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Metalation of Iminium Ions Formed in the Reaction of Tertiary Amines with $TiCl_4$

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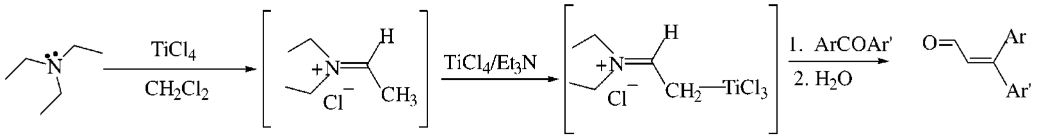
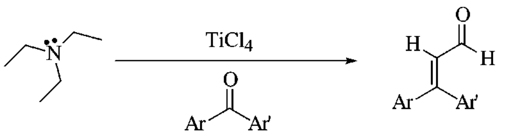
ABSTRACT



$TiCl_4$ reacts with trialkylamines at 0–25 °C to give iminium ions that on metalation followed by reaction with diaryl ketones, produce α,β-unsaturated aldehydes.

The $TiCl_4/R_3N$ reagent system has been extensively used in the preparation of titanium enolates for application in aldol reactions.[1] Also, it has been used for the oxidative coupling of phenylacetic acid esters and amides to obtain the corresponding 2,3-diphenylsuccinic acid derivatives.[2]

Previously, we examined the use of the $TiCl_4/Et_3N$ reagent system for the oxidative coupling of aryl methyl ketimines to 2,5-diarylpyrroles[3a] and for the direct metalation of 1-alkynes.[3b] Herein, we report that the reaction of trialkylamines with $TiCl_4$ gives iminium ions which undergo metalation followed by reaction with diaryl ketones to produce the corresponding α,β-unsaturated aldehydes (eq 1).



(1)

This transformation was examined with various aromatic ketones and benzaldehyde. It was found to be general, and the results are summarized in Table 1.[4] The symmetric diaryl ketones, **1−4** and **7**, produced the corresponding α,β-unsaturated aldehydes in good yields. The unsymmetric ketone, 4-methylbenzophenone (**6**), gave a 1:1 mixture of *E*

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(2) (a) Matsumara, Y.; Nishimura, M.; Hiu, H.; Watanabe, M.; Kise, N. *J. Org. Chem.* **1996**, *61*, 2809.

(3) (a) Periasamy, M.; Srinivas, G.; Bharathi, P. *J. Org. Chem.* **1999**, *64*, 4204. (b) Bharathi, P.; Periasamy, M. Unpublished results.

(4) **Representative Procedure for the Reaction of Diaryl Ketones.** In DCM (25 mL), benzophenone (0.456 g, 2.5 mmol) and $TiCl_4$ (2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$, 10 mmol) were taken at 0 °C under N_2. The Et_3N (1.4 mL, 10 mmol) was added to this solution and stirred for 0.5 h at 0 °C. It was stirred further at 25 °C for 8 h. A saturated NH_4Cl solution (20 mL) was added and stirred for 0.5 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. The unreacted ketone was eluted using 2:98 EtOAc/hexane mixture. The aldehyde **1a**, 3,3-diphenyl-2-propenal, was separated using 4:98 EtOAc/hexane mixture as eluent (0.374 g, 72%). **Procedure for the Reaction of Benzaldehyde.** In DCM (25 mL), $TiCl_4$ (2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$, 10 mmol) was taken, and the Et_3N (1.4 mL, 10 mmol) was added at −78 °C under N_2. The contents stirred at −78 °C for 1 h. Benzaldehyde (1.02 mL, 10 mmol) was added at −78 °C. The contents were brought to 25 °C in 1 h and stirred further for 2 h. A saturated NH_4Cl (20 mL) solution was added and stirred for 0.5 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was chromatographed on a silica gel column. The unreacted benzaldehyde was eluted using 2:98 EtOAc/hexane mixture. The cinnamaldehyde was separated using 4:98 EtOAc/hexane mixture as eluent (0.607 g, 46%).

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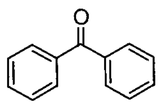
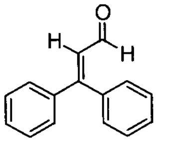
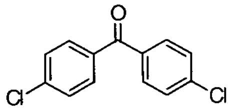
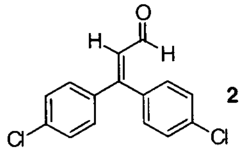
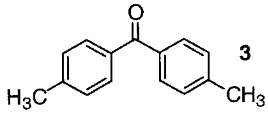
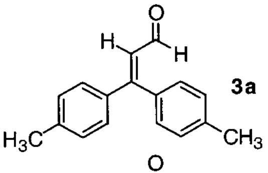
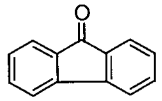
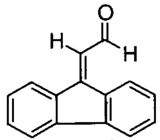
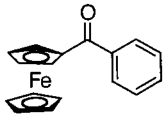
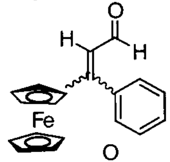
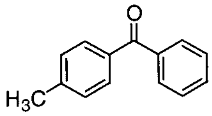
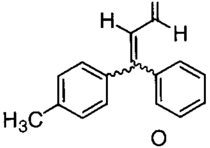
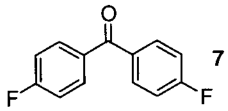
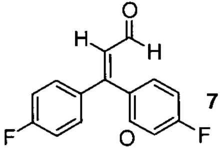
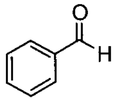
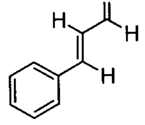
Table 1. Reaction of Diaryl Ketone/Aldehyde with $TiCl_4/Et_3N$

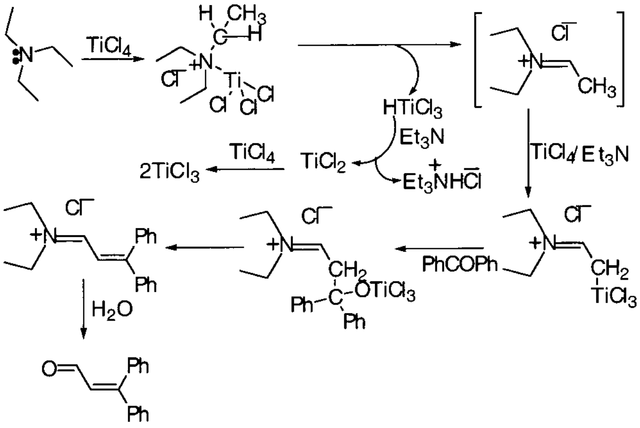
No.	Substrate	Product	Yield %
1.	 **1**	 **1a**	78
2.	 **2**	 **2a**	82
3.	 **3**	 **3a**	74
4.	 **4**	 **4a**	58
5.	 **5**	 **5a**	76
6.	 **6**	 **6a**	72
7.	 **7**	 **7a**	85
8.	 **8**	 **8a**	46

[a] The products were identified by ^1H,^{13}C-NMR and mass spectral data.[8]
[b] The yields are based on the ketone/aldehyde used.

and *Z* isomers. However, the ferrocenyl phenyl ketone (**5**) gave only one isomer. In the case of flourenone (**4**), the McMurry coupling product 9,9′-bifluorene (4%) was also isolated. The benzaldehyde yielded cinnamaldehyde in addition to some unidentified polar compounds.

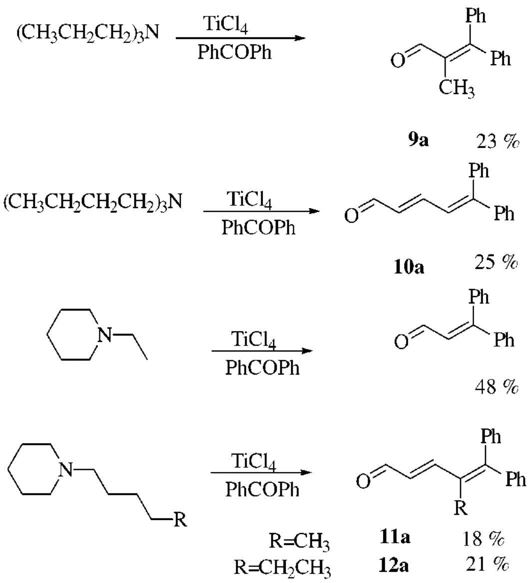
In 1955, it was reported that the reaction of $TiCl_4$ with $N(CH_3)_3$ leads to "$(CH_3)_2NCH_2Cl$" and $TiCl_3$.[5] Accordingly, this transformation may be explained by the tentative mechanistic pathway involving iminium ion intermediate as outlined in Scheme 1. The reaction of $TiCl_4$ with trialkylamine may proceed with the initial formation of an amine–$TiCl_4$ complex. Elimination of β-hydrogen from the amine moiety of this complex would produce the iminium ion species that on metalation followed by reaction with diaryl ketone would give the product as shown in Scheme 1. There is precedence for such processes in the Pd(II)[6] and Hg(II)[7] chemistry.

Scheme 1



We have also examined this transformation using other tertiary amines (Scheme 2). Whereas the Et_3N gave good yields of the aldehydes, other amines produced the aldehydes in low yields. However, the reaction of tributylamine is interesting since there is further dehydrogenation. Presumably, the initially formed iminium ion undergoes metalation

Scheme 2



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(6) (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principle and application of organotransition metal chemistry*; University Science Books: Mill Valley, 1987; p 725. (b) McCrindle, R.; Ferguson, G.; Arsenault, G. J.; McAlees, A. J.; Stephenson, D. K. *J. Chem. Res. (S)* **1984**, 360.

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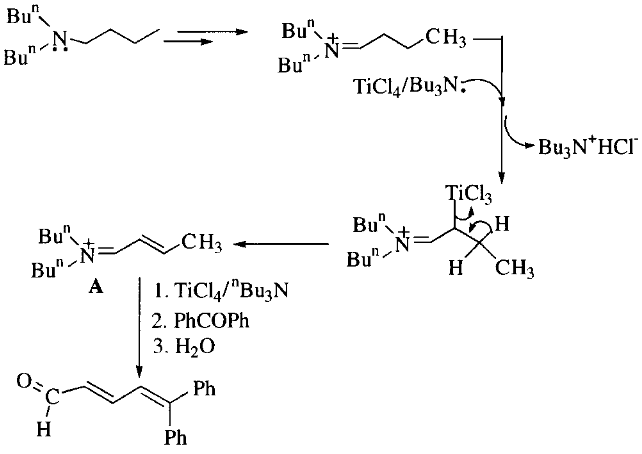
followed by elimination of "HTiCl$_3$" to give the conjugated iminium ion **A** which on further reactions produces the corresponding aldehyde (Scheme 3). Similar results were also realized with some *N*-alkyl piperidine derivatives (Scheme 2).

Scheme 3



We have also observed that the reaction of TiCl$_4$ with tribenzylamine gives dibenzylamine (22%) and benzaldehyde (18%) under these conditions. This observation further illustrates the formation of iminium ion intermediates.

In conclusion, the iminium ions and the corresponding novel metalated iminium species reported here have good potential for further synthetic applications.

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Supporting Information Available: ^{13}C NMR spectra of compounds **1a**−**12a** and ^{1}H NMR spectra of compounds **1a**, **5a**, **6a**, and **9a**−**12a.** This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) **1a**: ^{13}C NMR (δ ppm) 193.02, 161.91, 139.77, 136.79, 130.68, 130.43, 129.40, 128.62, 128.36, 127.37; ^{1}H NMR (δ ppm) 6.6 (d, 1H), 7.2−7.6 (m, 10H), 9.5 (d, 1H); M^{+} (e/m) 208. **2a**: ^{13}C NMR (δ ppm) 192.41, 159.18, 137.81, 136.94, 136.02, 134.66, 131.93, 129.80, 129.05, 128.88, 127.76; ^{1}H NMR (δ ppm) 6.6 (d, 1H), 7.25−7.6 (m, 8H), 9.55(d, 1H); M^{+} (e/m) 277. **3a**: ^{13}C NMR (δ ppm) 193.30, 162.25, 140.84, 139.51, 137.20, 134.05, 130.78, 129.33, 128.98, 128.69, 126.53, 21.28; ^{1}H NMR (δ ppm) 2.35 (s, 3H), 2.45 (s, 3H), 6.65 (d, 1H), 7.2−7.4 (m, 8H), 9.6 (d, 1H). **4a**: ^{13}C NMR (δ ppm) 190.08, 151.12, 142.68, 141.08, 138.50, 135.00, 131.48, 131.38, 127.94, 127.59, 122.93, 122.30, 120.47, 120.12; ^{1}H NMR (δ ppm); 6.8 (d, 1H), 7.2−7.4 (m, 8H), 10.8 (d, 1H); M^{+} (e/m) 206. **5a**: ^{13}C NMR (δ ppm) 192.56, 165.28, 136.52, 129.38, 128.72, 128.02, 124.24, 81.99, 71.63, 70.23, 69.01; ^{1}H NMR (δ ppm) 4.28−4.5 (m, 9H), 6.5 (d, 2H), 7.25−7.55 (m, 5H), 9.35 (d, 1H); M^{+} (e/m) 316. **6a**: ^{13}C NMR (δ ppm) 193.33, 162.29, 162.13, 140.99, 140.06, 139.68, 136.90, 133.85, 130.84−126.59, 21.35; ^{1}H NMR (δ ppm) 2.39 (s, 3H), 2.44 (s, 3H), 6.57 (d, 1H), 6.61 (d, 1H), 7.20−7.46 (m, 18H). **7a**: ^{13}C NMR (δ ppm) 192.42, 166.70, 166.01, 161.70, 161.02, 159.47, 135.77, 132.58, 132.41, 131.28, 130.64, 130.46, 129.83, 129.67, 127.41, 116.00, 115.85, 115.57, 115.42, 114.84, 114.29, 114.28; ^{1}H NMR (δ ppm) 6.5 (d, 1H), 7−7.4 (m, 8H), 9.45 (d, 1H); M^{+} (e/m) 244. **8a**: ^{13}C NMR (δ ppm) 193.55, 152.65, 134.05, 131.23, 129.09, 128.51; ^{1}H NMR (δ ppm) 6.7 (d, 1H), 6.8 (d, 1H), 7.3−7.7 (m, 5H), 9.75, (d, 1H). **9a**: ^{13}C NMR (δ ppm) 194.12, 159.33, 140.87, 138.90, 135.30, 131.17, 129.61, 128.92, 128.66, 128.26, 128.11, 14.26 (data of DEPT experiments correspond to the structure); ^{1}H NMR (δ ppm) 2.0 (s, 3H), 7.2−7.5 (m, 10H), 9.6 (s, 1H); M^{+} (e/m) 222. **10a**: ^{13}C NMR (δ ppm) 193.70, 153.07, 149.62, 140.85, 138.37. 132.50, 130.37, 129.24, 128.66, 128.50, 128.28, 125.27 (data of DEPT experiments correspond to the structure); ^{1}H NMR (δ ppm) 6.25 (d, 1H), 6.35 (d, 1H), 6.95 (d, 1H), 7.2−7.65 (m, 11H), 9.48 (d, 1H); M^{+} (e/m) 234. **11a**: ^{13}C NMR (δ ppm) 194.35, 153.77, 151.94, 141.82, 141.08, 130.63, 129.83, 129.17, 128.15, 127.87, 17.04; ^{1}H NMR (δ ppm) 2.0 (s, 3H), 6.35 (d, 1H), 6.45 (d, 1H), 9.55 (d, 1H 1H), 7.2−7.6 (m, 10H), 9.55 (s, 1H); M^{+} (e/m) 248. **12a**: ^{13}C NMR (δ ppm) 194.52, 152.49, 151.50, 141.96, 141.08, 136.89, 130.48, 129.11, 128.95, 128.27, 128.17, 127.75, 23.43, 14.08 (data of DEPT experiments correspond to the structure);^{1}H NMR (δ ppm) 1.2 (t, 3H), 2.45 (q, 2H), 6.4 (d, 1H), 6.35 (d, 1H) 7.2−7.5 (m, 10H), 9.5 (s, 1H); M^{+} (e/m) 262.