Pure Appl. Chem., Vol. 82, No. 9, pp. 1835–1844, 2010.
doi:10.1351/PAC-CON-09-09-06

Synthesis of heterocycles via alkoxyallenes*

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Abstract: Lithiated alkoxyallenes are very versatile components for the synthesis of heterocycles such as furans, pyrroles, and 1,2-oxazines, easily allowing the preparation of natural products via these heterocyclic intermediates. A surprising three-component synthesis of N-acylated enaminones allowed the synthesis of highly functionalized 4-hydroxypyridines, 5-acetyloxazoles, and pyrimidines. All these heterocyclic products are ready for further functionalizations, in particular for palladium-catalyzed reactions, leading to libraries of new interesting heterocycles.

Keywords: allenes; carbonyl compounds; imines; multicomponent reactions; natural products; nitriles; palladium-catalyzed reactions.

INTRODUCTION

Alkoxyallenes are very versatile building blocks for the preparation of a variety of useful heterocycles [1]. This has been demonstrated by the (stereoselective) preparation of furan, pyrrole, piperidine [2], and 1,2-oxazine derivatives [3]. The obtained heterocyclic intermediates can smoothly serve for the synthesis of a variety of interesting natural products and their analogs. The synthetic utility of alkoxyallenes is due to the reactivity pattern depicted in Fig. 1. By lithiation at C1 various electrophiles can be connected with the allene moiety, which subsequently allows reactions with a nucleophile at the terminal C3, whereas a second electrophile can add to the central C2 carbon. The formation of heterocycles is generally induced by intramolecular nucleophilic addition to the terminal carbon (see Schemes 1 and 2). The synthesis of alkoxyallenes is fairly simple. After preparation of the corresponding propargylic ether this intermediate is converted into the more stable allenyl isomer by treatment with catalytic amounts of base [4]. This method is also applicable to alkoxyallenes with other alkyl groups at oxygen and to aryl-substituted allene derivatives.

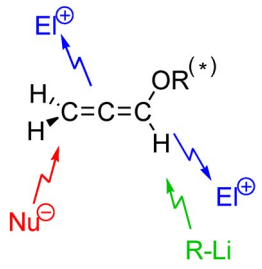

Fig. 1 Reactivity pattern of alkoxyallenes.

*Paper based on a presentation at the 22nd International Congress on Heterocyclic Chemistry (ICHC-22), 2–7 August 2009, St. John's, Newfoundland and Labrador, Canada. Other presentations are published in this issue, pp. 1735–1853.

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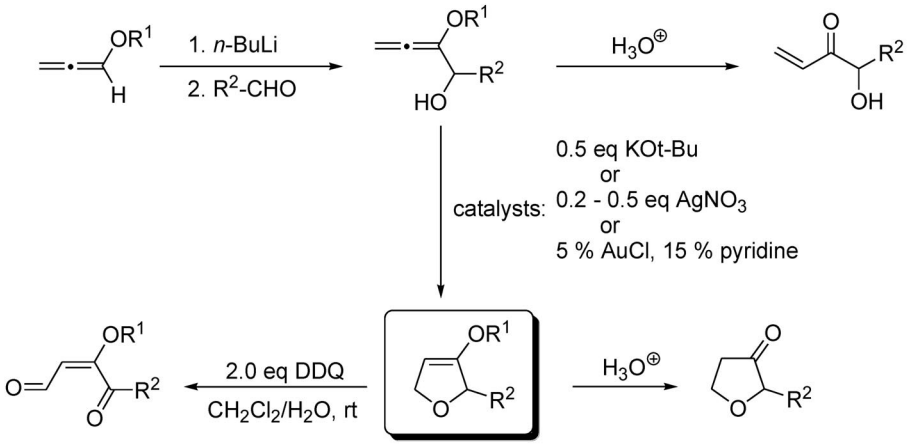
RESULTS AND DISCUSSION

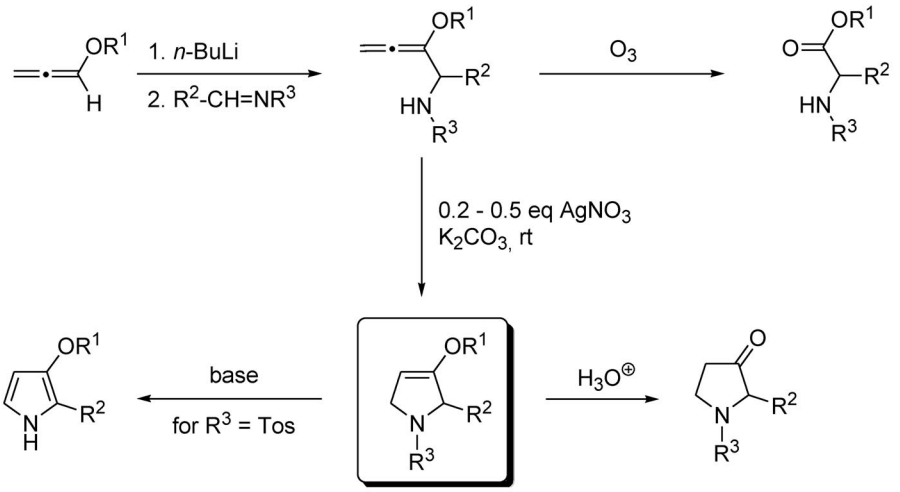
Additions of lithiated alkoxyallenes to carbonyl compounds and imines

Lithiation with *n*-butyllithium and subsequent addition of aldehydes or ketones provides primary adducts which can be hydrolyzed to provide α-hydroxy enones (Scheme 1) [5]. More importantly, cyclization under different conditions allows the preparation of dihydrofuran derivatives [6]. We recently disclosed that the gold-catalyzed process is of particular efficacy [7]. The dihydrofurans can be ring-opened again by oxidation to furnish unsaturated 1,4-dicarbonyl compounds which allow the synthesis of pyridazines [8]. Starting from enantiopure lactaldehyde derivatives we could recently use this route to prepare four desoxy sugar derivatives in a stereodivergent manner [9].

Similarly to carbonyl compounds, imines as electrophiles smoothly provide the corresponding allenyl amines (Scheme 2), which could be converted into α-amino esters by ozonolysis [10] or by cyclization into dihydropyrrole derivatives [10,11]. These dihydropyrrole intermediates have been used to



Scheme 1 Addition of lithiated alkoxyallenes to carbonyl compounds and subsequent reactions.



Scheme 2 Addition of lithiated alkoxyallenes to imines and subsequent reactions.

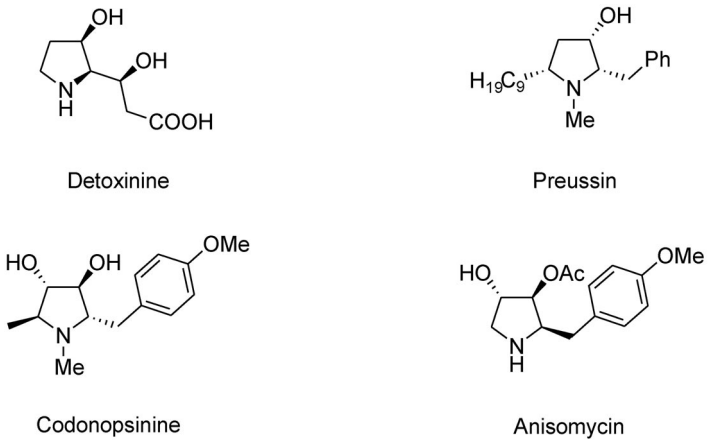
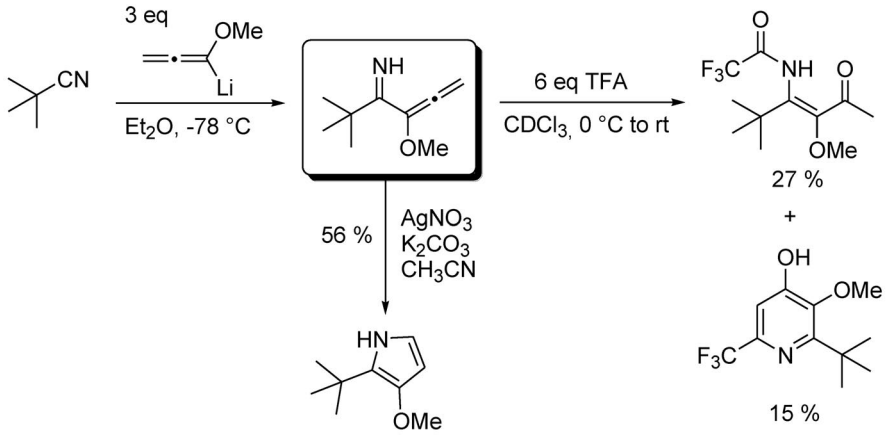


Fig. 2 Natural products with 3-hydroxypyrrolidine substructure prepared from alkoxyallenes.

prepare natural products with a 3-hydroxypyrrolidine substructure [12] or of key intermediates of fairly complex targets such as FR 901483 [13] in a stereoselective fashion (see Fig. 2).

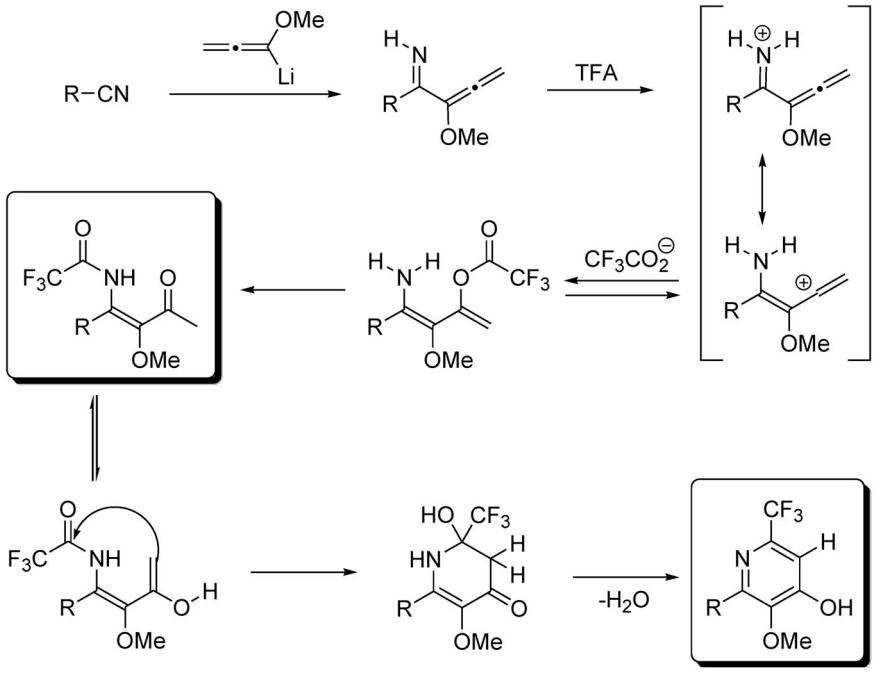
A new three-component synthesis of functionalized pyridine derivatives

When we examined nitriles as electrophiles, lithiated alkoxyallenes provided the expected primary adducts (Scheme 3). They could be converted into the expected 3-methoxypyrrole derivatives, however, treatment of the primary intermediates with an excess of trifluoroacetic acid surprisingly furnished a mixture of two completely different products incorporating the carboxylic acid. In the first experiment, an enaminone and a 4-hydroxypyridine derivative were isolated in fairly low yield [14].



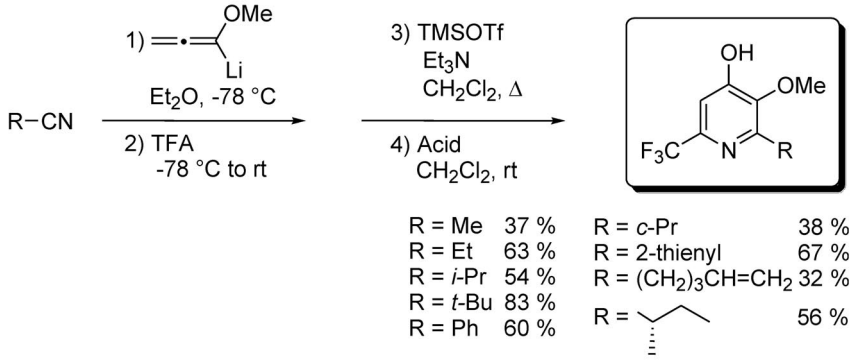
Scheme 3 Reaction of lithiated methoxyallene with pivalonitrile and subsequent reactions.

The mechanism of this unusual reaction sequence is depicted in Scheme 4, revealing that protonation to give an iminium salt and subsequent reaction of this species with trifluoroacetate are crucial steps. Migration of the acyl group provides the enaminone, which can undergo an intramolecular aldol-type condensation to deliver the 4-hydroxypyridine derivative. Quite remarkably, an amide carbonyl group serves as electrophilic center in this ring-closure process.



Scheme 4 Mechanism of enaminone and 4-hydroxypyridine formation.

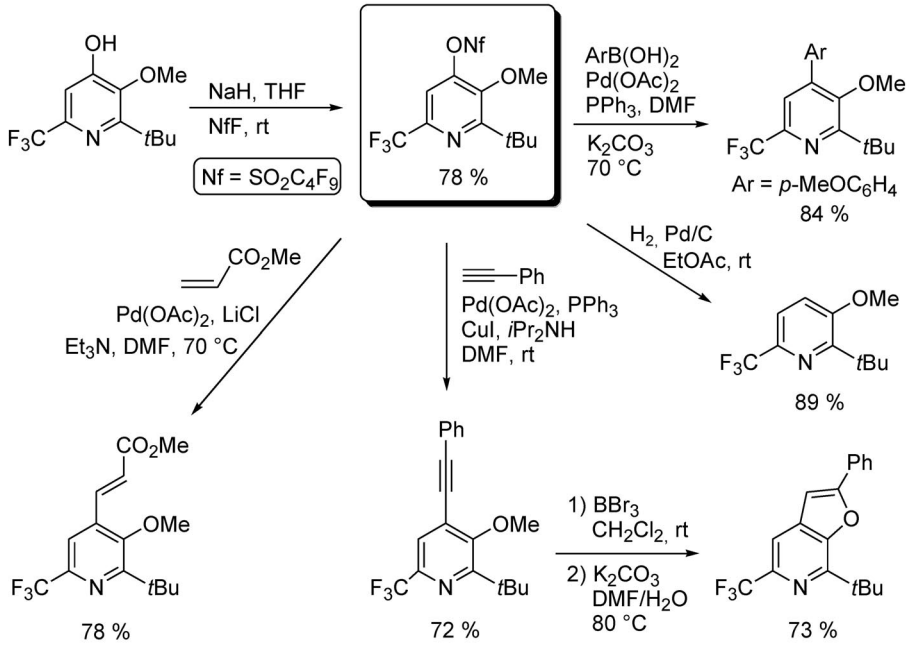
After understanding the mechanism, we were in the position to develop a new three-component synthesis of highly functionalized pyridine derivatives, which has a very broad scope with respect to the nitrile, carboxylic acid, and alkoxyallene components, thus allowing us to prepare a variety of new highly functionalized pyridine derivatives (Scheme 5) [15]. Even enantiopure components could be used, which led to pyridine derivatives being of interest as promising ligands in asymmetric catalysis [16]. Several of the 4-hydroxypyridine derivatives actually exist in preference in their tautomeric pyridin-4-one form.



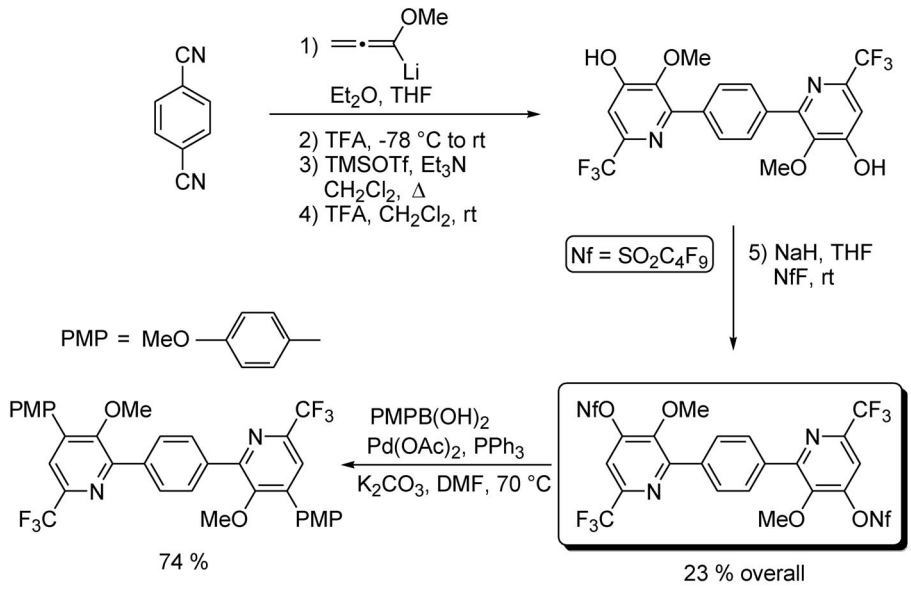
Scheme 5 Scope of the three-component synthesis of 4-hydroxypyridines from lithiated methoxyallene, nitriles, and trifluoroacetic acid.

The 4-hydroxypyridines obtained are of interest as components for palladium-catalyzed coupling reaction since their activation as nonaflate allowed a variety of efficient couplings such as Suzuki,

Sonogashira, Heck, and Stille reactions as illustrated in Scheme 6 [14,15,17]. Sonogashira products could be converted in furo[2,3-c]pyridine derivatives by deprotecting the alkoxy group, which resulted in an attack of the oxygen function to the alkyne moiety to generate the furan ring. Reactions with aromatic dinitriles opened a simple access to dipyridine derivatives, which, after nonaflation, smoothly provided Suzuki coupling products as depicted in Scheme 7 [15].

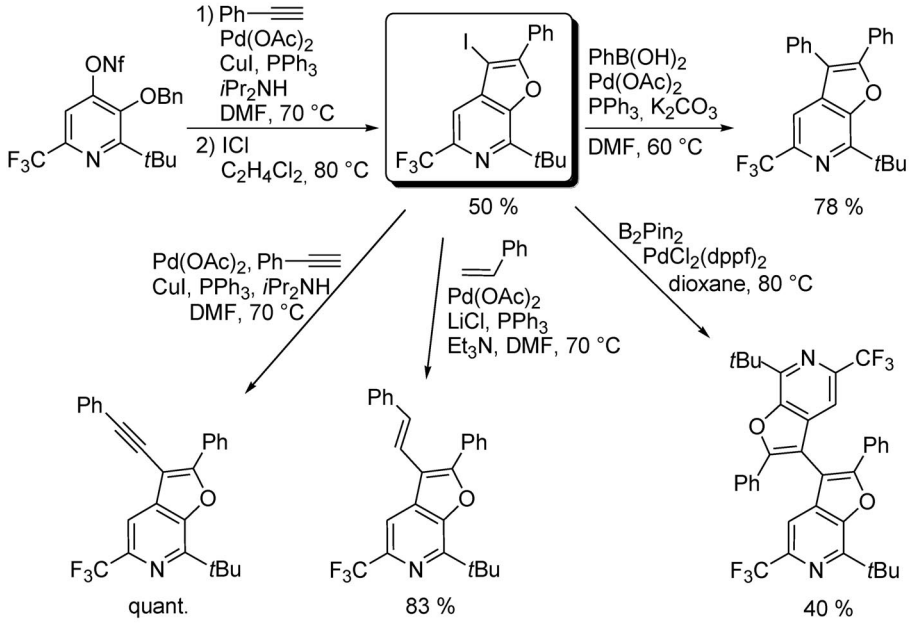


Scheme 6 Examples for palladium-catalyzed coupling reactions with 4-pyridyl nonaflates.



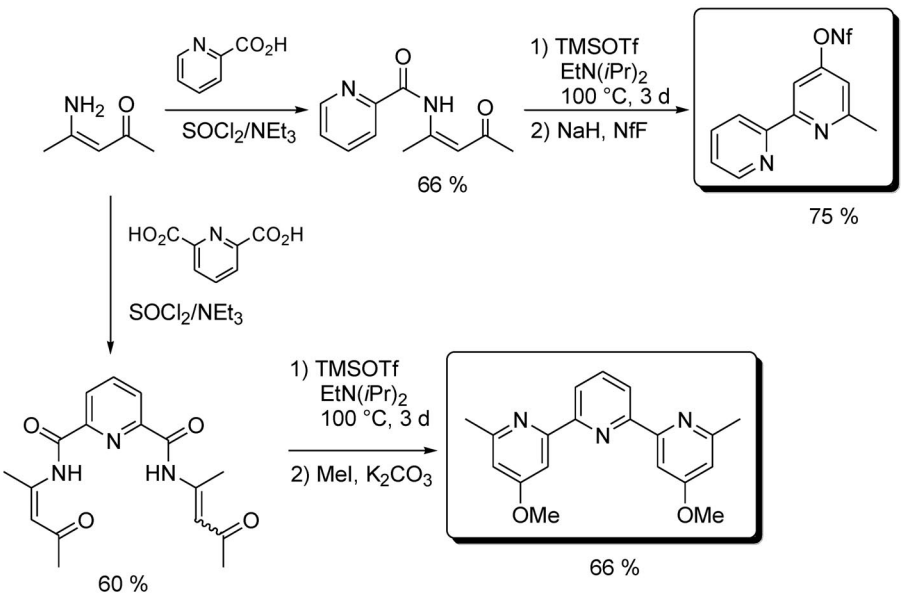
Scheme 7 Reaction with dinitriles leading to extended π-systems.

An alternative cyclization method employing iodo monochloride furnished 3-iodinated furo[2,3-*c*]pyridines as shown in Scheme 8. These iodinated compounds could be used for the generation of a library of new highly substituted furopyridine derivatives by a second palladium-catalyzed process. Actually, five components have been combined to prepare these heterocycles: alkoxyallene, nitrile, carboxylic acid, alkyne, and a final coupling partner. Several of these conjugated furopyridines show highly interesting photophysical properties, e.g., Stokes shifts up to 120 nm [17].



Scheme 8 Iodo monochloride-induced cyclizations and subsequent coupling reactions.

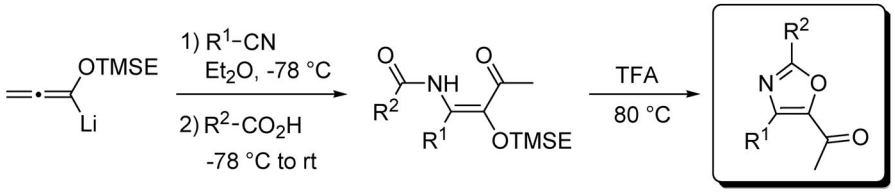
The mechanism of the pyridine-forming step led us to envision the synthesis of 4-hydroxypyridine derivative in a sequence **not** including alkoxyallenes. N-Acylation of the easily available 1,3-ketone-derived enaminones provided intermediates similar to those shown in Scheme 4. In fact, these compounds could be cyclized to provide the expected pyridine derivatives [18]. In Scheme 9, we depict two examples demonstrating the very simple and fairly efficient preparation of bipyridine and terpyridine derivatives following this route. Compounds of this type are very interesting and versatile ligands. Even antibiotic natural products (caerulomycin A and E) could easily be prepared along these lines.



Scheme 9 Rapid access to functionalized bipyridine and terpyridine derivatives.

New multicomponent approaches to oxazoles and pyrimidines

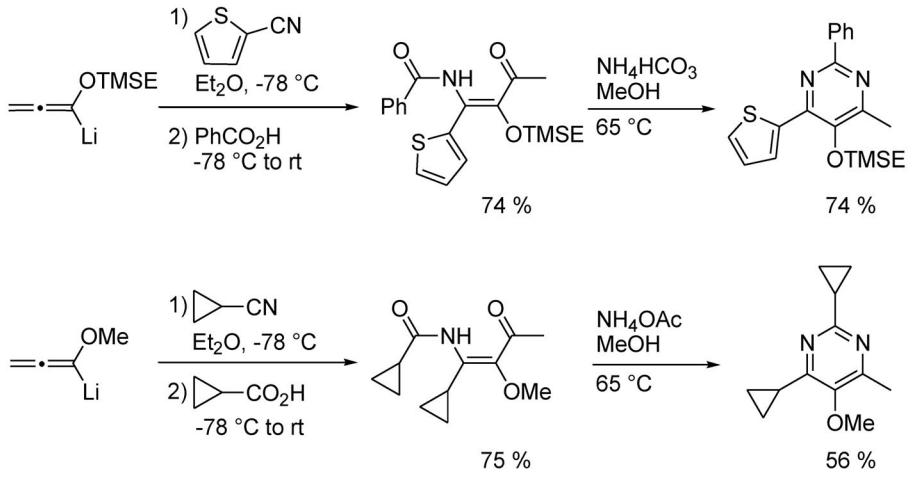
The N-acylated enaminones, which are crucial intermediates in the preparation of 4-hydroxypyridines (Scheme 4), could also be used to prepare other heterocyclic systems. An alternative cyclization mode of the 2-(trimethylsilyl)ethoxy-substituted derivatives was achieved by treatment with trifluoroacetic acid. After removal of the (trimethylsilyl)ethyl (TMSE) group, the enol oxygen cyclizes to the amide carbonyl group to furnish 5-acetyloxazole derivatives (Scheme 10). This new approach was used to prepare a set of functionalized oxazole derivatives which easily allow subsequent reactions at the reactive methyl ketone moiety [19].



R^1 = Ph, R^2 = 2-thienyl	75 %	68 %
R^1 = Ph, R^2 = C≡CH	21 %	74 %
R^1 = *c*-Pr, R^2 = *c*-Pr	75 %	67 %
R^1 = Ph, R^2 = 2-pyridyl	24 %	99 %

Scheme 10 Preparation of 5-acetyl oxazole derivatives starting from alkoxyallenes.

The N-acylated enaminones could also be employed for the preparation of pyrimidine derivatives. Their condensation with ammonium salts smoothly provided highly functionalized pyrimidines (Scheme 11) which could again be used in subsequent palladium-catalyzed reactions by oxygen depro-



Scheme 11 Synthesis of functionalized pyrimidine derivatives starting from alkoxyallenes.

tection and nonaflation. Alternatively, oxidation of the methyl group allows conversion into carboxylic acids or aldehydes [20].

CONCLUSION

All these new procedures to highly functionalized heterocycles demonstrate that the standard reactivity pattern of alkoxyallenes as expressed in Fig. 1 was remarkably expanded when the corresponding iminium salts (obtained by addition to nitriles) are involved. Now a nucleophilic species will add to the central allene carbon, whereas the terminal carbon acts as an electrophilic center. Figure 3 reveals that these two positions now suffered an **Umpolung of reactivity** with respect to the pattern shown in Fig. 1!

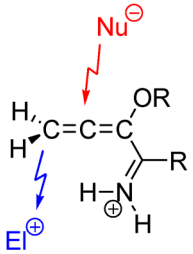
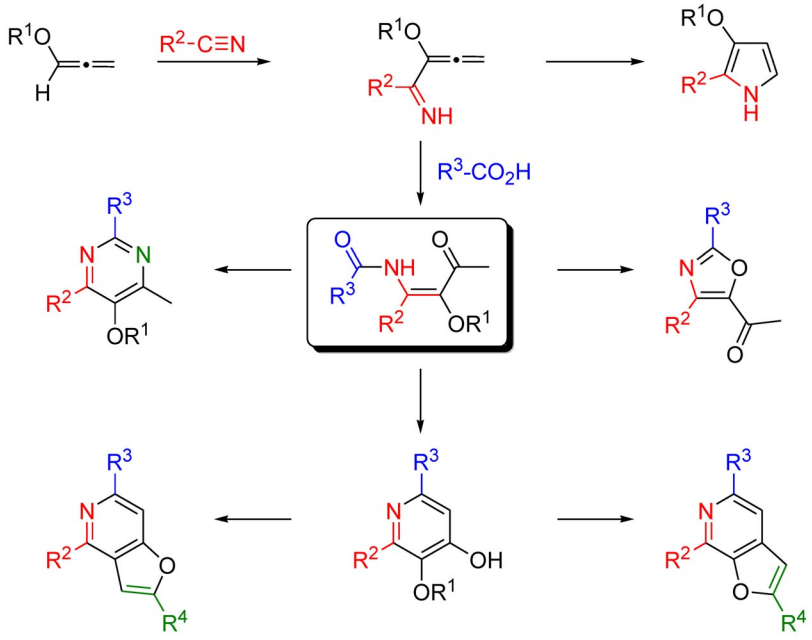


Fig. 3 New reactivity pattern involving Umpolung of reactivity of alkoxyallenes.

The new reactivity pattern leads to the smooth formation of N-acylated enaminones by the aforementioned three-component approach as depicted in Scheme 12. These enaminones not only provide highly functionalized pyridine derivatives, but they furnish by alternative protocols either oxazole or pyrimidine derivatives, both highly suitable intermediates for subsequent functionalizations. The combination of lithiated alkoxyallenes with nitriles (and carboxylic acids) allows the synthesis of a broad range of interesting heterocycles. Hence, the existing methods employing alkoxyallenes as functionalized C3 building blocks for the synthesis of heterocycles has been considerably expanded.



Scheme 12 Multicomponent reactions of lithiated alkoxyallenes and nitriles via allenyl imine intermediates.

ACKNOWLEDGMENTS

We gratefully acknowledge the intellectual and experimental contributions of our colleagues Oliver Flögel, Jyotirmayee Dash, Christian Eidamshaus, and Paul Hommes and the generous support of the Deutsche Forschungsgemeinschaft (SFB 765), the Alexander von Humboldt-Stiftung, the Fonds der Chemischen Industrie, and the Bayer Schering Pharma AG.

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