Palladium-Catalyzed Direct C–H Arylation of *N*-Iminopyridinium Ylides: Application to the Synthesis of (±)-Anabasine

Research by A. Larivée, J.J. Mousseau, and A.B. Charette, J. Am. Chem. Soc. ***2008***, 130, *52*

Condensation and commentary by ***R.M. Kellogg****, Syncom BV*

Condensation of the Research

Purpose of the Study

To develop a synthetic route for the direct, selective arylation of pyridine and derivatives thereof at the 2-position by means of synthetically reversible activation at the pyridine nitrogen atom

Background

Substituted pyridines are often required either as intermediates or end products in many synthesis chemistry projects. Commercially available pyridine derivatives are limited in their scope of substitution and are, on the whole, rather expensive. For preparation of 2-substituted pyridines, cross-coupling with 2-halopyridines is often the only recourse. A method of direct arylation would allow one to bypass either purchase or synthesis of halogenated intermediates for such cross-coupling reactions.

What Researchers Accomplished

The present article complements a publication from the Fagnou group that appeared in 2005.[1] Fagnou et al. described the palladium-catalyzed arylation of pyridine *N*-oxide with a range of aryl bromides. Catalytic reduction of the 2-substituted pyridine *N*-oxide to reform the pyridine is readily achieved. A drawback to the method is that moderate excesses (4-fold) of the pyridine *N*-oxide must be used to suppress formation of 2,6-disubstituted product.

The Charette group has already developed good protocols for the synthesis of *N*-iminopyridinium salts.[2] They now have shown that *N*-iminopyridinium ylide **1** can achieve 2-arylation of the pyridine ring (Scheme 1). Under optimized conditions, ylide **2** is obtained in 80% isolated yield. A protocol for reduction to the pyridine has also been developed (see later discussion).

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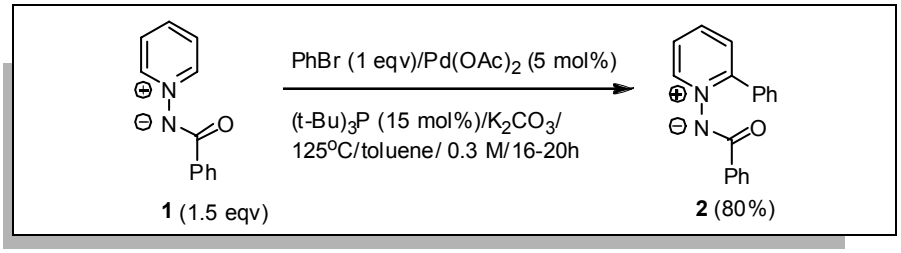
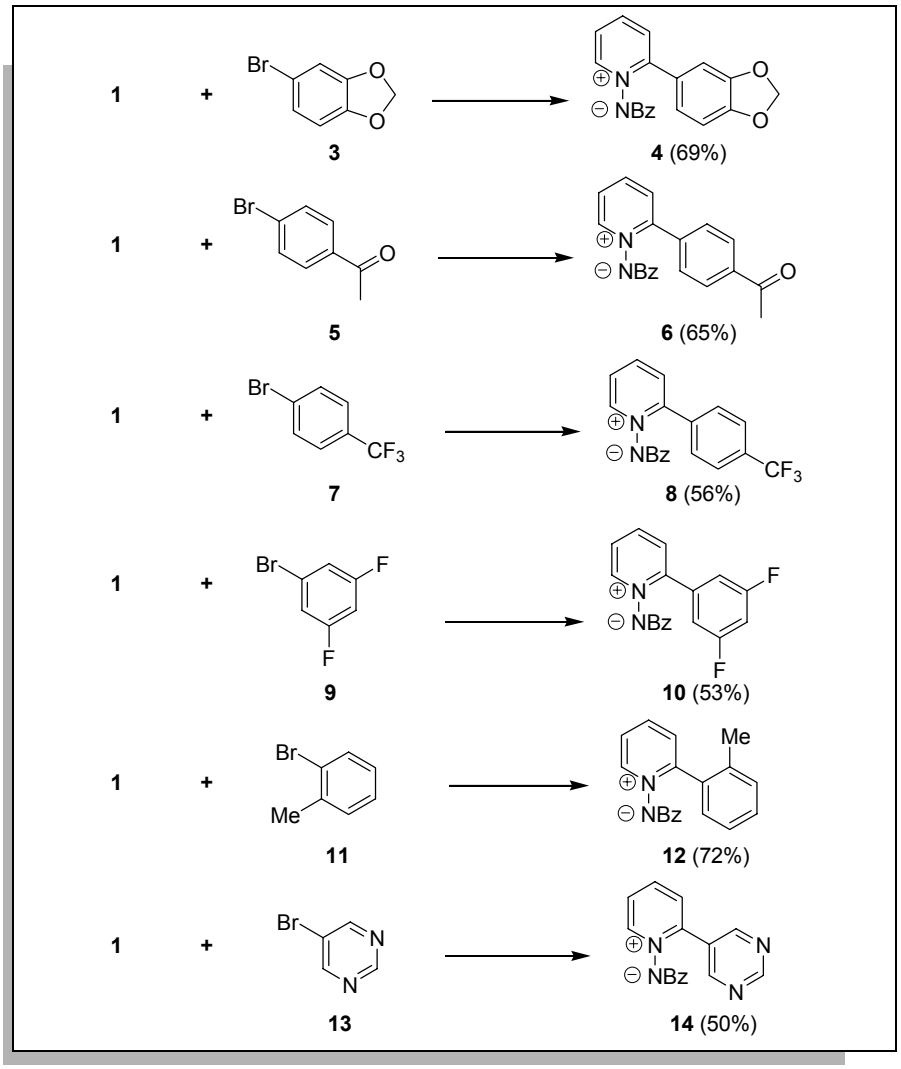
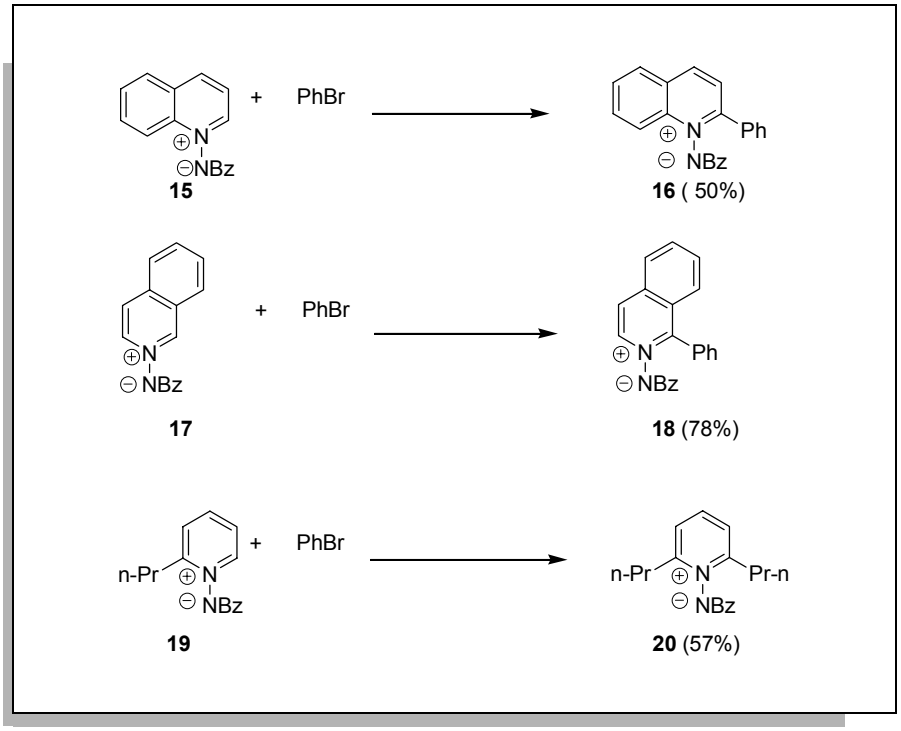


Scheme 1

A broad range of aryl bromides can be coupled with **1** (Scheme 2). Yields are moderate to good. For **6**, **8**, and **12**, 2.5 eq of **1** were required to obtain these results (1.5 eq for the other examples). Other *N*-iminopyridinium ylides could also be substituted in reasonable yields (Scheme 3), although the larger amounts of phenyl bromide generally were required to obtain a



Scheme 2

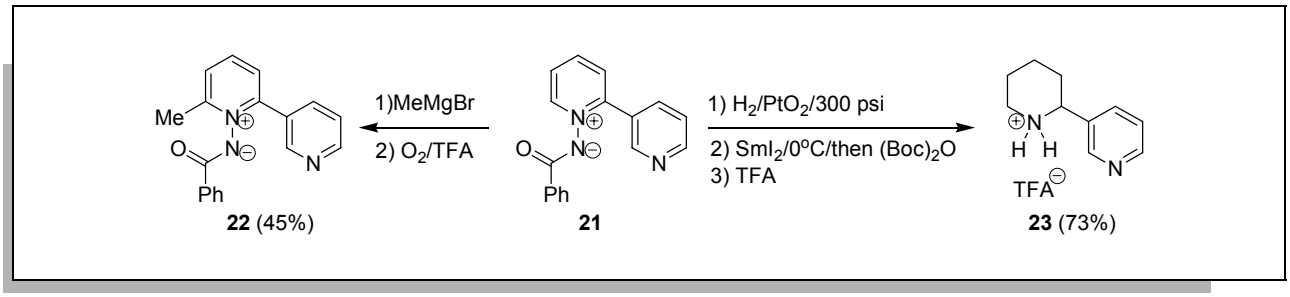


Scheme 3

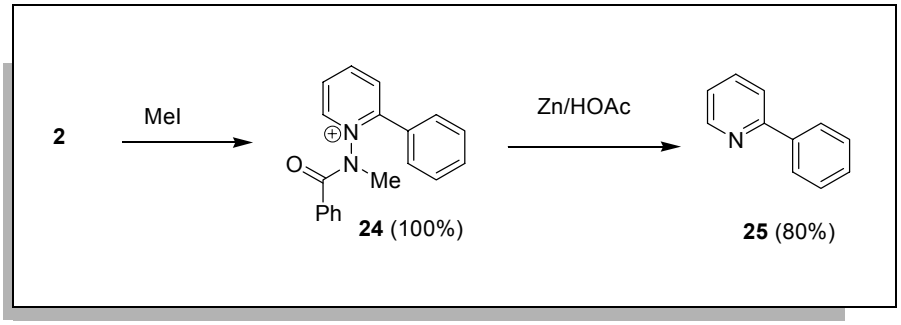
successful reaction. The exclusive substitution at the 1-position in **17** to provide **18** is remarkable but is not commented on further. For the 3-methyl derivative of **1**, substitution occurs exclusively at the 6-position apparently owing to steric hindrance.

Addition of organometallic reagents to the arylated *N*-iminopyridinium ylide products appears to proceed as expected at the unsubstituted position of **21** adjacent to nitrogen to produce **22** (Scheme 4). The 1,2-dihydropyridine intermediate (not isolated) is readily oxidized to **22**.

The reaction is reported only for the addition of methyl Grignard reagent. Ylide **21** is formed in 83% yield in the coupling reaction with **1**. Reduction and deprotection of **21** leads to racemic anabasine salt in good yield.



Scheme 4



Scheme 5

Deprotection as reported involves a two-step procedure as illustrated with **2** in Scheme 5. Methylation of **2** provides **24**, which is reduced with Zn dust to 2-phenylpyridine **25**. Reduction of **25** can also be carried out with HCO_2NH_4 and Pt (83%) or with $[(CH_3)_3Si]_3SiH$ and AIBN (85%). Several other *N*-iminopyridinium ylides were also successfully reduced with the Zn dust protocol. This procedure for reduction is clearly more involved than the direct reduction with Zn dust application to pyridine *N*-oxide derivatives.[1]

Commentary on the Research

As pointed out in the introduction, very similar results have been obtained using pyridine *N*-oxides. Two definite shortcomings of this research reported are that all reactions have been carried out only on a small (less than millimole) scale and the purification of most products was accomplished using preparative high-performance liquid chromatography. For larger scale applications, assuming that the methodology can be scaled up, other purification methods would be essential. In most cases, it is reasonable to expect that other chromatographic procedures would be successful.

The selectivity of substitution using the *N*-iminopyridinium salts appears to be higher than with the *N*-oxides. For cases in which there are no selectivity problems, the use of readily available pyridine oxide to prepare 2-arylated pyridines would probably be preferred because of the straightforward reduction procedure. Where selectivity plays a role, recourse can be taken using the *N*-iminopyridinium salts. With this report, chemists appear to have the luxury of choice, although with either pyridine *N*-oxide or *N*-iminopyridinium ylides, procedures for upscaling and easy purification still need to be developed.

References

1. Campeau, LC., Rousseaux, S., Fagnou, K. *J. Am. Chem. Soc*. **2005**, *127*, 18020.
2. Legault, C., Charette, A.B. *J. Org. Chem*. **2003**, *68*, 7119.