Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3819–3822

Regioselective Barbier reactions of 2-bromomethylcyclohexenone

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

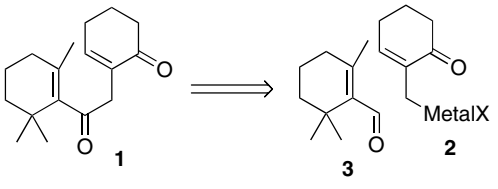
[a]Department of Chemistry, Binghamton University, Binghamton, NY 13902, United States
[b]Department of Chemistry, Middle Tennessee State University, Murfreesboro, TN 37132, United States

Received 8 March 2007; revised 27 March 2007; accepted 28 March 2007
Available online 3 April 2007

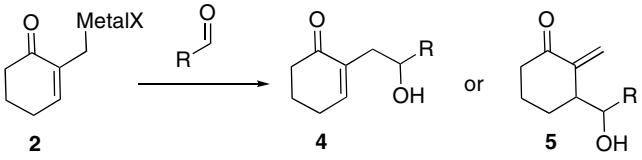
Abstract—Although the addition of crotyl or prenyl organometallic reagents has certainly found application in organic synthesis, the use of other non-symmetric allylic organometallic reagents has not received much attention. In part this is due to potential problems in controlling the regioselectivity 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.

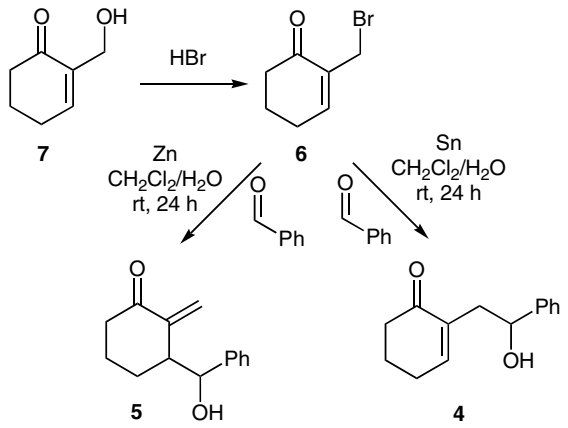


Scheme 2. Regioselectivity in the addition to aldehydes.

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

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

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.03.158



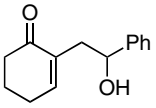
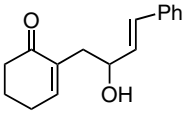
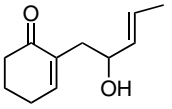
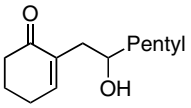
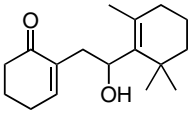
Scheme 3. Reactions with benzaldehyde.

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.

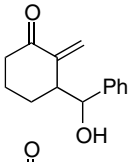
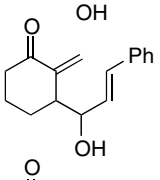
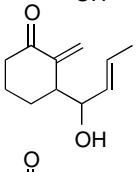
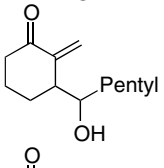
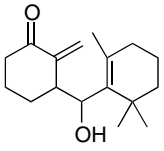
The zinc-mediated conditions also worked for a range of aldehydes, affording the γ products (Table 2).[7,8] These products were obtained as 1:1 mixtures of the *syn* and *anti* diastereomers. Although the yields were modest in methylene chloride/water, improved yields could be obtained by switching the 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]

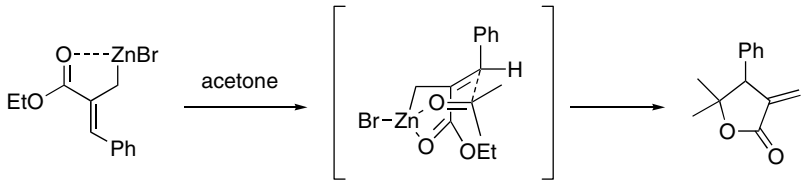
Entry	Carbonyl	Product	Time (h)	Yield[b] (%)
1	Benzaldehyde		24	27
2	Cinnamaldehyde		48	47
3	Crotonaldehyde		48	53
4	Hexanal		48	30
5	β-Cyclocitral		48	46

[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.



Scheme 4. Zinc-mediated reaction pathway by Lambert.[9]

Based upon the results reported by Loh, there is some question as to the source of the selectivity observed under these two sets of conditions. Loh noted in studies of crotyl and cinnamyl organometalic additions under aqueous Barbier conditions that the initially formed γ adduct slowly equilibrates to the α adduct.[5] To determine if a similar effect was operational in the present reactions, the reaction of bromide **6** with benzaldehyde under tin and zinc conditions was followed by TLC and ^{1}H NMR. In both cases, only the initially formed isomer (α for tin and γ for zinc) was observed and no equilibration was noted, even after following the reaction for 48 h (which was sufficient time for at least partial equilibration in Loh's studies). As a result, this selectivity does not appear to be the result of equilibration.

Our preliminary hypothesis regarding the origin of this metal-dependent selectivity is that the Lewis basic ketone functionality is important. This is borne out by the observation that the application of identical reaction conditions to the addition of crotyl bromide to benzaldehyde does not result in α selectivity for tin and γ selectivity for zinc, but rather essentially no selectivity for tin and α selectivity for zinc, as noted earlier by Loh.[5] Additional support for this hypothesis comes from earlier work by Lambert in which they reported the potential role of a Lewis basic group in the zinc-mediated Barbier addition of some ester-containing allylic systems.[9] Coordination between the zinc and the ester group was proposed. This reagent then reacted via a Zimmerman–Traxler transition state as seen in Scheme 4. A similar reaction pathway presumably is operational with bromide **6**.

For the tin-mediated reaction, we propose that it does not proceed via a transition state similar to that of the zinc-mediated reaction due to the poorer Lewis acidity of tin in the aqueous environment.[10] As a result, the tin may or may not be capable of coordinating to the ketone present in **6**, but is undoubtedly incapable of forming the highly coordinated transition state observed with zinc. The exact nature of the transition state in the tin-mediated reactions is not yet clear and will be the subject of future efforts.

In conclusion, we report the regioselective addition of a functionalized allylic organometallic reagent that can afford either the α or γ addition product depending upon the choice of metal. These reactions are simple to perform and afford the desired products in modest to good yield. Should this combination of Lewis basic functionality and metal prove to be a general method to control the regioselectivity of Barbier reactions of these types of allylic systems, it will open a new, practical disconnection for the synthesis of a wide range of natural and non-natural products. Already, the short sequence employing bromide **6** provides ready access to compounds of utility in the synthesis of drimane-type natural products via intramolecular hydrodimerization reactions. Further studies of the generality of this Lewis basic/metal combination to control the regioselectivity of Barbier reactions of allylic systems and synthetic applications are underway and will be reported in due course.

Acknowledgment

The authors thank Binghamton University for financial support of this research.

References and notes

1. Little, R. D.; Schwaebe, M. K. *Top. Curr. Chem.* **1997**, *185*, 1–48; Pandey, G.; Hajra, S.; Ghorai, M. K.; Kumar, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 8777–8787; Pandey, G.; Ghorai, M. K.; Hajra, S. *Tetrahedron Lett.* **1998**, *39*, 1831–1834; Pandey, G.; Chorai, M. K.; Hajra, S. *Tetrahedron Lett.* **1998**, *39*, 8341–8344; Enholm, E. J.; Kinter, K. S. *J. Org. Chem.* **1995**, *60*, 4850–4855; Cabrera, A.; Lagadec, R. L.; Sharma, P.; Arias, J. L.; Toscano, R. A.; Velasco, L.; Gavino, R.; Alvarez, C.; Salmon, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3609–3617; Mandell, L.; Daley, R. F.; Day, R. A., Jr. *J. Org. Chem.* **1976**, *26*, 4087–4089; Anderson, J. D.; Baizer, M. M.; Petrovich, J. P. *J. Electrochem. Soc.* **1966**, *31*, 3890–3897; Amputch, M. A.; Little, R. D. *Tetrahedron* **1991**, *47*, 383–402; Terem, B.; Utley, J. H. P. *Electrochim. Acta* **1979**, *24*, 1181–1184.
2. (a) Handy, S. T.; Omune, D. *Org. Lett.* **2005**, *7*, 1553–1555; (b) Handy, S. T.; Omune, D. *Tetrahedron* **2007**, *63*, 1366–1371.
3. For a review, see: Roush, W. R. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 1.
4. Yanagisawa, A.; Habaue, S.; Yasue, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 6130–6141.
5. (a) Tan, K. T.; Chang, S. S.; Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 2958–2963; (b) Loh, T. P.; Tan, K. T.; Yang, J. Y.; Xiang, C. L. *Tetrahedron Lett.* **2001**, *42*, 8701–8703.
6. Representative procedure: A mixture of aldehyde (2.2 mmol), bromide **6** (2.6 mmol), and tin powder (3.3 mmol) was combined in 2.6 mL of a 1:1 mixture of methylene chloride and water. The mixture was stirred at room temperature until TLC indicated complete consumption of starting material. The reaction was then diluted with ether and washed with water. The organic

layer was washed further with brine and dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude mixture was purified via column chromatography (30% ethyl acetate/hexanes as eluent) to afford the product as a clear oil.

7. All compounds exhibited spectral properties consistent with the assigned structures. ^{1}H and ^{13}C data are as follows: Table 1, entry 1—^{1}H (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 6.7 (br s, 1H), 4.8 (dd, $J = 6.2$, 11.5 Hz, 1H, X or ABX), 4.2 (br s, 1H, OH), 2.7–2.5 (AB of ABX, 2H), 2.5–2.3 (m, 4H), 2.1–1.8 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 201.7, 149.4, 146.7, 137.2, 128.1 (2C), 127.1, 125.6 (2C), 73.5, 41.0, 38.2, 26.1, 22.8. Entry 2—^{1}H (300 MHz, $CDCl_3$) δ 7.4–7.1 (m, 6H), 6.7 (d, $J = 12$ Hz, 1H), 6.3 (br d, $J = 12$ Hz, 1H), 4.6 (br s, 1H, OH), 4.1 (t, $J = 6.2$ Hz, 1H), 2.6–1.6 (m, 8H); ^{13}C (75 MHz, $CDCl_3$) δ 204.9, 152.1, 136.2, 135.5, 133.2, 128.9, 128.6 (2C), 128.0, 126.8 (2C), 73.5, 40.1, 36.1, 26.3, 22.6. Entry 3—^{1}H (300 MHz, $CDCl_3$) δ 6.9 (s, 1H), 5.7 (br d, $J = 12.1$ Hz, 1H), 5.2 (d, $J = 12.2$ Hz, 1H), 4.2 (t, 1H), 2.8–1.6 (m, 11H); ^{13}C (75 MHz, $CDCl_3$) δ 211.9, 142.9, 134.2, 128.5, 126.2, 74.7, 49.4, 41.5, 32.3, 25.8, 12.4. Entry 4—^{1}H (300 MHz, $CDCl_3$) δ 6.7 (s, 1H), 4.2 (m, 1H), 2.7–0.9 (m, 19H); ^{13}C (75 MHz, $CDCl_3$) δ 195.5, 148.7, 145.5, 67.1, 39.9, 38.5, 38.2, 28.4, 25.9, 25.6, 23.0, 22.7, 13.8. Entry 5—^{1}H (300 MHz, $CDCl_3$) δ 7.2 (br s, 1H), 4.3 (br s, 1H), 2.9 (m, 1H), 2.6–0.9 (m, 23H); ^{13}C (75 MHz, $CDCl_3$) δ 204.6, 151.7, 151.4, 136.2, 133.5, 75.4, 55.2, 51.4, 40.2, 39.9, 37.6, 36.4, 36.3, 33.9, 29.4, 28.7, 26.3, 24.8, 23.0, 22.6, 22.6, 21.1, 19.2. Table 2, entry 1—^{1}H (300 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5H), 5.6 (s, 1H), 5.4 (s, 1H), 5.0 (s, 1H, OH), 4.8 (d, $J = 7.1$ Hz, 1H), 2.9–2.8 (m, 2H), 2.4–2.3 (m, 1H), 1.8–1.2 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 212.8, 148.6, 143.3, 138.9, 128.0 (2C), 127.0 (2C), 115.1, 74.6, 51.5, 36.9, 28.4, 20.0. Entry 2—^{1}H (300 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5H), 6.7 (d, $J = 12$ Hz, 1H), 6.4 (br d, $J = 12$ Hz, 1H), 5.4 (s, 1H), 5.3 (s, 1H), 4.5 (br s, 1H, OH), 2.4–2.2 (m, 1H), 1.8–1.2 (m, 5H); ^{13}C (75 MHz, $CDCl_3$) δ 195.6, 148.6, 136.5, 132.8, 131.1, 128.5 (2C), 127.8, 126.6 (2C), 115.1, 73.1, 49.6, 36.5, 28.3, 19.7. Entry 3—^{1}H (300 MHz, $CDCl_3$)δ 5.8–5.6 (m, 2H), 5.3 (s, 1H), 5.2 (s, 1H), 4.3 (br s, 1H, OH), 4.2 (d, $J = 6.2$ Hz, 1H), 2.4–1.4 (m, 10H); ^{13}C (75 MHz, $CDCl_3$) δ 189.9, 151.0, 130.4, 128.2, 109.3, 72.9, 46.1, 36.5, 26.6, 20.8, 17.9. Entry 4—^{1}H (300 MHz, $CDCl_3$) δ 5.2 (s, 1H), 5.0 (s, 1H), 3.8 (d, $J = 6.4$ Hz, 1H), 2.4–0.8 (m, 18H); ^{13}C (75 MHz, $CDCl_3$) δ 195.0, 151.3, 114.0, 72.8, 50.7, 48.1, 37.2, 36.8, 34.7, 31.9, 29.4, 26.4, 25.5, 22.6, 19.9, 14.0. Entry 5—^{1}H (300 MHz, $CDCl_3$) δ 5.6 (br s, 1H, OH), 5.0 (s, 1H), 4.9 (s, 1H), 4.5 (s, 1H), 2.6–0.9 (m, 22H); ^{13}C (75 MHz, $CDCl_3$) δ 213.1, 138.2, 134.4, 125.6, 104.5, 70.6, 41.3, 39.9, 39.2, 36.6, 34.2, 29.4, 28.7, 27.5, 25.9, 21.5, 19.1, 18.4.
8. Representative procedure: A mixture of aldehyde (2.2 mmol), bromide **6** (4.4 mmol) and zinc powder (6.6 mmol) were combined in 3.0 mL of a 2:1 mixture of tetrahydrofuran and saturated aqueous ammonium chloride. The mixture was stirred at room temperature until TLC indicated complete consumption of starting material. The reaction was then diluted with ether and washed with water. The organic layer was washed further with brine and dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude mixture was purified via column chromatography (30% ethyl acetate/hexanes as eluent) to afford the product as a clear oil.
9. Lambert, F.; Kirschlege, B.; Villieras, J. *J. Organomet. Chem.* **1991**, *406*, 71–86.
10. Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287–8288.