

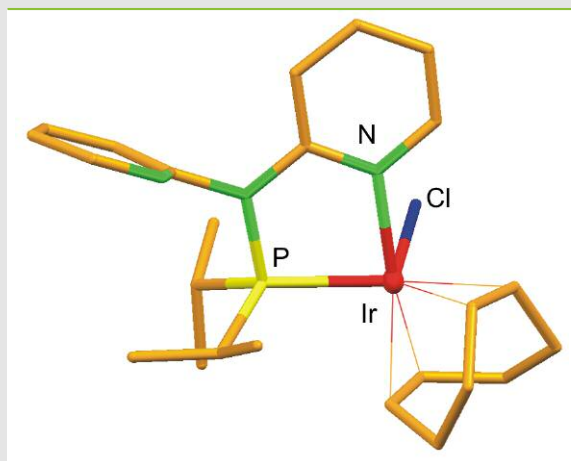
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2010/04

SYNSTORIES ■ ■ ■ ■

■ **Catalytic Alkylation of Methyl N-Heteroaromatics with Alcohols**



■ **Novel Highly Efficient Cu(I)-Catalyzed Synthesis of N-Hetero - cycles**

CONTACT ++++

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



Dear readers,

This issue of **SYNFORM** is thinner than usual because its journalistic nature and monthly frequency is not always in line with the busy agenda of the protagonists, namely the scientists who contribute with their time and material to the production of **SYNFORM**. However, quality and quantity are very different measures and this quantitatively light issue, very much focused on nitrogen heterocycles, can count on two high-quality pieces of organic chemistry. The first one reports on a novel catalytic homologation of a methyl substituent of azines (pyridine, pyrimidine, etc.) developed by Professor R. Kempe (Germany). The second **SYNSTORY** is all about a copper(I)-catalyzed synthesis of five-, six- and seven-membered N-heterocycles starting from alkynes. Quality is already here, for more quantity let's wait for the next issue...

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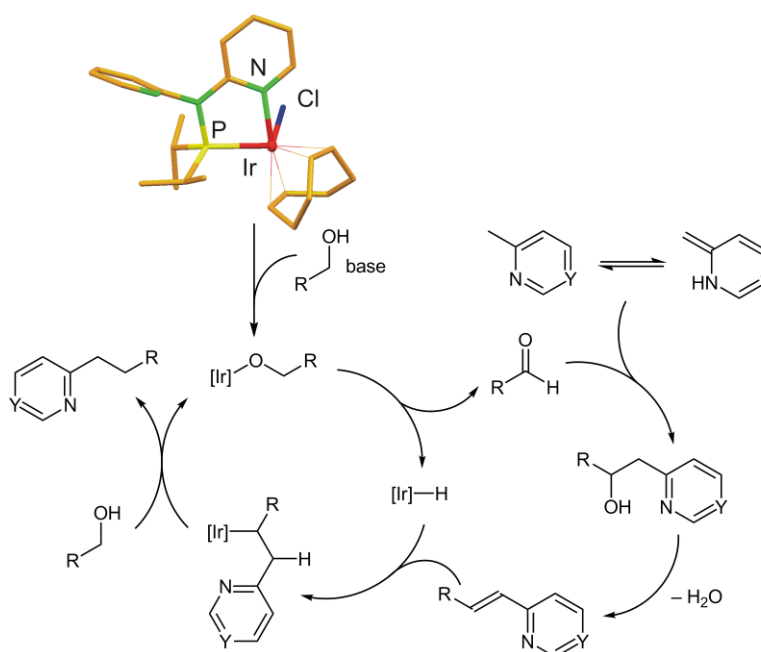
NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

Catalytic Alkylation of Methyl N-Heteroaromatics with Alcohols

J. Am. Chem. Soc. **2010**, *132*, 924–925

■ Alcohols are not among the most versatile compounds in organic synthesis. Indeed, they have a rather limited reactivity, but it is possible to temporarily convert alcohols into the corresponding carbonyl compounds, which are more amenable to different synthetic transformations, through a metal-catalyzed removal of hydrogen. This technique is known as “borrowing hydrogen” methodology (as proposed by J. M. J. Williams: *Adv. Synth. Catal.* **2007**, *349*, 1555) or “hydrogen autotransfer” reaction (as named by M. Yus: *Angew. Chem. Int. Ed.* **2007**, *46*, 2358). Recently, the group of Professor Rhett Kempe from the University of Bayreuth (Germany) has reported a novel reaction based on this technique. This methodology allows for the homologation of a methyl substituent of different azines (pyridine, pyrimidine, etc.) exploiting primary alcohols (mainly substituted benzylic alcohols), which are

probably converted into transient reactive aldehydes by means of an iridium catalyst, as alkylating agents. The reaction produces a rather wide range of homologated alkyl azines in generally good yields with a turnover number (TON) of up to ca. 50 with 2-amino-4-methylpyrimidines, whereas lower TONs were observed with other substrates. Concerning the efficiency aspect, Professor Kempe said “We need more active catalysts to be able to efficiently homologate methyl groups of whatever N-heterocycles are out there.” Professor Kempe acknowledged the great contributions given by the paper’s co-author, Dr. Benoit Blank: “Dr. Blank is a highly talented student who graduated recently and decided to work with BASF. He performed all of the experimental work.” According to Professor Kempe, the “borrowing hydrogen” or “hydrogen autotransfer” methodology is of great potential not just in



Mechanism (proposal based on substrate scope and the catalyst's performance in amine alkylation chemistry)

C–N but also in catalytic C–C coupling chemistry. “Let’s just imagine the large variety of bond formations that aldehydes can undergo,” concluded Professor Kempe. This reaction certainly expands the arsenal of useful methods available to organic chemists. ■

Matteo Zanda

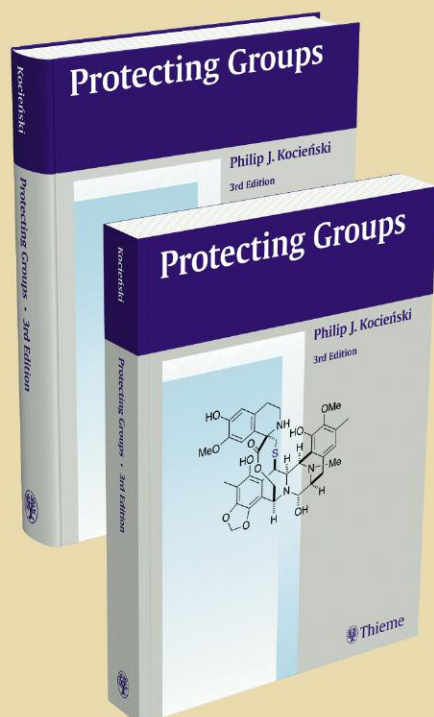


Dr. B. Blank



Prof. R. Kempe

INFORMATION ++++



Do you already have your Protecting Groups?

“... it is well organized, covers useful information, and is eminently readable – an excellent combination.”

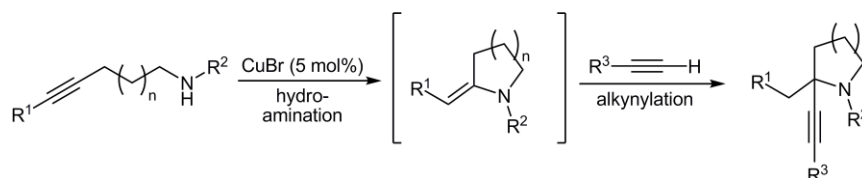
P. DeShong, University of Maryland, USA,
J. AM. CHEM. SOC., 2006

“... by far the best book on protection groups ...”

T. Laird, Scientific Update, UK, Organic
Process Research & Development, 2005

Novel Highly Efficient Cu(I)-Catalyzed Synthesis of N-Heterocycles

J. Am. Chem. Soc. **2010**, *132*, 916–917



■ Quick and efficient access to diversified classes of biologically active lead compounds is an essential part of drug discovery. In the search for bioactivity, heterocycles of different ring sizes, with different substitution patterns, constitute extremely important structure classes (e.g., alkaloids). Recently, the group led by Professors Gerald B. Hammond and Bo Xu from the University of Louisville (Kentucky, USA) reported a novel methodology which represents a useful addition to the arsenal of synthetic tools available to organic and medicinal chemists. The method makes use of a starting amino-alkyne which undergoes a tandem Cu(I)-catalyzed intramolecular hydroamination/intermolecular alkynylation reaction with a terminal alkyne, affording an array of five-, six- and seven-membered 2-alkynyl N-heterocycles in excellent yields.

“The need to map new chemical spaces through cascade reactions in an atom-economical fashion inspired us to develop an efficient and environmentally friendly method to access biologically important N-heterocycles containing five-, six-, or seven-membered rings with various substitution patterns,” said Professor Hammond.

According to Professor Xu, addition of a nucleophile to an alkyne using late transition metal catalysts like gold or palla-

dium is a well-known process. “But a tandem addition of two different nucleophiles to an alkyne is not a common strategy,” he said. “In our approach, we envisioned an intramolecular secondary amine attack on an electrophilically activated alkyne, with the resulting activated cyclic enamine intermediate then becoming a new electrophilic precursor capable of reacting with a second nucleophile – such as a terminal alkyne – to give a new addition product.” Professor Hammond and his associate, Professor Xu, explained that this essentially corresponds to a double addition to a triple bond. “The virtue of this transformation is that it sets up the stage for further transformations (e.g., cycloisomerization) that will furnish even more diverse N-heterocyclic products.” They call this strategy a ‘cyclization-triggered addition’. “Our method has some clear advantages over the literature methods: i) it is highly efficient (close to quantitative yields); ii) it uses cheap and environmentally friendly copper(I) bromide catalyst; iii) N-heterocycles containing either five-, six-, or seven-membered rings can be accessed in a one-pot procedure, using one single method for all cases; iv) it has a broader scope (unactivated alkynes – both terminal and non-terminal alkynes – can be used); and v) there is no need to protect the amine,” concluded Professor Hammond. ■

Matteo Zanda



J. Han



Prof. B. Xu



Prof. G. B. Hammond

COMING SOON ►► COMING SOON ►►

SYNFORM 2010/05

is available from
April 20, 2010

In the next issues:

SYNSTORIES ■ ■ ■ ■ ■

■ Palladium-Catalyzed Intermolecular Addition of Formamides to Alkynes

(Focus on an article from the current literature)

■ Direct Conversion of Arylamines to Pinacol Boronates

(Focus on an article from the current literature)

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

(Focus on an article from the current literature)

FURTHER HIGHLIGHTS + + + + +

SYNTHESIS

Review on: Transition-Metal-Catalyzed Oxidative Heck Reactions

(by B. Karimi)

SYNLETT

Account on: Deracemisation of Secondary Alcohols via Biocatalytic Stereoinversion

(by W. Kroutil)

SYNFACTS

Synfact of the Month in category "Synthesis of Natural Products and Potential Drugs": [Synthesis of \(E\)- and \(Z\)-Tamoxifen](#)

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