

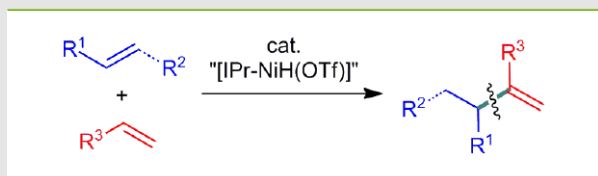
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2011/02

SYNSTORIES ■ ■ ■ ■

■ **Catalytic Intermolecular Tail-to-Tail Hydroalkenylation of Styrenes with α -Olefins**



■ **Chiral Brønsted Acid Catalyzed Enantioselective α -Aminoxylation of Enecarbamates**

■ **Highly Enantioselective Hydroxycarbonylation and Alkoxy-carbonylation of Alkenes Using Dipalladium Complexes as Precatalysts**

CONTACT ++++

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Dear readers,

This issue of **SYNFORM** features three **SYNSTORIES**, one from Europe and two from Asia. The first one comes from Scotland, where Dr. Matthew L. Clarke and his group envisaged a very interesting method for producing carboxylic acids in enantiocontrolled manner directly from olefins through a hydroxycarbonylation process. The second **SYNSTORY** comes from Singapore, where Professor Guofu Zhong and coworkers developed a novel organocatalytic α -aminoxylation of enecarbamates, eventually resulting in the production of stereodefined *N*-alkoxycarbonyl β -aminoalcohols. The third **SYNSTORY** comes from China, and more specifically from Hong Kong, where the group of Professor Chun-Yu Ho discovered an extremely interesting tail-to-tail hydroalkenylation of styrenes with α -olefins leading to the corresponding elongated alkenes. Great science for a great issue!

Enjoy your reading!

Matteo Zanda

Editor of **SYNFORM**

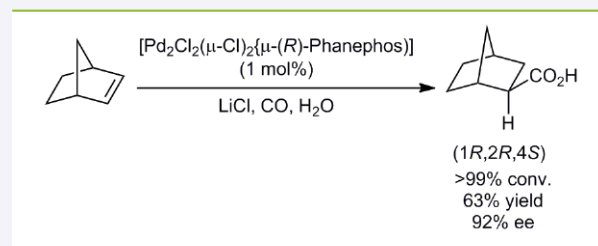
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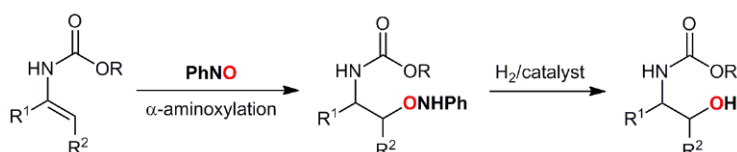
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Chiral Brønsted Acid Catalyzed Enantioselective α -Aminoxylation of Enecarbamates

Angew. Chem. Int. Ed. **2010**, *49*, 8588–8592



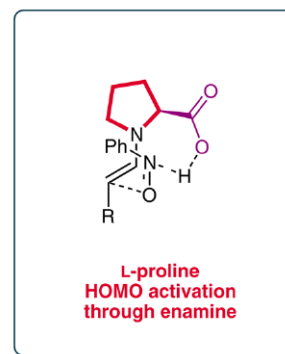
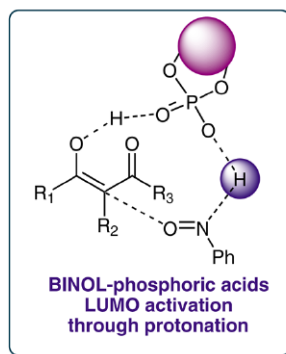
■ A number of biologically and pharmaceutically interesting compounds contain a stereodefined α -hydroxy-carbonyl framework, which is therefore a target of great interest for synthetic chemists. The stereocontrolled introduction of the hydroxy group through α -aminoxylation reactions is an attractive methodology, but the protocol is difficult to apply to linear ketones, which normally feature lower reactivity and stereoselectivity. Recently, the group of Professor Guofu Zhong from the Nanyang Technological University (NTU, Singapore) has developed a novel strategy which holds promise in alleviating this problem.

“Our research group has a long-standing interest in the organocatalytic α -aminoxylation reactions using nitroso compounds as terminal oxidants,” said Professor Zhong. “In 2003, we first reported the facile process converting unmodified aldehydes into enantiopure 1,2-diols via α -aminoxylation catalyzed by L-proline, demonstrating the debut of organocatalysis in this chemistry (*Angew. Chem. Int. Ed.* **2003**, *42*, 4247).” Professor Zhong explained that the contracted term ‘aminoxylation’ is new and was first applied in his *Angewandte* paper above (a VIP paper), and is, according to Professor Zhong, easier to use and write than the traditional term ‘aminoxylation’. “Now, most people accept this term in their publications,” he said. In subsequent years, exciting advancements have been made with the aminoxylation reaction. “With extremely high and predictable enantioselectivity, operational simplicity, and catalyst availability in both enantiomeric forms holding a touch of ‘green’ aspect, the proline-catalyzed α -aminoxylation of carbonyl compounds and its tandem protocols quickly moved up the ranks to a well-established tool for

constructing complex chiral molecules,” said Professor Zhong. “However, certain limitations that come along with L-proline and its derivatives persist with respect to the low catalyst turnover numbers and limited substrate scope, which prompted us to design new alternative activation modes.”

Professor Zhong and co-workers envisioned that by the judicious choice of Brønsted acids, selective protonation of the basic nitrogen of nitroso compounds will facilitate the subsequent nucleophilic attack at the oxygen atom through electrophilic activation. “In light of this blueprint, we identified the first BINOL–phosphoric acid catalyzed α -aminoxylation of β -dicarbonyl compounds with concomitant N/O bond heterolysis (*J. Am. Chem. Soc.* **2009**, *131*, 4562). This finding sets up a novel platform with tremendous opportunities in α -aminoxylation chemistry,” said Professor Zhong.

Phosphoric acid-catalyzed α -aminoxylation vs L-proline version

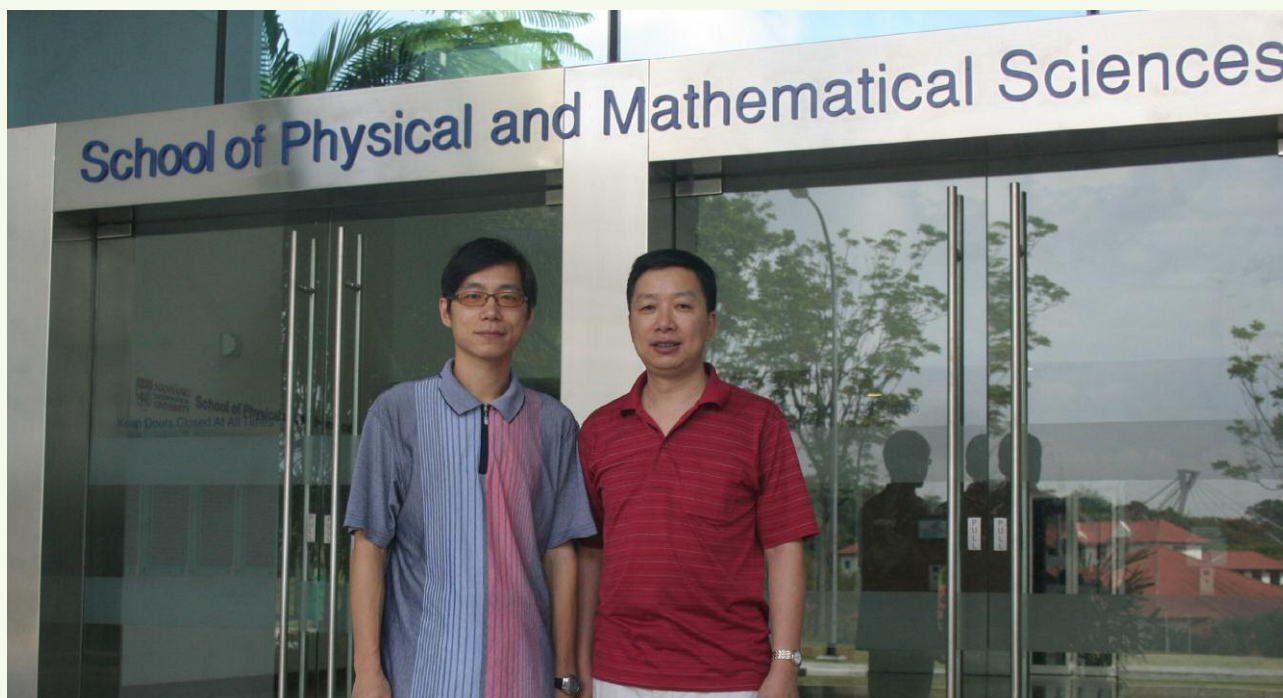


Next, the Singapore researchers set out to address the most challenging substrates in the field of α -aminoxylation, namely, aromatic ketones. “Steric hindrance accompanying extended conjugation made this type of compound extremely reluctant to succumb to the reign of proline,” explained Professor Zhong. “However, by implementing an enecarbamate moiety as activation group with an ideal H-bond handle, the long-desired α -aminoxylation finally took place with excellent enantiocontrol and can be finished in a couple of minutes,” he

said. The usefulness of the transformation was demonstrated through facile access to biologically important building blocks such as α -hydroxy ketones, orthogonally protected vicinal amino alcohols, and *cis*-oxazolidinones. “The fact that *E*- and *Z*-isomers of enecarbamates lead to different regioselective products provided further insights into the origin of O/N selectivity,” concluded Professor Zhong. ■

Matteo Zanda

About the authors



From left: M. Lu, Prof. G. Zhong (The picture was taken in front of the SPMS building at NTU on December 13, 2010)

Guofu Zhong is a faculty member at the Division of Chemistry & Biological Chemistry (CBC), School of Physical & Mathematical Sciences (SPMS), Nanyang Technological University (NTU), Singapore. He obtained his PhD from The Scripps Research Institute (USA) in 1998 under the direction of Professors R. A. Lerner and C. F. Barbas III. He started his academic career at Scripps as Assistant Professor (1999–2004), accepted the Changjiang Professorship (granted by the Chinese Ministry of Education) in the Department of Chemistry at Fudan University, Shanghai (P. R. of China) (2005–2006) and Outstanding PI in the Institutes of Biomedical Sciences (IBS) at the same university (2005–2006), and then moved to NTU in Singapore as

Associate Professor in 2006. His research fields cover synthetic methodologies, asymmetric catalysis, and medicinal and bioorganic chemistry.

Min Lu was born in Suzhou (P. R. of China) in 1983. He obtained his BSc in 2006 from Fudan University. He has been studying for his PhD at NTU since April 2007 under the guidance of Professor Guofu Zhong. Due to the excellence of his research at NTU, he was awarded the prestigious Chinese Government Outstanding Student Award for overseas Chinese students in May 2010.

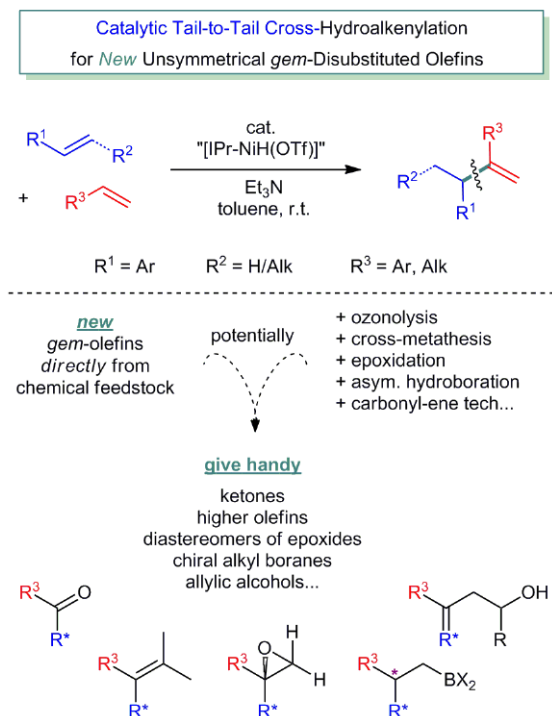
Catalytic Intermolecular Tail-to-Tail Hydroalkenylation of Styrenes with α -Olefins

Angew. Chem. Int. Ed. **2010**, *49*, 9182–9186

Simple alkenes represent an important chemical feedstock in industry, where they are used as primary starting materials for the large-scale preparation of important classes of compounds at a relatively low cost. While olefin cross-metathesis and hydrovinylation with ethylene have proven to be particularly important to construct *internal* and *monosubstituted* olefins in modern chemical industry, the selective construction of various asymmetric *gem-disubstituted* olefins from the feedstock remains challenging. Recently the group of Professor Chun-Yu Ho from the Chinese University of Hong Kong (P. R. of China) described a novel process for the efficient tail-to-tail hydroalkenylation of styrenes with α -olefins mediated by a nickel–N-heterocyclic carbene (Ni–NHC) complex.

“*gem-Disubstituted* olefins can be very useful building blocks for the construction of value-added molecules by making use of a large variety of alkene functionalization technologies, which are well documented in the literature,” said Professor Ho. “Unfortunately, they are of limited availability; therefore, we recently started a research program to develop new catalytic methodology to synthesize them. This was mainly based on the very important nickel chemistry reported by several research groups, namely those of Professors RajanBabu, Cavell, Sigman, Montgomery and Jamison,” acknowledged Professor Ho, “and was partly initiated by our related finding in the Ni–NHC-mediated cyclization reaction (*Chem. Commun.* **2010**, *46*, 466).” Professor Ho explained that he felt that one of the major implications in the cyclization was that the IPr–Ni(II) combination may have a positive effect by attenuating the facile β -H elimination at a certain point and provide enough time for a new C–C bond formation to take place, complementary to other approaches using bi/tridentate ligands. “After that work, I thought that another area for testing the potential of the IPr–Ni(II) combination was that represented by processes of intermolecular C–C bond formation directed by benzylic stabilization, for example revisiting the hydrovinylation reaction by joining the advantages of NHC ligand effects with the aforementioned elegant Ni–H and Ni(0) chemistry.”

Professor Ho explained that besides the concerns of isomerization and regio- and chemoselectivity, the major question in his mind before the testing was whether the steric bulk offered by the first insertion product was strong enough to stop oligomerization. “Pleasingly, the cross-hydroalkenylation between simple styrene and a long-chain α -olefin worked at the first trial,” he said. “Later, Lisi He, who is a first-year M.Phil student in my group, took on the challenge related to process optimization and scope expansion. She did well by picking up everything rapidly; notably, she had received no organometallic chemistry training prior to that,” said Professor Ho. “Once the process becomes more efficient, the hurdles of accessing the subsequent chemical products will be lowered accordingly,” said Professor Ho. The researchers are now working towards that goal. Meanwhile they are also exploring the potential applications of the products and exploring the NHC–Ni effect on other transformations.



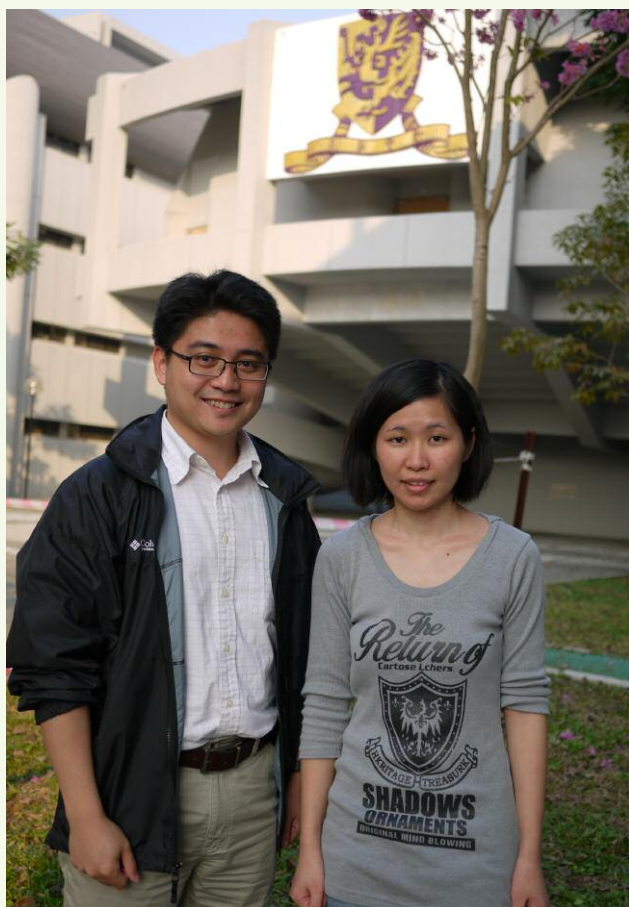
Key: IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene

“We hope that our research can stimulate further developments in the field of Ni-NHC chemistry and related insertion processes. Finally, I would like to give my most sincere thanks

to Professor Tim Jamison for providing me with a research opportunity in his group,” concluded Professor Ho.

Matteo Zanda

About the authors



From left: Professor C.-Y. Ho, L. He

Chun-Yu Ho was born in Hong Kong and received his BSc from The University of Hong Kong (P. R. of China). His interest in alkene research stems from his undergraduate projects on organocatalytic asymmetric epoxidation in 1999. He received his PhD in 2005 from the same institution under the supervision of Professor Dan Yang. After pursuing postdoctoral research at MIT with Professor Timothy F. Jamison (2005–2007), he joined the Center of Novel Functional Molecules, The Chinese University of Hong Kong (CUHK) as an independent Research Assistant Professor. He is the recipient of The Croucher Foundation Fellowship and Asian Core Program Lectureship Award. His current research interests include the applications of NHC in catalytic asymmetric synthesis, and the development of phosphorylation and cyanation methods for the synthesis of biologically important molecules.

Lisi He was born in China in 1986. She obtained her BSc from Sun Yat Sen University (P. R. of China) in 2009 and started her graduate study as an M.Phil student under Professor Chun-Yu Ho's supervision at CUHK.

Highly Enantioselective Hydroxycarbonylation and Alkoxy-carbonylation of Alkenes Using Dipalladium Complexes as Precatalysts

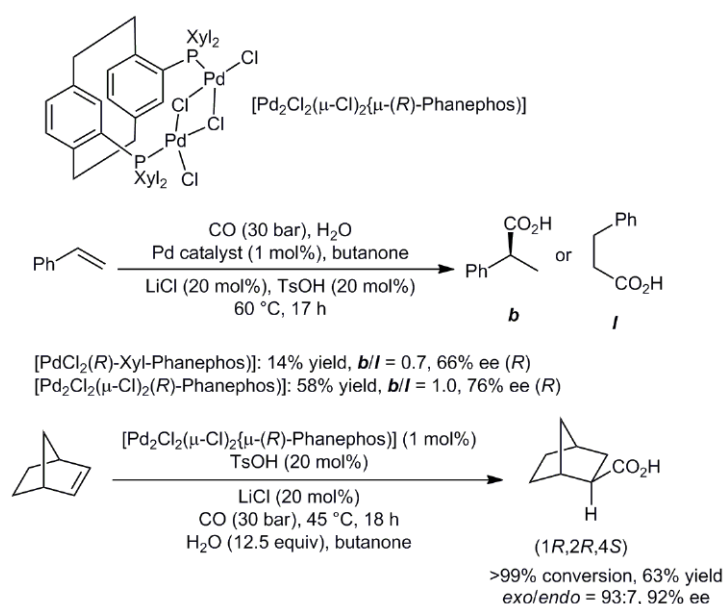
Angew. Chem. Int. Ed. **2010**, *49*, 9197–9200

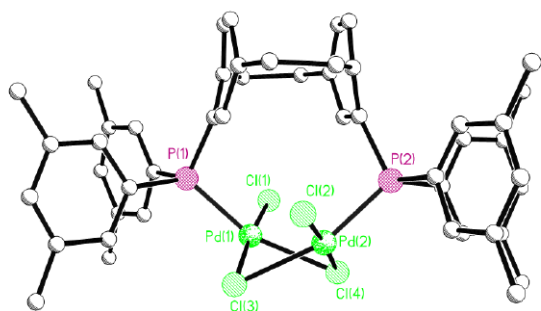
■ A stereoselective synthesis of carboxylic acids by direct enantiocontrolled installation of the carboxylic group (hydroxycarbonylation) on an olefin substrate is potentially a very powerful approach, but until recently no truly practical and user-friendly methods were available for standard laboratory applications. A breakthrough was recently achieved by the group of Dr. Matthew L. Clarke from the University of St. Andrews (UK), who developed a highly efficient methodology for both hydroxy- and alkoxy-carbonylation of alkenes based on the use of dipalladium complexes as precatalysts.

“We started work on this goal about six years ago,” said Dr. Clarke. “I am quite odd for a synthetic chemist, in that I am attracted to reactions that don’t work!” According to the Scottish researchers, asymmetric hydroxycarbonylation had been known about for about 30 years, but the only ee values that seemed to be reproducible were about 11% for a BINAP system, and an example with about 40% ee. “There had been some good ee values for alkoxy-carbonylation, but in both reactions there were issues with the yield, the amount of co-

catalyst, temperature and, for styrene derivatives, regioselectivities,” said Dr. Clarke. “If it were not for all these problems, it would be one of the most useful reactions for research and industry alike; carboxylic acid derivatives are everywhere, and making them this way uses the most economic precursors, alkenes, carbon monoxide and a nucleophile, and all of the atoms in these substrates go into the products.”

“We did some work that helped in sorting out regioselectivities for making racemic products (*Chem. Eur. J.* **2009**, *15*, 10504; *J. Mol. Catal.* **2010**, *330*, 18) and by 2006, we had our own 40% ee,” he continued. “However, most of the ligands failed to give any ee. I like to think we deserved a bit of luck, when we came across the dimetallics. Tina, the PhD student who did most of the work, did the right thing by not ignoring a mystery side product when making the monometallic complexes of Pye and Rossen’s planar-chiral PhanePhos ligand. She decided to make this and found out it was the dipalladium species,” (see X-ray crystal structure).





“However, I was not too optimistic they would do much in asymmetric carbonylations,” said Dr. Clarke; “bridging diphosphines are not the way to do asymmetric catalysis, right? If they re-arranged to chelates, you would expect them to be a bit worse than the mono-metallic catalysts. Anyway, I was wrong, and we got some very promising enantioselectivity in both hydroxycarbonylation (up to 85% ee) and alkoxy-carbonylation (up to 95% ee).” Dr. Clarke argued that it may be important that they were able to work at much lower temperatures and lower acid co-catalyst concentration than other studies. “We think this is the first big hurdle overcome towards making this long-desired process a reality, and it is probably the only project I have worked on where the results were much better than I dreamed of! A colleague in industry suggested we file a patent, which we did in 2009, and they are now supporting a student to tune these up for possible industrial application,” said Dr. Clarke. “We still have some work to do, for sure. Either the activity has to go up a bit more or we have to be able to recycle in a convenient way and we are working on both approaches.” The authors pointed out that this article mainly deals with styrene, since that was the benchmark substrate, and from a synthesis point of view, the regioselectivities make it useless for that aryl-propanoic acid. “However, since the paper was written, we have now fixed the regioselectivity to get only the chiral regioisomer, while keeping the same sort of level of ee, and this important modification will be one of the first papers we will write next year,” said Dr. Clarke. “In any case, quite a few substrates of interest to industry don’t present this problem (norbornene is the only one of these noted in the paper). Anyway, we are very excited about these catalysts and about the relatively untapped potential of alkene carbonylations in organic synthesis in general. I hope some readers have a go at using them; both asymmetric hydroformylations (also one of our favorite reactions to apply in synthesis) and palladium carbonylations are not only appealing for large scale, they are a piece of cake to do in a

research lab,” he said. “Finally, there is this tantalizing possibility regarding the pre-catalyst structure; we are dead keen to piece together the mechanism of this reaction. Maybe there will be lots of other catalytic reactions where a bridging diphosphine does the business when chelates do not?” concluded Dr. Clarke. ■

Matteo Zanda

About the authors



From left: T. M. Konrad, Dr. M. L. Clarke, J. A. Fuentes

COMING SOON ► ► COMING SOON ► ►

SYNFORM 2011/03 is available from February 16, 2011

In the next issues:

SYNSTORIES ■ ■ ■ ■ ■

■ Ni-Catalyzed Reduction of Inert C–O Bonds

(Focus on an article from the current literature)

■ Pd(II)-Catalyzed Carbonylation of C(sp³)-H Bonds

(Focus on an article from the current literature)

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

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + +

SYNTHESIS

Review on: α -Functionalization of Carbonyl Compounds Using Hypervalent Iodine Reagents

(by E. A. Merritt, B. Olofsson)

SYNLETT

Account on: Synthesis and Application of Redox-Active Hybrid Catalytic Systems Consisting of Polyanilines and Transition Metals

(by T. Amaya, T. Hirao)

SYNFACTS

Synfact of the Month in category "Metal-Mediated Synthesis":

[Palladium\(II\)-Catalyzed Decarboxylative Addition of Benzoic Acids to Nitriles](#)

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