

Halogeno Aldol Reaction of Ethyl Vinyl Ketone and Aldehydes Mediated by Titanium Tetrachloride[‡]

Han-Xun Wei, Subramanian Karur and Guigen Li*

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock TX 79409-1061, USA.

Fax: ++1-806-742-1289. <http://www.ttu.edu/~chem/faculty/li/li.html>

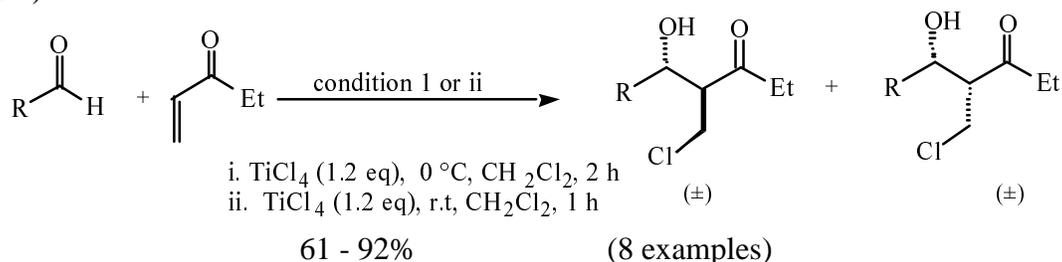
[‡] Presented at the 4th Electronic Conference on Synthetic Organic Chemistry, September 1-30, 2000, (Paper A0059). The preliminary results of this paper were reported at the Gordon Research Conference on Organic Reactions and Processes (paper no. 25), Bristol, RI, July 16 - 21, 2000.

*Author to whom correspondence should be addressed. E-mail: qeggli@ttu.edu

Received: 29 August 2000; in revised form 6 December 2000 / Accepted: 6 December 2000 /

Published: 22 December 2000

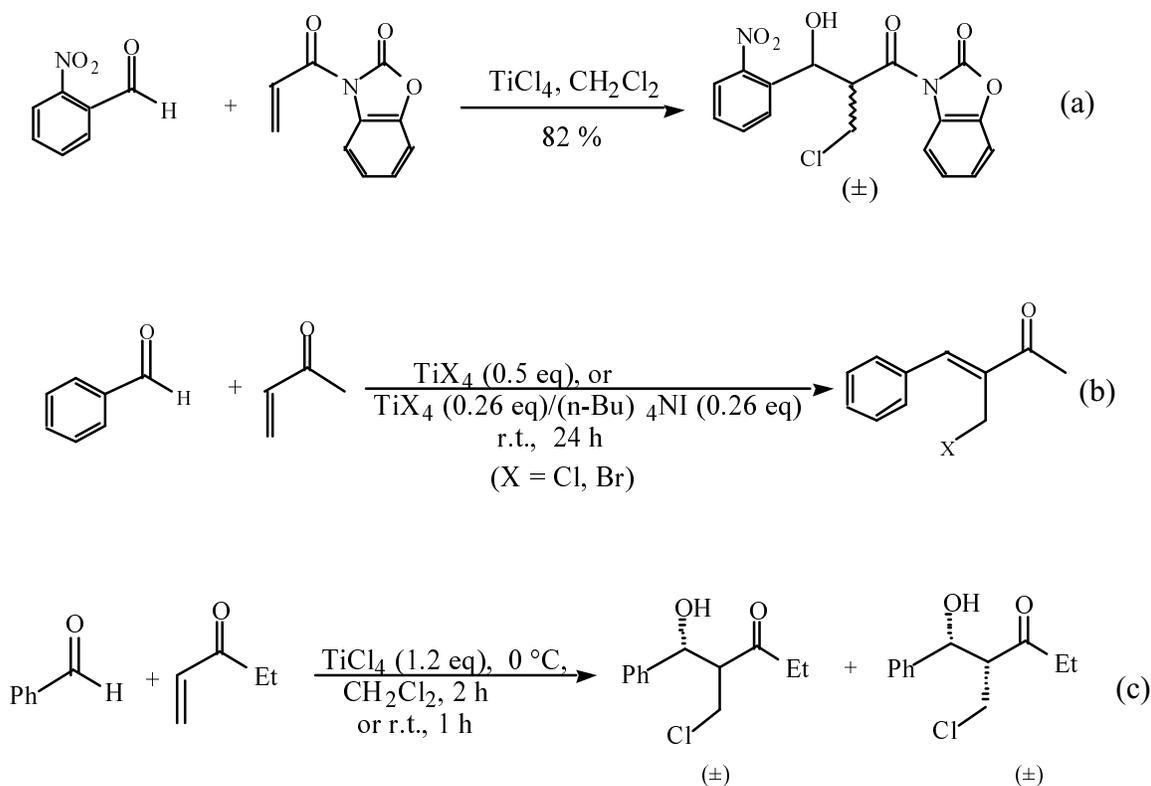
Abstract: A three-component halogeno aldol reaction has been developed by using titanium tetrachloride as the halogen source as well as the Lewis acid mediator. The dehydration and elimination of hydrogen chloride were inhibited by conducting the reaction at 0 °C in dichloromethane or at room temperature with a shortened reaction time. Seven examples were examined, giving good to high yields (61 - 92%) and modest stereoselectivity (*syn/anti*: 2.2/1.0 - 8.4/1.0).



Keywords: halides; aldol reaction; titanium tetrachloride.

Introduction

The formation of C(sp³)-C(sp³) bond via aldol reaction represents an important topic in organic chemistry [2-4]. It also acts as the key step of the Baylis-Hillman reaction [5-6]. Recently, we developed the TiCl₄-mediated Baylis-Hillman-type reaction without the direct use of a Lewis base [7a], which was confirmed to proceed through a halogeno aldol reaction by using α,β -unsaturated *N*-acyl benzoxalinone as the Michael acceptor (Scheme 1a). When we attempted to extend the reaction scope to the use of α,β -unsaturated ketones, we failed to obtain the anticipated Baylis-Hillman adducts or halogeno aldol products under the established conditions [7b]. The dehydration products of C=C bond formation were produced dominantly. Only 0.5 equivalent of titanium (IV) halides or 0.25 equivalent of TiX₄/(*n*-Bu)₄Ni [8] were needed to furnish the reaction with high stereoselectivity and yield (Scheme 1b). While the further study of the new C=C bond formation is ongoing in our laboratories, we concurrently made efforts to control the ketone-based system to produce halogeno aldol adducts prior to dehydration. In this report, we describe the preliminary results of this method which is represented in Scheme 1c.

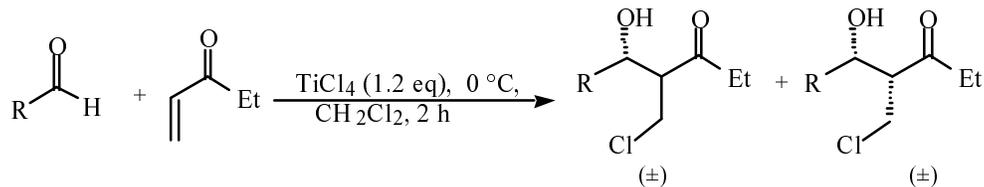


Scheme 1.

Results and Discussion

This halogeno aldol reaction was achieved by using an excess amount of α,β -unsaturated ketone (2.0 eq) and TiCl_4 (1.2 eq) and performed at 0 °C in dichloromethane. The three-component starting materials, ethyl vinyl ketone, aldehyde and TiCl_4 , were simply mixed together in a convenient vial without the protection of inert gases. The reaction was completed within a shortened period (2 h) as revealed by gas chromatography monitoring. Unlike the C=C formation system, the combination of $\text{TiCl}_4/(n\text{-Bu})_4\text{NI}$ was proven to be inefficient for the present ketone-based halogeno aldol reaction. Indeed, only a trace amount of desired halogeno aldol adducts were observed in more than 2 hours. The data in Table 1 shows that good to excellent yields have been obtained for both aromatic and aliphatic aldehyde substrates. The stereoselectivity for aromatic cases were well controlled. However, the individual *syn/anti* stereoisomers of all seven cases failed to be separated via flash column chromatography.

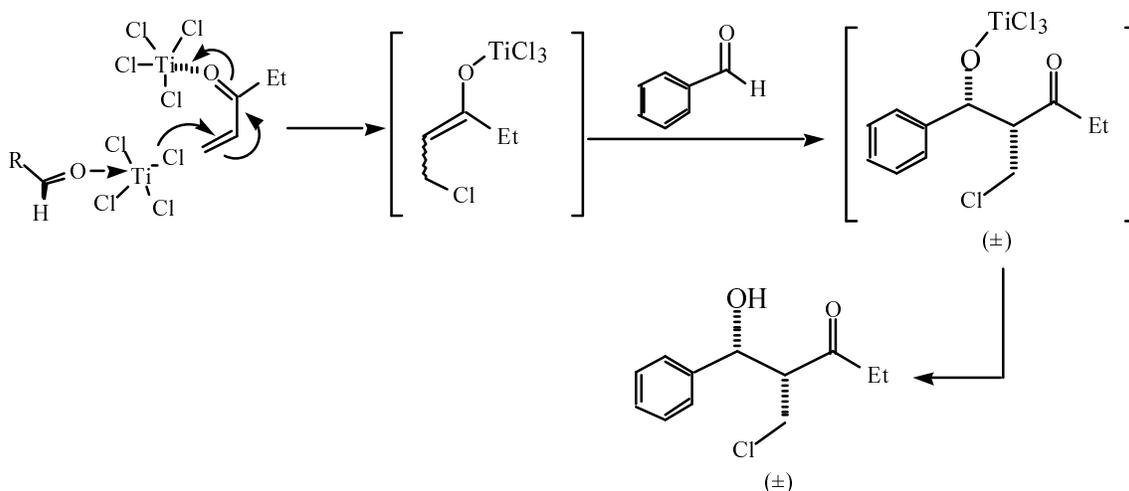
The *anti/syn* stereoselectivity was determined by $^1\text{H-NMR}$ analysis where the chemical shift of β proton (CH_2OH) of the *anti* isomer is farther downfield as compared with that of the corresponding *syn* isomer for most cases. The *syn* and *anti* isomers can be distinguished by the coupling constants between α and β protons of aldol adducts [9]. For entry 1 of Table 1, the β proton (CH_2OH) triplet of the *anti* isomer (d 5.11, $J = 6.35$ Hz) and the doublet-doublet of the *syn* isomer (d 5.05, $J = 2.75, 6.08$ Hz) were observed. The stability of these ethyl vinyl ketone-derived products and the resolution of their $^1\text{H-NMR}$ spectra made this determination possible. In contrast, the methyl vinyl ketone-derived products can be very easily dehydrated under the current conditions. The *syn* selectivity suggests that this aldol reaction is dynamically controlled. This is similar to α,β -unsaturated aldehyde-based system where the dynamically controlled *syn* stereoselection was proven to be dominant at -78 °C in the same solvent in which $\text{TiCl}_4/(n\text{-Bu})_4\text{NI}$ combination was employed as the halogen source (I⁻) [8c].

Table 1. Results of TiCl_4 -Mediated Halogeno Aldol Reaction

Entry	R	yield ^a	<i>syn/anti</i> ^b
1		80	2.9/1.0
2		67	5.4:1.0
3		68	8.4:1.0
4		81	5.1:1.0
5		61	7.2:1.0
6		87	1.0:1.0
7		79	4.0:1.0
8		92	2.2:1.0

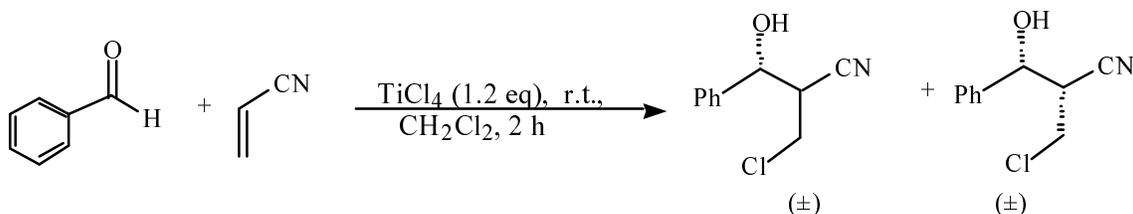
^a Yield of *syn/anti* mixture. ^b Determined by ^1H NMR analysis

The working hypothesis of this reaction is proposed as shown in Scheme 4 [7,10]. The initial step involves the addition of TiCl_4 to the ethyl vinyl ketone to generate the titanium enolate. The formation of this enolate intermediate could be accelerated by the coordination of carbonyl oxygen to the titanium center ($\text{C}=\text{O}\cdots\text{Ti}$ interaction) [11], to further polarize the π -conjugate double bond and to free the chlorine anion from TiCl_4 prior to the π -conjugate addition. The resulting Lewis acid species can also activate aldehyde for the subsequent aldol reaction by coordinating with aldehyde oxygen.



Scheme 2.

The resulting halo aldol adducts can be transformed into Baylis-Hillman adducts by treating with DBU at room temperature. These products can also be converted to dehydration products in prolonged reaction period. Interestingly, the dehydration products are much easier to form even at 0 °C when ethyl vinyl ketone was employed as the Michael acceptor. Acrylonitrile can also be used as the starting material by reacting at room temperature to give around 70% yield (Scheme 3).



Scheme 3.

Conclusions

The vinyl ketone-based halogeno aldol reaction has been achieved by using an excess amount of ketone and titanium tetrachloride. The reaction can occur to completion at 0 °C in dichloromethane within two hours or at room temperature for 1 hour. The scope of this reaction will be extended to the use of other substrates. Titanium tetrabromide and related chiral metal halides will also be employed as the halogen sources and Lewis acids in the future.

Experimental

General

Dichloromethane and propionitrile was dried and freshly distilled from calcium hydride under the nitrogen atmosphere. Other commercial chemicals were used without further purification and their stoichiometries were calculated based on the reported purities from the manufacturers. Flash chromatography was performed on E. Merck silica gel 60 (230-400 mesh). Thin layer chromatography was performed on Merck Kieselgel 60 GF254 plates (0.2 mm thickness). $^1\text{H-NMR}$ spectra (CDCl_3 solutions) were recorded on a Varian 500 MHz NMR spectrometer. The spectral data are reported in the following format: chemical shift (all relative to Me_4Si as an internal reference standard unless otherwise indicated), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, b = broad).

Synthetic Method

The typical procedure is represented by the reaction of entry 1 in Table 1. Into a dry vial was added freshly distilled dichloromethane (1.0 mL), 4-nitrobenzaldehyde (0.151 g, 1.0 mmol) and ethyl vinyl ketone (0.17 mL, 2.0 mmol). The vial with the stirring reaction mixture was cooled to 0 °C, and then added titanium tetrachloride (1.2 mL, 1.0M solution in dichloromethane, 1.2 mmol). The resulting solution in the capped vial was stirred at the same temperature for 2 h without argon protection. The reaction was finally quenched by dropwise addition of saturated aqueous NaHCO_3 solution (2.0 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness. Purification by flash chromatography (EtOAc/hexane, 1/5, v/v) provided **1** (216 mg, 80 %) as colorless oil.

1a (syn): $^1\text{H-NMR}$: d 0.95 (t, $J=5.2\text{Hz}$, 3H), 2.28 (q, $J=5.2\text{Hz}$, 1H), 2.51 (q, $J=5.2\text{Hz}$, 1H), 3.12 (d, $J=3.0\text{Hz}$, 1H, OH), 3.28 (m, 1H), 3.59 (dd, $J=4.0, 11.0\text{Hz}$, 1H, CH_2Cl), 3.89 (dd, $J=9.0, 11.0\text{Hz}$, 1H, CH_2Cl), 5.04 (dd, $J=3.0, 5.0\text{Hz}$, benzylic 1H), 7.50 (dd, $J=2.9, 8.9\text{Hz}$, 2H), 8.20 (dd, $J=2.9, 8.9\text{Hz}$, 2H).

1b (anti): $^1\text{H-NMR}$: d 1.01 (t, $J=6.8\text{Hz}$, 3H), 2.26 (q, $J=6.8\text{Hz}$, 1H), 2.62 (q, $J=6.8\text{Hz}$, 1H), 3.31 (m, 1H), 3.54 (dd, $J=7.0, 11.0\text{Hz}$, 1H, CH_2Cl), 3.93 (dd, $J=5.0, 11.0\text{Hz}$, 1H, CH_2Cl), 5.10 (t, $J=6.0\text{Hz}$, benzylic 1H), 7.52 (dd, $J=2.9, 8.9\text{Hz}$, 2H), 8.22 (dd, $J=2.9, 8.9\text{Hz}$, 2H).

2a (syn): $^1\text{H-NMR}$: d 0.86 (t, $J=4.6\text{Hz}$, 3H), 2.09 (q, $J=4.6\text{Hz}$, 1H), 2.35 (q, $J=4.6\text{Hz}$, 1H), 2.75 (d, $J=2.6\text{Hz}$, 1H, OH), 3.26 (m, 1H), 3.74 (dd, $J=3.8, 10.0\text{Hz}$, 1H, CH_2Cl), 3.87 (dd, $J=8.0, 10.0\text{Hz}$, 1H, CH_2Cl), 4.79 (dd, $J=2.6, 5.0\text{Hz}$, benzylic 1H), 7.07 (dd, $J=2.7, 9.0\text{Hz}$, 2H), 7.25 (dd, $J=2.7, 9.0\text{Hz}$, 2H).

2b (anti): $^1\text{H-NMR}$: d 1.00 (t, $J=7.1\text{Hz}$, 3H), 2.03 (q, $J=7.1\text{Hz}$, 1H), 2.45 (q, $J=7.1\text{Hz}$, 1H), 3.10 (d, $J=5.4\text{Hz}$, 1H, OH), 3.24 (m, 1H), 3.43 (dd, $J=6.5$, 10.0Hz, 1H, CH_2Cl), 3.53 (dd, $J=6.0$, 10.0Hz, 1H, CH_2Cl), 4.86 (t, $J=5.9\text{Hz}$, benzylic 1H), 7.00 (dd, $J=2.7$, 9.0Hz, 2H), 7.27 (dd, $J=2.7$, 9.0Hz, 2H).

3a (syn): $^1\text{H-NMR}$: d 0.89 (t, $J=7.1\text{Hz}$, 3H), 2.14 (q, $J=7.1\text{Hz}$, 1H), 2.38 (q, $J=7.1\text{Hz}$, 1H), 2.83 (d, $J=2.7\text{Hz}$, 1H, OH), 3.22 (m, 1H), 3.76 (dd, $J=4.0$, 11.0Hz, 1H, CH_2Cl), 3.81 (dd, $J=9.0$, 11.0Hz, 1H, CH_2Cl), 4.79 (dd, $J=2.7$, 5.0Hz, benzylic 1H), 7.22 (dd, $J=2.8$, 9.0Hz, 2H), 7.35 (dd, $J=2.8$, 9.0Hz, 2H).

3b (anti): $^1\text{H-NMR}$: d 1.00 (t, $J=7.2\text{Hz}$, 3H), 2.04 (q, $J=7.2\text{Hz}$, 1H), 2.48 (q, $J=7.2\text{Hz}$, 1H), 3.16 (d, $J=5.5\text{Hz}$, 1H, OH), 3.24 (m, 1H), 3.47 (dd, $J=7.0$, 10.0Hz, 1H, CH_2Cl), 3.58 (dd, $J=5.0$, 10.0Hz, 1H, CH_2Cl), 4.88 (t, $J=7.0\text{Hz}$, benzylic 1H), 7.22 (dd, $J=2.8$, 7.0Hz, 2H), 7.36 (dd, $J=2.8$, 7.0Hz, 2H).

4a (syn): $^1\text{H-NMR}$: d 0.90 (t, $J=7.0\text{Hz}$, 3H), 2.15 (q, $J=7.0\text{Hz}$, 1H), 2.39 (q, $J=7.0\text{Hz}$, 1H), 2.83 (d, $J=2.7\text{Hz}$, 1H, OH), 3.20 (m, 1H), 3.75 (dd, $J=4.0$, 11.0Hz, 1H, CH_2Cl), 3.81 (dd, $J=8.0$, 11.0Hz, 1H, CH_2Cl), 4.78 (dd, $J=3.0$, 9.0Hz, benzylic 1H), 7.16 (dd, $J=2.6$, 9.0Hz, 2H), 7.51 (dd, $J=2.6$, 9.0Hz, 2H).

4b (anti): $^1\text{H-NMR}$: d 0.99 (t, $J=7.4\text{Hz}$, 3H), 2.06 (q, $J=7.4\text{Hz}$, 1H), 2.52 (q, $J=7.4\text{Hz}$, 1H), 3.26 (m, 1H), 3.47 (dd, $J=7.0$, 10.0Hz, 1H, CH_2Cl), 3.57 (dd, $J=5.0$, 10.0Hz, 1H, CH_2Cl), 4.84 (t, $J=7.0\text{Hz}$, benzylic 1H), 7.20 (dd, $J=2.8$, 7.5Hz, 2H), 7.52 (dd, $J=2.8$, 7.5Hz, 2H).

5a (syn): $^1\text{H-NMR}$: d 0.84 (t, $J=4.6\text{Hz}$, 3H), 2.07 (q, $J=4.6\text{Hz}$, 1H), 2.35 (q, $J=4.6\text{Hz}$, 1H), 2.61 (d, $J=1.1\text{Hz}$, 1H, OH), 3.27 (m, 1H), 3.82 (dd, $J=5.0$, 11.0Hz, 1H, CH_2Cl), 3.90 (dd, $J=8.0$, 11.0Hz, 1H, CH_2Cl), 4.80 (dd, $J=3.0$, 9.0Hz, benzylic 1H), 7.31 (m, 5H).

5b (anti): $^1\text{H-NMR}$: d 0.99 (t, $J=7.2\text{Hz}$, 3H), 2.01 (q, $J=7.2\text{Hz}$, 1H), 2.45 (q, $J=7.2\text{Hz}$, 1H), 2.95 (d, $J=5.0\text{Hz}$, 1H, OH), 3.29 (m, 1H), 3.43 (dd, $J=6.5$, 10.5Hz, 1H, CH_2Cl), 3.62 (dd, $J=5.0$, 10.5Hz, 1H, CH_2Cl), 4.89 (t, $J=7.0\text{Hz}$, benzylic 1H), 7.29 (m, 5H).

6a (syn): $^1\text{H-NMR}$: d 0.86 (t, $J=7.0\text{Hz}$, 3H), 2.21 (q, $J=7.0\text{Hz}$, 1H), 2.27 (s, 3H), 2.35 (q, $J=7.0\text{Hz}$, 1H), 2.64 (d, $J=2.7\text{Hz}$, 1H, OH), 3.28 (m, 1H), 3.83 (dd, $J=5.0$, 10.0Hz, 1H, CH_2Cl), 3.92 (dd, $J=7.0$, 10.0Hz, 1H, CH_2Cl), 4.98 (dd, $J=2.7$, 10.0Hz, benzylic 1H), 7.09-7.40 (m, 4H).

6b (anti): $^1\text{H-NMR}$: d 0.96 (t, $J=7.2\text{Hz}$, 3H), 2.08 (q, $J=7.2\text{Hz}$, 1H), 2.34 (s, 3H), 2.44 (q, $J=7.2\text{Hz}$, 1H), 3.00 (d, $J=5.8\text{Hz}$, 1H, OH), 3.32 (m, 1H), 3.38 (dd, $J=6.5$, 11.0Hz, 1H, CH_2Cl), 3.67 (dd, $J=5.0$, 11.0Hz, 1H, CH_2Cl), 5.11 (t, $J=7.0\text{Hz}$, benzylic 1H), 7.10-7.49 (m, 4H).

7a (syn): $^1\text{H-NMR}$: d 0.83 (t, $J=7.3\text{Hz}$, 3H), 2.05 (q, $J=7.3\text{Hz}$, 1H), 2.37 (q, $J=7.3\text{Hz}$, 1H), 2.79 (d, $J=2.6\text{Hz}$, 1H, OH), 3.42 (m, 1H), 3.79 (dd, $J=5.0$, 10.0Hz, 1H, CH_2Cl), 3.94 (dd, $J=8.0$, 10.0Hz, 1H, CH_2Cl), 4.96 (dd, $J=2.6$, 9.0Hz, benzylic 1H), 7.48 (m, 3H), 7.81 (m, 4H).

7b (anti): $^1\text{H-NMR}$: d 0.98 (t, $J=7.2\text{Hz}$, 3H), 2.02 (q, $J=7.2\text{Hz}$, 1H), 2.52 (q, $J=7.2\text{Hz}$, 1H), 3.07 (d, $J=5.4\text{Hz}$, 1H, OH), 3.38 (m, 1H), 3.64 (dd, $J=7.0$, 11.0Hz, 1H, CH_2Cl), 3.68 (dd, $J=5.0$, 11.0Hz, 1H, CH_2Cl), 5.03 (t, $J=6.8\text{Hz}$, benzylic 1H), 7.42 (m, 3H), 7.76 (m, 4H).

8a (syn): $^1\text{H-NMR}$: d 1.07 (t, $J=7.2\text{Hz}$, 3H), 2.23 (d, $J=3.1\text{Hz}$, 1H, OH), 2.60 (dd, $J=7.1$, 10.0Hz, 2H), 2.71 (q, $J=7.2\text{Hz}$, 1H), 2.77 (q, $J=7.2\text{Hz}$, 1H), 3.05 (m, 1H), 3.82 (dd, $J=4.0$, 10.0Hz, 1H, CH_2Cl), 3.88 (dd, $J=7.0$, 10.0Hz, 1H, CH_2Cl), 4.03 (m, benzylic 1H), 7.15-7.35 (m, 5H).

8b (anti): $^1\text{H-NMR}$: d 1.09 (t, $J=7.0\text{Hz}$, 3H), 2.64 (dd, $J=6.0$, 11.0Hz, 2H), 2.74 (m, 2H), 3.02 (m, 1H), 3.73 (dd, $J=6.0$, 11.0Hz, 1H, CH_2Cl), 3.77 (dd, $J=5.0$, 11.0Hz, 1H, CH_2Cl), 4.05 (m, benzylic 1H), 7.15-7.41 (m, 5H).

Acknowledgments

We gratefully acknowledge the National Institutes of Health, General Medical Sciences (GM-60261) and the Robert A. Welch Foundation (D-1361) for the generous support of this work, the National Science Foundation (CHE-9808436) for partial funding of the 500 MHz NMR spectrometer. We also thank Ms. Sun Hee Kim for her assistance.

References and Notes

1. During the preparation of this manuscript, two halogeno aldol reaction papers have appeared in which the combinations of TiCl_4 and Lewis bases were subjected to the Michael-type addition to methyl vinyl ketone followed by aldol reaction with aldehydes: (a) Kataoka, T.; Kinoshita, H.; Iwama, T.; Tsujiyama, S-i.; Iwamura, T.; Watanabe, S-i.; Muraoka, O.; Tanabe, G. *Tetrahedron* **2000**, *56*, 4725. (b) Shi, M.; Jiang, J.-K.; Feng, Y.-S., *Organic Letters* **2000**, *2*, 2397.
2. (a) Evans, D. A. Nelson, J. V.; Taber, T. R. *Topics in Stereochemistry* **1982**, *13*, 1. (b) Heathcock, C. H. In *Comprehensive Carbonion Chemistry*, Buncl, E., Durst, T., Eds., Elsevier, New York, **1984**, vol. 5B, p177. (c) Kim, B. M.; Williams, S. F.; Masumune, S. in *Comprehensive Organic Synthesis* (Eds. Trost, B. M.; Fleming, I.; Heathcock, C. H.), vol. 2, Chapter 1.7, Pergamon, Oxford, **1991**, p 239.
3. For several recent reviews see: (a) Nelson, S. G. *Tetrahedron Asymmetry* **1998**, *9*, 357. (b) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (c) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917.
4. For representative references on asymmetric catalytic Aldol reactions see: (a) Parmee, E. R.; Tempkin, O.; Masumune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365. (b) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907. (c) Evans, D. A.; Kozlowski, M. C.; Murray, J.

- A.; Burgey, C. S.; Campos, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (d) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982. (e) Taylor, S.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528.
- For recent reviews regarding the Baylis-Hillman reaction see: (a) Ciganek, E., *Org. React.*, **1997**, *51*, 201; (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.
 - Brzezinski, L. J.; Rafel, S.; Leahy, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 4317. (b) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219. (c) Barrett, A. G. C.; Cook, A. S.; Kamimura, A. *Chem. Commun.*, **1998**, 2533. (d) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539.
 - (a) Li, G.; Wei, H.-X.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1. In this preliminary report, the mechanistic experiments of Baylis-Hillman system resulted in the halo aldol process as an extra synthetic bonus. The mixture of *syn/anti* isomers were generated, although the coupling contents-based *anti* structural demonstration was temporally used. (b) Li, G.; J. Gao, Wei, H.-X.; Enright, M. *Organic Letters* **2000**, *2*, 617.
 - For TiCl₄/(*n*-Bu)₄NI combination see: (a) Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *39*, 4767. (b) Yachi, K.; Maeda, K.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1997**, *38*, 5161. (c) Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Organic Lett.* **1999**, *1*, 1383.
 - (a) Heng, K.; Smith, R. A. J. *Tetrahedron* **1979**, *35*, 425. (b) Kamimura, A.; Mitsudera, H.; Asano, S.; Kidera, S.; Kakehi, A. *J. Org. Chem.* **1999**, *64*, 6353.
 - Wei, H. X.; Caputo, T. D.; Purkiss, D. W.; Li, G. *Tetrahedron* **2000**, *56*, 2397.
 - For a comprehensive review about Lewis acid carbonyl complexation including TiCl₄ see: Shambayati, S.; Schreiber, S. L. in *Comprehensive Organic Synthesis* (Eds. Trost, B. M.; Fleming, I.), vol. 1, Pergamon, Oxford, **1991**, pp. 283-321.

Sample Availability: Available from the authors