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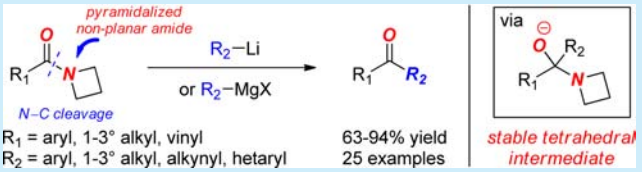
# Chemoselective Ketone Synthesis by the Addition of Organometallics to *N*-Acylazetidines

Chengwei Liu, Marcel Achtenhagen, and Michal Szostak*

Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States

Supporting Information

**ABSTRACT:** A general and highly chemoselective method for the synthesis of ketones by the addition of organometallics to *N*-acylazetidines via stable tetrahedral intermediates is reported for the first time. The transformation is characterized by its wide substrate scope and exquisite selectivity for the ketone products even when a large excess of nucleophilic reagents is used. Even of broader interest is the use of *N*-acylazetidines as bench-stable, readily available amide acylating reagents, in which the reactivity is controlled by amide pyramidalization and strain of the four-membered ring to afford synthetically valuable building blocks.




Nucleophilic addition of organometallics to carboxylic acid derivatives is a fundamental method for the synthesis of ketones that is widely used in academic and industrial settings.[1] Ketones are valuable compounds that are found in a large number of biologically active molecules and also serve as important building blocks in the synthesis of pharmaceuticals, functional materials, and agrochemicals.[2] The major challenge associated with these protocols is overaddition of the reactive nucleophilic reagents to ketone products, resulting in the formation of tertiary alcohols and other side reactions (e.g., disproportionation and formation of secondary alcohols).[3]

In this context, based on the pioneering studies by Weinreb, *N*-methoxy-*N*-methyl amides have been identified as arguably the most versatile acylating reagents for the synthesis of ketones, in which the presence of a chelating functional group prevents collapse of the tetrahedral intermediate (Figure 1).[4,5] Significant progress in the development of new methods to control the stability of metal-chelated tetrahedral intermediates has been made.[5] In contrast, Evans demonstrated that *N*-acylpyrroles form stable tetrahedral intermediates upon addition of organometallics due to pyrrole aromaticity and the lack of $n_{Olp}$ to $\sigma^*_{C-N}$ overlap.[6] The recent report on the pyrrole-bearing dication linchpin for the synthesis of ketones by the Sarpong group is noteworthy.[7] Other notable advances in the organometallic addition to amides include electrophilic activation of the amide bond reported by the groups of Charette and Huang[8] and cyclopropanation of amides by the Kulinkovich–de Meijere reaction.[9] Despite these advances, however, there is an urgent need to develop new bench-stable acylating reagents for the direct synthesis of ketones using cheap and readily available organometallics with high chemoselectivity.[10]

Our group has an ongoing interest in the activation of amide bonds.[11] While the selective nucleophilic addition to amides (resonance of 15–20 kcal/mol)[12] presents a significant challenge, in 2015, we introduced a new mode of amide N–C activation by geometric distortion.[13] This reactivity platform allows utilization of amides in a broad range of previously elusive transition-metal-catalyzed transformations to form carbon–carbon bonds (Suzuki, Heck, directed arylation). Independently, Garg and Zou reported Suzuki reactions of nonplanar imides.[14] A unique feature of these reactions is ground-state amide distortion, with N-coordination increasing amide electrophilicity toward N–C cleavage.[15] Interestingly, in all examples examined to date, amide bond twist (cf. pyramidalization) was required for productive metal insertion.[16]

Expanding upon this theme, we recently hypothesized that stable, pyramidalized amides[16] (cf. twisted amides) might be employed as highly chemoselective acylating reagents for organometallic 1,2-addition by using pyramidalization as the reactivity-controlling feature. In particular, we considered *N*-acylazetidines[17] based on the following features: (i) approximately half pyramidalization of the amide bonds ($\tau = 3.3°$; $\chi_N = 32.5°$;[18] 4-TolC(O)-azetidine, Winkler–Dunitz parameters) should allow enhanced N–C(O) reactivity due to diminished $n_{Nlp}$ to $\pi^*_{C=O}$ overlap, while preserving high bench stability of the precursors; (ii) large ring strain in a four-membered ring of 25.4 kcal/mol (cf. aziridines, 27.5 kcal/mol) and high nitrogen inversion barrier (90° angle) should decrease the aptitude for collapse of the tetrahedral intermediate;[19] (iii) large amide bond resonance energy in the ground state of 17.7 kcal/mol (cf. aziridines, 10.5 kcal/mol) should enable high bench stability, while obviating the need for handling sensitive *N*-acylating precursors.[20] The unique geometric properties of *N*-acylazetidines (ca. 30% amide distortion) might provide an opportunity to interrogate the effect of amide strain on the stability of tetrahedral intermediates.[21,22]

Herein, we report the first general and highly chemoselective method for the addition of organometallics to *N*-acylazetidines to give ketones via stable tetrahedral intermediates. The transformation is characterized by its operational simplicity,

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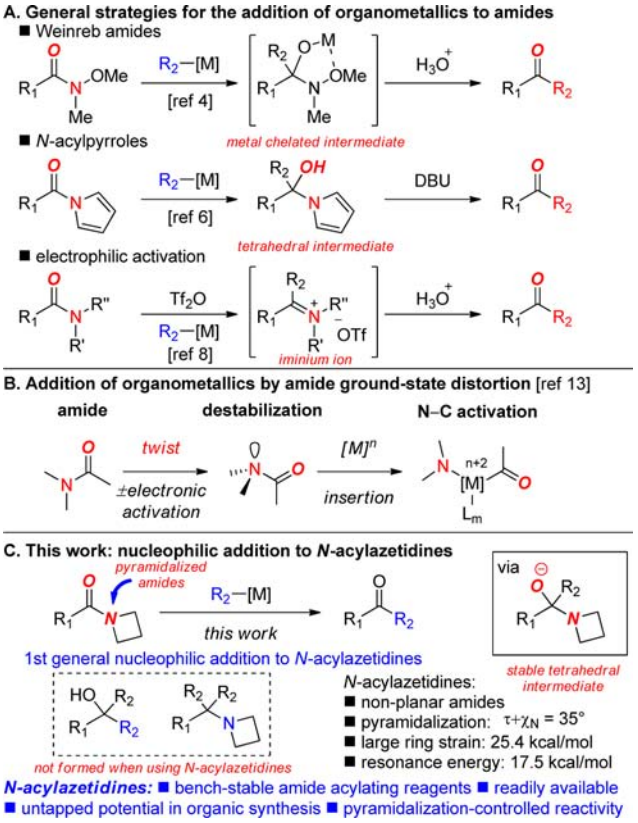
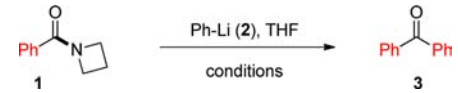



**Figure 1.** (A) General strategies for ketone synthesis from amides. (B) Activation of N−C amide bonds by ground-state distortion. (C) Organometallic addition to *N*-acylazetidines (*pyramidalization control*).

wide substrate scope, and exquisite selectivity for the ketone products. This report introduces *N*-acylazetidines as bench-stable, readily available amide acylating reagents, in which the reactivity is controlled by amide pyramidalization and strain of the four-membered ring,[16] which might be exploited in ways beyond the organometallic addition described.

We started our investigations by examining 1,2-nucleophilic addition of phenyllithium to *N*-acylphenylazetidine under a variety of conditions (Table 1). *N*-Acylazetidinyl aryl amide was selected as a standard electrophile with the aim of providing a complementary method to the recently reported metal-catalyzed synthesis of aryl ketones from amides.[13,14] After preliminary experiments, we found that the proposed addition occurs readily at −78 °C (entry 1). As expected, the reaction time, temperature, reagent stoichiometry, and addition mode had a significant influence on the reaction efficiency (entries 1−10). Importantly, in all cases examined, the overaddition alcohol and ring-opening products were not detected in crude reaction mixtures (selectivity >95:5), attesting to the high stability of the tetrahedral intermediate.[6] The best results were obtained in reactions at −78 °C (entry 10). Experiments designed to probe the stability of the tetrahedral intermediate (vide infra) demonstrated that reverse addition of *N*-acylazetidinyl amide (entry 10), prolonged reaction time (entry 11), and even high temperatures (entry 12) did not significantly affect its propensity to collapse. Similar stability experiments were conducted with MeLi as the nucleophile (not shown) and demonstrated that the corresponding tetrahedral intermediate is stable under the reaction conditions (selectivity >95:5). We note that the high stability of tetrahedral intermediates resulting

**Table 1. Optimization of 1,2-Addition of Organometallics to *N*-Acylazetidines**[a]



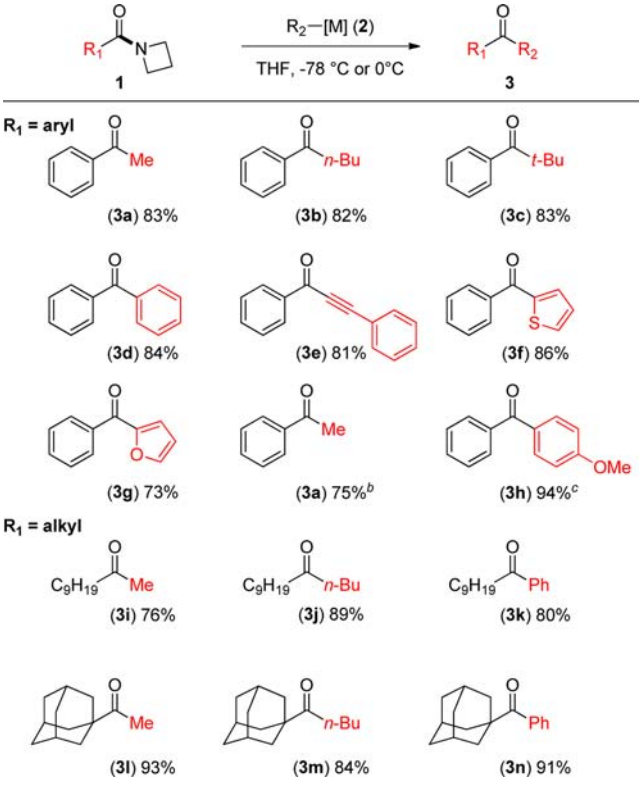

| entry | PhLi (equiv) | temp (°C) | time | conv (%)[b] | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | 1.05 | −78 | 15 min | 71 | 48 |
| 2 | 1.05 | −78 | 1 h | 62 | 19 |
| 3[c] | 1.05 | −78 | 1 h | 69 | 37 |
| 4 | 2.00 | −78 | 15 min | >95 | 88 |
| 5 | 2.00 | −78 | 1 h | >95 | 74 |
| 6[c] | 2.00 | −78 | 1 h | >95 | 78 |
| 7 | 2.00 | 0 | 1 h | >95 | 84 |
| 8 | 2.00 | rt | 1 h | >95 | 77 |
| 9[c] | 2.00 | rt | 1 h | 89 | 66 |
| 10[c] | 3.00 | −78 | 15 min | >95 | 93 |
| 11 | 3.00 | −78 to rt | 18 h | >95 | 80 |
| 12 | 3.00 | 0 to 60 | 1 h | >95 | 81 |

[a]Conditions: amide (0.5 mmol), PhLi (1−3 equiv, 1.9 M), THF (0.1 M). [b]Determined by $^1$H NMR and/or GC. [c]Reverse addition.

from the nucleophilic addition to *N*-acylazetidines provides important practical and mechanistic considerations (vide infra).

Next, the preparative scope of the reaction was explored (Scheme 1). As shown, the reaction accommodates a broad range of aryl and alkyl amide and organometallic coupling partners, providing advantageous selectivity (aryl−aryl, aryl−alkyl, alkyl−alkyl) to the metal-catalyzed protocols.[13,14] A

**Scheme 1. Addition of Organometallics to *N*-Acylazetidines: Nucleophile and Amide Scope**[a]




[a]Amide (0.50 mmol), RLi, THF (0.10 M), −78 or 0 °C. [b]MeMgBr, rt. [c]ArMgBr, 0−60 °C. See Supporting Information for full details.



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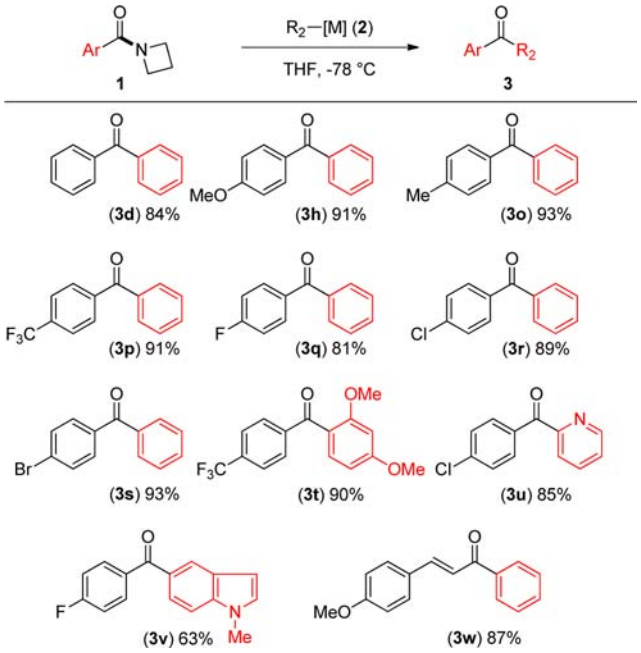
variety of organometallic reagents, including simple (**3a**–**3b**) and sterically hindered (**3c**) alkyl, aryl (**3d**), alkynyl (**3e**), and heterocyclic aryl lithium reagents, such as thienyl (**3f**) and furyl (**3g**), are perfectly accommodated. Note that these reagents can be readily generated by halogen–lithium exchange (**3d**), direct deprotonation (**3e**), or directed metalation (**3f**–**3g**).[10] Alkyl and aryl Grignard reagents could be equally accommodated, highlighting the high electrophilicity of *N*-acylazetidines (**3a**,**3h**). Furthermore, the procedure could be extended to simple alkyl (**3i**–**3k**) and sterically hindered alkyl *N*-acylazetidines as electrophilic coupling partners in high yields (**3l**–**3n**) using both alkyl and aryl nucleophiles. This reactivity is particularly noteworthy as metal-catalyzed cross-coupling of alkyl amide electrophiles by N–C insertion cannot be easily accomplished due to decarbonylation/$\beta$-hydride elimination.[13a]

The scope with respect to functional group tolerance on both coupling partners was next investigated (Scheme 2). The

**Scheme 2. Addition of Organometallics to *N*-Acylazetidines: Scope of Ketones**[a]

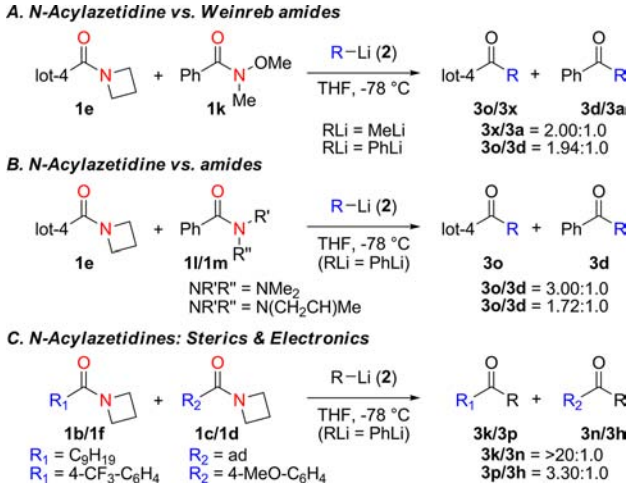



[a]Amide (0.50 mmol), RLi, THF (0.10 M), −78 °C.

reaction tolerates a range of electronically varied substituents under the standard reaction conditions (**3d**, **3h**, **3o**, **3p**). Valuable electrophilic functional groups such as *para*-fluoro (**3q**), chloro (**3r**), and bromo (**3s**) are readily tolerated, providing handles for nucleophilic addition/cross-coupling manipulation. Functionalized (**3t**) and heterocyclic nucleophiles, such as pyridinyl (**3u**) and indolyl (**3v**), are compatible. Finally, we found that alkenyl *N*-acylazetidinyl amides undergo selective 1,2-addition to give valuable chalcone products (**3w**). The utility of the present reaction is underscored by the synthesis of ketones with biological activity, such as substituted benzophenones with fungicidal activity (**3t**), chloropheniramine metabolite (**3u**), and an intermediate in the synthesis of potent aromatase inhibitors (**3v**).[23]

Studies were conducted to gain insight into the reaction mechanism (Scheme 3). Most importantly, intermolecular competition studies showed that organometallic addition to *N*-acylazetidines is preferred over Weinreb amides (Scheme

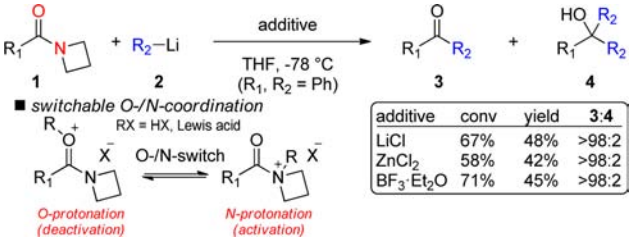
**Scheme 3. Selectivity Studies with *N*-Acylazetidines**




3A),[4] attesting to the high electrophilicity of *N*-acylazetidines. Experiments with electronically biased amides revealed that *N*-acylazetidines are inherently more reactive substrates (Scheme 3B). Experiments between *N*-acylazetidines (Scheme 3C) are consistent with the ease of nucleophilic addition.[1,2] The competition experiments suggest that synthetically useful levels of selectivity are possible with these substrates.

To probe further the stability of tetrahedral intermediates, the effect of Lewis acid additives was examined (Scheme 4). It is

**Scheme 4. Stability of Tetrahedral Intermediates**




well-known that Lewis acids increase the reactivity of N-containing electrophiles in organometallic addition;[24] however, a profound decrease was found in the present reaction, while maintaining high selectivity. We hypothesize that switchable *N*-/*O*-Lewis acid coordination[15] in azetidinyl amides ($\tau + \chi_N$ = 35°)[16] attenuates the reactivity. In the absence of Lewis acids, azetidinyl amides react via direct nucleophilic addition, while N-coordination increases the pathway selectivity.

In summary, we have reported the first general addition of organometallics to *N*-acylazetidines via stable tetrahedral intermediates. The reaction adds to the toolbox of traditional techniques for ketone synthesis from amides, complementing the recently disclosed methods by N–C amide bond activation. In a broader context, the present method introduces *N*-acylazetidines as bench-stable, readily available amide acylating reagents, in which the reactivity is controlled by the amide bond pyramidalization. We anticipate that this mode of amide bond activation will find widespread use in organic synthesis.

## ■ ASSOCIATED CONTENT

### Supporting Information

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Experimental procedures and characterization data (PDF)

## AUTHOR INFORMATION


### Corresponding Author

*E-mail: michal.szostak@rutgers.edu.


### Notes

The authors declare no competing financial interest.

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