Pergamon

Tetrahedron Letters 40 (1999) 4227–4230

TETRAHEDRON LETTERS

Catalytic TMSCl Promoted Powerful Aldol Addition and Claisen Condensation Mediated by $TiCl_4/Bu_3N$ Agent: Comparison and Evaluation with the Mukaiyama Aldol Addition

Yoshihiro Yoshida, Noriaki Matsumoto, Ryota Hamasaki, and Yoo Tanabe*

School of Science, Kwansei Gakuin University, 1-1-155 Uegahara, Nishinomiya, Hyogo 662-8501, Japan

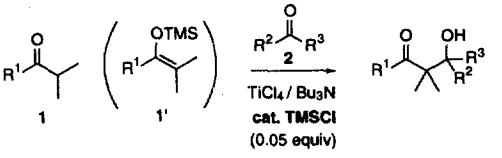
Received 22 February 1999; revised 23 March 1999; accepted 26 March 1999

Abstract: TMSCl catalyst (0.05 equiv) signifiantly promoted the $TiCl_4/Bu_3N$-mediated direct cross aldol additions of sterically crowded ketones and α-hetero substituted ketones, and also the direct Claisen condensation between methyl esters.

$TiCl_4$-mediated aldol additions,[1] originally called the Mukaiyama aldol reaction,[2] have attained a prominent position in the wide field of organic syntheses. In view of the restrictions during the expanding elaborate syntheses of complex organic compounds, the research on more efficient methods has become increasingly significant. We report here one of the most powerful protocols for *direct* cross aldol additions and the related Claisen condensation using $TiCl_4/Bu_3N$ promoted by *catalytic* TMSCl (0.05 equiv).

Initial comparison experiments were guided by the nonaccessible cross aldol coupling using sterically crowded and less reactive α, α-dimethylketones **1**. Actually, the effectiveness of the co-existing TMSCl catalyst was demonstrated as shown in Table 1. It is worth noting that the $TiCl_4/Bu_3N$ direct method (A) using **1**,[3] and the original Mukaiyama aldol addition (B)[2a] or the related titanium trichloride enolate reaction (C)[4] using the enol silyl ether of ketones **1'**, which rank hitherto as the most powerful system, however, were inferior in every case in Table 1.[5] Meanwhile, both the reactions using $Sn(OTf)_2$/*N*-ethylpiperidine[6] and Bu_2BOTf/*i*-Pr_2NEt,[7] which are efficient direct cross aldol addition systems, failed to proceed (no reaction) in the case of entry 1.

Table 1. Direct cross aldol reactions of α, α-dimethylketones **1** using $TiCl_4/Bu_3N$/cat. TMSCl.[a)]



1 1'

entry	R^1	R^2	R^3	time / h	Yield / %	(Yield / %; A, B, C)[b)]
1[c)]	*i*-Pr	*i*-Pr	H	0.5	87[d)]	(54, 71, 57)
2[e)]	*i*-Pr	*t*-Bu	H	16.5	51	(44, trace, trace)
3[c)]	*i*-Pr	Ph	H	2.0	98	(81, 46, 75)
4[c)]	Ph	*i*-Pr	H	0.5	73	(59, 58, 44)
5[e)]	*i*-Pr	*n*-Hex	Me	2.5	42	(35, --, trace)

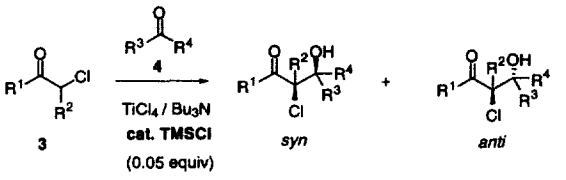
a) These reactions were carried out in CH_2Cl_2 at 0-5 °C. b) A; $TiCl_4/Bu_3N$ method without TMSCl. B; Mukaiyama aldol reaction ($TiCl_4$ was added into the mixture of **1'** and **2**). C; $TiCl_3$-enolate method ($TiCl_4$ and **2** were successively added into **1'**). c) Molar ratio / **1** : **2** : $TiCl_4$: Bu_3N = 1 : 1.2 : 1.2 : 1.4. d) In the place of Bu_3N; Et_3N (64%), *i*-Pr_2NEt (53%), and TMEDA (trace). e) **1** : **2** : $TiCl_4$: Bu_3N = 1 : 1.2 : 1.5 : 2.0.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00682-6

Encouraged by the results, we next evaluated this protocol for the reaction of α-hetero substituted ketones, not only because these are important substrates for obtaining multi-functionalized aldols, but because preparations of these enol silyl ethers are quite limited. Table 2 lists these results in the case of α-chloroketones **3**.[8] The salient features are as follows: [a] The presence of the TMSCl catalyst (0.05 equiv) had a dramatic effect on the reaction of α-chloroacetophenone (**3a**) and significantly enhanced higher yields and *syn*-selectivities in the cases using α-chloropropiophenone (**3b**) and α-chloropinacolone (**3c**); [b] An equimolar amount of TMSCl or 0.05 equiv of TMSOTf showed a somewhat reduced yield in the case of **3a** with PhCHO; [c] The cross coupling between α-chloroketones **3a**, **3c** and diethylketone was also performed, wherein Bu_3N was superior to Et_3N; and [d] ^{13}C NMR characterization supported the speculation that TMSCl effectively contributed to the smooth enolate formation of α-chloroacetophenone.[9]

The obtained *syn*-α-chloroaldols are worthwhile precursors for preparing the normally nonaccessible and thermodynamically unfavorable *cis*-α,β-epoxyketone[10] and would be a promising intermediate for the radical-type manipulation through reductive dechlorination.[11]

Table 2. Direct aldol addition of α-chloroketones (**3**) using $TiCl_4/Bu_3N$/cat. TMSCl.[a]

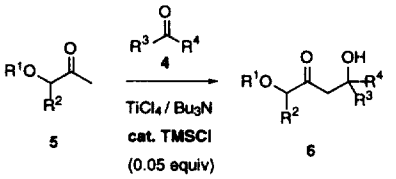


Substrate	R^1	R^2	R^3	R^4	Yield /% (/%)[b]	*syn/anti*[c]
3a	Ph	H	Ph	H	81 (trace)	89:11
3a	Ph	H	Ph	H	63[d] (trace)	91:9
3a	Ph	H	Ph	H	48[e] (trace)	88:12
3a	Ph	H	Bu	H	71 (trace)	94:6
3a	Ph	H	Et	Et	66 (trace)	--
3a	Ph	H	Et	Et	15[f] (trace)	--
3b	Ph	Me	*i*-Pr	H	63 (36)	92:8 (82:18)
3c	*t*-Bu	H	Ph	H	72 (44)	83:17 (70:30)
3c	*t*-Bu	H	*i*-Pr	H	58 (18)	80:20 (66:34)
3c	*t*-Bu	H	Et	Et	43 (10)	--

a) These reactions were carried out in CH_2Cl_2 at -78 °C for 2-3 h. Molar ratio / **3** : **4** : $TiCl_4$: Bu_3N = 1.0 : 1.2 : 1.4 : 1.2. Parentheses indicate the cases without using TMSCl. b) They were based on the yields of their TMS ethers. c) These ratios were determined by ^1H NMR (400 MHz) of the crude product. d) 1.0 Equiv of TMSCl was used. e) 0.05 Equiv of TMSOTf was used. f) Et_3N was used in the place of Bu_3N. Self coupling aldol of phenacyl chloride was mainly obtained in 79% yield.

Next, we investigated the aldol additions of several α-oxygenated methyl ketones **5**. Table 3 lists these results. In all the cases examined, *catalytic* TMSCl considerably increased the yields of regiocontrolled aldol adducts **6**, among them, a remarkable effect was observed in the cases of pyruvic aldehyde dimethylacetal (**5a**) and *t*-butyldimethylsiloxy acetone (**5c**). The reactions of phenacyl chloride as a basic labile acceptor also smoothly proceeded.

Table 3. Direct aldol addition of α-oxyketones (**5**) using $TiCl_4/Bu_3N$/cat. TMSCl.[a]

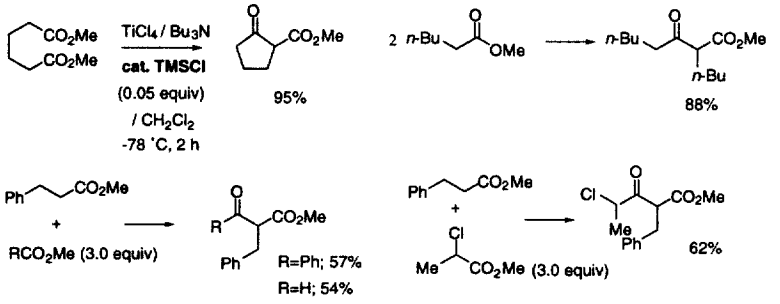


Substrate	R^1	R^2	R^3	R^4	Yield /% (/%)[b]	
5a	Me	MeO	Ph	H	80	(trace)
5a	Me	MeO	Ph	H	67[c]	(trace)
5a	Me	MeO	Bu	H	71	(trace)
5a	Me	MeO	Ph	CH_2Cl	63	(trace)
5b	PhCO	H	Ph	H	86	(68)
5c	TBS	H	Ph	H	78	(23)
5c	TBS	H	Ph	CH_2Cl	94	--

a) These reactions were carried out in CH_2Cl_2 at -78 °C for 2-3 h. Molar ratio / **5** : **4** : $TiCl_4$: Bu_3N = 1.0 : 1.2 : 1.4 : 1.2. b) Parentheses indicate the cases without using TMSCl. c) Et_3N was used in the place of Bu_3N.

Finally, the present agent was successfully applied to the direct and powerful Claisen condensation between methyl esters (Table 4). The reported reaction using the titanium triflate[12] or $TiCl_4$/cat. TMSOTf[3] requires rt-60 °C for completing the reaction. Therefore, it should be noted that the TMSCl catalyst promoted the desired reaction even at -78 °C,[13] which is one of the most powerful methods ever known. Namely, TMSCl showed superior reactivity to TMSOTf. Benzoylation and formylation were also performed. In the last decade, there have appeared a number of TMSCl catalyzed C-C bond forming reactions, wherein TMSCl works as an activator of organometallic reagents or substrates. However, to the best of our knowledge, all known those TMSCl mediated reactions require at least equimolar amount of TMSCl *vs.* the metal reagents and/or substrates.

Table 4. Direct Claisen condensation between methyl esters using $TiCl_4/Bu_3N$/cat. TMSCl.



The role of the *catalytic* TMSCl in the present system is not clarified at present. We presume that TMSCl facilitates smooth enolate generation and/or activates the carbonyl oxygen of acceptors.[14] As another possibility, intermediary formations of enol silyl ethers and ketene silyl acetals are expected. However, this speculation could be ruled out, because these species can hardly be generated under the present acidic conditions.

In conclusion, $TiCl_4$/Bu_3N/catalytic TMSCl conducts some useful C-C bond forming reactions including a powerful aldol addition of α, α-dimethylketones, an aldol addition of α-chloro- or α-oxy-substituted ketones, and the Claisen condensation between methyl esters, wherein *catalytic* TMSCl works as an efficient and consistent activator. Compared with the original $TiCl_4$-mediated Mukaiyama aldol reaction, this method has merits being a direct procedure (not using enol TMS ethers) with higher reactivities. These general and powerful protocols would heighten the practical level of the $TiCl_4$-mediated aldol additions and the Claisen condensation.

Acknowledgment: This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture (Japan). One of the authors (Y. Y) acknowledges Sasakawa Scientific Research Grant from the Japan Science Society.

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(5) The reaction mode of the present method resembles that of trichlorotitanium enolate reaction (C) rather than the original Mukaiyama aldol addition (B), judging from the stereochemical results of cyclohexanone with benzaldehyde (79%; *syn* : *anti* = 95:5).

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(8) Since these α-chloroaldol adducts were relatively unstable, these yields were based on their TMS-ethers, which were obtained by nearly neutral trimethylsilylation using TMS-imidazole/catalytic TBAF (Tanabe, Y.; Murakami, M.; Kitaichi, K.; Yoshida, Y. *Tetrahedron Lett.* **1994**, *35*, 8409). For example, 3-hydroxy-2-chloro-1,3-diphenyl-1-propanone: $TiCl_4$ (1M-CH_2Cl_2; 1.2 ml) was added to a stirred solution of phenacyl chloride (**1a**; 155 mg, 1.0 mmol) in CH_2Cl_2 (2.0 ml) at -78 °C under an Ar atmosphere. TMSCl (5 mg, 0.05 mmol) and Bu_3N (259 mg, 1.4 mmol) was successively added to the mixture, which was stirred for 30 minutes. Then, benzaldehyde (127 mg, 1.2 mmol) was added to the mixture followed by being stirred at -78 °C for 2 h. The mixture was quenched with water (10 ml), extracted twice with ether. The organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. To the obtained crude oil (282 mg) was added *N*-TMS-imidazole (281 mg, 2.0 mmol) and TBAF (1M-THF; 0.02 ml). The mixture was allowed to stand for 10 min. at room temp., then, was quenched with water (10 ml) and the organic phase was extracted twice with ether, washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude oil was purified by SiO_2-column chromatography (hexane-AcOEt = 14:1) to give 2-chloro-1,3-diphenyl-3-trimethylsiloxy-1-propanone (268 mg, 81 %). ^1H NMR (400 MHz) [*syn*-isomer] δ 0.21 (9H, s), 5.22 (1H, d, J = 8.0 Hz), 5.26 (1H, d, J = 8.0 Hz), 7.22-7.99 (10H, m); [*anti*-isomer] δ -0.15 (9H, s), 5.08 (1H, d, J = 9.2 Hz), 5.16 (1H, d, J = 9.2 Hz), 7.22-7.99 (10H, m).

(9) ^{13}C NMR (400 MHz) of three independent experiments with three molar ratios (**3a** : $TiCl_4$: Bu_3N : TMSCl = 1.0 : 1.0 : 1.0 : 0.0, 0.5, and 1.0) in CD_2Cl_2 at -78 °C showed progressive appearance of enol carbon peak (δ 135.85 and 151.20) of the titanium enolate.

(10) a) Mukaiyama, T.; Haga, T.; Iwasawa, N. *Chem. Lett.* **1982**, 1601. b) Mukaiyama, T.; Yura, T.; Iwasawa, N. *Chem. Lett.* **1985**, 809.

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(13) A typical procedure is as follows. $TiCl_4$ (1M-CH_2Cl_2; 1.2 ml) was added to a stirred solution of methyl 3-phenylpropionate (164 mg, 1.0 mmol) and methyl benzoate (408 mg, 3.0 mmol) in CH_2Cl_2 (2.0 ml) at -78 °C under an Ar atmosphere. TMSCl (5 mg, 0.05 mmol) and Bu_3N (259 mg, 1.4 mmol) was successively added to the mixture, which was stirred for 2 h. Usual work up and purification by SiO_2 column chromatography (hexane-AcOEt = 8:1) gave methyl 2-benzyl-3-oxo-3-phenylpropionate (216 mg, 81%).

(14) Related speculation was reported: Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1987**, 463.