ORGANIC LETTERS

2000
Vol. 2, No. 5
617−620

New C=C Bond Formation via Nonstoichiometric Titanium(IV) Halide Mediated Vicinal Difunctionalization of α,β-Unsaturated Acyclic Ketones

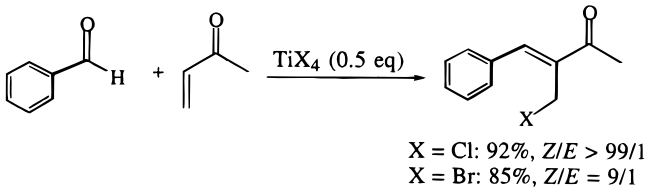
Guigen Li,* Joe Gao, Han-Xun Wei, and Mason Enright

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

qeggl@ttu.edu

Received December 20, 1999

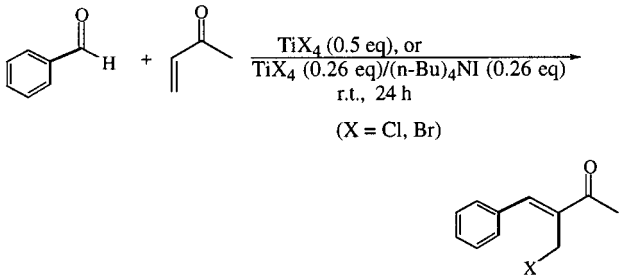
ABSTRACT



Highly stereoselective vicinal difuctionalization of α,β-unsaturated ketones for the synthesis of multifunctionalized trisubstituted alkenes is described. The new reaction employs titanium(IV) halides (0.5 equiv) as promoters and inexpensive commercial chemicals as starting materials. The reaction can be performed at room temperature in a convenient vial without the protection of inert gases. Good to excellent yields and high *Z*/*E* stereoselectivity have been realized in most cases presented (16 examples).

The application of the Baylis−Hillman reaction to carbon−carbon single bond formation has become increasingly important in modern organic chemistry.[1] However, the utilization of a Baylis−Hillman-type procedure in forming carbon−carbon double bonds has not been well documented so far.[2] This process can result in (halomethyl)acrylates and 2-(halomethyl)vinyl ketones, which are versatile building blocks for organic synthesis.[3] To date, the synthesis of these important molecules has been done by treating Baylis−Hillman adducts with various halogen reagents such as NBS/Me_2S, hydrogen halides and $CuBr_2/SiO_2$, etc.[3] During our study of Baylis−Hillman-type processes,[4] we found these compounds can be readily generated by using a one-pot tandem difunctionalization of α,β-unsaturated ketones mediated by a nonstoichiometric amount of titanium(IV) halides (TiX_4, X = Cl, Br) or the combination of $TiX_4/(n\text{-}Bu)_4NI$[5]

Scheme 1



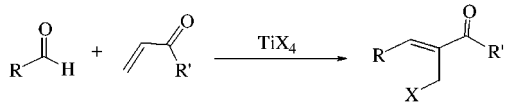
(1) (a) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219. (b) Brzezinski, L. J.; Rafel, S.; Leahy, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 4317. For recent reviews, see: (c) Ciganek, E. *Org. React.* **1997**, *51*, 201. (d) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.

(2) During the preparation of this manuscript, a paper has appeared that mentions two examples of similar C=C formation by using different conditions (*Z*/*E* selectivity, 46/54 and 34/66; yield, 51% and 57%): Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1*, 1383.

(3) (a) Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1991**, *74*, 1213. (b) Xu, L.-X. Kundig, E. P. *Helv. Chim. Acta* **1994**, *77*, 1480. (c) Basavaiah, D.; Hyma, R. S.; Padmaja, K.; Krishnamacharyulu, M. *Tetrahedron* **1999**, *55*, 6971 and references therein.

10.1021/ol9904040 CCC: $19.00
Published on Web 02/16/2000

Scheme 2

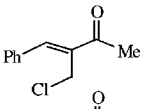
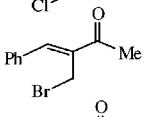
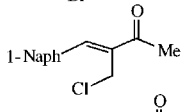
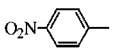
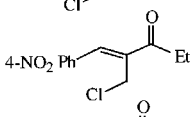
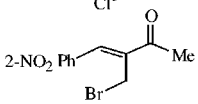
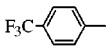
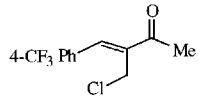
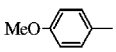
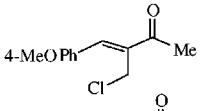
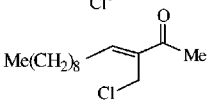
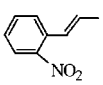
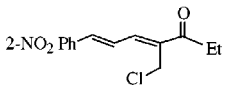
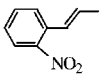
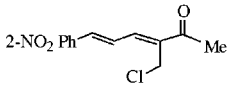


in highly stereoselective fashions. In this communication, we present our preliminary research results about this reaction, which is represented in Scheme 1, with the results collected in Tables 1 and 2.

This one-pot, three-component reaction was performed simply by mixing aldehyde, α,β-unsaturated ketone, and TiX_4 in dichloromethane solution at room temperature. The reaction went to completion in 24 h and gave good to excellent yields (Table 1). Both $TiCl_4$ and $TiBr_4$ worked very well as promoters in this new process in which the latter was inferior to the former with regard to controlling *Z*/*E* stereoselectivity. As indicated in Table 1, both aromatic and aliphatic aldehydes can be utilized as the electrophilic acceptors. Excellent *Z*/*E* selectivity was realized for most cases, only in cases **2** and **5** were the minor *E* isomers observed with the *Z*/*E* selectivity of 9:1 and 6:1, respectively, when $TiBr_4$ was employed as the promoter. Only 0.5 equiv of $TiCl_4$ or $TiBr_4$ is needed for the complete conversion, which reveals that two halogen atoms of each TiX_4 molecule participated in halogen transformations. The reaction did not proceed to completion with less than 0.5 equiv of TiX_4 even in prolonged period (>30 h). However, a stoichiometric amount of $TiCl_4$ or $TiBr_4$ can drive the reaction to completion within 5 h with yields and *Z*/*E* selectivity similar to those of Table 1.

Dichloromethane appears to be the best solvent for the present reaction system. The effort to improve *Z*/*E* selectivity for cases **2** and **5** by using other solvents, such as toluene, THF, and acetonitrile, was unsuccessful. The anticipated products were obtained with good yields by using the above solvents, but a stoichiometric amount of titanium halides turned out to be necessary. A variety of conditions including the use of various solvents/cosolvents will be studied so that

Table 1. Results of TiX_4-Mediated New C=C Bond Formation[7a,8]

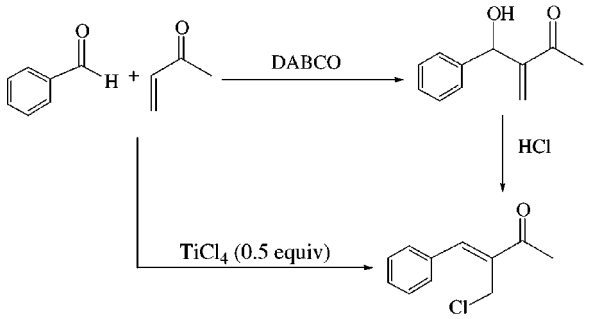
entry	R-	R'-	X	product	m.p.(°C)	yield (%)[a]
1		Me	Cl		36-38	92
2[b]		Me	Br		oil	87
3		Me	Cl		95-96	85
4[c]		Et	Cl		98-100	62
5[b]		Me	Br		125-127	94
6		Me	Cl		48-49	75
7		Me	Cl		72-74	70
8	$Me(CH_2)_8$-	Me	Cl		oil	68
9		Et	Cl		103-105	66
10		Me	Cl		164-166	76

[a] Purified yields by column chromatography. [b] Two isomers were observed by crude ^1H NMR determination, *Z*/*E* = 9:1 and 6:1 for **2** and **5**, respectively. [c] Baylis−Hillman adduct was isolated in 10% yield.

acrylates and similar derivatives can be employed as the substrates, which has not been successful under the present conditions.

The stereochemical assignment was carried out by converting one of the products (entry **1**) to an authentic sample, which was synthesized by a literature procedure.[3c] In this procedure, the Baylis−Hillman adduct was treated with hydrogen chloride at room temperature for a few minutes to afford (3*Z*)-3-(chloromethyl)-4-phenylbut-3-en-2-one (Scheme 3). The *Z*/*E* geometric selectivity was determined by ^{1}H

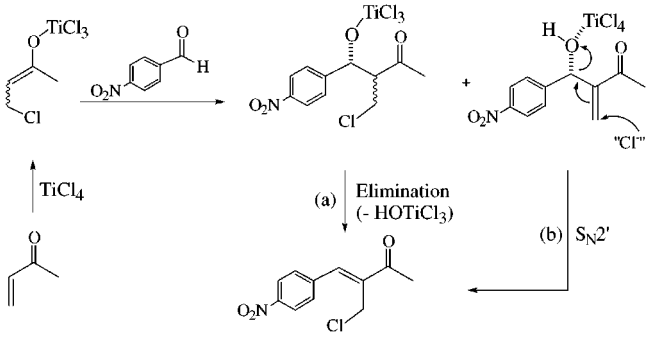
Scheme 3



NMR analysis in which the singlet peak of the β-CH_2 protons of the *Z*-isomer shifts to farther upfield as compared with that of *E*-isomer.

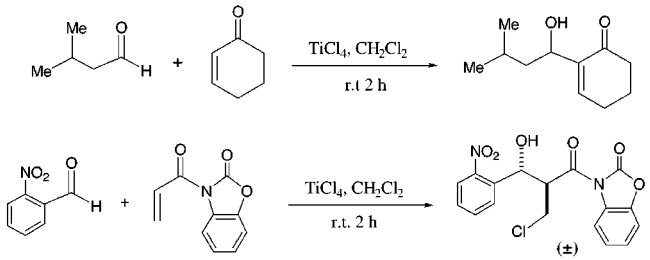
It seems reasonable to suggest that the reaction proceeds through the formation of aldol and Baylis−Hillman intermediates and the subsequent reactions involving these intermediates. As shown in Scheme 4, these intermediates

Scheme 4



are initially generated from the reactions of aldehydes with titanium enolates derived from the $TiCl_4$-mediated α,β-unsaturated additions.[6] Routes a and b of Scheme 4, involving β-elimination and S_N2' reactions, respectively, could proceed at the same time. This mechanistic hypothesis can be supported by the observation of aldol (minor) and Baylis−Hillman adducts (major) for entry **4** by quenching the reaction at 0 °C within 2 h. It can also be supported by our recent research results on the similar reaction promoted by $TiCl_4$ in which α,β-unsaturated cycloketones and *N*-acyl benzoxalinone were employed as Micheal-type acceptors.[4a] This reaction predominantly yielded Baylis−Hillman olefins with α,β-unsaturated cycloketones as the substrate, whereas β-halogenated aldol adducts became the major products when α,β-unsaturated *N*-acyl benzoxalinone was employed as the substrate (Scheme 5). Interestingly, these *N*-acyl benzoxalinone derived products could not undergo the dehydration reaction under the present conditions.

Scheme 5



After we succeeded in the above $TiCl_4$- and $TiBr_4$-mediated difunctionalization reaction, we then tried to incorporate an iodine moiety onto (*Z*)-2-(halomethyl)vinyl ketones by taking advantage of the TiX_4/$(n\text{-Bu})_4$NI combination.[2] Surprisingly, the products obtained by using this combination were not what we anticipated (Scheme 6). The resulting products were essentially identical to those generated from solely pure $TiBr_4$- or $TiCl_4$-promoted process. The reaction went to completion in 24 h at room temperature to afford the relevant chloro or bromo products. Good yields and excellent stereoselectivity were obtained with further reduced loading of titanium halides [TiX_4/$(n\text{-Bu})_4$NI = 0.26

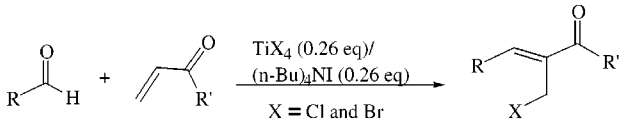
(4) (a) Li, G.; Wei, H.-X.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1. (b) Li, G.; Wei, H.-X.; Whittlesey, B.; Batrice, N. N. *J. Org. Chem.* **1999**, *64*, 1061. (c) Wei, H.-X.; Hook, J. D.; Fitzgerald, K. A.; Li, G. *Tetrahedron: Asymmetry* **1999**, *10*, 661.

(5) For the $TiCl_4$/$(n\text{-Bu})_4$NI 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.

(6) Ferreri, C.; Palumbo, G.; Caputo, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 139−172. (b) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986.

(7) **(a) Typical Procedure (Entry 1, Table 1).** Into a dry vial was added freshly distilled dichloromethane (1.5 mL), benzaldehyde (0.1 mL, 1.0 mmol), and methyl vinyl ketone (0.10 mL, 1.2 mmol). The reaction mixture was stirred at room temperature and then loaded with titanium tetrachloride (0.5 mL, 1 M solution in dichloromethane, 0.5 mmol). The resulting solution in the capped vial was stirred at the same temperature for 24 h without argon protection. The reaction was finally quenched by dropwise addition of saturated aqueous $NaHCO_3$ solution (5 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated to dryness. Purification by flash chromatography (EtOAc/hexane, 1/8, v/v) provided **1** (184 mg, 92%) as light yellow solid. **(b) Typical Procedure (Entry 1, Table 2).** To a stirred mixture of benzaldehyde (0.10 mL, 1.0 mmol), methyl vinyl ketone (0.10 mL, 1.2 mmol), and $(n\text{-Bu})_4$NI (96 mg, 0.26 mmol) in dichloromethane (1.5 mL) was added 0.26 mL of a 1 M $TiCl_4$ (0.26 mmol) solution in dichloromethane. The reaction mixture was stirred at room temperature for 24 h and then quenched by dropwise addition of saturated aqueous $NaHCO_3$ solution (5 mL). The product was isolated by extraction with dichloromethane (3 × 10 mL), dried over anhydrous sodium sulfate, and concentrated to dryness. Purification by flash chromatography (EtOAc/hexane, 1/8, v/v) provided **1** (135 mg, 69%).

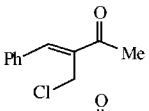
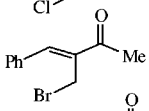
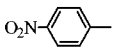
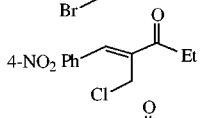
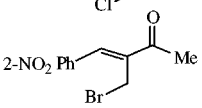
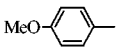
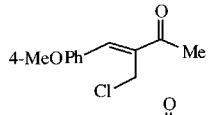
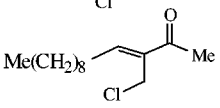
Scheme 6



equiv each] (Table 2), which is in contrast to the former system where the reaction could not proceed to completion with less than 0.5 equiv of TiX_4. Less than 5% of iodinated products were observed for all cases shown in Table 2. These results suggest that four chlorine ions per $TiCl_4$ molecule instead of the iodine anion of $(n\text{-Bu})_4NI$ were all consumed during the reaction process. At this stage, it is not clear why the affinity of α,β-unsaturated ketones for chlorine ion is superior to that for the iodine counterpart under the present conditions.

In summary, we have demonstrated a new nonstoichiometric $TiCl_4$- and $TiBr_4$-mediated vicinal difuctionalization of α,β-unsaturated acyclic ketones for the stereoselective synthesis of mutifunctionalized (*Z*)-keto allyl bromides, chlorides, and the relevant diene derivatives. The reaction can be carried out at room temperature without the need for inert atmosphere to give good to excellent yields and complete *Z*/*E* stereoselectivity. This new method has the advantage of the Baylis−Hillman reaction by using inexpensive and readily available starting materials.

Table 2. Results of $TiX_4/(n\text{-Bu})_4NI$-Mediated C=C Bond Formation[7b]

entry	R-	R'-	X	product	yield (%)
1		Me	Cl		70
2		Me	Br		85
3		Et	Cl		71
4		Me	Br		66
5		Me	Cl		65
6	$Me(CH_2)_8$-	Me	Cl		54

Acknowledgment. Generous support from the Robert A. Welch Foundation (grant D-1361) and the South Plains Foundation are gratefully acknowledged. We thank the National Science Foundation (CHE-9808436) and Texas Tech University for purchasing the 500 MHz NMR. We thank Mr. David W. Purkiss for his assistance in NMR spectroscopic analysis.

Supporting Information Available: ^1H and ^{13}C NMR spectra for all pure products. These materials are available free of charge via the Internet at http://pubs.acs.org.

OL9904040

(8) **^1H NMR Data, Table 1 (200 MHz, $CDCl_3$). 1**: δ 7.70 (s, 1H), 7.62−7.40 (m, 5H), 4.44 (s, 2H), 2.50 (s, 3H). **2**: δ 7.65−7.58 (m, 3H), 4.44 (s, 0.2H), 4.35 (s, 1.8H), 2.50 (s, 3H). **3**: δ 8.26 (s, 1H), 7.95−7.74 (m, 4H), 7.60−7.52 (m, 3H), 4.39 (s, 2H), 2.62 (s, 3H). **4**: δ 8.35−8.30 (d, 2H, *J* = 8.8), 7.75−7.70 (d, 2H, *J* = 8.8), 7.72−7.68 (d, 1H *J* = 5.4), 4.39 (s, 2H), 2.95−2.84 (q, 2H, *J* = 14.4, 7.2), 1.26−1.18 (t, 3H, *J* = 7.2); **5** δ 8.30−8.24 (q, 1H, *J* = 8.2, 1.2), 8.02 (s, 1H), 7.80−7.63 (m, 3H), 4.21 (s, 1H), 2.55 (s, 3H). **6**: δ 7.78−7.68 (q, 4H), 4.39 (s, 1H), 2.53 (s, 3H). **7**: δ 7.65 (s, 1H), 7.62−7.57 (d, 2H, *J* = 8.8), 7.01−6.97 (d, 2H, *J* = 8.8), 4.49 (s, 2H), 3.86 (s, 3H), 2.48 (s, 3H). **8**: δ 6.89−6.81 (t, 1H, *J* = 7.4), 4.31 (s, 2H), 2.45−2.33 (q, 2H, *J* = 7.4, 14.8), 2.35 (s, 3H), 1.42−1.18 (m, 14H), 0.92−0.85 (t, 3H, *J* = 6.4). **9**: δ 8.05−8.01 (d, 1H, *J* = 8.0), 7.79−7.45 (m, 4H), 7.42−7.36 (d, 1H, *J* = 11.0), 7.24−7.10 (q, 1H, *J* = 14.8, 11.0), 4.53 (s, 2H), 2.89−2.77 (q, 2H, *J* = 14.4, 7.2), 1.23−1.14 (t, 3H, *J* = 7.2). **10**: δ 8.06−8.01 (q, 1H, *J* = 8.2, 1.2), 7.81−7.49 (m, 4H), 7.42−7.35 (d, 1H, *J* = 11.2), 7.24−7.10 (q, 1H, *J* = 13.2, 11.2), 4.51 (s, 2H), 2.47 (s, 3H). **^{13}C NMR Data, Table 1 (125 MHz, $CDCl_3$). 1**: δ 197.3, 143.6, 136.9, 134.0, 129.8, 129.5, 128.8, 37.5, 25.8. **2**: δ 197.1, 142.7, 137.1, 134.1, 129.0, 129.6, 128.8, 37.4, 25.1. **3**: δ 197.1, 141.4, 138.9, 133.3, 131.1, 131.1, 130.0, 128.8, 126.8, 126.7, 126.4, 125.4, 123.9, 38.0, 26.2. **4**: δ 199.4, 148.0, 140.6, 139.2, 138.9, 130.1, 124.0, 37.1, 31.2, 8.2. **5**: δ 196.7, 147.0, 140.3, 137.7, 134.1, 130.5, 130.2, 125.2, 37.0, 26.0. **6** δ 197.0, 141.4, 138.8, 137.6, 129.6, 125.9, 125.8, 125.8, 37.0, 25.0. **7**: δ 197.3, 161.0, 143.8, 134.9, 131.9, 126.5, 114.4, 55.3, 37.9, 25.7. **8**: δ 196.8, 149.1, 138.2, 35.5, 31.8, 29.4, 29.4, 29.3, 29.2, 28.4, 25.4, 22.6, 14.0. **9**: δ 199.2, 148.0, 140.6, 136.9, 136.8, 133.4, 131.3, 129.6, 128.6, 127.6, 124.6, 35.7, 30.6, 8.2. **10** δ 196.6, 148.1, 141.9, 137.6, 137.2, 133.5, 131.4, 129.8, 128.7, 127.6, 125.0, 35.4, 25.6.