

1,4-Addition of Secondary and Tertiary Alkylzinc Bromides to α,β -Unsaturated Ketones without a Copper Catalyst

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
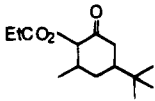



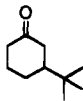

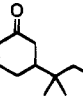

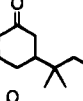

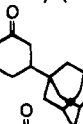

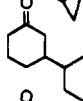

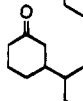
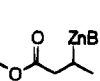
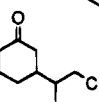
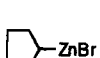

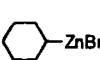
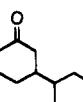
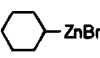
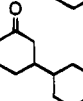
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Significant advances in organocopper chemistry have been developed in recent years, including methods to prepare cuprates bearing remote electrophilic centers. These new approaches include (1) oxidative addition of Rieke copper to alkyl and aryl halides,¹ (2) oxidative addition of Zn(0) to alkyl halides followed by metathesis with $\text{CuCN} \cdot 2 \text{LiCl}$ ² (this was extended to alkyl bromides and aryl bromides and iodides with the use of Rieke zinc³), (3) Lipshutz's novel low-temperature metathesis between functionalized vinylzirconocenes and higher order cyanocuprates,⁴ and (4) Lipshutz's recently published ingenious method involving the catalytic use of a cyanocuprate in conjugate additions of *in situ* formed lithiocuprates.⁵

However, the direct use of organozinc halides in synthetically useful conjugate additions to enones has been limited to alkynylzinc halides using TMSI as a Lewis acid.⁶ Organozinc reagents are capable of forming the 1,4-addition products without a copper catalyst if a lithium or magnesium triorganozincate approach is used.⁷ Direct use of primary alkylzinc halide reagents has been demonstrated not to be effectual in the formation of Michael products.^{2a,e,5} We recently reported an efficient procedure to generate secondary and tertiary alkylzinc bromides^{3a} in high yield and now report that 1,4-addition of these reagents to enones proceeds directly, in good yield, without the presence of a copper(I) catalyst.

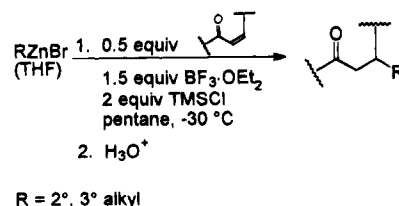
tert-Butylzinc bromide (1) reacted with cyclohexenone (2) to form the 1,4-addition product (Table 1, entry 3) in good yield in THF, using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.5 equiv)/ TMSCl (2.0 equiv) as a Lewis acid combination at -78°C . Unfortunately, under these reaction conditions, the use of other secondary and tertiary alkylzinc bromides gave only low yields of the desired products (entries 4, 7, and 11). Performing the reactions in a mixed polar/nonpolar solvent system proved to be advantageous in that when the alkylzinc bromide reagents (prepared in THF) were transferred to solutions of the enones in pentane, forming hetero-

Table 1. Conjugate Addition of Secondary and Tertiary Alkylzinc Bromides to Enones^a

Entry	RZnBr	Enone ^b	Product ^c	Yield(%) ^d
1	 ZnBr	A		54 ^{e,f}
2	 ZnBr	B		71
3	 ZnBr	C		89 ^e
4	 ZnBr	C		35 ^e
5	 ZnBr	C		74
6	 ZnBr	C		54
7	 ZnBr	C		34 ^{e,f}
8	 ZnBr	C		65 ^f
9	 ZnBr	C		51 ^f
10	 ZnBr	B		40
11	 ZnBr	C		36 ^e
12	 ZnBr	C		73

^a Reaction conditions: RZnBr (1 M, 10 mL THF), pentane (90 mL), 2 equiv of TMSCl , 1.5 equiv of $\text{BF}_3 \cdot \text{OEt}_2$, 0.5 equiv of enone, -30°C . ^b Enones: A, ethyl 6-methyl-2-oxo-3-cyclohexene-1-carboxylate; B, 3-penten-2-one; C, 2-cyclohexen-1-one. ^c NMR, IR, HRMS, and elemental analyses were consistent with structure or in agreement with the literature. ^d Isolated yield. ^e Reaction performed in THF. ^f Ratio of diastereomers not determined.

Scheme 1



geneous reaction mixtures, the yields of the resulting ketones increased dramatically (entries 5, 8, and 12).⁸ The 1,4-addition reactions were most efficiently performed at -30°C , as the reactions were sluggish at -78°C , except for the case of 1,

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which readily transferred the *tert*-butyl group⁹ at the lower temperature. A slight modification in the structure from the *tert*-butyl group, as in the case of 2-methyl-2-butylzinc bromide (entry 4), resulted in a sluggish reaction in THF with **2** and performed well only in a mixed solvent system (entry 5). The reaction of **1** with **2** in pentane alone gave a low yield of the desired product (17%). Primary alkyl- and arylzinc bromides did not react with enones under any of the above reaction conditions.

Though the use of a mixed solvent system in the 1,4-addition enabled an effective transfer of alkyl groups to enones, the product yields suffered when the active zinc was not washed with THF prior to the reaction with the starting alkyl bromides. Washing removed most of the lithium salts and naphthalene. Accordingly, it appeared that the reaction was inhibited by the presence of lithium salts. To confirm this observation, the reaction of **1**, in THF, prepared from washed active zinc, with enone **2** in the presence of added lithium chloride (1 equiv) led

(8) Representative procedure: To a flask charged with finely cut lithium (24.8 mmol), naphthalene (2.5 mmol), and THF (10 mL) under argon was transferred by cannula a THF (20 mL) solution of zinc chloride (11.8 mmol) dropwise such that addition was complete in ~1.5 h with moderate stirring. The stirring was stopped when the lithium was totally consumed, and the active zinc was allowed to settle. The supernatant was then removed. Fresh THF (25 mL) was added, the mixture briefly stirred and then allowed to settle, and the supernatant subsequently removed. The active zinc was then washed an additional time. THF (10 mL) was added to the flask, and the active zinc was ready for use. To the stirring mixture of active zinc was added methyl 3-bromobutyrate (7.59 mmol), and the mixture was refluxed for 2 h. The reaction mixture was allowed to cool to room temperature, and the zinc settled in 4 h. The alkylzinc bromide reagent was added dropwise to a solution of 2-cyclohexen-1-one (4.14 mmol), BF₃·OEt₂ (11 mmol), and TMSCl (15 mmol) in pentane (90 mL) at -30 °C, such that addition was complete in 20 min. The heterogeneous reaction mixture was stirred for 3.5 h at -30 °C. The reaction was then quenched by addition to saturated NH₄Cl (30 mL) and was then taken up in ether (20 mL). The aqueous layer was extracted with ether (2 × 20 mL). The combined organics were washed sequentially with water (20 mL) and brine (20 mL), dried over MgSO₄, and concentrated. Methyl 3-(3'-oxocyclohexyl)butanoate (2.10 mmol, 51%) was isolated from the crude reaction mixture by flash chromatography (hexanes/ethyl acetate).

(9) For exclusive transfer of the *tert*-butyl group to aldehydes under salt-free conditions for *tert*-butylmethylzinc, see: Laloë, E.; Srebnik, M. *Tetrahedron Lett.* **1994**, 35, 5587-5590.

to a 54% yield of product (cf. entry 3). The possibility of performing the 1,4-addition catalytically in BF₃·OEt₂ was investigated. The reaction of 2-butylzinc bromide with enone **2** using BF₃·OEt₂ catalytically (10 mol %) and 2 equiv of TMSCl resulted in a 50% yield of product, as opposed to a yield of 65% (entry 8) with 1.5 equiv of BF₃·OEt₂. Reactions conducted without the use of TMSCl resulted in the appearance of side products.

The reactions run in the mixed solvent system proceeded well at -30 °C, with typical reaction times of 2-12 h. The transfer of bulky groups in the organozinc was efficient as in the cases of adamantyl- and cyclohexylzinc bromides (entries 6 and 12). The tolerance of the methyl ester under the reaction conditions was apparent in the methyl-3-butyrylzinc bromide reaction with **1**, as a 51% yield (entry 10) was realized. Additionally, the nature of the enone was important in the reaction rate. The reactions of cyclic enones proceeded more readily than those of acyclic enones, the latter requiring longer reaction times.

In summary, methods have been developed which allow for the first time the 1,4-addition of secondary and tertiary alkylzinc bromides to α,β -unsaturated ketones without the need for a copper catalyst or without the presence of cyanide ion. The method is general and will tolerate functional groups. The ability to carry out conjugate additions without copper or cyanide ions represents an economical and an exceedingly "environmentally friendly" approach. Moreover, the reaction temperature need only be -30 °C, rather than -78 °C as most procedures require.

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Supporting Information Available: Spectral data for all new compounds listed in Table 1 (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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