JOC Article

Steric Factors Direct Baylis−Hillman and Aldol Reactions in Titanium Tetrachloride Mediated Coupling between α-Keto Esters and Cyclohex-2-enone Derivatives

Deevi Basavaiah,* Bandaru Sreenivasulu, and Anumolu Jaganmohan Rao

School of Chemistry, University of Hyderabad, Hyderabad-500 046, India

dbsc@uohyd.ernet.in

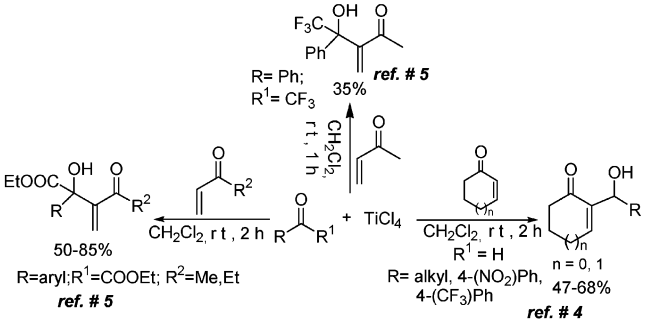
Received February 23, 2003

The titanium tetrachloride mediated reaction of α-keto esters with 5,5-dimethylcyclohex-2-enone provides the corresponding Baylis−Hillman adducts exclusively whereas a similar reaction of α-keto esters with cyclohex-2-enone furnishes the corresponding aldol adducts (with high syn-diasteroeselectivity) as the major product (along with the Baylis−Hillman adducts as the minor product), thus clearly demonstrating the role of the steric factors in directing the reaction pathway.

Introduction

The Baylis−Hillman reaction is an atom economical carbon−carbon bond forming reaction between the α-position of activated alkenes and carbon electrophiles under the influence of a tertiary amine catalyst (most commonly DABCO) producing an interesting class of highly functionalized molecules that have been extensively used in various organic transformation methodologies often involving high levels of stereoselectivities.[1−3] In a broad sense the Baylis−Hillman reaction can be regarded as a one-pot combination of Michael and aldol reactions. Recently, numerous non-amine catalysts/catalytic systems/reagents such as trialkylphosphines,[2i] dimethyl sulfide/titanium tetrachloride,[2m] and titanium tetrachloride[4,5] have been employed for performing the Baylis−Hillman reaction. During the course of our work in the titanium tetrachloride mediated Baylis−Hillman reaction we have observed interesting steric factors governed competition between the Baylis−Hillman reaction and the aldol reaction, i.e. the titanium tetrachloride mediated reaction of α-keto esters with 5,5-dimethylcyclohex-2-enone provides the corresponding Baylis−Hillman adducts exclusively whereas a similar reaction of α-keto esters with cyclohex-2-enone furnishes the corresponding aldol adducts, with high syn-diasteroeselectivity, as the major product (along with the Baylis−Hillman adducts as the minor product). We herein describe these results.

SCHEME 1. Baylis−Hillman Reaction of Aldehydes with Cyclic Enones and α-Keto Esters/ Trifluoromethyl Phenyl Ketone with Acyclic Enones



Li and co-workers reported an important Baylis−Hillman reaction between aldehydes and cyclic enones under the influence of titanium tetrachloride to produce the desired adducts (Scheme 1).[4] We have recently described an interesting titanium tetrachloride mediated Baylis−Hillman coupling of α-keto esters and trifluoromethyl phenyl ketone with acyclic enones to provide the functionalized tertiary alcohols (Scheme 1).[5]

Results and Discussion

During our ongoing research program on the Baylis−Hillman reaction we required the *tertiary*-allylic alcohols,

* To whom correspondence should be addressed. Fax: +91-40-23012460.

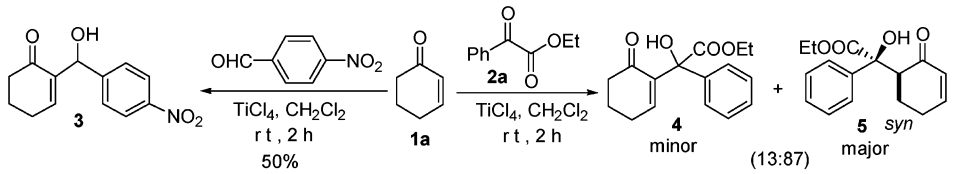
(1) (a) Basavaiah, D.; Jaganmohan Rao, A.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Ciganek, E. *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1997; Vol. 51, p 201. (c) Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001. (d) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

(2) (a) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Synlett* **2003**, 357. (b) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692. (c) Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **2003**, *44*, 937. (d) Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. *J. Org. Chem.* **2003**, *68*, 915. (e) Patra, A.; Roy, A. K.; Joshi, B. S.; Roy, R.; Batra, S.; Bhaduri, A. P. *Tetrahedron* **2003**, *59*, 663. (f) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507. (g) Barrett, A. G. M.; Dozzo, P.; White, A. J. P.; Williams, D. J. *Tetrahedron* **2002**, *58*, 7303. (h) Kaye, P. T.; Nocanda, X. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1318. (i) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402. (j) Yu, C.; Hu, L. *J. Org. Chem.* **2002**, *67*, 219. (k) Ram Reddy, M. V.; Rudd, M. T.; Ramchandran, P. V. *J. Org. Chem.* **2002**, *67*, 5382. (l) Racker, R.; Doring, K.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 6932. (m) Kataoka, T.; Iwama, T.; Tsujiyama, S.-i.; Iwamura, T.; Watanabe, S.-i. *Tetrahedron* **1998**, *54*, 11813. (n) Amri, H.; El Gaied, M. M.; Ayed, T. B.; Villieras, J. *Tetrahedron Lett.* **1992**, *33*, 7345. (o) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795.

(3) (a) Basavaiah, D.; Jaganmohan Rao, A. *Chem. Commun.* **2003**, 604. (b) Basavaiah, D.; Satyanarayana, T. *Tetrahedron Lett.* **2002**, *43*, 4301. (c) Basavaiah, D.; Sharada, D. S.; Kumaragurubaran, N.; Reddy, R. M. *J. Org. Chem.* **2002**, *67*, 7135. (d) Basavaiah, D.; Satyanarayana, T. *Org. Lett.* **2001**, *3*, 3619. (e) Basavaiah, D.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron Lett.* **2001**, *42*, 85. (f) Basavaiah, D.; Krishnamacharyulu, M.; Suguna Hyma, R.; Sarma, P. K. S.; Kumaragurubaran, N. *J. Org. Chem.* **1999**, *64*, 1197. (g) Basavaiah, D.; Bakthadoss, M.; Pandiaraju, S. *Chem. Commun.* **1998**, 1639. (h) Basavaiah, D.; Gowriswari, V. V. L. *Tetrahedron Lett.* **1986**, *27*, 2031.

10.1021/jo0342424 CCC: $25.00
Published on Web 07/02/2003

SCHEME 2. Reaction of Cyclohex-2-enone with Ethyl Phenylglyoxylate and *p*-Nitrobenzaldehyde in the Presence of Titanium Tetrachloride



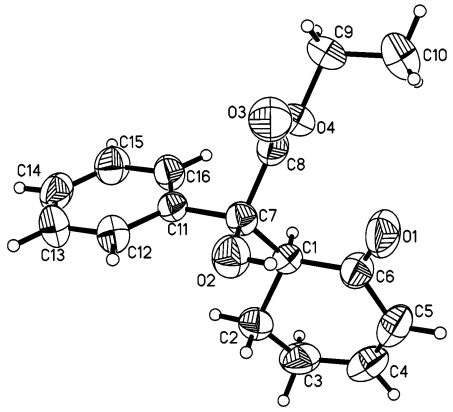


FIGURE 1. ORTEP diagram of compound **5**.

which would be obtained via the reaction between α-keto esters and cyclic enones. In this direction, with a view to obtaining the desired Baylis−Hillman adducts, that is, alkyl 2-hydroxy-2-aryl-2-(cyclohex-2-en-1-on-2-yl)ethanoates, we first carried out the reaction between ethyl phenylglyoxylate (**2a**, 1 mmol) and cyclohex-2-enone (**1a**, 3 mmol) under the influence of $TiCl_4$ (1 mmol) in dichloromethane at room temperature for 2 h. Astonishingly, this reaction provided Baylis−Hillman adduct **4** only as a minor product (≈13% as evidenced by the ^{1}H NMR spectrum of the crude product) (in fact, we have isolated **4** in 7% yield by carrying out the reaction on a 2-mmol scale: Experimental Section). As the major product we have obtained ethyl *syn*-2-hydroxy-2-phenyl-2-(cyclohex-5-en-1-on-2-yl)ethanoate (**5**) (aldol adduct) in 80% isolated yield after column chromatography followed by crystallization (Scheme 2). The syn-stereochemistry,[6] as well as the structure of this molecule, was established by single-crystal X-ray data (Figure 1).[7]

This unexpected formation of aldol adduct as the major product in the reaction of ethyl phenylglyoxylate (**2a**) with cyclohex-2-enone (Scheme 2) led us to perform the reaction of 4-nitrobenzaldehyde with cyclohex-2-enone in the presence of titanium tetrachloride under similar conditions, which provided only the Baylis−Hillman adduct[8,9] in 50% isolated yield (Scheme 2) and did not indicate the presence of any aldol product.[8,9] This result is in accordance with Li's work, that is, the titanium tetrachloride mediated reaction of 4-nitrobenzaldehyde with cyclohex-2-enone provided the desired Baylis−Hillman adduct in 56% isolated yield (Scheme 1).[4]

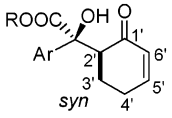
These two different results [the titanium tetrachloride mediated coupling of aldehydes[4,10] with cyclohex-2-enone provides the desired Baylis−Hillman adducts[4] (Scheme 1) whereas similar coupling of ethyl phenylglyoxylate (**2a**) with cyclohex-2-enone leads to the aldol reaction, Scheme 2][11] indicate that these reactions might possibly proceed through two different transition states, that is, through two different titanium-enolates. It can be easily envisioned that the treatment of cyclohex-2-enone with titanium tetrachloride in principle can result either in the formation of Michael type enolate (**A**) or dienolate (aldol type) (**B**) thus creating a competition between Baylis−Hillman and aldol reactions (Scheme 3).

In fact, we have recorded the ^{1}H NMR and ^{13}C NMR spectra of the crude reaction mixture obtained by the treatment of cyclohex-2-enone with $TiCl_4$ (1:1) for 30 min at room temperature in $CDCl_3$. In the ^{1}H NMR spectrum there is a considerable change (deshielding) in the chemical shifts of α- and *β*-vinylic protons (from that of cyclohex-2-enone). The ^{13}C NMR spectrum also shows a considerable change in the chemical shift (deshielding),

(4) Li, G.; Wei, H. X.; Gao, J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1. In this paper Li and co-workers have clearly mentioned that the electron-withdrawing group is necessary on the aromatic ring for obtaining modest yields and a better reaction rate in the titanium tetrachloride mediated Baylis−Hillman reaction between aromatic aldehydes and cyclic enones and they employed 4-nitrobenzaldehyde and 4-(trifluoromethyl)benzaldehyde as electrophiles in this reaction.

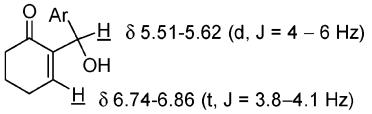
(5) Basavaiah, D.; Sreenivasulu, B.; Reddy, R. M.; Muthukumaran, K. *Synth. Commun.* **2001**, *31*, 2987.

(6) We have assigned the syn-stereochemistry to the structure as shown below [the hydroxy group and $C_{2'}$ and $C_{3'}$ (of the cyclohex-2-enone moiety) are on the same side in the extended conformation].



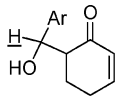
(7) Detailed X-ray crystallographic data for compound **5** is available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K. (CCDC no. 184079).

(8) ^{1}H NMR data (particularly the chemical shifts of benzylic and/or olefinic protons) of Baylis−Hillman and aldol compounds obtained from cyclohex-2-enone and aromatic aldehydes were reported in the literature.



Ar = aryl

Baylis–Hillman[2m,4]

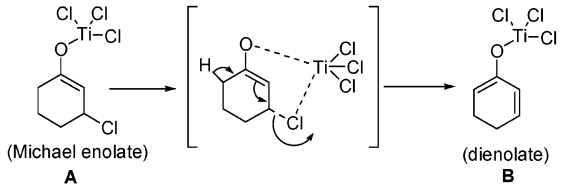


aldol

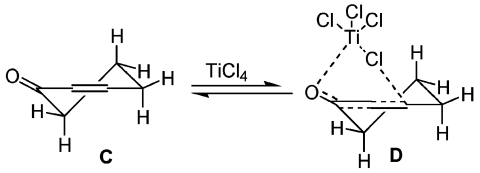
Ar = phenyl; [**ref.11**]
anti: δ 4.82 (d, J = 8.9 Hz); *syn*: δ 5.55 (d, J = 2.8 Hz)
Ar = 4-nitrophenyl; [**ref. 2m**]
δ 4.98 (dd, J = 1.5 & 9 Hz) (stereochemistry not mentioned)

(9) The ^{1}H NMR spectrum of the crude reaction mixture shows a triplet at *δ* 6.81 and a singlet at *δ* 5.61 in the ratio of 1:1 indicating the presence of Baylis−Hillman compound.[8] The absence of any other peak in the *δ* 4.50−5.90 region indicates the absence of *syn*- or *anti*-aldol adduct.[8]

SCHEME 3. Reaction of Cyclohex-2-enone with Titanium Tetrachloride: Possible Enolate Formation

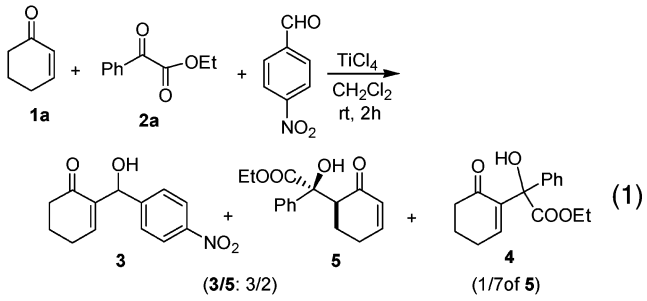


appearance (broad), and size (small) of β-vinylic and carbonyl carbons, thus probably indicating the presence of structures **C** and **D** in equilibrium. To realize this



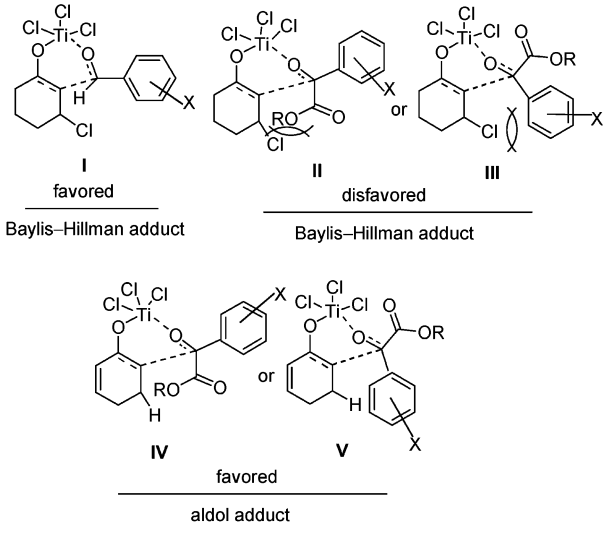
observation, we have treated the reaction mixture with water and recorded the ^{1}H NMR spectrum of the crude mixture, which shows a multiplet at δ 4.27−4.42 probably arising from the −C*H*Cl proton. The ^{13}C NMR spectrum of this crude mixture shows a peak at δ 206.48 (in addition to the peak at δ 199.41 due to the carbonyl carbon of cyclohex-2-enone) probably arising from the −*C*═O carbon of 3-chlorocyclohexanone.[12] These observations also indicate that there is no formation of dienolate (**B**) in the reaction.

To understand the formation of enolates (**A** and/or **B**) and also to investigate competition between Baylis−Hillman and aldol reactions, we have treated cyclohex-2-enone (**1a**, 1 mmol) with 4-nitrobenzaldehyde (1 mmol) and ethyl phenylglyoxylate (**2a**, 1 mmol) in the presence of $TiCl_4$ (1 mmol). As expected the ^{1}H NMR spectrum of the crude mixture shows the formation of Baylis−Hillman product **3** (derived from the enolate **A**) and aldol product **5** [derived from the dienolate **B**, which probably was obtained from **A** in the presence of keto ester (Scheme 3)] in the ratio of ca. 60:40 (probably indicating that 4-nitrobenzaldehyde is more reactive than ethyl phenylglyoxylate). We have also noticed the formation of ethyl 2-hydroxy-2-phenyl-2-(cyclohex-2-en-1-on-2-yl)-ethanoate (**4**) (Baylis−Hillman adduct from ethyl phenylglyoxylate and cyclohex-2-enone) in minor amounts (ca. 1/7 of **5**) (eq 1, competition between Baylis−Hillman and aldol reactions).



(1)

The formation of the Baylis−Hillman and aldol adducts in the reactions of aldehydes and α-keto esters with cyclohex-2-enone respectively possibly can be explained by considering the transition state models **I**, **II**, **III**, **IV**, and **V**. Our results as well as Li's results[4] indicate that the transition state **I** is more favored in the case of aldehydes leading to the formation of Baylis−Hillman



(10) As suggested by the referee, we have also performed the reaction between the less reactive electrophile, that is, 4-methoxybenzaldehyde (1 mmol), and cyclohex-2-enone (3 mmol) under the influence of titanium tetrachloride (1 mmol, 0.5 mL of 2 M solution in CH_2Cl_2) for 2 h at room temperature (similar conditions as in the case of 4-nitrobenzaldehyde). Since 4-methoxybenzaldehyde is less reactive, we have also performed the same reaction for 5 h at room temperature. In both cases, the ^{1}H NMR spectrum of the crude reaction mixture did not show the presence of either Baylis−Hillman or aldol adducts (absence of any peak at ca. δ 4.50−5.80)[8] and also ^{1}H NMR and TLC examinations indicated a mixture of products (unidentified).[4] Our observation is consistent with that of Li and co-workers.[4] Since the reaction of 4-methoxybenzaldehyde with cyclohex-2-enone did not provide any additional information, we have used benzaldehyde (because it is more reactive than 4-methoxybenzaldehyde and less reactive than 4-nitrobenzaldehyde) as the electrophile in this reaction, with a view to understand the course of the reaction. Thus, we have performed the reaction between benzaldehyde (1 mmol) and cyclohex-2-enone (3 mmol) under the influence of titanium tetrachloride (1 mmol, 0.5 mL of 2 M solution in CH_2Cl_2) for 2 h at room temperature (following similar conditions as in the case of 4-nitrobenzaldehyde). The ^{1}H NMR spectrum of crude compound shows the presence of a triplet at δ 6.73 (with a low intensity) and a singlet at δ 5.56 (with a low intensity) (in the ratio of 1:1) indicating the presence of Baylis−Hillman compound. In fact, we have also isolated the Baylis−Hillman adduct, that is, 2-[hydroxy(phenyl)methyl]cyclohex-2-en-1-one (**3a**), in very low yield (10%) by performing this reaction on 5 mmol of benzaldehyde with cyclohex-2-enone (15 mmol) in the presence of titanium tetrachloride (5 mmol, 2.5 mL of 2 M solution in CH_2Cl_2) for 2 h. The ^{1}H NMR spectrum of crude also shows a multiplet at δ 5.42−5.52 (unidentified) (with very low intensity, the intensity ratio of singlet at δ 5.56 and this multiplet is 3:1). The absence of any peak in the δ 4.70−5.20 region clearly indicates the absence of *anti*-aldol product. Since the chemical shift of the multiplet, that is, δ 5.42−5.52 (observed in our case), is similar to that of *syn*-aldol [δ 5.55 (d, J = 2.8 Hz)][8,11] it may not be possible to confirm the complete absence of *syn*-aldol product because of the possibility of the doublet (or dd in case benzylic-H couples with the OH proton) hidden in this multiplet. Because the intensity of this multiplet itself (at δ 5.42−5.52) is much lower than that of singlet at δ 5.56, the *syn*-aldol product, even if formed, might be in much smaller amounts in comparison with that of the Baylis−Hillman adduct. These observations might, therefore, suggest that aldehydes undergo preferentially the Baylis−Hillman reaction.

(11) It is worth mentioning here the work of Zaidlewich and co-workers, who reported an interesting enolization−aldolization of cyclohex-2-enone derivatives via dienolborinates. During their studies they also observed the formation of Baylis−Hillman adducts in minor amounts in the case of dienolborinates derived from hindered cyclohexenones (3,4,5-trisubstituted cyclohexenone derivatives) along with major aldol adducts; see: Zaidlewicz, M.; Sokol, W.; Wojtczak, A.; Neumann, P.; Nissinen, M. *Tetrahedron Lett.* **2002**, *43*, 3525.

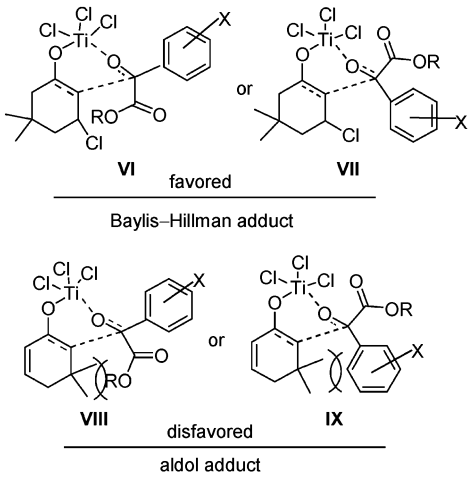
TABLE 1. Reactions of α-Keto Esters with 5,5-dimethylcyclohex-2-enone in the Presence of Titanium Tetrachloride[a−d]

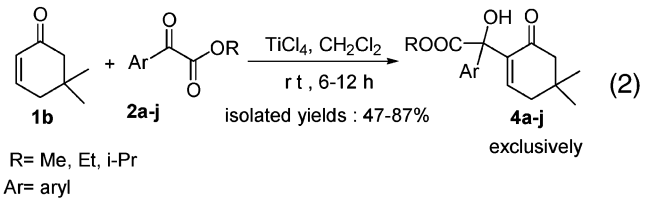
enone	keto ester	Ar	R	product	mp (°C)	yield (%)	aldol:BH
1b	**2a**	phenyl	Et	**4a**	44−46	85	00:100
1b	**2b**	4-methylphenyl	Et	**4b**	60−62	81	00:100
1b	**2c**	4-ethylphenyl	Et	**4c**		86	00:100
1b	**2d**	4-methoxyphenyl	Et	**4d**		85	00:100
1b	**2e**	2-methylphenyl	Et	**4e**		47	00:100
1b	**2f**	phenyl	Me	**4f**	58−60	80	00:100
1b	**2g**	3-methoxyphenyl	Me	**4g**	52−54	87	00:100
1b	**2h**	2-methylphenyl	Me	**4h**	102−104	53	00:100
1b	**2i**	2-methoxyphenyl	Me	**4i**	74−75	50	00:100
1b	**2j**	4-methylphenyl	*i*-Pr	**4j**	62−64	82	00:100

[a] All reactions were carried out on a 1-mmol scale (α-keto ester). To a stirred solution of α-keto ester (1 mmol) and 5,5-dimethylcyclohex-2-enone (3 mmol) in dichloromethane was added titanium tetrachloride (1 mmol) at 0 °C stirred at room temperature for 6 h (12 h for **4e**,**h**,**i** and 10 h for **4j**). [b] All the products (**4a**−**j**) were characterized by IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz), and elemental analyses; compounds **4a**, **4g**, and **4j** were also characterized by mass spectral analysis. [c] ^{1}H NMR spectra of the crude products did not indicate the formation of any aldol product. ^{1}H NMR spectra of the crude products (**4e**,**h**,**i**) clearly indicated the presence of the starting materials, that is, keto esters (**2e**,**h**,**i**) ≈ 38, 35, 40%, respectively. In fact, we isolated the starting materials (the α-keto esters) in 29% (**2e**), 24% (**2h**), and 32% (**2i**) yields in the corresponding reactions. [d] Yields are of the pure products (**4a**−**j**) (based on α-keto esters) after column chromatography (silica gel, 10% EtOAc in hexanes).

adducts. However, in the case of α-keto esters, the transition states **II** and **III** leading to the Baylis−Hillman adduct may be disfavored due to the steric interaction between Cl and the ester (or aryl) group whereas transition states **IV** and **V** leading to the aldol product may be favored due to the absence of any such interactions.

The above transition states clearly suggest that if we have some group sterically more demanding than the chloride at the fifth position of the cyclohex-2-enone there is a possibility of obtaining Baylis−Hillman compound predominantly. Accordingly, we have selected 5,5-dimethylcyclohex-2-enone for coupling with ethyl phenylglyoxylate in the presence of $TiCl_4$, and in fact, this reaction provided the corresponding Baylis−Hillman compound exclusively as predicted. Thus the reaction of ethyl phenylglyoxylate (**2a**, 1 mmol) with 5,5-dimethylcyclohex-2-enone (**1b**, 3 mmol) in the presence of $TiCl_4$ (1 mmol) at room temperature for 6 h provided the corresponding Baylis−Hillman adduct, that is, ethyl 2-hydroxy-2-phenyl-2-(5,5-dimethylcyclohex-2-en-1-on-2-yl)ethanoate (**4a**), exclusively in 85% isolated yield (eq 2, Baylis−Hillman reaction of 5,5-dimethylcyclohex-2-enone with α-keto esters in the presence of titanium tetrachloride; Table 1) (the ^{1}H NMR spectrum of the crude product did not indicate the presence of any aldol product). This observation clearly supports our hypothesis, that is, since the *gem*-dimethyl group is sterically more demanding than the Cl group the Baylis−Hillman adduct is produced in larger amounts (here exclusively) than the corresponding aldol product (transition states **VI**, **VII**, **VIII**, and **IX**).





(2)

In fact, with a view to understanding the nature of titanium enolate in the case of 5,5-dimethylcyclohex-2-enone we have also recorded the ^{1}H NMR and ^{13}C NMR spectra of the crude reaction mixture obtained by the treatment of 5,5-dimethylcyclohex-2-enone with $TiCl_4$ (1:1) for 30 min at room temperature in $CDCl_3$ and found similar observations as in the case of cyclohex-2-enone and $TiCl_4$ (Experimental Section and Supporting Information).

To study the generality of this reaction we have then extended this methodology to representative α-keto esters (**2b**−**j**) to provide the expected Baylis−Hillman adducts **4b**−**j** exclusively in 47−87% yields respectively (eq 2; Table 1). We did not observe the formation of any aldol products in all these cases as evidenced by the ^{1}H NMR spectrum of the crude products. The slow reactivity and low yields obtained in the case of α-keto esters with the α-substituted aryl group (**2e**,**h**,**i**) might be attributed to the steric factors, and in fact, we have recovered (isolated) substantial amounts of α-keto esters in these experiments (Table 1).

Thus, we have established conditions for obtaining the Baylis−Hillman adducts in the reaction of cyclohex-2-enone derivatives with α-keto esters under the influence of titanium tetrachloride. Although our main aim was

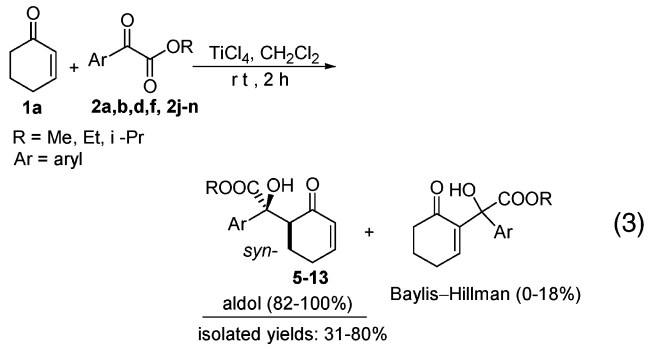
(12) It is reported that the reaction between aldehydes and alkyl vinyl ketones in the presence of titanium tetrachloride/amines or sulfides provided the corresponding allyl chlorides[4,5] or chloroaldols.[12a,b] (a) Shi, M.; Feng, Y.-S. *J. Org. Chem.* **2001**, *66*, 406. (b) Shi, M.; Jiang, J.-K.; Cui, S.-C. *Tetrahedron* **2001**, *57*, 7343. (c) Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett.* **2000**, *2*, 2397.

TABLE 2. Reactions of α-Keto Esters with Cycloalk-2-enones in the Presence of Titanium Tetrachloride[a−c]

enone	keto ester	Ar	R	product[d]	mp (°C)[e]	yield (%)[f]	aldol:BH[g]
1a	**2a**	phenyl	Et	**5**[h]	88	80	87:13
1a	**2b**	4-methylphenyl	Et	**6**[i]	112−114	63	90:10
1a	**2d**	4-methoxyphenyl	Et	**7**[i]	94−95	50	100:00
1a	**2f**	phenyl	Me	**8**[i]	117−119	70	85:15
1a	**2j**	4-methylphenyl	*i*-Pr	**9**[i]	95−96	65	95:5
1a	**2k**	4-bromophenyl	Et	**10**[i]	82	57	82:18
1a	**2l**	naphth-1-yl	Et	**11**[i]	118−120	31	100:00
1a	**2m**	4-methylphenyl	Me	**12**[i]	132−134	61	100:00
1a	**2n**	4-ethylphenyl	Me	**13**[i]	80−82	66	88:12
1c	**2a**	phenyl	Et	**14**[i,j]		65	95:5

[a] All reactions were carried out on a 1-mmol scale (α-keto ester). To a stirred solution of α-keto ester (1 mmol) and cycloalk-2-enone (3 mmol) in dichloromethane was added titanium tetrachloride (1 mmol) at 0 °C stirred at room temperature for 2 h. [b] All the products (**5**−**14**) were characterized by IR, ^{1}H NMR (200 MHz), ^{13}C NMR (50 MHz), and elemental analyses; compounds **5** and **9**−**12** were also characterized by mass spectral analysis. [c] ^{1}H NMR spectra of the crude products (**6**−**8**, **10**−**12**, **14**) clearly indicated the presence of the starting materials, that is, keto esters (**2b**,**d**,**f**, **2k**−**m**, **2a**) in ≈ 20, 25, 8, 17, 30, 5, 5% respectively. In fact, we isolated the starting materials (the α-keto esters) in 16% (**2d**) and 23% (**2l**) yields in their respective reactions. ^{1}H NMR spectra of the crude products also indicated the formation of Baylis−Hillman adducts in small amounts. In fact, we have isolated the minor Baylis−Hillman adduct (**4**) in 7% isolated yield as a colorless solid in the reaction between **1a** and **2a** and this was fully characterized. The ^{1}H NMR spectrum of the crude product **11** indicated the formation of presumably the anti isomer in ca. 10%. [d] The products (**5**−**13**) were obtained as colorless solids with pure syn-stereochemistry after column chromatography (silica gel, 5% EtOAc in hexanes) followed by crystallization (hexanes); compound **14** was obtained as liquid after column chromatography (silica gel, 5% EtOAc in hexanes). [e] Melting points are of the pure syn-diastereomers (**5**−**13**). [f] Yields are of the pure syn products (**5**−**13**) (based on α-keto esters) after column chromatography followed by crystallization. In the case of **14**, yield is of pure syn product after column chromatography. [g] The ratio of the Baylis−Hillman and aldol compounds was determined by ^{1}H NMR studies of the crude products. [h] The stereochemistry[7] of compound **5** was established by single crystal (obtained from hexanes) X-ray data (Figure 1). [i] The syn-stereochemistry was assigned in analogy to **5**. [j] The ^{1}H NMR spectrum of the crude product shows two singlets at δ 4.04 and 4.00 (ca. 12:88) for the OH proton. The underlined chemical shift value might be attributed to the minor anti-diastereomer. The ^{1}H NMR spectrum of the crude compound also shows the presence of ca. 5% Baylis−Hillman compound as indicated by the appearance of a triplet at δ 6.68.

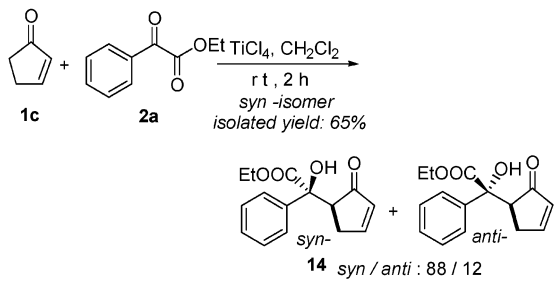
not directed toward aldol reaction we were fascinated by the formation of ethyl 2-hydroxy-2-phenyl-2-(cyclohex-5-en-1-on-2-yl)ethanoate (**5**), that is, the aldol adduct as the major product with high syn-diastereoselectivity in the titanium tetrachloride mediated reaction of cyclohex-2-enone with ethyl phenylglyoxylate (**2a**). A careful literature survey reveals that although the aldehydes have been very extensively used as electrophiles in various stereoefficient aldol carbon−carbon bond-forming reactions,[13] applications of α-keto esters,[14] which represent yet another potential class of electrophiles, in aldol reactions have been relatively less studied and the aldol reactions of α-keto esters with cyclohex-2-enone have not been reported so far. Since tertiary α-hydroxy acids/esters constitute an important class of molecules because of the presence of this structural framework in various biologically active molecules and natural products,[15] the development of convenient facile methodologies for the diastereoselective aldol reaction of α-keto esters with appropriate metal enolates to provide the desired tertiary α-hydroxy esters is an attractive endeavor in organic chemistry. Therefore, we have extended the above methodology to representative α-keto esters (**2b**,**d**,**f**, **2j**−**n**) to provide the corresponding alkyl *syn*-2-hydroxy-2-aryl-2-(cyclohex-5-en-1-on-2-yl)ethanoates (**6**−**13**) in 31−70% yields (eq 3, reaction of cyclohex-2-enone with a-keto



(3)

esters in the presence of titanium tetrachloride; Table 2). The stereochemistry of these compounds was assigned in analogy to that of compound **5**. In some cases we have noticed the formation of the Baylis−Hillman adducts in small amounts (Table 2).

Then we extended this methodology to the reaction between ethyl phenylglyoxylate (**2a**) and cyclopent-2-enone (**1c**) in the presence of titanium tetrachloride. Under similar conditions, we have noticed the formation



(4)

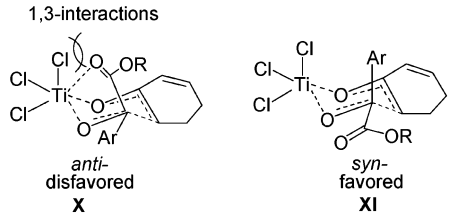
(13) (a) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (b) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Oshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466. (c) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (d) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (e) Mahrwarld, R. *Chem. Rev.* **1999**, *99*, 1095.

(14) (a) Jorgensen, K. A.; Johannsen, M.; Yao, S.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605. (b) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893. (c) Ito, Y.; Sawamura, M.; Hamashima, H.; Emura, T.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 4681.

(15) (a) Saxton, J. E. *Nat. Prod. Rep.* **1990**, *7*, 191. (b) Robins, D. J. *Nat. Prod. Rep.* **1989**, *6*, 221. (c) Vedejs, E.; Ahmed, S.; Larsen, S. D.; Westwood, S. *J. Org. Chem.* **1987**, *52*, 3937. (d) White, J. D.; Ohira, S. *J. Org. Chem.* **1986**, *51*, 5492.

of presumably ca. 12% anti-isomer along with the major ethyl *syn*-2-hydroxy-2-phenyl-2-(cyclopent-4-en-1-on-2-yl)ethanoate (**14**) (eq 4, reaction of cyclopent-2-enone with ethyl phenylglyoxylate in the presence of titanium tetrachloride). However, the pure syn-isomer was isolated in 65% yield after column chromatography. The syn-stereochemistry was tentatively assigned in analogy to **5**.

Possible Explanation for Syn-Stereoselectivity. The syn-stereoselectivity in aldol products possibly can be explained through a six-membered cyclic transition state (**X** and **XI**). Due to the simultaneous coordination



of Ti with carbonyl oxygens of the ester and keto groups, the 1,3-interactions between the ester group and Cl in transition state **X** may be more dominating than the 1,3-interactions between the aryl group and Cl in the transition state **XI**, thus leading to the formation of syn-product.

In conclusion, our work describes the role of steric factors in the selection of reaction pathways, that is, Baylis−Hillman or aldol reactions, particularly in the reaction between α-keto esters and cyclohex-2-enone derivatives. Thus we have successfully demonstrated that the reaction of 5,5-dimethylcyclohex-2-enone with α-keto esters in the presence of titanium tetrachloride proceeds in the Baylis−Hillman fashion affording the corresponding adducts alkyl 2-hydroxy-2-phenyl-2-(5,5-dimethylcyclohex-2-en-1-on-2-yl)ethanoates exclusively, whereas a similar reaction between α-keto esters and cyclohex-2-enone in the presence of titanium tetrachloride proceeds in the highly syn-diastereoselective aldol fashion thus for the first time providing a convenient methodology for synthesis of pure alkyl *syn*-2-hydroxy-2-aryl-2-(cyclohex-5-en-1-on-2-yl)ethanoates. Further work in understanding and exploring the various aspects of steric factors in directing the reaction pathway is in progress in our laboratory.

Experimental Section

General. Melting points were uncorrected. IR spectra were recorded on a FT-IR spectrometer with samples as KBr plates (solids) and liquid samples as neat. ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS, $\delta = 0$) as an internal standard. Elemental analyses were recorded on a CHN analyzer. Mass spectra were recorded on a micromass instrument. The X-ray diffraction measurements were carried out at 293 K, using graphite monochromated, Mo Kα (λ = 0.71073 Å) radiation with CAD4 software.

Typical Experimental Procedure: Ethyl 2-Hydroxy-2-phenyl-2-(5,5-dimethylcyclohex-2-en-1-on-2-yl)ethanoate (4a). To a stirred solution of ethyl phenylglyoxylate (1 mmol, 0.178 g) and 5,5-dimethylcyclohex-2-enone (3 mmol, 0.372 g) in CH_2Cl_2 (3 mL) was added titanium tetrachloride (1 mmol, 0.5 mL of a 2 M solution in CH_2Cl_2) at 0 °C. After stirring at room temperature for 6 h, the reaction mixture was quenched with water (5 mL) and extracted with ether (3 × 10 mL). The combined organic layer was dried over anhydrous sodium sulfate. Solvent was evaporated and the residue, thus obtained, was purified by column chromatography (silica gel, 10% EtOAc in hexanes) to furnish the pure molecule (**4a**) in 85% (0.257 g) isolated yield, as a colorless solid. IR (KBr) 3503, 1736, 1676 cm^{-1}; ^{1}H NMR δ 1.04 (s, 3H), 1.08 (s, 3H), 1.26 (t, 3H, J = 7.2 Hz), 2.21 (d, 2H, J = 4.4 Hz), 2.36 (s, 2H), 4.25 (q, 2H, J = 7.2 Hz), 4.33 (s, 1H), 6.27 (t, 1H, J = 4.4 Hz), 7.28−7.46 (m, 3H), 7.55−7.66 (m, 2H); ^{13}C NMR δ 13.91, 27.42, 28.54, 33.88, 39.86, 51.97, 62.00, 78.10, 126.74, 128.05, 138.06, 141.53, 146.69, 173.55, 199.31; FABMS 303 (M^++ H). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.66; H, 7.27.

Ethyl 2-hydroxy-2-(4-methylphenyl)-2-(5,5-dimethylcyclohex-2-en-1-on-2-yl)ethanoate (4b): IR (KBr) 3504, 1736, 1676 cm^{-1}; ^{1}H NMR δ 1.03 (s, 3H), 1.07 (s, 3H), 1.25 (t, 3H, J = 6.9 Hz), 2.21 (d, 2H, J = 4.0 Hz), 2.35 (s, 5H), 4.24 (q, 2H, J = 6.9 Hz), 4.30 (s, 1H), 6.30 (t, 1H, J = 4.0 Hz), 7.18 (d, 2H, J = 8.2 Hz), 7.46 (d, 2H, J = 8.2 Hz); ^{13}C NMR δ 13.98, 21.01, 27.42, 28.62, 33.97, 39.84, 51.96, 62.05, 77.97, 126.63, 128.84, 134.90, 137.76, 141.47, 146.93, 173.77, 199.60. Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.25; H. 7.68.

Ethyl 2-hydroxy-2-(4-ethylphenyl)-2-(5,5-dimethylcyclohex-2-en-1-on-2-yl)ethanoate (4c): IR (neat) 3503, 1736, 1678 cm^{-1}; ^{1}H NMR δ 1.03 (s, 3H), 1.07 (s, 3H), 1.24 (t, 3H, J = 7.2 Hz), 1.26 (t, 3H, J = 7.2 Hz), 2.21 (d, 2H, J = 4.2 Hz), 2.35 (s, 2H), 2.66 (q, 2H, J = 7.2 Hz), 4.24 (q, 2H, J = 7.2 Hz), 4.30 (s, 1H), 6.30 (t, 1H, J = 4.2 Hz), 7.20 (d, 2H, J = 8.0 Hz), 7.48 (d, 2H, J = 8.0 Hz); ^{13}C NMR δ 13.99, 15.34, 27.41, 28.40, 28.64, 33.98, 39.84, 51.96, 62.06, 77.99, 126.69, 127.62, 135.09, 141.48, 144.07, 146.97, 173.79, 199.61. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.95; H, 7.80.

Ethyl 2-hydroxy-2-(4-methoxyphenyl)-2-(5,5-dimethylcyclohex-2-en-1-on-2-yl)ethanoate (4d): IR (neat) 3489, 1736, 1678 cm^{-1}; ^{1}H NMR δ 1.04 (s, 3H), 1.07 (s, 3H), 1.26 (t, 3H, J = 7.4 Hz), 2.22 (d, 2H, J = 4.0 Hz), 2.35 (s, 2H), 3.82 (s, 3H), 4.24 (q, 2H, J = 7.4 Hz), 4.30 (s, 1H), 6.31 (t, 1H, J = 4.0 Hz), 6.90 (d, 2H, J = 8.7 Hz), 7.50 (d, 2H, J = 8.7 Hz); ^{13}C NMR δ 13.99, 27.43, 28.62, 33.98, 39.87, 51.97, 55.22, 62.04, 77.76, 113.54, 127.99, 129.88, 141.61, 146.86, 159.43, 173.81, 199.61. Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28. Found: C, 68.39; H, 7.36.

Ethyl 2-hydroxy-2-(2-methylphenyl)-2-(5,5-dimethylcyclohex-2-en-1-on-2-yl)ethanoate (4e): reaction time 12 h; IR (neat) 3495, 1732, 1664 cm^{-1}; ^{1}H NMR δ 1.07 (s, 6H), 1.30 (t, 3H, J = 7.4 Hz), 2.25 (d, 2H, J = 4.0 Hz), 2.38 (s, 3H), 2.39 (s, 2H), 4.24−4.48 (m, 2H), 4.85 (s, 1H), 6.22 (t, 1H, J = 4.0 Hz), 7.11−7.34 (m, 4H); ^{13}C NMR δ 14.05, 22.04, 27.64, 28.55, 34.23, 40.06, 52.29, 62.05, 81.73, 125.63, 127.18, 128.25, 132.58, 136.15, 138.13, 138.34, 147.30, 173.67, 201.05. Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.35; H. 7.76.

Methyl 2-hydroxy-2-phenyl-2-(5,5-dimethylcyclohex-2-en-1-on-2-yl)ethanoate (4f): IR (KBr) 3449, 1745, 1672 cm^{-1}; ^{1}H NMR δ 0.95 (s, 3H), 0.99 (s, 3H), 2.07 and 2.19 (doublet of ABq, 2H, J = 4.0 and 18.8 Hz), 2.23 and 2.32 (ABq, 2H, J = 16.0 Hz), 3.68 (s, 3H), 4.30 (s, 1H), 6.20 (t, 1H, J = 4.0 Hz), 7.19−7.38 (m, 3H), 7.45−7.55 (m, 2H); ^{13}C NMR δ 27.72, 28.39, 33.98, 39.86, 51.92, 53.03, 78.29, 126.71, 128.21, 137.74, 141.35, 147.20, 174.19, 199.89. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.52; H, 7.02.

Methyl 2-hydroxy-2-(3-methoxyphenyl)-2-(5,5-dimethylcyclohex-2-en-1-on-2-yl)ethanoate (4g): IR (KBr) 3501, 1724, 1657 cm^{-1}; ^{1}H NMR δ 1.03 (s, 3H), 1.07 (s, 3H), 2.17 and 2.28 (doublet of ABq, 2H, J = 4.0 and 19.0 Hz), 2.31 and 2.41 (ABq, 2H, J = 16.0 Hz), 3.78 (s, 3H), 3.82 (s, 3H), 4.38 (s, 1H), 6.32 (t, 1H, J = 4.0 Hz), 6.86−6.94 (m, 1H), 7.08−7.35 (m, 3H); ^{13}C NMR δ 27.66, 28.33, 33.92, 39.82, 51.87, 52.96,

55.21, 78.19, 112.53, 113.67, 119.04, 129.09, 139.37, 141.14, 147.19, 159.63, 174.03, 199.76; FABMS 319 ($M^+ + H$). Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.85; H, 6.89.

Methyl 2-hydroxy-2-(2-methylphenyl)-2-(5,5-dimethylcyclohex-2-en-1-on-2-yl)ethanoate (4h): reaction time 12 h; IR (KBr) 3472, 1745, 1647 cm^{-1}; ^1H NMR δ 1.07 (s, 6H), 2.25 (d, 2H, $J = 4.0$ Hz), 2.35 (s, 3H), 2.40 (s, 2H), 3.83 (s, 3H), 4.96 (s, 1H), 6.22 (t, 1H, $J = 4.0$ Hz), 7.10−7.30 (m, 4H); ^{13}C NMR δ 21.93, 27.81, 28.38, 34.21, 40.08, 52.25, 52.87, 81.90, 125.71, 127.16, 128.33, 132.56, 136.03, 137.98, 138.15, 147.50, 174.12, 201.38. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.69; H, 7.38.

Methyl 2-hydroxy-2-(2-methoxyphenyl)-2-(5,5-dimethylcyclohex-2-en-1-on-2-yl)ethanoate (4i): reaction time 12 h; IR (KBr) 3416, 1734, 1655 cm^{-1}; ^1H NMR δ 0.97 (s, 3H), 1.07 (s, 3H), 2.17 and 2.31 (doublet of ABq, 2H, $J = 4.1$ and 19.0 Hz), 2.32 and 2.55 (ABq, 2H, $J = 15.9$ Hz), 3.67 (s, 3H), 3.71 (s, 3H), 6.02 (s, 1H), 6.20 (t, 1H, $J = 4.1$ Hz), 6.87 (d, 1H, $J = 8.0$ Hz), 6.95−7.05 (m, 1H), 7.21−7.35 (m, 1H), 7.54 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR δ 27.78, 28.44, 34.04, 40.15, 52.41, 52.51, 55.70, 79.04, 111.34, 121.34, 128.03, 128.18, 129.59, 136.96, 147.13, 156.35, 173.39, 202.35. Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.70; H, 6.93.

Isopropyl 2-hydroxy-2-(4-methylphenyl)-2-(5,5-dimethylcyclohex-2-en-1-on-2-yl)ethanoate (4j): reaction time 10 h; IR (KBr) 3522, 1728, 1672 cm^{-1}; ^1H NMR δ 1.04 (s, 3H), 1.07 (s, 3H), 1.21 (d, 3H, $J = 6.0$ Hz), 1.26 (d, 3H, $J = 6.0$ Hz), 2.20 (d, 2H, $J = 4.0$ Hz), 2.35 (s, 2H), 2.36 (s, 3H), 4.26 (s, 1H), 5.09 (sept, 1H, $J = 6.0$ Hz), 6.29 (t, 1H, $J = 4.0$ Hz), 7.18 (d, 2H, $J = 8.1$ Hz), 7.48 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR δ 21.02, 21.56, 27.18, 28.87, 33.97, 39.83, 51.99, 69.86, 77.75, 126.67, 128.78, 135.05, 137.68, 141.51, 146.77, 173.26, 199.23; FABMS 331 ($M^+ + H$). Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.75; H, 7.91.

2-[Hydroxy(4-nitrophenyl)methyl]cyclohex-2-en-1-one (3): mp 84−86 °C (lit.[2m] mp 87−89 °C); IR (KBr) 3402, 1649 cm^{-1}; ^1H NMR δ 1.95−2.10 (m, 2H), 2.38−2.55 (m, 4H), 3.52 (d, 1H, $J = 6.0$ Hz), 5.61 (d, 1H, $J = 6.0$ Hz), 6.81 (t, 1H, $J = 4.0$ Hz), 7.55 (d, 2H, $J = 8.6$ Hz), 8.20 (d, 2H, $J = 8.6$ Hz); ^{13}C NMR δ 22.27, 25.68, 38.27, 71.19, 123.31, 127.08, 140.20, 147.02, 148.11, 149.67, 199.76. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.40; H, 5.31; N, 5.63. This molecule is known in the literature[2m,4] and our spectral data are consistent with reported data.

2-[Hydroxy(phenyl)methyl]cyclohex-2-en-1-one (3a):[10] yield 10%; IR (neat) 3404, 1656 cm^{-1}; ^1H NMR δ 1.90−2.08 (m, 2H), 2.32−2.53 (m, 4H), 3.43 (d, 1H, $J = 4.8$ Hz), 5.56 (d, 1H, $J = 4.8$ Hz), 6.73 (t, 1H, $J = 4.0$ Hz), 7.18−7.43 (m, 5H); ^{13}C NMR δ 22.47, 25.71, 38.48, 72.09, 126.43, 127.36, 128.21, 141.13, 141.88, 147.17, 200.12. This molecule is known in the literature[2m] and our spectral data are consistent with reported data.

Typical Experimental Procedure: Ethyl *syn*-2-Hydroxy-2-phenyl-2-(cyclohex-5-en-1-on-2-yl)ethanoate (5). To a stirred solution of ethyl phenylglyoxylate (1 mmol, 0.178 g) and cyclohex-2-enone (3 mmol, 0.288 g, 0.29 mL) in CH_2Cl_2 (3 mL) was added titanium tetrachloride (1 mmol, 0.5 mL of a 2 M solution in CH_2Cl_2) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched with water (5 mL) and extracted with ether (3 × 10 mL). The combined organic layer was dried over anhydrous sodium sulfate. Solvent was evaporated and the residue, thus obtained, was purified by column chromatography (silica gel, 5% EtOAc in hexanes) followed by crystallization from hexanes to furnish the pure molecule (**5**) in 80% (0.219 g) yield, as a colorless solid. IR (KBr) 3520, 1724, 1674 cm^{-1}; ^1H NMR δ 1.28 (t, 3H, $J = 7.2$ Hz), 1.48−1.72 (m, 1H), 1.78−2.05 (m, 1H), 2.27−2.48 (m, 2H), 3.48 (dd, 1H, $J = 4.5$ and 13.8 Hz), 3.85 (s, 1H), 4.26 (q, 2H, $J = 7.2$ Hz), 5.98−6.12 (m, 1H), 6.88−7.09 (m, 1H), 7.22−7.48 (m, 3H), 7.59−7.72 (m, 2H); ^{13}C NMR δ 13.99, 22.95, 26.09, 55.18, 62.35, 77.56, 125.75, 127.79, 128.38, 129.93, 139.55, 150.66, 174.75, 198.94; FABMS 275 ($M^+ + H$). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.14; H, 6.63. Crystal data for **5**: empirical formula, $C_{16}H_{18}O_4$; formula weight, 274.30; crystal color and habit, colorless, needle; crystal dimensions, 0.40 × 0.15 × 0.15 mm; crystal system, monoclinic; lattice type, primitive; lattice parameters, $a = 8.7653(18)$ Å, $b = 9.2536(19)$ Å, $c = 17.751(4)$ Å; $\beta = 93.18(3)°$; $V = 1437.6(5)$ Å^3; space group, $P2_1/n$; $Z = 4$; $D_{calcd} = 1.267$ g/cm^3; $F_{ooo} = 584.00$; λ(Mo Kα) = 0.71073 Å; $R = 0.0605$, $wR^2 = 0.1783$.

Typical Experimental Procedure for the Isolation of Ethyl 2-Hydroxy-2-phenyl-2-(cyclohex-2-en-1-on-2-yl)-ethanoate (4) (minor Baylis−Hillman adduct). To a stirred solution of ethyl phenylglyoxylate (2 mmol, 0.356 g) and cyclohex-2-enone (6 mmol, 0.576 g, 0.58 mL) in CH_2Cl_2 (5 mL) was added titanium tetrachloride (2 mmol, 1 mL of a 2 M solution in CH_2Cl_2) at 0 °C and stirred for 2 h at room temperature. Compound **4** was isolated (following a similar workup procedure as described for **5**) after column chromatography (silica gel, 8% EtOAc in hexanes) in 7% (0.038 g) yield along with major aldol adduct **5** in 81% (0.445 g) isolated yield. mp 56−58 °C; IR (KBr) 3449, 1743, 1664 cm^{-1}; ^1H NMR δ 1.26 (t, 3H, $J = 6.8$ Hz), 1.94−2.13 (m, 2H), 2.25−2.42 (m, 2H), 2.45−2.60 (m, 2H), 4.15−4.34 (m, 2H), 4.37 (s, 1H), 6.40 (t, 1H, $J = 4.0$ Hz), 7.27−7.49 (m, 3H), 7.56−7.65 (m, 2H); ^{13}C NMR δ 13.98, 22.39, 25.86, 38.42, 62.15, 78.41, 126.88, 128.15, 138.07, 142.53, 149.01, 173.60, 199.32; FABMS 275 ($M^+ + H$). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.25; H, 6.57.

Ethyl *syn*-2-hydroxy-2-(4-methylphenyl)-2-(cyclohex-5-en-1-on-2-yl)ethanoate (6): IR (KBr) 3452, 1720, 1662 cm^{-1}; ^1H NMR δ 1.27 (t, 3H, $J = 7.4$ Hz), 1.55−1.70 (m, 1H), 1.78−2.05 (m, 1H), 2.28−2.50 (m, 5H), 3.45 (dd, 1H, $J = 4.4$ and 14.0 Hz), 3.80 (s, 1H), 4.24 (q, 2H, $J = 7.4$ Hz), 5.98−6.10 (m, 1H), 6.92−7.05 (m, 1H), 7.16 (d, 2H, $J = 8.0$ Hz), 7.51 (d, 2H, $J = 8.0$ Hz); ^{13}C NMR δ 13.95, 20.99, 22.89, 26.06, 55.06, 62.22, 77.40, 125.60, 129.05, 129.88, 136.51, 137.43, 150.62, 174.84, 198.98. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.58; H, 7.03.

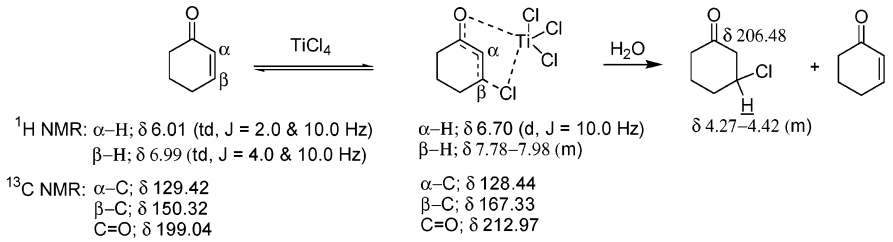
Ethyl *syn*-2-hydroxy-2-(4-methoxyphenyl)-2-(cyclohex-5-en-1-on-2-yl)ethanoate (7): IR (KBr) 3443, 1718, 1662 cm^{-1}; ^1H NMR δ 1.28 (t, 3H, $J = 7.0$ Hz), 1.54−1.68 (m, 1H), 1.78−2.05 (m, 1H), 2.25−2.42 (m, 2H), 3.43 (dd, 1H, $J = 4.6$ and 13.8 Hz), 3.81 (s, 4H), 4.25 (q, 2H, $J = 7.0$ Hz), 5.96−6.08 (m, 1H), 6.84−7.02 (m, 3H), 7.54 (d, 2H, $J = 8.8$ Hz); ^{13}C NMR δ 13.96, 22.88, 26.06, 55.06, 55.25, 62.18, 77.22, 113.73, 126.93, 129.92, 131.46, 150.57, 159.24, 174.88, 198.94. Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.88; H, 6.57.

Methyl *syn*-2-hydroxy-2-phenyl-2-(cyclohex-5-en-1-on-2-yl)ethanoate (8): IR (KBr) 3431, 1730, 1658 cm^{-1}; ^1H NMR δ 1.47−1.64 (m, 1H), 1.77−2.05 (m, 1H), 2.28−2.42 (m, 2H), 3.48 (dd, 1H, $J = 4.6$ and 13.8 Hz), 3.79 (s, 3H), 3.81 (s, 1H), 5.98−6.10 (m, 1H), 6.89−7.02 (m, 1H), 7.22−7.42 (m, 3H), 7.60−7.70 (m, 2H); ^{13}C NMR δ 22.86, 26.05, 53.14, 55.24, 77.57, 125.69, 127.82, 128.40, 129.85, 139.34, 150.71, 175.26, 199.01. Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.48; H, 6.23.

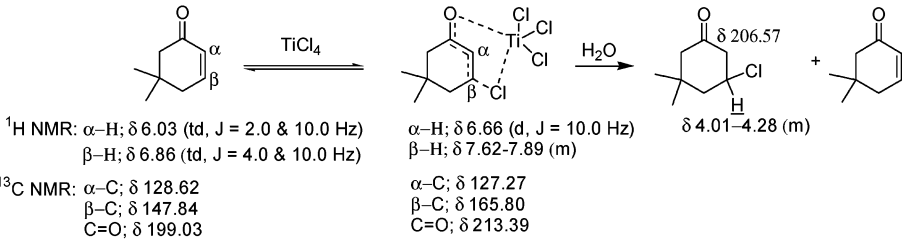
Isopropyl *syn*-2-hydroxy-2-(4-methylphenyl)-2-(cyclohex-5-en-1-on-2-yl)ethanoate (9): IR (KBr) 3503, 1722, 1678 cm^{-1}; ^1H NMR δ 1.23 and 1.27 (2d, 6H, $J = 6.0$ Hz), 1.51−1.68 (m, 1H), 1.77−2.04 (m, 1H), 2.25−2.43 (m, 5H), 3.42 (dd, 1H, $J = 4.4$ and 13.8 Hz), 3.83 (s, 1H), 5.08 (sept, 1H, $J = 6.0$ Hz), 5.96−6.10 (m, 1H), 6.88−7.04 (m, 1H), 7.16 (d, 2H, $J = 8.2$ Hz), 7.52 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR δ 21.01, 21.53, 22.97, 26.06, 54.95, 70.02, 77.42, 125.64, 128.99, 129.96, 136.77, 137.34, 150.48, 174.31, 198.69; FABMS 303 ($M^+ + H$). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.38; H, 7.28.

Ethyl *syn*-2-hydroxy-2-(4-bromophenyl)-2-(cyclohex-5-en-1-on-2-yl)ethanoate (10): IR (KBr) 3414, 1739, 1662 cm^{-1}; ^1H NMR δ 1.27 (t, 3H, $J = 7.2$ Hz), 1.46−1.66 (m, 1H), 1.76−2.06 (m, 1H), 2.25−2.45 (m, 2H), 3.41 (dd, 1H, $J = 4.3$ and

SCHEME 4. Chemical Shifts of Cyclohex-2-enone and the Cyclohex-2-enone−$TiCl_4$ Complex (^{1}H and ^{13}C NMR)



SCHEME 5. Chemical Shifts of 5,5-Dimethylcyclohex-2-enone and the 5,5-Dimethylcyclohex-2-enone−$TiCl_4$ Complex (^{1}H and ^{13}C NMR)



14.0 Hz), 3.84 (s, 1H), 4.25 (q, 2H, J = 7.2 Hz), 5.97−6.08 (m, 1H), 6.90−7.07 (m, 1H), 7.45−7.58 (m, 4H); ^{13}C NMR δ 13.95, 22.83, 25.99, 55.06, 62.50, 77.35, 122.05, 127.64, 129.82, 131.48, 138.75, 150.67, 174.23, 198.50; FABMS 353 (M^+ + H), 355 (M^+ + H + 2). Anal. Calcd for $C_{16}H_{17}O_4Br$: C, 54.41; H, 4.85. Found: C, 54.53; H, 4.88.

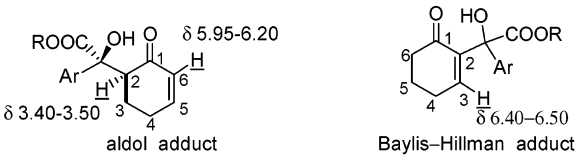
Ethyl *syn*-2-hydroxy-2-(naphth-1-yl)-2-(cyclohex-5-en-1-on-2-yl)ethanoate (11): IR (KBr) 3510, 1730, 1666 cm^{-1}; ^{1}H NMR δ 1.22 (t, 3H, J = 7.6 Hz), 1.48−1.68 (m, 1H), 1.78−2.10 (m, 1H), 2.25−2.40 (m, 2H), 4.09 (dd, 1H, J = 4.4 and 13.8 Hz), 4.18−4.36 (m, 3H), 6.07−6.16 (m, 1H), 6.88−7.02 (m, 1H), 7.42−7.54 (m, 3H), 7.77−7.90 (m, 2H), 8.00 (d, 1H, J = 7.2 Hz), 8.79−8.91 (m, 1H); ^{13}C NMR δ 13.94, 23.68, 26.25, 54.15, 62.33, 79.70, 125.07, 125.33, 125.88, 126.06, 129.22, 129.63, 130.04, 131.06, 134.34, 134.75, 150.58, 174.08, 200.04; FABMS 325 (M^+ + H). Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 73.90; H, 6.19.

Methyl *syn*-2-hydroxy-2-(4-methylphenyl)-2-(cyclohex-5-en-1-on-2-yl)ethanoate (12): IR (KBr) 3425, 1730, 1660 cm^{-1}; ^{1}H NMR δ 1.50−1.68 (m, 1H), 1.78−2.06 (m, 1H), 2.24−2.40 (m, 5H), 3.47 (dd, 1H, J = 4.5 and 14.0 Hz), 3.78 (s, 4H), 5.97−6.09 (m, 1H), 6.90−7.02 (m, 1H), 7.17 (d, 2H, J = 8.0 Hz), 7.51 (d, 2H, J = 8.0 Hz); in the ^{1}H NMR spectrum of the compound (5 mg) in the presence of Eu(fod)$_3$ (4 mg) the singlet originally at δ 3.78 separated into two singlets at δ 4.36 and δ 6.10 in the ratio of 3:1 indicating that original singlet contains four protons (COO*CH*$_3$ + *OH*); ^{13}C NMR δ 21.00, 22.84, 26.07, 53.12, 55.14, 77.43, 125.58, 129.12, 129.85, 136.29, 137.54, 150.77, 175.41, 199.17; FABMS 275 (M^+ + H). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.87; H, 6.64.

Methyl *syn*-2-hydroxy-2-(4-ethylphenyl)-2-(cyclohex-5-en-1-on-2-yl)ethanoate (13): IR (KBr) 3441, 1736, 1658 cm^{-1}; ^{1}H NMR δ 1.23 (t, 3H, J = 7.6 Hz), 1.52−1.70 (m, 1H), 1.78−2.04 (m, 1H), 2.26−2.40 (m, 2H), 2.64 (q, 2H, J = 7.6 Hz), 3.46 (dd, 1H, J = 4.6 and 14.0 Hz), 3.78 (s, 4H), 5.98−6.08 (m, 1H), 6.90−7.02 (m, 1H), 7.18 (d, 2H, J = 8.0 Hz), 7.52 (d, 2H, J = 8.0 Hz); in the ^{1}H NMR spectrum of the compound (5 mg) in the presence of Eu(fod)$_3$ (4 mg) the singlet originally at δ 3.78 separated into two singlets at δ 3.82 and δ 3.89 in the ratio of 3:1 indicating that the original singlet contains four protons (COO*CH*$_3$ + *OH*); ^{13}C NMR δ 15.23, 22.85, 26.04, 28.34, 52.97, 55.17, 77.49, 125.61, 127.83, 129.88, 136.56, 143.76, 150.47, 175.32, 199.00. Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.83; H, 6.97.

Ethyl *syn*-2-hydroxy-2-phenyl-2-(cyclopent-4-en-1-on-2-yl)ethanoate (14): IR (neat) 3522, 1724, 1672 cm^{-1}; ^{1}H NMR δ 1.33 (t, 3H, J = 7.2 Hz), 2.47−2.61 (m, 2H), 3.56 (dd, 1H, J = 4.0 and 6.0 Hz), 3.99 (s, 1H), 4.18−4.51 (m, 2H), 6.19 (td, 1H, J = 2.0 and 6.0 Hz), 7.27−7.43 (m, 3H), 7.59−7.72 (m, 3H); ^{13}C NMR δ 14.02, 31.97, 52.37, 62.98, 77.44, 125.92, 127.99, 128.42, 134.18, 140.50, 164.45, 174.33, 208.02. Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 68.94; H, 6.25.

^{1}H NMR Data of Crude Compounds. In the ^{1}H NMR spectrum of the crude products (**5**−**13**) the methine proton (at C_2) in aldol products appears at ca. δ 3.40−3.50 (dd, 1H) (in the case of **11**, the doublet of doublet appears at ca. δ 4.09) and the β-vinylic proton (at C_3) in the Baylis−Hillman products appears at ca. δ 6.40−6.50 (t, 1H). The integration of these protons provides the ratio of aldol and Baylis−Hillman products in 82−100:0−18%, respectively.



The ^{1}H NMR spectrum of crude compounds (**4a**−**j**) did not indicate the formation of any aldol product as evidenced by the absence of methine proton peaks. The ^{1}H NMR spectra of the crude products (**5**−**10**, **12**, and **13**) do not show the presence of any other diastereomers (anti). The ^{1}H NMR spectrum of the crude product **11** shows a doublet of doublet at ca. δ 4.09 (for methine proton of the *syn*-aldol compound) and a multiplet at ca. δ *3.48*−*3.72* in the ratio of ca. 90:10 (^{1}H NMR spectrum of the mother liquor also shows the presence of a multiplet at ca. δ *3.48*−*3.72*). We have assigned a minimum of 90% syn-selectivity (even if the doublet of doublet arising from the methine proton of the *anti*-aldol product is hidden in the multiplet at δ *3.48*−*3.72*).

See Scheme 4 for the chemical shifts of cyclohex-2-enone and the cyclohex-2-enone−$TiCl_4$ complex and Scheme 5 for the chemical shifts of 5,5-dimethylcyclohex-2-enone and the 5,5-dimethylcyclohex-2-enone−$TiCl_4$ complex.

Acknowledgment. We thank DST (New Delhi) for funding this project. We thank UGC (New Delhi) for a

Special Assistance Program in Organic Chemistry in the School of Chemistry, University of Hyderabad. B.S. and A.J.R. thank CSIR (New Delhi) for their research fellowship. We also thank the National Single Crystal X-ray Facility, School of Chemistry, University of Hyderabad funded by DST (New Delhi). We thank Dr. T. P. Radhakrishnan for helpful discussions regarding the X-ray crystal structure.

Supporting Information Available: ^{13}C NMR spectra of all the compounds (**3**, **3a**, **4**, **4a**−**j**, **5**−**14**); ^{13}C NMR spectra of cyclohex-2-enone and its $TiCl_4$ complex; ^{13}C NMR spectra of 5,5-dimethylcyclohex-2-enone and its $TiCl_4$ complex; crystallographic information data file for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0342424