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A Single Step Approach to Piperidines via Ni-Catalyzed β-Carbon Elimination

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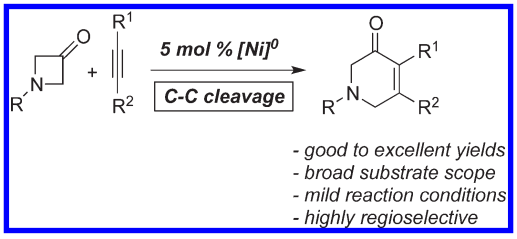
ABSTRACT

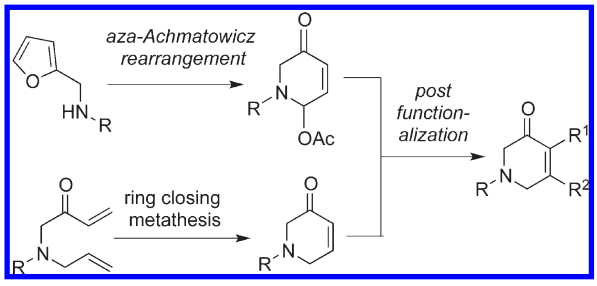


An easy and expeditious route to substituted piperidines is described. A Ni-phosphine complex was used as catalyst for [4 + 2] cycloaddition of 3-azetidinone and alkynes. The reaction has broad substrate scope and affords piperidines in excellent yields and excellent regioselectivity. In the reaction of an enantiopure azetidinone, complete retention of stereochemistry was observed.

The ubiquity of piperidines in pharmaceuticals and natural products makes them attractive targets for organic synthesis.[1] Over the past few years, tremendous progress has been made in accessing substituted piperidines.[2] Specifically, aza-Achmatowicz rearrangement[3] and ring closing metathesis[4] provide access to these motifs in an efficient fashion (Scheme 1). However, synthesizing highly substituted piperidines is still a challenging problem. Also, most of the existing strategies rely on multistep routes, which urges the need for an operationally simple, expeditious, and efficient methodology to access these heterocycles.

Recently, we and others have reported a Ni-catalyzed coupling of carbonyl compounds with alkynes and alkenes.[5] Most importantly, the nickel-catalyst system has enabled the oxidative coupling of alkynes/alkenes and unactivated ketones to provide dienones and pyrans.[5a,5b,6] This is in contrast to other reports where use of activated ketones was critical for the success of the reaction.[7] Murakami and co-workers discovered that transition metal catalysts can be utilized to exploit the ketone moiety of cyclobutanone that can render β-carbon elimination in reactive intermediates.[8]

Scheme 1. Existing Strategies to 3-Piperidones



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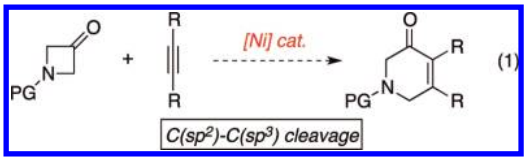
Recently, Murakami reported that cyclobutanone can be very elegantly coupled with alkynes to afford highly substituted cyclohexenones.[9] We surmised the coupling of 3-aza-cyclobutanones with alkynes could provide piperidines in a single step (eq 1).



For reaction optimization, we chose commercially available 1-Boc-3-azetidinone and 3-octyne as model substrates. Gratifyingly, a combination of $Ni(COD)_2$ and a variety of monodentate as well as bidentate ligands effected the desired cycloaddition. However, PPh_3 ligand proved to be optimal in our case.[10] A report recently appeared with a similar finding that the combination of Ni(0) and PPh_3 catalyzes the coupling of azetidinones and alkynes.[11] However, in contrast to their findings, we found that the cycloaddition of alkyne and 3-azetidinones proceeds with lower catalyst loading (5 mol % rather than 10−20 mol %), lower ligand loading (10 mol % rather than 30−80 mol %), at lower temperatures (60−100 °C rather than 90−110 °C), and in shorter times (6 h rather than 17 h).

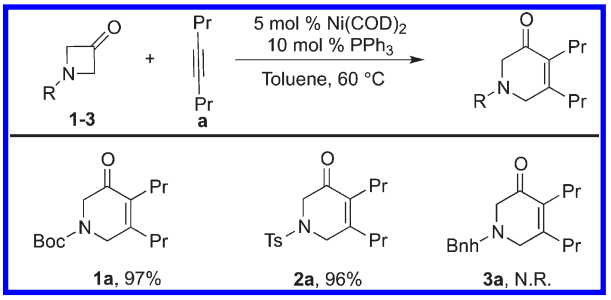


Figure 1. Investigation of protecting groups on "N" of azetidinones. Reaction conditions: azetidinone (1 equiv, 0.2 M), 3-octyne (1.5 equiv), 6 h. Isolated yields.

Several azetidinones bearing different N-protecting groups were prepared and investigated. The *tert*-butoxycarbonyl- and tosyl-azetidinones could be converted to piperidone products in excellent yields (Figure 1). However, the use of a benzhydryl protecting group did not lead to the desired cycloadduct under our optimized reaction conditions. Notably, the reaction of 3-octyne and N-Ts-azetidinone proceeded smoothly under our optimized conditions. Higher catalyst/ligand loading, higher temperature (110 °C), and prolonged reaction times were not necessary.[11]

The substrate scope of this reaction was then investigated using 1-Boc-3-azetidinone with a variety of alkynes (Figure 2). The reaction with 3-octyne afforded the piperidine (**1a**) in excellent yields. We also investigated the cycloaddition with a volatile alkyne, i.e., 2-butyne, which resulted into the desired product (**1b**) in 95% yield. To test the effect of sterics on cycloaddition, *tert*-butyl-methyl and trimethylsilyl-methyl alkynes were investigated. Surprisingly, both alkynes exhibited contrary regioselectivity patterns; i.e., the silyl group prefers to be on α-position and *tert*-butyl group on *β*-position (**1c**, **2c** vs **1e**). The structure of

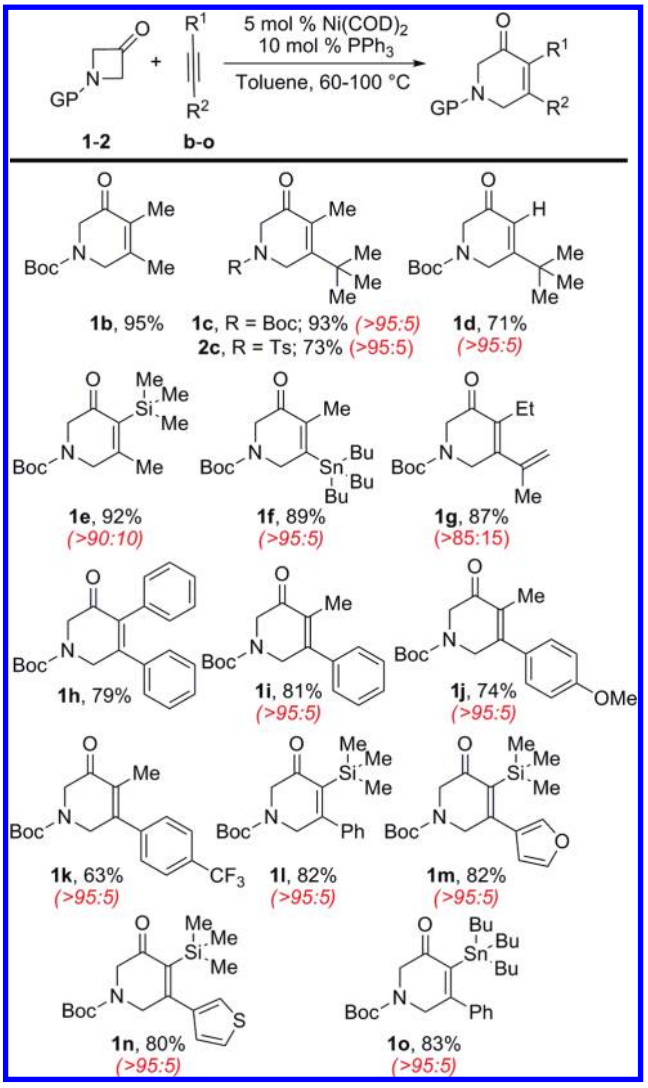


Figure 2. Ni-catalyzed coupling of azetidinones and alkynes. Method A (for **1b**−**ag** except **1d**): 5 mol % $Ni(COD)_2$, 10 mol % PPh_3, toluene, 60 °C, azetidinon (1 equiv, 0.2 M), alkyne (1.5 equiv). Method B (for **1d** and **1h**−**1o**): 5 mol % $Ni(COD)_2$, 10 mol % PPh_3 toluene, 100 °C, azetidinone (1 equiv, 0.2 M), alkyne (3.0 equiv and slow addition). Isolated yield. Regioselectivty (denoted in parentheses) was calculated by NMR of crude reaction mixture.

(8) Murakami, M.; Amii, H.; Ito, Y. *Nature* **1994**, *370*, 540.
(9) (a) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 6932. (b) Murakami, M.; Ashida, S.; Matsuda, T. *Tetrahedron* **2006**, *62*, 7540.
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2c was unambiguously determined by single crystal X-ray crystallography (Figure 3).

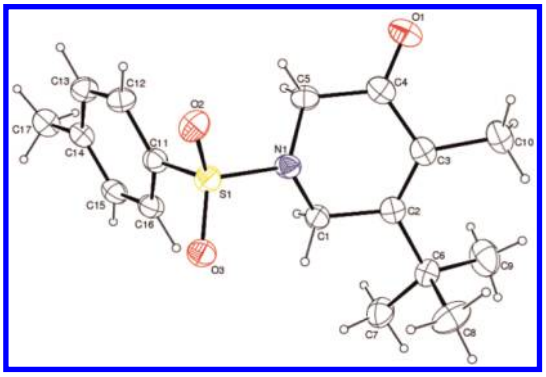
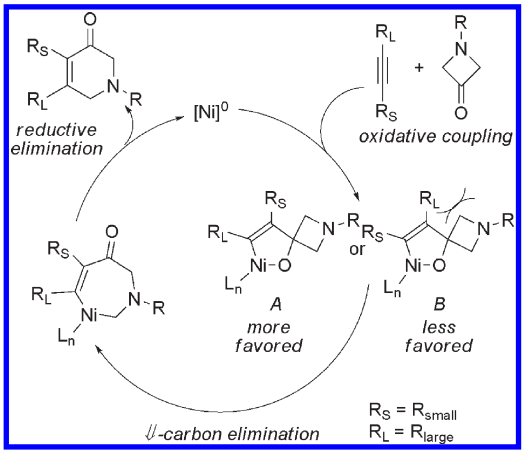


Figure 3. Ortep diagram of **2c**.

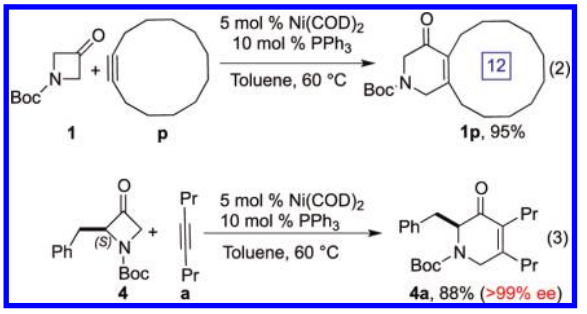
Scheme 2. Proposed Mechanism of Cycloaddition



The regioselective outcome of the reaction may be explained on the basis of mechanism shown in Scheme 2. Initially, oxidative coupling between the alkyne and the carbonyl of the azetidinone occurs. Two intermediates, A or B, are possible. However, metallacycle A is favored over metallacycle B since the regioselectivity of A positions the R_L away from the quaternary center. Intermediate A undergoes β-carbon elimination to form a seven-membered nickelacycle, which undergoes subsequent reductive elimination to afford the piperidine product.

Terminal alkynes are one of the most challenging substrates because of their rapid oligomerization. After a brief screening, we successfully incorporated terminal alkynes in our cycloaddition. That is, *tert*-butyl acetylene couples with azetidinone regioselectively (**1d**). Interestingly, these results are in contrast to the reactivity of cyclobutanones, which fail to react with terminal alkynes as well as sterically hindered alkynes.[9] Stannyl piperidine (**1f**) can also be obtained regioselectively in excellent yields when tributylstannyl-methyl alkyne was employed as a substrate. The use of 1,3-enyne led to selective formation of vinyl-piperidine (**1g**) with good regioselectivity. The reaction is not limited to alkyl substituted alkynes, as diphenyl acetylene can also be successfully coupled with azetidinone to afford the piperidine (**1h**).[11,12] However, these alkynes were less reactive than alkyl−alkyl alkynes, and higher temperature (100 °C) was necessary to effect the desired cycloaddition.[13] The mixed alkynes (i.e., aryl−alkyl alkynes) also react to yield the piperidine (**1i**−**1k**) in a regioselective fashion. Retention of regioselectivity was observed even when the electronics on the aryl ring of aryl−alkyl alkynes were perturbed (**1j**, **1k**). The extremely challenging aryl−silyl alkynes afforded the product (**1l**) in very good yields and excellent regioselectivity, for the desired cycloadduct was observed. Furanyl (**1m**) as well as thiophenyl (**1n**) piperidine skeleton can also be easily accessed. Interestingly, when stannyl-phenyl alkyne is employed, the product (**1o**) is obtained where the stannyl group is on the α-carbon. Thus, the aryl group, instead of the large stannyl group, seems to have a stronger affect on the regioselectivity.

Because of recent interest in macrocyclic heterocycles,[14] we subjected the cyclododecyne **p** under our reaction conditions. Gratifyingly, excellent yield of the piperidine product (**1p**) was obtained (eq 2).



To gain insight into the migratory aptitude of a 2-substituted azetidinone, we prepared 2-benzyl-3-Boc-azetidinone (**4**) from Boc-protected phenylalanine amino acid. When we subjected substituted azetidinone **4** to our standard reaction conditions, regioselective formation of the piperidine product (**4a**) with complete retention of enantioselecitivity (>99% ee) was obtained (eq 3). This observation reveals the preference for the migration of less

(12) A trace of amount of an unidentified side product was formed. This side product is possibly an α-alkenylation product, which has been observed by Aïssa and co-workers (see ref 11).

(13) The reaction can also be performed with less alkyne (i.e., 1.5 equiv); however, consistently excellent conversions and yields were obtained in short reaction times with 3.0 equiv of aryl substituted alkynes.

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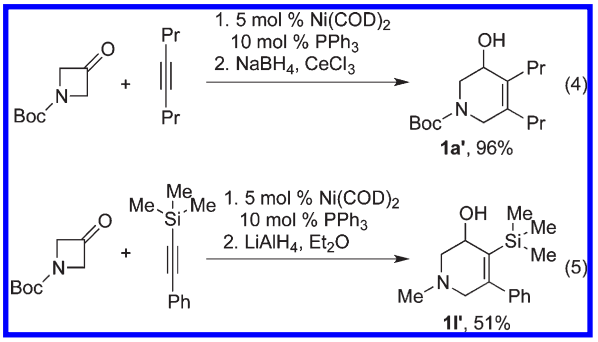
substituted β-carbon of azetidinone on the metal (Ni) center.



Further functionalization of the piperidine skeleton is also possible. The carbonyl moiety can be selectively reduced to the alcohol (**1a**′) using $NaBH_4/CeCl_3$ (eq 4). No loss of yield was observed for this two-step one-pot protocol. Similarly, ketone and carbamate can be reduced using LAH and the hydroxylated *N*-methyl piperidine (**1l**′) can be accessed in good yields (eq 5).

In conclusion, we have developed a Ni-catalyzed method for the [4 + 2]-cycloaddition reaction of azetidinones and alkynes. This reaction mechanism includes an interesting C−C bond cleavage that ultimately affords 3-piperidone products. Reaction conditions are both mild and practical and afford the N-heterocycles in excellent yields. Importantly, minimal side products such as C−H activation products are formed.

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Supporting Information Available. Experimental details, ^1H and ^{13}C NMR spectra, and crystal structure data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.