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One-pot Unsymmetrical Ketone Synthesis Employing a Pyrrole-Bearing Formal Carbonyl Dication Linchpin Reagent**

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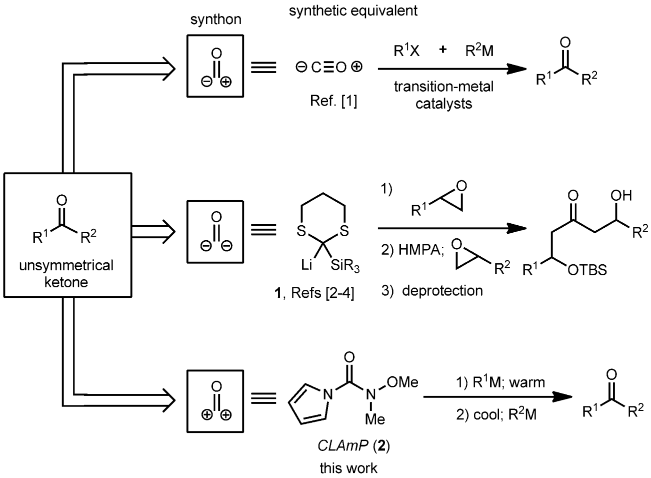
Abstract: *A one-pot procedure for the synthesis of unsymmetrical ketones utilizing a pyrrole-bearing carbonyl linchpin reagent (carbonyl linchpin N,O-dimethylhydroxylamine pyrrole; CLAmP) is reported. In contrast to other carbonyl dielectrophile equivalents, CLAmP enables the synthesis of ketones from a variety of organolithium and Grignard reagents. The electrophilic nature of CLAmP enables the addition of less reactive as well as thermally unstable nucleophiles. CLAmP was designed to form kinetically stable tetrahedral intermediates upon the addition of organometallic nucleophiles. Evidence for the existence of persistent tetrahedral intermediates was obtained through in situ IR studies.*

Unsymmetrical ketones are ubiquitous building blocks in chemical synthesis. Retrosynthetically, the ketone carbonyl may be thought of as one of three possible synthons—the carbonyl dication, dianion, or carbene (i.e., carbon monoxide)—and could serve as a linchpin upon which two carbon ligands can be appended (Scheme 1). Sequential attachment of carbon ligands through multiple steps is the most popular approach to ketone synthesis. However, the ketone linkage can conceivably be forged with a single synthetic operation (a one-pot synthesis) by combining the two carbon ligands with a synthetic equivalent of one of the above synthons. The preparation of unsymmetrical ketones by this approach would be synthetically empowering, but is particularly challenging as the carbonyl synthetic equivalent must exhibit differential reactivity toward the two carbon ligands.

Of the three possible carbonyl synthons, only two have been successfully employed in one-pot syntheses of unsymmetrical ketones. Transition-metal-catalyzed carbonylative cross-coupling is essentially a one-pot ketone synthesis involving carbon monoxide as the carbonyl linchpin.[1] The carbonyl dianion synthetic equivalent, has been reduced to practice by the groups of Tietze[2] and Smith[3] by using the sequential alkylation of dithianes such as **1** (Scheme 1).[4] Surprisingly, a carbonyl dication equivalent, which enables a general synthesis of unsymmetrical ketones, has not been developed,[5] though several groups have reported tactics and reagents with a very narrow scope. Herein we report that *N*-methoxy-*N*-methyl-1*H*-pyrrole-1-carboxamide (**2**; CLAmP) is a versatile electrophilic carbonyl linchpin reagent for the synthesis of unsymmetrical ketones.



Scheme 1. Retrosynthetic analysis of the ketone group: Synthons and synthetic equivalents.

In order to effect the selective formation of unsymmetrical ketones, an electrophilic carbonyl linchpin must feature two nucleofuges, each of which generate differentially stable tetrahedral intermediates upon sequential monoaddition of organometallic nucleophiles. Specifically, initial reaction of a carbonyl dication synthon (e.g., **2**) with the first nucleophile equivalent should afford a tetrahedral intermediate that persists throughout the addition but whose rate of collapse can be modulated by experimental conditions. Controlled collapse of the first tetrahedral intermediate generates a new carbonyl electrophile (acylium ion synthon) that is available for reaction with a second organometallic nucleophile. Ideally, persistence of the tetrahedral intermediate derived from the second addition prevents overalkylation at the electrophilic carbon, preserving the ketone oxidation state.

Several tactics that enable controlled monoaddition of organometallic nucleophiles to carbonyls have been reported. The groups of Weinreb,[7] Meyers,[8] and Mukaiyama[9] each developed carboxylic acid derivatives bearing chelating nucleofuges that retard the collapse of the initially formed

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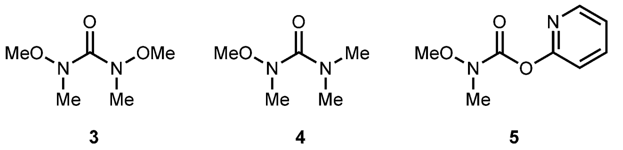
tetrahedral intermediates. It has been shown that some carbonyl electrophiles with poor nucleofuges (e.g., amides) also form unusually stable tetrahedral intermediates.[10] However, the same structural features that give rise to poor nucleofugality typically also reduce the inherent electrophilicity of the carbonyl group. For instance, the ideal electrophilic carbonyl linchpin, CO_2, forms unsymmetrical ketones from only the most reactive organolithium derivatives.[11] Exceptions to this general trend are *N*-acylpyrroles, which Evans et al. showed to form stable tetrahedral intermediates upon reaction with either organolithium or Grignard reagents.[12]

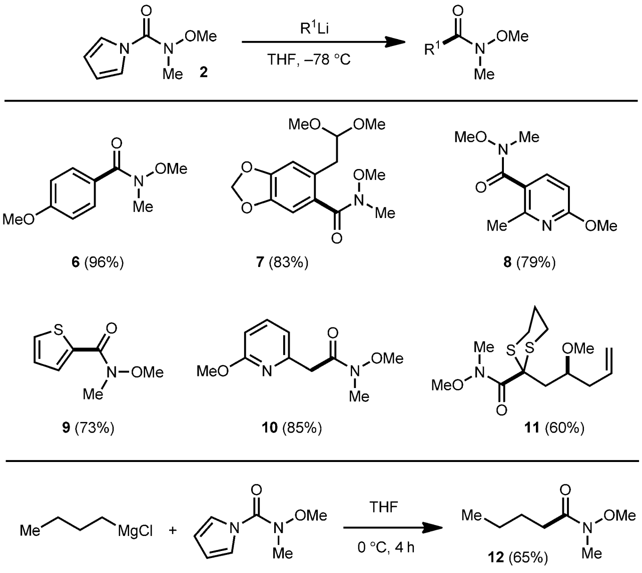
The groups of Reich, Hlasta, and Lee have all reported potential 'double' electrophilic carbonyl linchpin reagents employing chelative stabilization (**3**–**5**; Scheme 2), but the properties of the first departing nucleofuge have severely limited their use. The symmetrical urea **3**[13] reacts only at a relatively high temperature with strongly nucleophilic Grignard and organolithium reagents and does not undergo in situ elimination, even under forcing conditions. Therefore, it cannot be employed in a one-pot unsymmetrical ketone synthesis. The unsymmetrical urea **4**[14] reacts only with organolithium species to yield a nearly 1:1 mixture of *N,N*-dimethylamide and Weinreb amide products, the former of which is so weakly electrophilic that only the most reactive organolithium nucleophiles (e.g., *n*BuLi) may be used in the second addition step. The carbamate **5**[15] reacts unselectively with organolithium reagents, presumably because of the relatively high nucleofugality of the 2-pyridoxy group.



Scheme 2. Carbonyl dication synthetic equivalents.

The carbonyl dication synthetic equivalent **2** combines the desirable nucleofugal properties of Weinreb amides and *N*-acylpyrroles, thus allowing facile one-pot synthesis of unsymmetrical ketones. This carbonyl bis-electrophile reacts rapidly with different organometallic reagents to generate a semi-persistent tetrahedral intermediate at −78 °C, and thus permits selective monoaddition of the first nucleophile. Upon warming to ambient temperature, the putative intermediate readily collapses to exclusively generate a Weinreb amide in situ, which can react with a suite of organometallic nucleophiles to append the second carbon ligand.

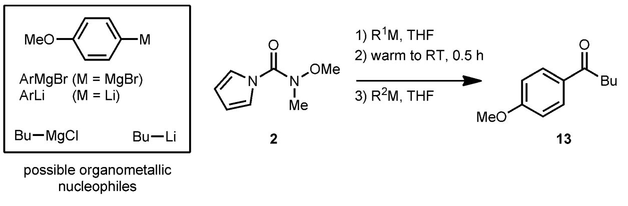
We first studied the reactivity and selectivity afforded by **2** in the presence of a single organometallic species to yield Weinreb amides (Scheme 3). In contrast to **5** and **4**, relatively non-nucleophilic lithiated picoline and dithiane species, as well as Grignard reagents can be employed to synthesize Weinreb amides. Although our primary goal was to identify a modular synthesis of unsymmetrical ketones, the synthesis of Weinreb amides is also synthetically useful. Thus, **2** should find use as a complement to **3** for one-carbon homologative synthesis of Weinreb amides, particularly in cases involving thermally unstable or relatively unreactive organometallic nucleophiles.



Scheme 3. Scope of Weinreb amides synthesis from organometallic reagents and **2**. Yields within parentheses are for the isolated compounds, with the exception of **12**, the yield of which is based on ^{1}H NMR analysis using an internal standard. THF = tetrahydrofuran.

In principle, both the type of organometallic nucleophile as well as the order in which it is appended to the carbonyl group of **2** could impact the outcome of the ketone synthesis. To better understand these factors, we synthesized 4′-methoxyvalerophenone (**13**; Table 1) using several permutations of nucleophile type and order of addition. Unlike the use of **5**, the best results with **2** were obtained when an aryllithium was used as the first nucleophile (entries 1 versus 2, and 3 versus 4). Unlike the use of **4**, the nature of the second nucleophile does not appear to strongly influence the overall yield of ketones, though it appears that organolithium nucleophiles

Table 1: Impact of nucleophile type and order of addition on unsymmetrical ketone synthesis.



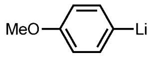
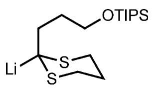
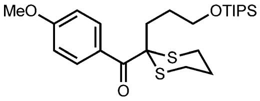
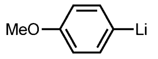
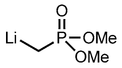
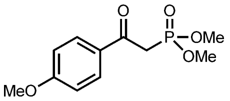
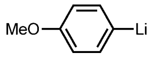
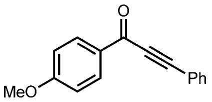
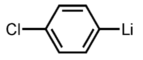
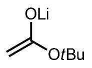
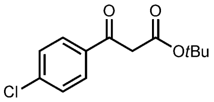
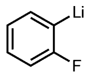
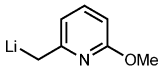
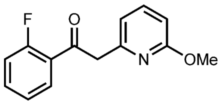
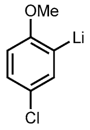
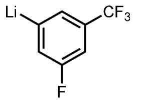
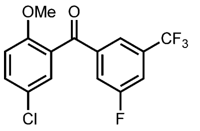
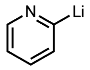
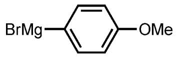
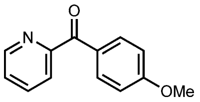
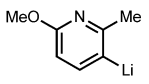
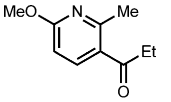
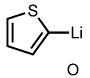
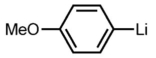
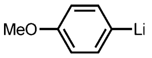
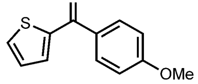
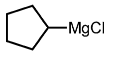
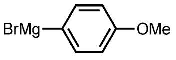
Entry	R^1 M	R^2 M	Yield [%][a]	Reaction conditions[b]
1	ArLi	AlkylLi	94	−78 °C, 1.5 h; −78 °C, 0.5 h
2	AlkylLi	ArylLi	63	−78 °C, 1 h; −78 °C, 1 h
3	AlkylLi	ArMgBr	54	−78 °C, 1 h; 23 °C, 8 h
4	ArLi	AlkylMgCl	80	−78 °C, 1 h; 0 °C, 3 h
5	AlkylMgCl	ArLi	36	0 °C, 5 h; 23 °C, 8 h
6	AlkylMgCl	ArMgBr	75	23 °C, 6 h; 23 °C, 8 h

[a] Yield of isolated product. [b] Reaction conditions are reported in the following format: conditions for first nucleophile; conditions for second nucleophile.

perform somewhat better (entries 1 versus 4, and 2 versus 3). Moreover, Grignard reagents may be used as the first nucleophile that is added to **2**, as the use of two different Grignard reagents is well-tolerated (entry 6). There are two important caveats: using sp^2-hybridized Grignard reagents as the first nucleophile with **2** leads to poor selectivity,[16] and the use of organolithium species following the addition of any Grignard reagent impairs the second addition step (entry 5). It is possible that in these cases, the lithium reagents react with magnesium salt byproducts to produce lithium magnesiate species, which may not be viable nucleophiles. In addition, bimetallic tetrahedral intermediates, which are less likely to undergo collapse, may form. Salt effects of this type have recently been discussed.[17] The former caveat can be avoided simply by using the sp^2-hybridized Grignard reagent as the second nucleophile, while the latter is readily solved by introducing the organolithium nucleophile first.

With a better understanding of the reactivity of **2**, the substrate scope of the one-pot unsymmetrical ketone synthesis was investigated further (Table 2). A variety of carbon nucleophiles can be utilized in the second addition step, including dithiane anions (entry 1), lithiophosphonates (entry 2), acetylides (entry 3), enolates (entry 4), and picolinyl anions (entry 5). Unlike **3**, the reagent **2** reacts rapidly with organolithium nucleophiles at low temperature, thus enabling the use of unstable organometallic species such as (2-fluorophenyl)lithium, which would otherwise decompose at noncryogenic temperatures.[18] Heteroaromatic nucleophiles are generally well tolerated (entries 7–9). Highly functionalized ketones can also be prepared using **2**. For instance, **19**, a key intermediate in the Boehringer Ingelheim synthesis of an NNRT inhibitor (HIV therapeutic),[19] was obtained in good yield. In general, the unsymmetrical ketones were formed with greater than 20:1 selectivity over the possible

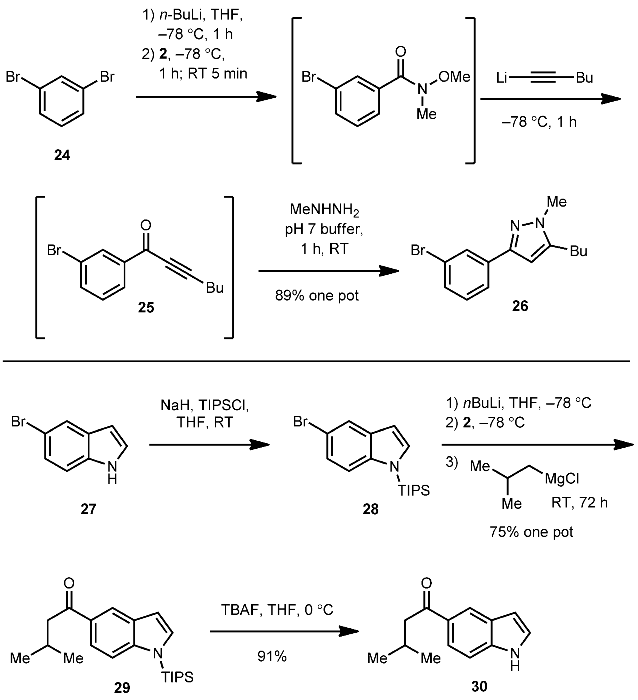
Table 2: Scope of unsymmetrical ketone synthesis using **2**.

Entry	First nucleophile (R^1M)	Second nucleophile (R^2M)[b]	Product		Yield [%][a]	Reaction conditions[c]
1				**14**	63	−78 °C, 1 h; −78 °C, 1 h, then warm to 0 °C
2				**15**	82	−78 °C, 1 h; −78 °C, 1 h, then warm to 0 °C
3				**16**	96	−78 °C, 1 h; −30 °C→0 °C over 3 h
4				**17**	84	−78 °C, 1.5 h; −78 °C, 2 h
5				**18**	78	−78 °C, 2 h; −78 °C, 3 h, then warm to 23 °C
6				**19**	67	−78 °C, 1 h; −78 °C, 3 h, then warm to 23 °C, R^2M added as a solution in Et_2O
7				**20**	60	−78 °C, 1 h; 23 °C, 8 h
8		Et−MgBr		**21**	58	−78 °C, 2 h; 23 °C, 24 h
9				**22**	64	−78 °C, 1 h; −78 °C, 1 h, then warm to 23 °C
10				**23**	79	0 °C, 1 h, then 23 °C for 24 h; 0 °C, 1 h, then 23 °C for 24 h

[a] Yield of isolated product. [b] Upon completion of the addition of the first nucleophile, the reaction mixture was warmed to 23 °C and stirred for 30 min prior to the addition of the second nucleophile. [c] Reaction conditions are reported as: conditions for first nucleophile; conditions for second nucleophile.

symmetrical congeners (except when alkyllithium nucleophiles were added first), and only trace amounts of the protonated organometallic nucleophiles were detected.

It also proved possible to telescope post-functionalization chemistry onto the unsymmetrical ketone synthesis sequence (Scheme 4). The ynone **25** is efficiently prepared in one pot from 1,3-dibromobenzene and 1-lithio-1-hexyne. Addition of methylhydrazine to the reaction vessel following ketone synthesis afforded the pyrazole **26** in 89 % overall yield. This set of transformations constitutes a four-component coupling of **2**, **24**, 1-hexyne, and methylhydrazine.



Scheme 4. Applications of the CLAmP unsymmetrical ketone synthesis to telescoped syntheses and the preparation of natural products. TBAF = tetra-*n*-butylammonium fluoride, TIPS = triisopropylsilyl.

Natural products that contain ketones are also accessible through short synthetic sequences which exploit the simplifying power of the one-pot ketone synthesis. For instance, verticillatine B[20] (**30**; Scheme 4,) was efficiently prepared by using **2** to couple **28** with isobutylmagnesium chloride.

In designing **2**, we speculated that addition of organometallic nucleophiles would result in a persistent tetrahedral intermediate resistant to nucleophilic attack. Experimental support for this hypothesis was obtained by monitoring the addition of organolithium nucleophiles to **2** using in situ IR spectroscopy. Carbonyl stretches corresponding to the Weinreb amide products (**33**, **12**) appeared and intensified over several hours after the consumption of **2** (Figure 1 A and B), and indirectly supports the existence of persistent tetrahedral intermediates arising from **2**. Interestingly, the tetrahedral intermediates that form from **2** and either PhLi or *n*BuLi (**31** and **32**, respectively), have dramatically different lifetimes (Figure 1 C and D). The tetrahedral intermediate **32** collapsed over about 5 hours at –78 °C[21] In contrast, the tetrahedral intermediate **31** had a significantly longer lifetime, as it had not completely collapsed even after 40 hours at –78 °C. Warming the reaction mixture to room temperature resulted in rapid and complete collapse of **31**.

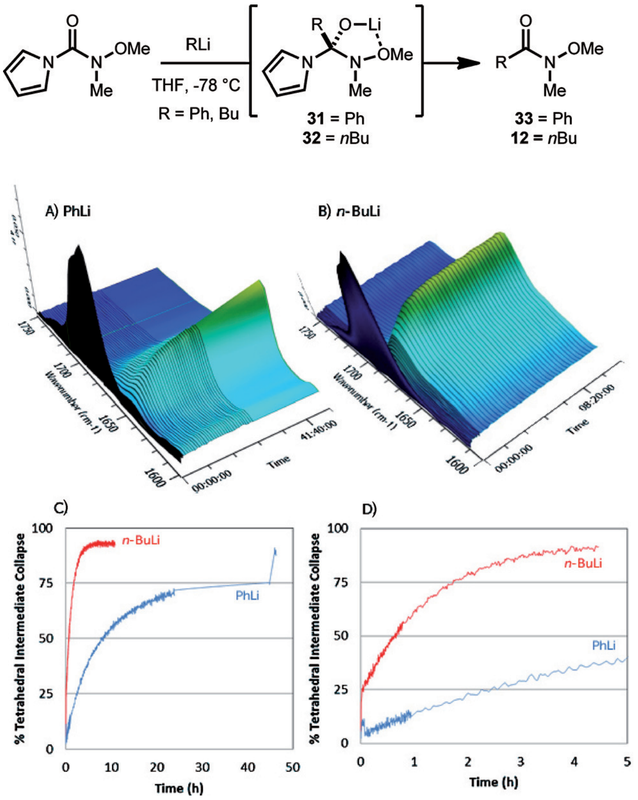


Figure 1. Persistence of lithio-tetrahedral intermediates studied by in situ IR. A) IR Surface of the collapse of **31**. B) IR Surface of the collapse of **32**. C,D) Plots of the disappearance of the tetrahedral intermediates versus time.

In conclusion, we have reported a carbonyl dication synthetic equivalent, **2**, which to our knowledge is the first carbonyl linchpin reagent that reacts with a wide variety of organometallic nucleophiles without the need for transition-metal catalysis. This versatile reagent can be used to prepare Weinreb amides or unsymmetrical ketones using a one-pot protocol. The success of these reactions hinges on the ability of **2** to form persistent tetrahedral intermediates upon the addition of the first organometallic reagent. Lifetimes of these tetrahedral intermediates range from a few hours to a few days at –78 °C, depending on the nucleophile. As a consequence of the broad product scope and the ease of the synthetic operations, this procedure should serve as a useful complement to existing unsymmetrical ketone synthesis methodology.

Keywords: acylation · amides · IR spectroscopy · ketones · synthetic methods

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