Communications to the Editor

Highly Regioselective Lewis Acid-Mediated Aldol Additions at the More Encumbered α-Side of Unsymmetrical Ketones

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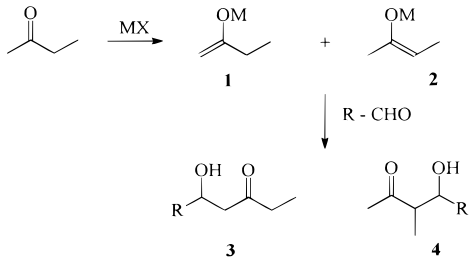
Regioselective reactions of enolates of unsymmetrical ketones are of fundamental importance in organic synthesis, the most familiar reactions being α-alkylations,[1] aldol additions,[2] and the Michael addition.[3] An unsymmetrical ketone can form the two regioisomeric enolates **1** and **2** upon deprotonation (Scheme 1).[2a,4]

The deprotonation of unsymmetrical ketones results in the less substituted enolate **1** by irreversible kinetic control, whereas those reactions under thermodynamical control usually yield the more substituted product **2**. The latter product is produced during an equilibrium with moderate regioselectivity.[5] In the more favorable cases, one regioisomer can greatly predominate in the equilibrium mixture, but often the equilibrium constant is not sufficiently high enough to achieve an acceptable regioselectivity. Furthermore, even if one prepares a regiodefined enolate, problems may occur with proton-transfer.[6] There do exist a few methods for generating the more-substituted enolates with high selectivity,[7] but examples of high regioselectivity obtained with these reactions are rare.

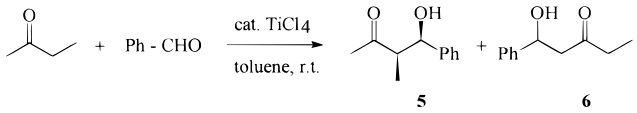
Recently, Yamamoto et al. have described a case of high regioselectivity obtained with α-alkylation. The reaction occurs at the more hindered α-side of unsymmetrical ketones, through the use of bulky aluminum alkoxides in the presence of lithium diisopropylamide.[8]

We describe here a very simple and efficient method for the direct aldol addition of aldehydes at the encumbered α-side of unsymmetrical ketones. In the presence of substoichiometric quantities of $TiCl_4$, reactions of ketones with aldehydes at room temperature resulted in high syn selectivity and good yields of 3-hydroxy ketones (Scheme 2).[9]

Scheme 1

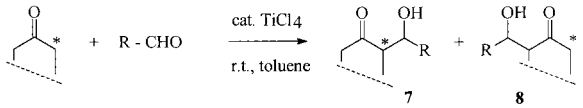


Scheme 2



yield: 83 %
regioselectivity **5** / **6**: 97 / 3
syn / *anti* ratio of **5**: 95 / 5

Table 1. Regioselective Aldol Addition of Unsymmetrical Ketones



entry	ketone	aldehyde	yield [%]	ratio of **7** : **8**[b]	*syn* / *anti* ratio of **7**
1		Ph - CHO	83	97 / 3[7f]	95 / 5
2		*i*Pr - CHO	72	91 / 9[13]	76 / 24
3		*n*Pr - CHO	68	89 / 11[14]	83 / 17
4	*nBu	Ph - CHO	87	89 / 11[12]	72 / 28
5		Ph - CHO	88	99 / 1[7e, 7d]	> 98 / 2
6		*i*Pr - CHO	81	95 / 5[7e]	84 / 16
7		Ph - CHO	67	89 / 11[7e, 7d]	75 / 25
8		*i*Pr - CHO	71	88 / 12[7e]	67 / 33
9		*n*Pr - CHO	62	86 / 14[7a]	73 / 27
10		Ph - CHO	91	> 99 / 1[11]	21 / 79
11	*Ph	*i*Pr - CHO	89	96 / 4[15]	37 / 63
12		*n*Pr - CHO	82	94 / 6[16]	25 / 75

[a] The carbon atoms indicated with an asterisk are the encumbered α-side. [b] Ratios were determined by ^1H and ^{13}C NMR ($CDCl_3$, 300 MHz) on the crude material. [c] For a representative aldol addition see ref 9c.

These reactions were carried out in the absence of base, in contrast to the previously reported method by Evans ($TiCl_4$ and base).[10] Ketones are used directly in this reaction: no formation of the activated corresponding silyl enol ether is required. As an example, the $TiCl_4$-mediated reaction of methyl ethyl ketone with aldehydes gave a highly syn selective and high regioselective

(1) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, pp 1−64.
(2) (a) Heathcock, C. H. In *Modern Synthetic Methods 1992*; Scheffold, R., Ed.; VCH: Weinheim, 1992; pp 1−102. (b) Braun, M. In *Houben-Weyl, Stereoselective Synthesis;* Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; G. Thieme: Stuttgart, 1995; Vol. 21b, pp 1603−1735. (c) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2; pp 181−258.
(3) (a) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4; pp 1−68. (b) Yamamoto, Y. In *Houben-Weyl, Stereoselective Synthesis;* Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; G. Thieme: Stuttgart, 1995; Vol. 21b, pp 2041−2155.
(4) Meckelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 99−132.
(5) (a) Negishi, E.; Matsushita, H.; Chatterjee, S.; John, R. A. *J. Org. Chem.* **1982**, *47*, 3188−3190. (b) Krafft, M. E.; Holton, R. A. *J. Org. Chem.* **1984**, *49*, 3669−3670.
(6) Patterson, J. W.; Fried, J. H. *J. Org. Chem.* **1974**, *47*, 2506−2509.
(7) (a) Yamago, S.; Machii, D.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2098−2106 and references cited therein. (b) Ando, A.; Miura, T.; Tatematsu, T.; Shiori, T. *Tetrahedron Lett.* **1993**, *34*, 1507−1510. (c) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598−1608 and references cited therein. (d) Duhamel, P.; Cahard, D.; Quesnel, Y.; Poirier, J.-M. *J. Org. Chem.* **1996**, *61*, 2232−2235. (e) Toru, T.; Wakayama, T.; Watanabe, Y.; Ueno, Y. *Phosphorus Sulfur Silic*on **1992**, *67*, 253−256. (f) Szymoniak, J.; Lefranc, H.; Besancon, J.; Moise, C. *Synthesis* **1995**, 815−819.
(8) Saito, S.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 611−612.

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aldol addition at the more encumbered α-side of the ketone (Scheme 2). To widen the applicability of our results, reactions utilizing various unsymmetrical ketones were conducted with the obtained results summarized in Table 1. Excellent discrimination between the more hindered α-side and the less-substituted α-side of the ketone was also observed.

The mechanism involved in this reaction still remains unknown, but investigations are currently in progress. Nonetheless, the unsually high regioselectivity can be interpreted from observations made by aldol additions of aldehydes to functionalized unsymmetrical ketones in the presence of substoichiometric amounts of $TiCl_4$. For example, no aldol addition occurs at all by reacting 2.4-pentanedione or fluoracetone with benzaldehyde. These ketones are too acidic for this reaction, due to their electron-withdrawing substituents. Furthermore, aldol addition at the unsubstituted α-side, through the reaction of 1-chloro-3-pentanone with benzaldehyde, resulted in only poor yields under our conditions. These results indicate the predominance of electronic effects in the regioselective outcome of this reaction. The aldol addition of aldehydes appears to occur at the less electronegative α-side of unsymmetrical ketones or, from the stereochemical point of view, at the more hindered and substituted α-side.

In conclusion, high regioselective addition of aldehydes at the more encumbered α-side of unsymmetrical ketones was achieved in a $TiCl_4$-mediated aldol addition.

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(9) (a) Mahrwald, R. *Chem. Ber*. **1995**, *128*, 919−921. (b) Mahrwald, R. *GIT* **1996**, *40*, 43−44. (c) Benzaldehyde (1.0 mL, 10 mmol) and 3-heptanone (1.4 mL, 10 mmol) were dissolved in 20 mL of anhydrous toluene. Under inert conditions 110 μL (1 mmol) of titanium(IV) chloride was added dropwise to this solution at room temperature. The solution was stirred for 16 h at room temperature. After that time, 50 mL of diethyl ether was added and the organic phase was rapidly extracted with water until the water phase was neutral. The organic layer was separated and dried (Na_2SO_4) and the filtrate concentrated in vacuo. The syn/anti ratio and the ratio of regioselectivity of the crude aldol product was determined by ^1H and ^{13}C NMR spectroscopy.

(10) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc*. **1991**, *113*, 1047−1049.

(11) Chow, H.-F.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 604−614.

(12) Masamune, S.; Mori, S.; van Horn, D.; Brooks, D. W. *Tetrahedron Lett*. **1979**, *20*, 1665−1668.

(13) Hoffmann, R. W.; Ditrich, K.; Fröbel, S. *Liebigs Ann. Chem*. **1987**, 977−985.

(14) Utaka, M.; Onoue, S.; Takeda, A. *Chem. Lett*. **1987**, 971−972.

(15) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc*. **1974**, *96*, 7503−7509.

(16) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc*. **1973**, *95*, 3310−3324.