Pergamon

Tetrahedron Letters 41 (2000) 1–5

TETRAHEDRON LETTERS

$TiCl_4$-Mediated Baylis–Hillman and aldol reactions without the direct use of a Lewis base

Guigen Li,* Han-Xun Wei, Joe J. Gao and Thomas D. Caputo

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

Received 17 August 1999; accepted 21 October 1999

Abstract

$TiCl_4$-Mediated Baylis–Hillman and aldol reactions were developed without the direct use of a Lewis base. These processes involve the conjugate addition of $TiCl_4$ to α,β-unsaturated substrates followed by carbonyl coupling. Baylis–Hillman olefins were obtained when α,β-unsaturated ketones were employed as the substrates, whereas β-halogenated aldol products were generated with an α,β-unsaturated *N*-acyl benzoxalinone as the Michael-type acceptor.

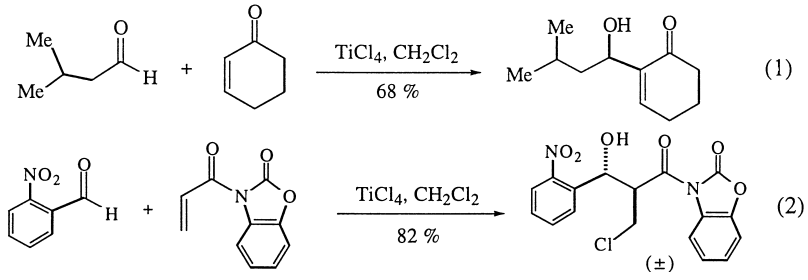
Keywords: titanium(IV) chloride; Baylis–Hillman reaction; aldol reaction.

The Baylis–Hillman reaction and related processes have become increasingly important in synthetic organic chemistry because the resulting adducts have an array of multifunctional groups which can be subjected to numerous transformations.[1–5] This carbon–carbon bond formation was typically catalyzed by DABCO or tertiary phosphines. The major drawbacks of the Baylis–Hillman reaction are shown by its slow reaction rate and limited scope of substrates. To overcome its shortcomings, much effort has been made on using Lewis acids or adding additives to the reaction system to activate carbonyl electrophiles.[6–10] Among various Lewis acids, $TiCl_4$ has been successfully utilized to promote the Baylis–Hillman reaction in the presence of Lewis base catalysts.[11] During our study on the Baylis–Hillman process, we found that this reaction can proceed smoothly in the presence of $TiCl_4$ with no need of a Lewis base. Concurrently, we also found that this C–C formation can be controlled to give β-chloro aldol adducts simply by choosing an α,β-unsaturated *N*-benzoxazolinone as the substrate. In this paper, we report our preliminary results of these new systems.

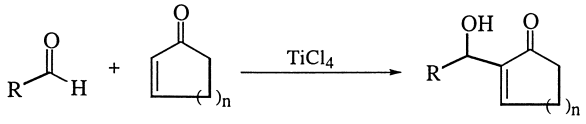
The new processes are represented in Scheme 1 with the results summarized in Tables 1 and 2. The Baylis–Hillman reaction was realized by simply mixing three components, aldehyde, α,β-unsaturated cycloketone and titanium(VI) chloride in dichloromethane at 0°C then to room temperature. Any convenient vessel of appropriate size can be used for the reaction without the protection of inert gases. An excess amount of cycloketone (ketone/aldehyde, 2/1, mol/mol) was found necessary for the complete consumption of aldehyde.

* Corresponding author. Fax: 806-742-1289; e-mail: qeggl@ttu.etu

0040-4039/00/$ - see front matter
PII: S0040-4039(99)01992-9



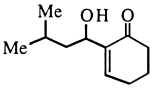
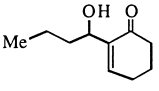
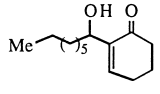
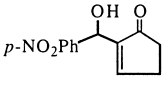
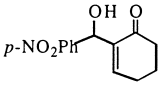
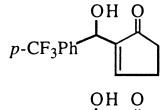
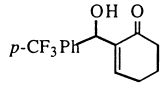
Scheme 1.



Scheme 2.

Table 1

Results of $TiCl_4$-mediated halogen-Baylis–Hillman reaction[12]

Entry	R-	Cycloketone	Product[a]	Yield (%)[b]
1	*i*-Propyl			68
2	Propyl			64
3	Heptyl			57
4	*p*-NO_2Ph			49
5	*p*-NO_2Ph			56
6	*p*-CF_3Ph			47
7	*p*-CF_3Ph			53

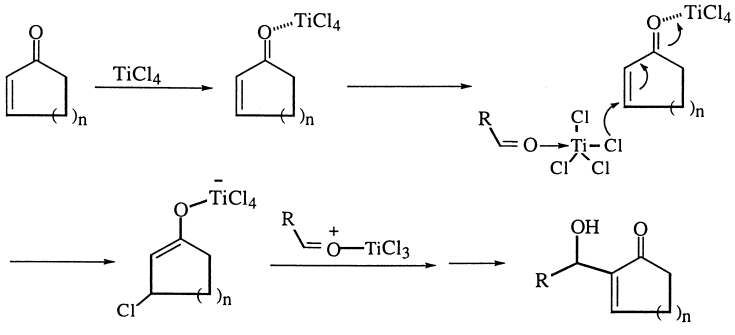
a All of the products were isolated as colorless oils. Dehydration products (~8%) were determined for **1** - **3**. Major unknown side-products (>10%) were observed for 4 - 7. b Purified yields based on aldehydes after column chromatography.

Examination of the results collected in Table 1 reveals that both aliphatic and aromatic aldehydes can be employed as electrophilic acceptors among which aliphatic aldehydes gave better yields. For aromatic aldehydes, electron withdrawing group attachment is necessary to achieve the modest reaction rate and yield. Benzaldehyde resulted in only a trace amount of desired product. About 8% of diene side-products were found in aliphatic cases **1**–**3**, which were generated from the dehydration of Baylis–Hillman

adducts. However, there was difficulty in identifying the major side-products (>10%) for cases **4**–**7**. Attempts to improve the yields under various conditions proved to be unsuccessful. A trace amount of desired product was detected in several other solvents, such as benzene, THF, etc. Among various metal promoters ($AlCl_3$, $ZnCl_2$, etc.) we examined, only $TiCl_4$ showed good efficiency for this new process. So far, only 2-cyclohexen-1-one and 2-cyclopenten-1-one have been employed as Michael-type acceptors. The cyclic ketones with larger cyclic rings and other similar derivatives, such as α,β-unsaturated lactones and lactams, will be subjected to this reaction in future. Acyclic methyl vinyl ketone was also utilized for this system and gave complex products. The modification of the present system by using Bu_4NI:$TiCl_4$ (1:1) mixture instead of $TiCl_4$ resulted in the expected Baylis–Hillman adducts with modest yields (51–67%) (Scheme 2).

As mentioned before, $TiCl_4$ has been previously utilized in the Baylis–Hillman system as the promoter to activate aldehydes or ketones via forming coordination complexes. Recently, Kataoka and co-workers reported the chalcogeno-Baylis–Hillman reaction using a series of sulfides and selenides as Lewis base catalysts, and $TiCl_4$ to activate α,β-unsaturated cycloketones (for Michael-type addition) and aldehydes (for the C–C coupling).[9,10] This reaction proceeded to completion using 3 equiv. of α,β-unsaturated cycloketones in the presence of 10 mol% of chalcogenides and 1.0 equiv. of $TiCl_4$ in dichloromethane. In our conditions (2.0 equiv. of α,β-unsaturated cycloketones and 1.2 equiv. of $TiCl_4$), there is no Lewis base catalyst specially added into the reaction mixture. However, the reaction took a little longer time to go to completion.

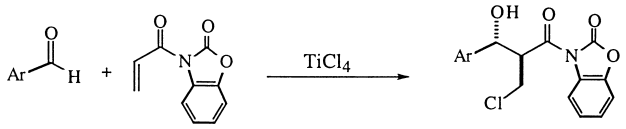
During the reaction process, we believe that the chlorine anion released from $TiCl_4$ acted as the actual Lewis base to participate in the conjugate addition to form the halogenated titanium enolate. This enolate will then react with the aldehyde to give the coupling adduct. The release of chlorine anion could be assisted by the coordination of aldehyde or cycloketone oxygen onto $TiCl_4$ metal center as shown in Scheme 3.



Scheme 3.

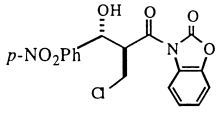
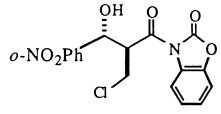
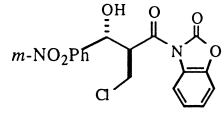
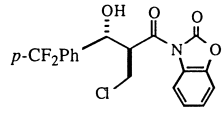
To confirm this hypothesis, we made the effort to isolate the chlorinated aldol adducts generated from the aldol addition without much success. Interestingly, the chlorinated aldol adducts became the major products when an α,β-unsaturated *N*-acyl benzoxalinone was utilized as the Michael-type acceptor (Scheme 4 and Table 2). The reaction was performed to completion under similar conditions (CH_2Cl_2, room temperature, 1 h). This process should also be synthetically useful because the resulting chlorinated aldol adducts can be readily transformed to Baylis–Hillman olefins by treating with DBU, or to many other compounds via S_N2 substitution of β-chlorine by various nucleophiles.

In conclusion, the new $TiCl_4$-based Baylis–Hillman reaction and aldol addition have been developed for the synthesis of Baylis–Hillman olefins and chlorinated aldol adducts. The reactions can be performed at room temperature in any convenient vial without the inert gase protection. These new procedures could provide novel strategies in order to achieve their asymmetric versions in the future.



Scheme 4.

Table 2
Results of $TiCl_4$-mediated halogen aldol reaction

Entry	R-	Product (±)	m.p.(°C)	Yield (%)
8	*p*-NO_2Ph		182-184	77
9	*o*-NO_2Ph		130-132	82
10	*m*-NO_2Ph		154-156	45
11	*p*-CF_3Ph		119-121	60

Acknowledgements

We would like to dedicate this paper to Professor Richard A. Bartsch on the occasion of his 60th birthday. We gratefully acknowledge generous support from the Robert A. Welch Foundation (grant no. D-1361) and the South Plains Foundation. We also would like to thank Ms. Sun Hee Kim for her assistance.

References

1. For reviews, see: (a) Ciganek, E. *Org. React.* **1997**, *51*, 201.1; (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001; (c) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.
2. Brzezinski, L. J.; Rafel, S.; Leahy, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 4317.
3. Marko, I. E.; Giles, P. G.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015.
4. Richter, H.; Jung, G. *Tetrahedron Lett*. **1998**, *39*, 2729.
5. Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun*. **1999**, 2533.
6. Kundig, E. P.; Xu, L. H.; Romanens, P; Bernardinelli, G. *Tetrahedron Lett*. **1993**, *34*, 7049.
7. Aggarwal, V.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem*. **1998**, *63*, 7183.
8. Kawamura, M.; Kobayashi, S. *Tetrahedron Lett*. **1999**, *40*, 1539.
9. Kataoka, T.; Iwama, T.; Tsujiyama, S.-i.; Iwamura, T.; Watanable, S.-i. *Tetrahedron* **1998**, *54*, 11813.
10. Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett*. **1999**, *40*, 1509.
11. (a) Nagaoka, Y.; Yomioka, K. *J. Org. Chem.* **1998**, *63*, 6428; (b) Harrowven, D.; Hannam, J. C. *Tetrahedron* **1999**, *55*, 9341.

12. Typical procedure (Table 1, entry 1): Into a dry vial was added isovaleraldehyde (86.1 mg, 1.0 mmol), 2-cyclohexen-1-one (192.3 mg, 2.0 mmol) and freshly distilled dichloromethane (1.5 mL). The reaction vial was immersed in a 0°C bath, and $TiCl_4$ (1.2 mL, 1.0 M in CH_2Cl_2, 1.2 mmol) was then added dropwise. The resulting solution was stirred at 0°C for 10 minutes and at room temperature for 2 hours. The reaction was finally quenched by saturated aqueous $NaHCO_3$ solution (3.0 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated to dryness. Purification by flash chromatography (EtOAc/hexane, 3/50, v/v) provided product **1** (124 mg, 68% yield) as colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.17 (t, J=4.25 Hz, 1H), 5.05 (dd, J=8.79, 4.41 Hz, 1H), 2.42–2.51 (m, 4H), 1.54–2.04 (m, 5H), 0.90–0.96 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.7, 147.1, 140.4, 54.8, 46.8, 38.3, 25.9, 25.6, 22.9, 22.4, 21.2. Compound **2**: colorless oil (107 mg, 64% yield); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.17 (t, J=4.33 Hz, 1H), 4.97 (t, J=6.38 Hz, 1H), 2.42–2.50 (m, 4H), 1.36–2.07 (m, 7H), 0.92 (t, J=7.39 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9, 147.2, 140.2, 56.5, 40.0, 38.3, 26.0, 22.5, 20.0, 13.4. Compound **3**: colorless oil (143 mg, 57% yield); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.16 (t, J=4.23 Hz, 1H), 4.95 (t, J=6.96 Hz, 1H), 2.44–2.50 (m, 4H), 1.96–2.04 (m, 2H), 1.67–1.82 (m, 2H), 1.25 (s, 16H), 0.88 (t, J=4.88 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.8, 147.2, 140.2, 56.8, 38.3, 37.9, 31.8, 29.5, 29.4, 29.3, 28.9, 26.8, 26.0, 22.6, 22.5, 14.0. Compound **4**: colorless oil (113 mg, 49% yield); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.21 (dd, J=6.95, 1.99 Hz, 2H), 7.59 (dd, J=7.30, 1.80 Hz, 2H), 7.32–7.34 (m, 1H), 5.67 (m, 1H), 3.76 (d, J=5.41 Hz, 1H), 2.61–2.67 (m, 2H), 2.46–2.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2, 159.9, 148.5, 147.5, 146.6, 127.0, 123.7, 68.9, 35.1, 26.8. Compound **5**: colorless oil (139 mg, 56% yield); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.20 (dd, J=7.02, 1.89 Hz, 2H), 7.56 (dd, J=6.43, 1.51 Hz, 2H), 6.83 (t, J=3.79 Hz, 1H), 5.61 (d, J=5.99 Hz, 1H), 3.58 (d, J=5.95 Hz, 1H), 2.40–2.50 (m, 4H), 1.95–2.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0, 149.3, 148.1, 147.2, 140.2, 127.1, 123.5, 72.1, 38.4, 25.7, 22.4. Compound **6**: colorless oil (121 mg, 47% yield); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.62 (d, J=9.40 Hz, 2H), 7.52 (d, J=8.30 Hz, 2H), 7.26–7.29 (m, 1H), 5.63 (s, 1H), 3.54 (b, 1H), 2.59–2.64 (m, 2H), 2.45–2.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 159.6, 147.1, 145.2, 126.6, 125.4, 125.5 (q), 69.3, 35.2, 26.7. Compound **7**: colorless oil (143 mg, 53% yield); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.60 (d, J=9.35 Hz, 2H), 7.48 (d, J=8.28 Hz, 2H), 6.77 (t, J=4.08 Hz, 1H), 5.58 (d, J=5.61 Hz, 1H), 3.57 (d, J=5.78 Hz, 1H), 2.38–2.49 (m, 4H), 1.97–2.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 147.8, 145.8, 140.5, 126.7, 125.2 (q), 72.1, 38.5, 25.7, 22.4.