It's a heavy load of great chemistry!

Enjoy your reading!

Matteo Zanda

Editor of SYNFORM

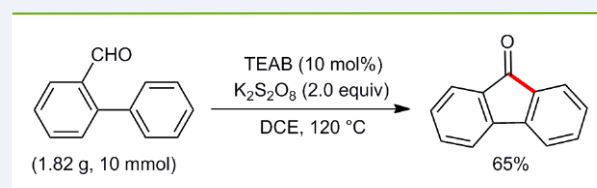
P.S. And I am still enjoying my Belgian beer ;-)

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CONTACT + + + +

If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it

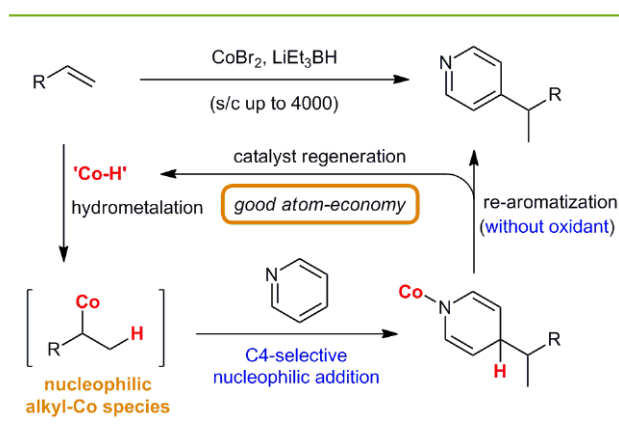
Cobalt-Catalyzed C4-Selective Direct Alkylation of Pyridines

Angew. Chem. Int. Ed. **2013**, *52*, 3213–3216

■ The nucleophilic addition of organometallic reagents to electrophiles is a fundamental C–C bond-forming reaction in organic synthesis. The generation of nucleophilic organometallic reagents, however, generally requires stoichiometric amounts of strong bases and/or reducing metals, such as Mg and Li, and stoichiometric salt waste is therefore inevitably produced. Thus, the development of atom-economical processes, involving the catalytic generation of nucleophilic organometallic species without any stoichiometric amounts of activating reagents, is highly desirable.

The group of Professor Motomu Kanai at The University of Tokyo (Japan) is trying to develop new methods to catalytically generate nucleophilic active species in situ under first-row transition-metal catalysis (for related recent works in this direction, see also: *Angew. Chem. Int. Ed.* **2013**, *52*, 2207 for the generation of nucleophilic aryl-Co species). In the communication covered by this article, Professor Kanai and Dr. Shigeki Matsunaga reported the utility of a low-valent ‘Co-hydride’ species for the generation of nucleophilic alkyl-Co species in the functionalization of pyridines at the C4-position. Although there are many reports on (catalytic) C2-selective pyridine functionalization by using the Lewis basic sp²-nitrogen atom in the pyridine ring as a directing group, examples of direct C4-selective functionalization are quite limited (see the works of Nakao and Hiyama as well as Ong, refs. 10a and 10b in the original paper). Professor Kanai said: “To realize C4-selective functionalization in a different manner from previous reports based on an oxidative addition/insertion/reductive elimination sequence under Ni(0) catalysis, we utilized ‘Co-hydride’ species.” He continued: “Our working hypothesis was as follows (see Scheme 1): Hydrometalation of alkenes with a metal hydride catalyst affords an alkyl-metal species. If the alkyl-metal species has sufficient nucleophilicity, its addition to pyridine would afford a dihydropyridine intermediate. To realize an atom-economical catalytic process, re-aromatization of pyridine without any oxidants and regeneration of the metal-hydride catalyst are the keys for success.”

After intensive screening and optimization studies to fulfill the above-mentioned requirements, the Japanese researchers

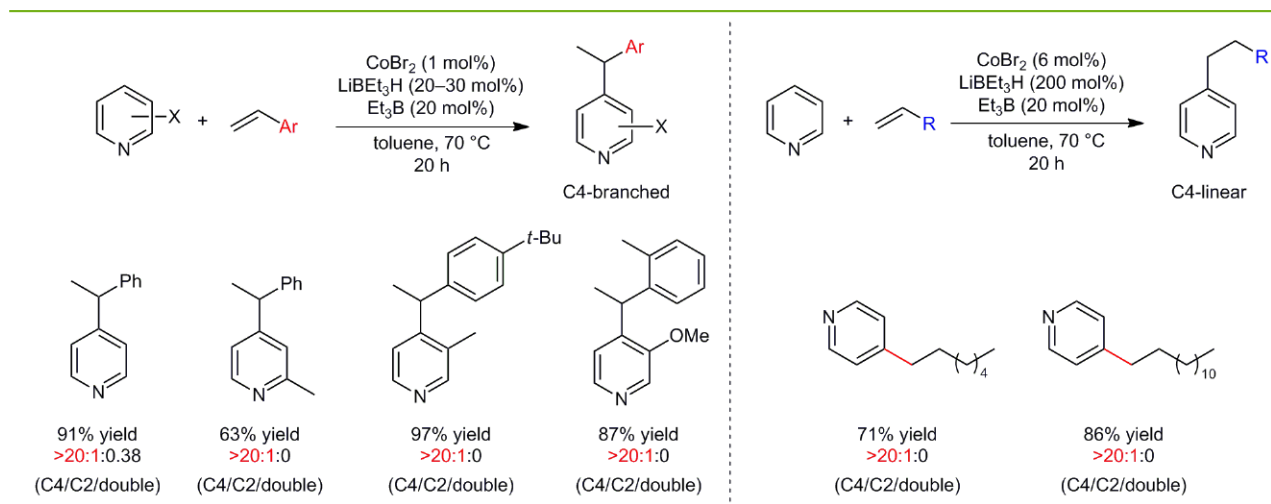


Scheme 1

found that the Co salt in combination with LiEt₃BH was quite effective. The catalyst was suitable for both styrene derivatives and aliphatic alkenes. “Styrene derivatives gave branched adducts in >20:1 selectivity, while aliphatic alkenes predominantly afforded linear adducts (1:>20),” explained Professor Kanai. In almost all cases, high C4-selectivity was observed (Scheme 2). A high catalyst turnover number (TON = 3.4 × 10³) based on the Co salt was observed as demonstrated in the gram-scale reaction with low catalyst loading (s/c=4000).

“Further mechanistic studies are essential for the precise understanding of the reaction mechanism, as well as for clarifying the reason for high C4-selectivity,” said Dr. Matsunaga, “but we believe the present communication clearly demonstrated the utility of first-row transition-metal catalysis for generating nucleophilic active species in situ. The process is ideal in terms of both atom- and step-economy. Further studies to expand the scope of heterocycles are actively ongoing in our group, and new results will be published in due course.”

For the future, the group wishes to see the application of their Co catalysis for the late-stage functionalization of complex biologically active compounds bearing heteroaromatic rings, such as pyridines and quinolines, but the limited functional group compatibility of the present catalyst system remains problematic for addressing the late-stage functional-



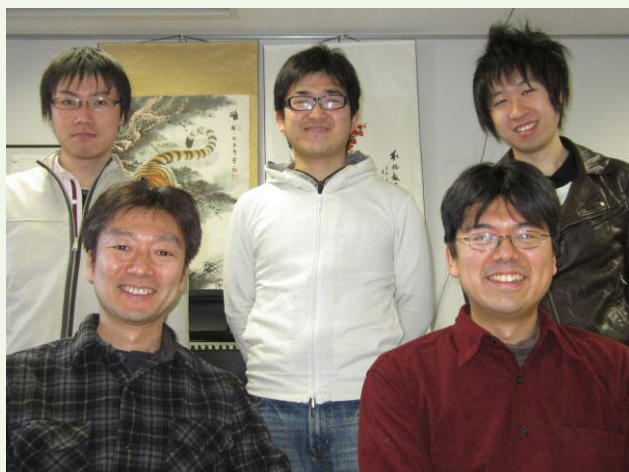
Scheme 2 Representative examples

ization. Because LiEt_3BH is utilized in the current system, applicable functional groups are limited at the moment. Professor Kanai concluded: “We are currently working hard to

develop alternative procedure(s) to generate ‘Co-hydride’ species without using LiEt_3BH .”

Matteo Zanda

About the authors



Front from left: Prof. Dr. M. Kanai, Prof. Dr. S. Matsunaga;
back from left: Dr. T. Andou, H. Komai, Y. Saga

Motomu Kanai was born in 1967 in Tokyo (Japan) and received his BSc from The University of Tokyo (UT, Japan) in 1989 under the direction of the late Professor Kenji Koga.

In the middle of his PhD course at UT (in 1992), he obtained an Assistant Professor position at Osaka University (Japan) under the direction of Professor Kiyoshi Tomioka. He obtained his PhD from Osaka University in 1995. Then, he moved to the University of Wisconsin (USA) for postdoctoral studies with Professor Laura L. Kiessling. In 1997 he returned to Japan and joined Professor Masakatsu Shibasaki's group at UT as an Assistant Professor. After some time as a Lecturer (2000–2003) and Associate Professor (2003–2010), he became a Full Professor at UT. He is also the PI of ERATO Kanai Life Science Catalysis Project (since 2011). He has received The Pharmaceutical Society of Japan Award for Young Scientists (2001), the Thieme Chemistry Journals Award (2003), the Merck-Banyu Lectureship Award (2005), the Asian Core Program Lectureship Award (2008 and 2010, from Thailand, Malaysia, and China), and the Novartis Lecturer in Organic Chemistry (2011). His research interests entail design and synthesis of functional molecules.

Shigeki Matsunaga is an Associate Professor at the University of Tokyo (Japan) in Professor Kanai's group. He was born in 1975 in Kyoto, and received his PhD from The University of

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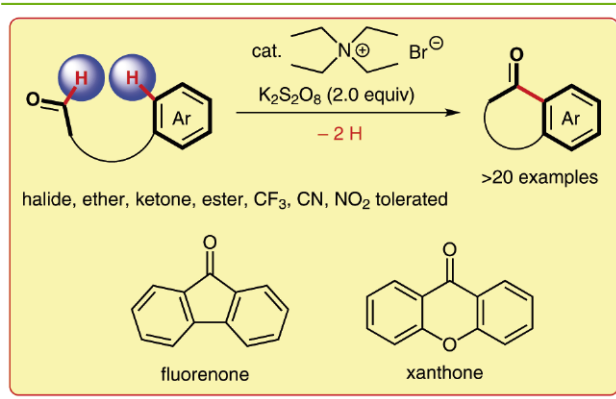
Tokyo under the direction of Professor Masakatsu Shibasaki. He started his academic career in 2001 as an Assistant Professor in Professor Shibasaki's lab at UT. He was promoted to a Senior Lecturer in 2008, and to his current position in 2011. He is the recipient of the Chemical Society of Japan Award for Young Chemists (2006), the Thieme Chemistry

Journals Award (2008), the Mitsui Chemicals Catalysis Award of Encouragement (2009), the Merck-Banyu Lectureship Award (2010), and others. His research interests are in homogeneous catalysis for C–H activation, asymmetric C–C bond formation, and in the synthesis of biologically active compounds.

Synthesis of Fluorenones via Quaternary Ammonium Salt Promoted Intramolecular Dehydrogenative Arylation of Aldehydes

Chem. Sci. **2013**, *4*, 829–833

Fluorenones and xanthenes are core motifs of many natural and biologically active compounds, as well as organic light-emitting materials. Existing synthetic routes to these compounds, such as Friedel–Crafts-type ring closures or the oxidation of fluorenes, are usually limited to electron-rich arenes or require multiple-step synthesis.



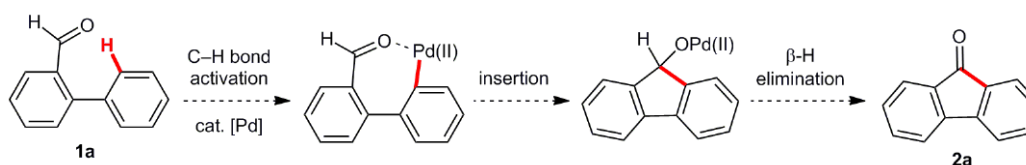
Scheme 1

Recently, Professor Frank Glorius and Dr. Zhuangzhi Shi of the Organic Chemistry Institute at the Universität Münster (Germany) developed a novel and efficient route for the synthesis of fluorenones via direct intramolecular dehydrogenative arylation of aldehydes. The Glorius group has focused its research activity on the catalytic selective functionalization of aldehyde C–H bonds to construct ketones via transition-metal complexes and N-heterocyclic carbene catalysts. Professor

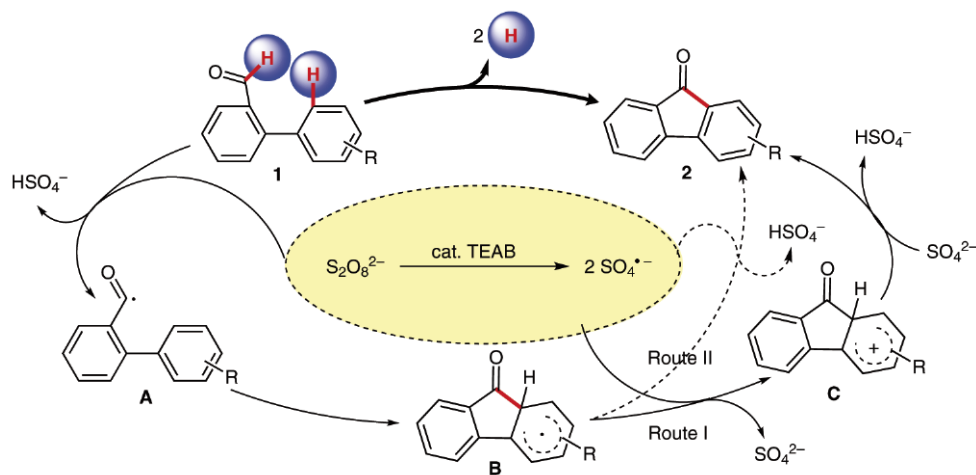
Glorius said: “Our initial intention in this project was to develop a Pd(OAc)₂-catalyzed direct acylation of 2-phenylbenzaldehyde (**1a**) to form fluorenone (**2a**); the desired acylation product **2a** was observed in 48% yield in the presence of 10 mol% Pd(OAc)₂ as the catalyst, 2.0 equivalents of K₂S₂O₈ as the oxidant and 2.0 equivalents of TBAB (tetrabutylammonium bromide) as the additive at 80 °C in DCE.” He continued: “We hypothesized that 2-phenylbenzaldehyde (**1a**), which incorporates an aldehyde group, might analogously function as a directing group to coordinate with palladium(II) followed by C–H bond activation/insertion and reductive elimination leading to fluorenones (Scheme 2).”

However, the researchers were surprised by the outcome of the control reactions, in which the desired cyclization product **2a** was observed in a similar yield even in the absence of any additional palladium catalyst. A further investigation of the cation identified that 10 mol% TEAB (tetraethylammonium bromide) was the optimum catalyst, affording **2a** in 68% yield. Dr. Zhuangzhi Shi suggested: “This direct acylation reaction might proceed via a free-radical pathway. This is actually more attractive than our originally proposed palladium-catalyzed process because it proceeds without the aid of any transition metals, acids or bases, and uses a catalytic amount of a quaternary ammonium salt in the presence of a persulfate oxidant.”

Dr. Shi continued: “A key step in this transformation involves TEAB, which may act as a special initiator for generating sulfate radical anions through an unexplored type of catalytic process. This radical could react with the aldehyde **1** through a hydrogen-abstraction process providing an acyl radical **A** and a bisulfate anion. The resulting acyl radical

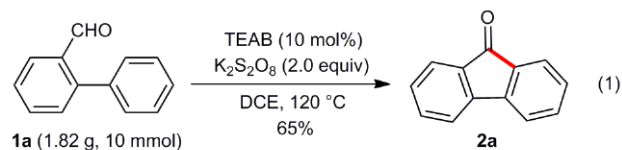


Scheme 2 Initial (incorrect) hypothesis: Pd-catalyzed C–H activation pathway

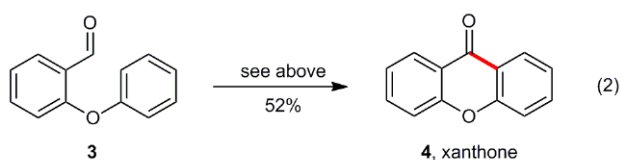


Scheme 3 Plausible reaction mechanism

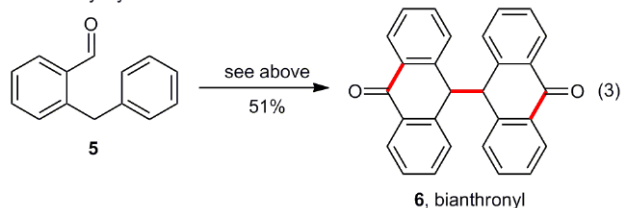
Gram-scale synthesis



Xanthone synthesis



Bianthranyl synthesis



Scheme 4

would then readily add to the arene to form radical intermediate **B**. Single-electron oxidation of **B** by another sulfate radical gives cation **C**, which is deprotonated by the formed sulfate dianion to give the annulation product and another bisulfate anion (Scheme 3)."

With the developed protocol in hand, the fluorenone synthesis could be readily scaled up to gram quantities without difficulty (Scheme 4, eq. 1). The researchers also expanded the scope of this method to the synthesis of xanthenes **4** in moderate yield (Scheme 4, eq. 2). Interestingly, for the reaction of substrate **5**, they isolated bianthranyl **6**, which may derive from the desired anthrone intermediate via homo-coupling (Scheme 4, eq. 3).

Professor Glorius concluded: "This reaction proceeds with an inexpensive system (i.e., catalytic TEAB + $\text{K}_2\text{S}_2\text{O}_8$) and displays a broad scope with respect to the substituents. We anticipate this transformation can complement Friedel–Crafts approaches in the synthesis of fluorenones and xanthenes." ■

Matteo Zanda

About the authors*Dr. Z. Shi*

His research interests include aerobic oxidations and C–H activation chemistry.

Zhuangzhi Shi was born in Nantong, Jiangsu Province (P. R. of China), in 1983. He received his BSc in chemistry and MSc in organic chemistry from Yangzhou University (P. R. of China) in 2005 and 2008, and obtained his PhD (2011) at Peking University (Beijing, P. R. of China), under the supervision of Professor Ning Jiao. He is currently an Alexander von Humboldt Postdoctoral Fellow in the laboratory of Professor Frank Glorius at the

*Prof. F. Glorius*

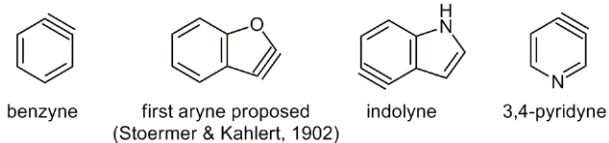
Kohlenforschung and in 2004 was promoted to Associate Professor for Organic Chemistry at the Philipps-Universität Marburg (Germany). Since 2007, he has been Full Professor at the Westfälische Wilhelms-Universität Münster. His research focuses on the development of new concepts for catalysis and their implementation in organic synthesis.

Frank Glorius was educated in chemistry at the Universität Hannover (Germany), at Stanford University (USA) with Professor Paul A. Wender, at the Max-Planck-Institut für Kohlenforschung (Mülheim/Ruhr, Germany) and the Universität Basel (Switzerland) with Professor Andreas Pfaltz, and at Harvard University (USA) with Professor David A. Evans. In 2001, he began his independent research career at the Max-Planck-Institut für

Regioselective Reactions of 3,4-Pyridynes Enabled by the Aryne Distortion Model

Nature Chem. **2013**, *5*, 54–60

■ Arynes are fascinating, yet synthetically useful and highly reactive intermediates, which occupy a pivotal role in organic synthesis. Although benzyne is probably the best known and most used aryne intermediate, a number of heterocyclic arynes have been described and successfully used in a wide range of synthetic methods. The first aryne proposed (over 100 years ago) in fact was a heterocyclic aryne, which was obtained from 3-bromobenzofuran (*Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1633). However, arguably the synthetic potential of such compounds has not been unlocked until recently.



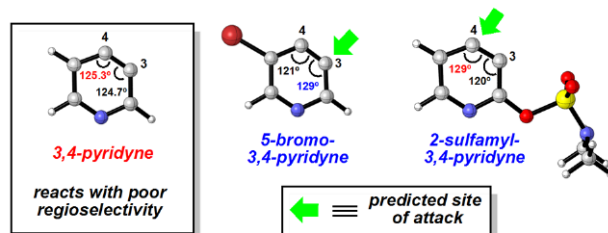
For some time, the research laboratory of Professor Neil Garg at the University of California, Los Angeles (UCLA, USA) has been interested in the chemistry of heterocyclic arynes. Professor Garg said: “In earlier efforts, we studied ‘indolynes’ as a means to prepare substituted indole derivatives. This work led to the synthesis of alkaloids, such as indolactam V and several welwitindolinone natural products.” Importantly, collaborative studies with Professor Ken Houk at UCLA also led to the establishment of the aryne distortion model. This model allows one to make reliable predictions about regioselectivity in reactions of unsymmetrical arynes, including hetarynes. Professor Garg continued: “The predictive powers of this model are best showcased by the computational predictions we made on >150 of heterocyclic arynes (*Angew. Chem. Int. Ed.* **2012**, *51*, 2758) and studies where indolyne regioselectivities could be controlled by a neighboring halide substituent (*J. Am. Chem. Soc.* **2011**, *133*, 3832).”

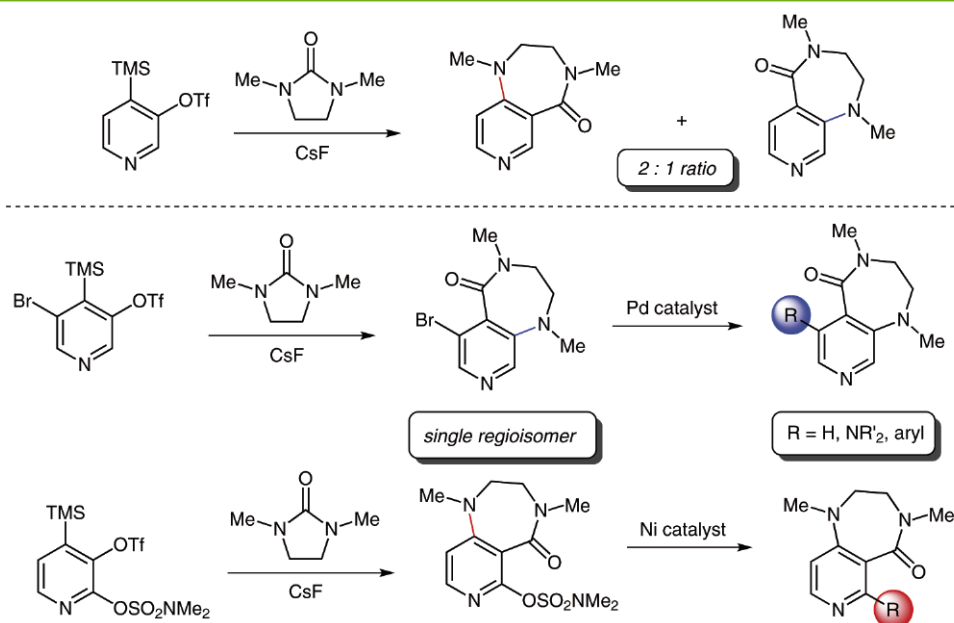
“Given the importance of pyridines in drug discovery,” said Professor Garg, “we hoped to further develop the chemistry of ‘pyridynes’ to enable their widespread use in synthesis. The 3,4-pyridyne seemed like a natural system for our studies because of its rich history.” The compound has been shown to

react with little or no regioselective preference in a variety of trapping agents over the past 50 years. However, a small set of examples, by Snieckus, Caubère, and Guitián, demonstrated that substituted 3,4-pyridynes could react with some regioselectivity. “We were therefore very excited by the possibility of controlling the reactivity of this intermediate to give highly substituted pyridines in a predictable and synthetically useful fashion,” said Professor Garg, adding: “I would like to emphasize that a stellar graduate student named Adam Goetz (first author of this paper) did all of the computational and experimental work from this manuscript single-handedly.”

He continued: “We first carried out a series of simple computational experiments to evaluate substituted 3,4-pyridynes using the aryne distortion model. This allowed us to make predictions regarding pyridyne regioselectivities that would guide future experimentation.” Taking the most promising results, while considering synthetic access to potential pyridyne precursors, they opted to synthesize three pyridyne precursors (precursors to the three pyridynes shown below). “Synthesizing the pyridyne precursors turned out to be a bigger challenge than we had anticipated,” explained Professor Garg. “Nonetheless, we developed syntheses that provided gram quantities of each of the corresponding silyltriflate precursors.” Although silyltriflate precursors to arynes are sometimes criticized because of the challenge in their preparation, it should be noted that they can be used in a tremendous variety of aryne-trapping experiments, using mild fluoride-based reaction conditions, and are therefore very attractive.

Professor Garg said: “With access to the pyridyne precursors, it was exciting to find that pyridynes could be generated





and trapped in nucleophilic addition and cycloaddition experiments. Moreover, the regioselectivity we observed experimentally was consistent with the predictions made by the aryne distortion model.”

One of the most useful aspects of this chemistry is the potential to further manipulate the products obtained from pyridine-trapping experiments, by virtue of the bromo or sulfamyl substituents. “To test this notion, we chose the products resulting from pyridine trapping with dimethylurea because they are obtained as single regioisomers and are structurally reminiscent of benzodiazepines,” explained Professor Garg. Using Pd or Ni catalysis, the bromide or sulfamate, respectively, could be readily manipulated in C–C, C–N, or C–H bond-forming events.

Professor Garg concluded: “We hope that others will now view pyridynes as a productive means to access highly substituted pyridines, especially those that represent new classes of compounds that might be difficult to access by other methods. We are working now with suppliers to make our pyridyne and indolyne precursors commercially accessible. We are also eager to synthesize other heterocyclic arynes as synthetic building blocks and as a means to further test predictions made by the aryne distortion model.” ■

Matteo Zanda

About the authors



A. E. Goetz

Adam E. Goetz was born in Dayton, OH (USA) in 1985. He received his B.A. in Chemistry from Carleton College in Northfield, MN (USA) and conducted summer research with Professor Robert Kempton at Northern Kentucky University (USA). After graduating, he spent a year as a research assistant for Segetis, Inc. in Minneapolis, MN (USA). He is currently a fourth-year graduate student in

Professor Neil Garg's laboratory at UCLA, where his graduate studies are focused on understanding and controlling selectivity in the reactions of heterocyclic arynes.



Prof. N. K. Garg

Neil K. Garg is an Associate Professor of Chemistry at UCLA. Professor Garg received a B.S. degree in Chemistry from New York University (USA) where he carried out undergraduate research with Professor Marc Walters. During his undergraduate years, he spent several months in Strasbourg (France) conducting research with Professor Wais Hosseini at the

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Université Louis Pasteur as an NSF REU Fellow. Subsequently, he obtained his Ph.D. degree in 2005 from the California Institute of Technology (Pasadena, CA, USA) under the direction of Professor Brian Stoltz. He then spent two years in Professor Larry Overman's research laboratory at the University of Cali-

fornia, Irvine (USA) as an NIH Postdoctoral Scholar. Professor Garg started his independent career at UCLA in 2007, where his laboratory develops novel synthetic strategies and methodologies to enable the total synthesis of complex bioactive molecules.

Palladium(0)-Catalyzed Alkynylation of C(sp³)-H Bonds

J. Am. Chem. Soc. **2013**, *135*, 3387–3390

■ α -Propargyl carboxylic acids and their derivatives are extremely important and valuable molecules having a number of applications as drugs, key building blocks for the synthesis of complex natural and bioactive compounds, tools for biomedical research, and innovative bio-materials. In fact, the propargylic function imparts increased reactivity and offers the possibility of introducing further bespoke functionalities for the fine-tuning of their biological activity, as well as acting as a bioconjugation site. An attractive strategy for the synthesis of α -propargyl carboxylic acid derivatives would be the conversion of a C–H bond positioned β to a carboxamide function into an alkyne by formation of a new C–C bond with an activated alkyne derivative. Unfortunately, this potentially versatile methodology has remained elusive owing to the apparent lack of reactivity of such an inactivated C–H bond and the absence of suitable catalytic systems. Recently, the group of Professor Jin-Quan Yu from the Scripps Research Institute (La Jolla, CA, USA) developed a methodology for achieving such a striking transformation, based on the use of Pd(0) catalysts with N-heterocyclic carbene (NHC) or phosphine (PR₃) ligands. Key to the success of the methodology was also the use of an electron-deficient amide derived from commercially available carboxylic acids and (4-CF₃)C₆F₄-NH₂ as substrates for the β -alkynylation with alkynyl bromides. The new synthetic method was thoroughly optimized and a number of catalysts, ligands, and conditions were carefully screened in order to identify the best reaction conditions.

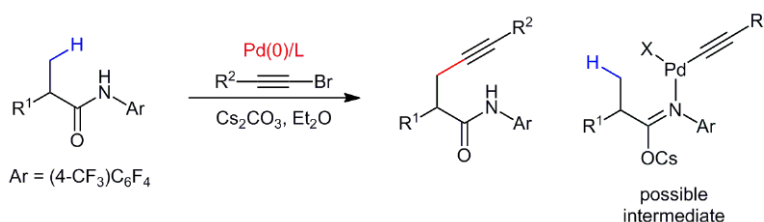
“Despite the long history of using Pd(0)/PR₃ and Pd(0)/NHC catalysts to functionalize aryl C–H bonds using aryl halides as coupling partners, intermolecular activation of C(sp³)-H bonds using this system has only been reported in a

single example of arylation (see the first example from our group: *J. Am. Chem. Soc.* **2009**, *131*, 9886),” said Professor Yu.

“This work uses alkynyl halides as coupling partners and converts C(sp³)-H bonds into synthetically versatile alkynyl groups. Mechanistically, this demonstrates for the first time that [L–Pd(II)-alkynyl] complexes can cleave and alkynylate C(sp³)-H bonds in an intermolecular fashion,” he continued.

Mechanistic studies on the reaction were conducted, showing that substrates incorporating a deuterium atom α to the carboxamide moiety fully retain deuterium, thus suggesting that a β -hydride elimination pathway, as previously observed in conceptually related reactions by Baudoin et al. (*Angew. Chem. Int. Ed.* **2010**, *49*, 7261), is unlikely. This and other experimental evidence led the authors to hypothesize the possible intermediate shown in Scheme 1. The new methodology has remarkably broad scope and allows for the synthesis of a number of structurally diverse propargylic carboxamides in good yields. “Practically, this reaction does not need any external oxidant compared to the Pd(II)-catalyzed C–H activation reactions. Most importantly, the use of optically enriched phosphine and carbene ligands in these transformations could lead to the development of enantioselective C(sp³)-H activation reactions,” concluded Professor Yu. ■

Matteo Zanda



Scheme 1

About the authors*Prof. J.-Q. Yu*

Jin-Quan Yu received his B.Sc. in Chemistry from East China Normal University (Shanghai, P. R. of China; undergraduate thesis study with Professor L.-X. Dai and B.-Q. Wu at the Shanghai Institute of Organic Chemistry, P. R. of China). He obtained his M.Sc. from the Guangzhou Institute of Chemistry (P. R. of China) with Professor X.-D. Xiao, and his Ph.D. from 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 (Waltham, MA, USA) from 2004–2007, and finally to The Scripps Research Institute (USA), where he is currently Frank and Bertha Hupp Professor of Chemistry.

*J. He*

Jian He obtained his first degree from Zhejiang University (Hangzhou, P. R. of China) in 2011, where he worked with Shengming Ma, and is now a second-year student in the Yu group at Scripps.

COMING SOON ►► COMING SOON ►►

SYNFORM 2013/07

is available from
June 17, 2013

In the next issues:

SYNSTORIES ■ ■ ■ ■ ■

■ Efficient and Stereoselective Nitration of Mono- and Disubstituted Olefins with AgNO₂ and TEMPO

(Focus on an article from the current literature)

■ Highly Efficient Cu(I)-Catalyzed Oxidation of Alcohols to Ketones and Aldehydes with Diaziridinone

(Focus on an article from the current literature)

■ N-Chlorosuccinimide, an Efficient Reagent for On-Resin Disulfide Formation in Solid-Phase Peptide Synthesis

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: Enantioselective Organocatalyzed Domino Synthesis of Six-Membered Carbocycles

(by D. Bonne, J. Rodriguez et al.)

SYNLETT

Account on: N-Alkyl Sulfonamides as Useful Carbon Electrophiles

(by Y. Gu, S.-K. Tian)

SYNFACTS

Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": [Synthesis of Tatanans A–C and Reinvestigation of their Glucokinase-Activating Properties](#)

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