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Simple One-pot Conversion of Aldehydes and Ketones to Enals

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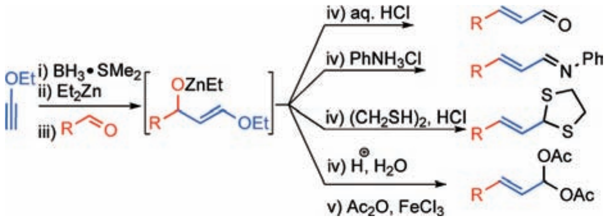
ABSTRACT



A simple and efficient method to convert aldehydes into α,*β*-unsaturated aldehydes with a two-carbon homologation is presented. Hydroboration of ethoxy acetylene with $BH_3 \cdot SMe_2$ generates tris(ethoxyvinyl) borane. Transmetalation with diethylzinc, addition to aldehydes or ketones, and acidic workup affords enals. When the addition is quenched with anilinium hydrochloride, 1,2-dithioglycol, or acetic anhydride, the unsaturated imine, dithiolane, or 1,1-diacetate is isolated in high yield. These transformations can be performed in a one-pot procedure.

The field of organocatalysis has witnessed explosive growth in the past decade and will continue to be a dynamic area of chemical research.[1] A wide variety of organocatalysts and reaction classes have been recently advanced, and many of these are based on α,*β*-unsaturated aldehydes as substrates. As a result, enals have arguably become the single most important class of substrates for development and applications of organocatalytic transformations[2] while remaining a mainstay of metal-based catalytic asymmetric processes.[1a,3] To keep pace with the ever-increasing demand for enals, current synthetic methods must be reevaluated and optimized or supplanted with new, direct, and more efficient approaches. Herein we disclose a simple and practical yet broadly applicable one-pot method for the conversion of aldehydes and ketones into α,*β*-unsaturated aldehydes.

A practical synthesis of enals would meet the following criteria: it must be general, employ commercially available and inexpensive reagents, use common laboratory techniques, be functional group compatible, and be tolerant of α-stereogenic centers in enantioenriched aldehydes and ketones. Furthermore, the transformation should be amenable to a one-pot procedure to enable rapid generation of an array of enals.

Existing methods for conversion of aldehydes and ketones to enals do not satisfy these criteria (Scheme 1). For example, cross aldol reactions with acetaldehyde enolates are not general, yielding self-condensation products with aliphatic aldehyde partners (Scheme 1, **A**).[4] This difficulty can be circumvented with *C*-silated imines (**B** and **C**),[5] but these imines must be prepared, silylated, and distilled, adding

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[1] (a) Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*; University Science Books: Sausalito, 2008. (b) Enders, D.; Grondal, C.; Hüttl, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175. (d) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79–87. (f) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724.

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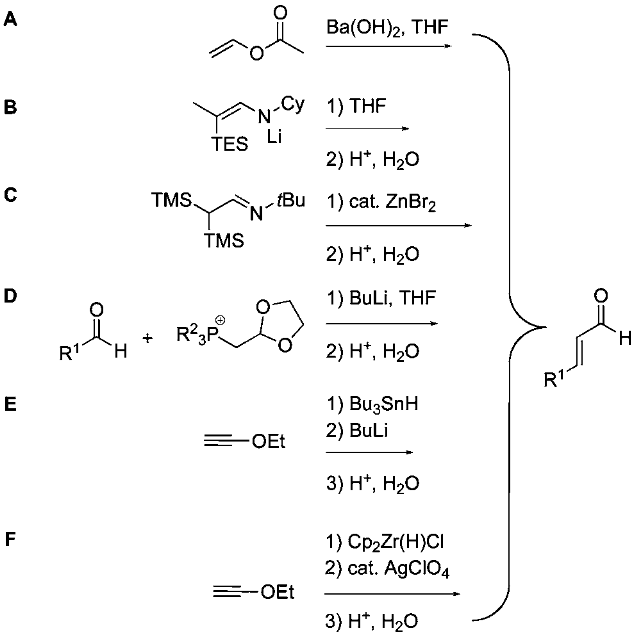
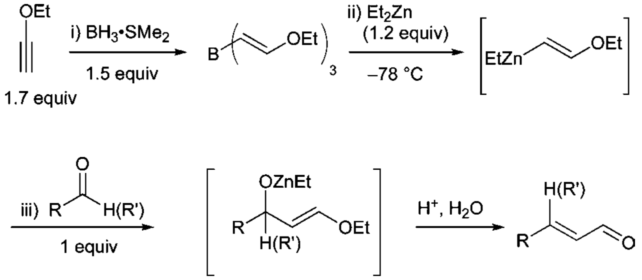
Scheme 1. Synthesis of Enals



additional steps. Wittig,[6] Horner–Emmons,[7] and Peterson-type reagents[8] are generally not compatible with base-sensitive functional groups and/or can require additional synthetic steps to generate enals (**D**).

Methods employing commercially available ethoxy acetylene are most attractive (Scheme 1, **E** and **F**). Hydrostannylation of ethoxy acetylene provides a vinylstannane. Transmetalation with *n*-BuLi leads to a highly reactive vinyllithium that readily adds to aldehydes and ketones to afford enals on acidic workup.[9] The drawback of such methods is the incompatibility of the vinyllithium with most functional groups. Suzuki introduced a method that combines the two steps above into one and circumvents the highly reactive vinyllithium intermediate in **E**.[10] Thus, hydrozirconation of ethoxy acetylene, in situ transmetalation of the vinylzirconocene intermediate with catalytic AgClO$_4$, addition to aldehydes, and elimination provides enals (**F**). Although this method has advantages over those outlined above, it is not economically viable because Schwartz's reagent is prohibitively expensive (>$2,000/mol from Aldrich).

Scheme 2. Our Synthesis of Enals



Our approach to α,*β*-unsaturated aldehydes involves hydroboration of ethoxy acetylene with BH$_3$•SMe$_2$ to generate the tris(vinyl) borane (Scheme 2).[11] This intermediate can be prepared on scale and stored for months under a nitrogen atmosphere or used directly in situ. Transmetalation from boron to zinc at −78 °C and addition to aldehydes or ketones affords zinc alkoxy enol ethers,[12] which readily undergo elimination on workup with 2 M HCl.

The broad substrate scope of this tandem reaction is illustrated in Table 1. Aliphatic (entries 1−3), aromatic (entries 4 and 8), and heteroaromatic aldehydes (entries 5−7) and conjugated enals (entries 9 and 10) and ynals (entry 11) undergo homologation to afford enals with 72−96% yield. Particularly noteworthy is the successful conversion of phenyl acetaldehyde to the expected enal in 89% yield, despite the acidic nature of its α-hydrogens (entry 3).

Ketone substrates were more challenging and exhibited variable results. Cyclohexanone (entry 12) was an excellent substrate and furnished the enal in 86% yield. Given the low reactivity of benzophenone and the mild nature of organozinc reagents,[13] we were surprised to isolate 54% yield of the enal (entry 13). Unsymmetrical ketones, such as acetophenone (entry 14), gave little *E*:*Z* selectivity (3:1) unless the two groups flanking the carbonyl were significantly different in size, such as *tert*-butyl versus methyl (*E*:*Z* = 15:1, 53% yield, entry 15). To examine the selectivity of the vinylzinc intermediate toward aldehydes versus ketones, a 1:1 mixture of cyclohexane carboxaldehyde and cyclohexanone were subjected to 1 equiv of ethoxy vinylzinc reagent. The more reactive aldehyde was converted to the enal product, and the ketone was left untouched.

In the case of *p*-phthalaldehyde the di(enal) was isolated in 70% yield (entry 16). The *o*-derivative (entry 17),

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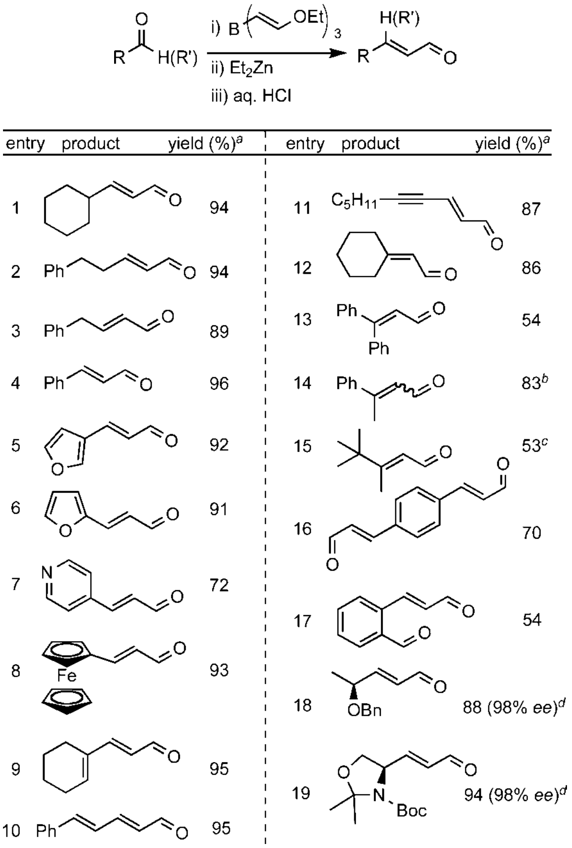
Table 1. Two-Carbon Homologation of Aldehydes and Ketones



entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	O	94	11	C_5H_{11}, O	87
2	Ph, O	94	12	O	86
3	Ph, O	89	13	Ph, Ph, O	54
4	Ph, O	96	14	Ph, O	83[b]
5	O, O	92	15	O	53[c]
6	O, O	91	16	O, O	70
7	N, O	72	17	O, O	54
8	Fe, O	93	18	OBn, O	88 (98% *ee*)[d]
9	O	95	19	O, N, Boc, O	94 (98% *ee*)[d]
10	Ph, O	95			

[a] Isolated yield. [b] *E*:*Z* ratio 3:1 (^{1}H NMR). [c] *E*:*Z* ratio >15:1 (^{1}H NMR). [d] ee determined by HPLC.

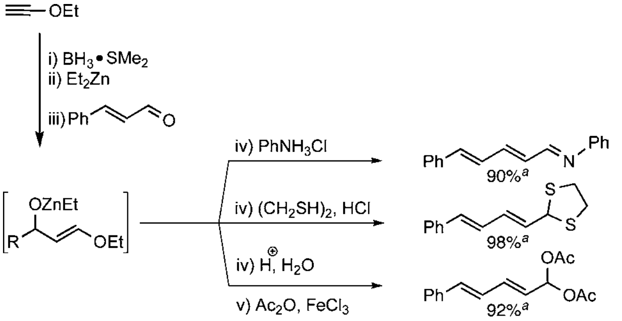
however, furnished the monoenal in 54% yield, most likely because the second aldehyde forms an internal hemiacetal derivative after the first addition, preventing further reaction.

Enantioenriched aldehydes are important starting materials and intermediates in synthesis. We therefore examined two optically active aldehyde substrates each with a stereocenter flanking the carbonyl. Benzyl-protected 2-hydroxy propanal and Garner's aldehyde were converted to enals in 88% and 94% yield, respectively (entries 18 and 19). Both enals had >98% ee after isolation and purification, indicating the organozinc intermediate in this process is indeed mild.

In the development of practical and useful methods, scalability must be demonstrated. The homologation of cyclohexenecarboxaldehyde was therefore performed on a 10 mmol scale, affording the dienal in 95% yield (entry 9).

Although enals are very important synthetic intermediates, derivatized enals are often desired. Under the assumption that the mechanism of conversion of hydroxy enol ethers to enals proceeds via oxocarbenium ions, we rationalized that these intermediates could be trapped by other nucleophiles. Thus, after addition of cinnamaldehyde to the vinylzinc to generate the alkoxide, 3 equiv of anilinium hydrochloride was added, leading to the imine in 90% isolated yield (Scheme 3). Likewise, trapping with 2 equiv of 1,2-dithioglycol afforded the unsaturated 1,3-dithiolane in 98% yield. Unsaturated 1,1-diacetates are useful intermediates in palladium allylation chemistry.[14] The diacetate was isolated in 92% yield after treatment of the alkoxide intermediate with aqueous HCl, removal of the volatile materials under reduced pressure and addition of 7 equiv of acetic anhydride and catalytic $FeCl_3$ (5 mol %).

Scheme 3. One-Pot Synthesis of Derivatized Enals[a]



[a] Isolated yield.

In summary, we have developed a simple and efficient one-pot procedure that enables rapid access to α,*β*-unsaturated aldehydes from aldehydes and ketones. The advantages of this method include its extensive substrate scope, functional group compatibility, tolerance of stereocenters α to carbonyl groups, and low cost. The method can also be employed in the one-pot synthesis of synthetically valuable unsaturated aldimines, dithiolanes, and 1,1-diacetates. We anticipate this method will facilitate advances in organocatalysis with enal substrates.

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Supporting Information Available: Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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