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Regioselective Barbier reactions of 2-bromomethylcyclohexenone

Renuka Manchanayakage[a] and Scott T. Handy[b,*]

[a]*Department of Chemistry, Binghamton University, Binghamton, NY 13902, United States*
[b]*Department of Chemistry, Middle Tennessee State University, Murfreesboro, TN 37132, United States*

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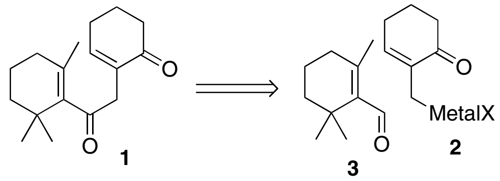
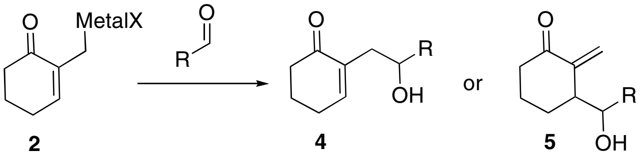
Abstract—Although the addition of crotyl or prenyl organometallic reagents has certainly found application in organic synthesis, the use of other non-symmetric allylic organometallic reagents has not received much attention. In part this is due to potential problems in controlling the regioselectivity of the addition products. We have noted that the tin and zinc reagents derived from 2-bromomethylcyclohexenone afford the complementary α and γ addition products, respectively. These conditions work for the reaction with a range of aldehydes, affording the products in good to modest yield.

During the course of studies directed at the development of the intramolecular reductive cyclization (hydrodimerization) reaction, we were interested in the preparation of substrates such as **1** (Scheme 1).[1,2] Although several routes could be envisioned, the most facile route to such compounds appeared to be the addition of an allyl organometallic reagent such as **2** to an aldehyde such as **3**. The bromide precursor to **2** is known and has been used in these labs in a manganese-mediated dimerization reaction, indicating that it should be possible to form an organometallic reagent from this bromide.[2]

At the same time, the addition of functionalized, non-symmetric allylic organometallic reagents such as **2** to aldehydes has never been reported and does have several potential pitfalls. One of the more troubling concerns is establishing the regioselectivity of reagent **2**, since it could afford either the direct addition (α) product **4** or the 'rearranged' (γ) product **5** (Scheme 2). This same problem has been encountered in the use of other non-symmetric allylic organometallic reagents, such as those derived from crotyl or prenyl bromide. In these cases, the observed regioselectivity generally favors reaction at the more substituted, γ, end.[3] This selectivity can be reversed in certain cases by the use of special organometallic reagents, such as the organobarium reagents developed by Yamamoto.[4] Also, in some cases, careful control of the reaction conditions can lead to selection of either the α or γ products, as has been demonstrated by Loh for the addition of crotyl reagents to aldehydes.[5] Still, the limited number of examples displaying such control and the intrinsic bias generally observed for the formation of the γ product, along with the potential reactivity of the ketone present in **2**, raised serious questions regarding the ability to selectively prepare α adduct **4**.



Scheme 1. General approach to cyclization substrates.



Scheme 2. Regioselectivity in the addition to aldehydes.

Bromide **6** was prepared as described previously.[2] It is worth noting that this bromide is of limited stability, particularly when neat. As a result, this bromide was

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Keywords: Barbier reaction; Regioselectivity; Tin; Zinc; Organometallic reagents.

* Corresponding author. Tel.: +1 615 904 8114; fax: +1 615 898 5182; e-mail: shandy@mtsu.edu

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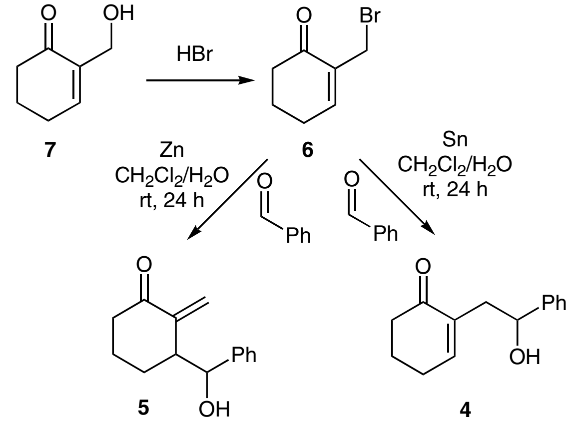


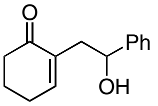
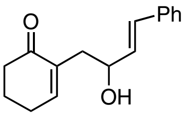
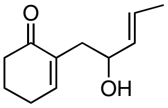
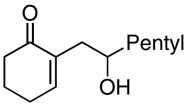
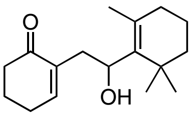
Scheme 3. Reactions with benzaldehyde.

prepared from the more stable Baylis–Hillman adduct **7** and then used directly without further purification. Initially, two sets of conditions for the reaction with benzaldehyde were studied: Sn with a mixture of H_2O and CH_2Cl_2 as the solvent and Zn with a mixture of H_2O and CH_2Cl_2 as the solvent (Scheme 3). These two metals were chosen since they have been frequently employed in aqueous Barbier chemistry and the fact that they are inexpensive and readily available. Much to our surprise, they did not afford the same product. Instead, the tin-mediated conditions afforded the α addition product **4** while the zinc-mediated conditions afforded the γ addition product **5**. The regiochemistry of product **4** was readily determined by the presence of the β proton of the enone near 7 ppm in the ^1H NMR spectrum. For product **5**, the presence of two olefinic signals, both as apparent singlets, signified the exocyclic position of the alkene. Although the yields of these reactions were modest (27% for the tin reaction and 50% for the zinc reaction), NMR analysis of the crude reaction mixture did not show any traces of the other isomer in either the tin or zinc reaction.

On the basis of this fortuitous discovery, application of these conditions to a range of aldehydes was undertaken. The tin-mediated reactions afforded the α products for simple aromatic, alkenyl, and alkyl-substituted aldehydes in modest yield (Table 1).[6,7] These conditions also worked with the more hindered β-cyclocitral (entry 5). This product is of particular interest in our study of the intramolecular hydrodimerization reaction and could afford a very facile route to a wide range of drimane-type natural products.

The zinc-mediated conditions also worked for a range of aldehydes, affording the γ products (Table 2).[7,8] These products were obtained as 1:1 mixtures of the *syn* and *anti* diastereomers. Although the yields were modest in methylene chloride/water, improved yields could be obtained by switching the reaction solvent to saturated aqueous ammonium chloride/THF and increasing the amount of bromide **6** and zinc dust. A similar switch for the tin-mediated reactions did not result in any increase in the isolated yield.

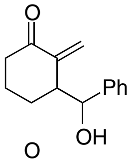
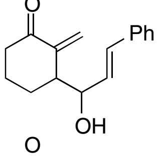
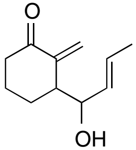
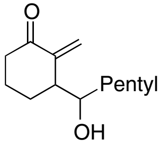
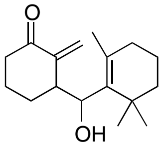
Table 1. Tin-mediated Barbier reactions[a]

Entry	Carbonyl	Product	Time (h)	Yield[b] (%)
1	Benzaldehyde		24	27
2	Cinnamaldehyde		48	47
3	Crotonaldehyde		48	53
4	Hexanal		48	30
5	β-Cyclocitral		48	46

[a] Aldehyde (1 equiv), bromide **6** (1.2 equiv), and tin powder (1.5 equiv) in an equivolume mixture of CH_2Cl_2 and water.

[b] Isolated yield.

Table 2. Zinc-mediated Barbier reactions[a]

Entry	Carbonyl	Product	Time (h)	Yield[c] (%)
1	Benzaldehyde		24[a] 7[b]	50 70
2	Cinnamaldehyde		48[a] 7[b]	47 96
3	Crotonaldehyde		48[a] 9[b]	43 72
4	Hexanal		36[a] 9[b]	52 69
5	β-Cyclocitral		48[a] 4[b]	60 79

[a] Aldehyde (1 equiv), bromide **6** (1.2 equiv), and zinc dust (1.5 equiv) in an equivolume mixture of CH_2Cl_2 and water.

[b] Aldehyde (1 equiv), bromide **6** (2 equiv), zinc dust (3 equiv) in a 2:1 mixture of THF and saturated aqueous NH_4Cl.

[c] Isolated yield.