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$TiCl_4/Bu_3N$/(catalytic TMSOTf): Efficient Agent for Direct Aldol Addition and Claisen Condensation

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***Abstract*:** $TiCl_4/Bu_3N$ conducts highly efficient cross aldol additions between different ketones and between ketones and aldehydes, in good to excellent yields with high *syn*-stereoselectivities. As an extension, direct Claisen condensation between methyl esters was also promoted by $TiCl_4/Bu_3N$ with 0.05 equiv of TMSOTf co-catalyst.

Among the numerous elaborated aldol-type addition reactions,[1] $TiCl_4$/amine-mediated systems (Evans protocol) have great merits in their efficiency: direct (straightforward) procedure, operational simplicity and accessibility, mild conditions, and its high level of diastereo- and enantioselective version.[2] The amine base employed in conjunction with $TiCl_4$ has been limited to Et_3N, *i*-Pr_2NEt, and TMEDA. In order to brush up this reaction we directed our attention to the use of another amine whose method was guided by the fundamental aldol addition of ketones and aldehydes. Consequently, an improved $TiCl_4/Bu_3N$ reagent demonstrates several significant advantages in enhanced *syn*-stereoselectivities, especially, in the performance of the cross coupling between two different ketones. To our knowledge, the general method for this ketone-ketone direct cross coupling is limited to the $Sn(OTf)_2$/amine mediated aldol additions.[3] In addition, we extended the present method to the direct Claisen condensation between methyl esters promoted by $TiCl_4/Bu_3N$ with catalytic TMSOTf.[4]

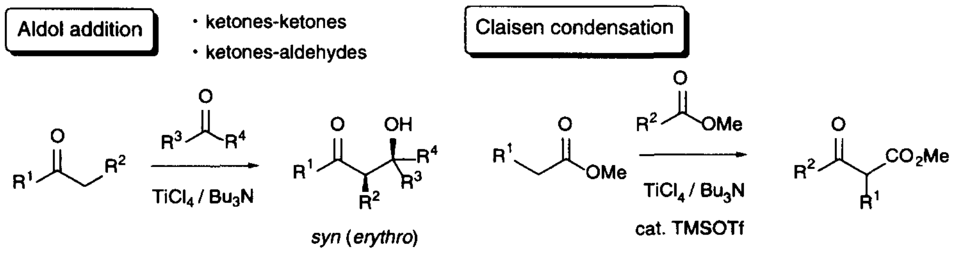
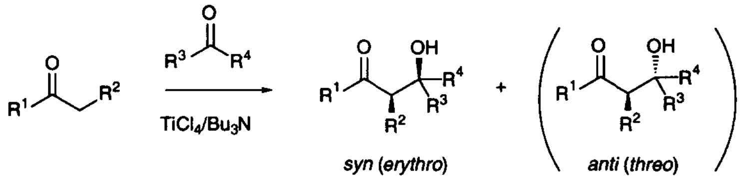


Table 1 lists the cross aldol additions between two different ketones (entries 1-11) and between ketones and aldehydes (entries 12-19) employing the $TiCl_4/Bu_3N$ reagent.[5] Their notable features are demonstrated as follows: [1] the use of Bu_3N successfully promoted the reaction between two different ketones, including aliphatic ketones (entries 10 and 11);[6] [2] when Et_3N, *i*-Pr_2NEt, and TMEDA were used for the reactions of entries 2 and 7, the yields were much lower in every case (conversion <20% under the identical conditions); [3] consistent *syn* (*erythro*)-stereoselectivity was observed[7] in clear contrast to the method using $Sn(OTf)_2$/amine, wherein the selectivity varies from *syn* to *anti* depending on the nature of carbonyl acceptors;[3] [4] α-chloro or α-benzoyloxy acetophenone, a basic labile substrate, could tolerate the reaction conditions (entries 5 and 6); and

[5] this method is also applicable to the conventional couplings between ketones and aldehydes with very higher *syn* (*erythro*)-stereoselectivity.

Table 1 $TiCl_4/Bu_3N$-Promoted Direct Aldol Addition between Ketones and Ketones or Aldehydes.[a]



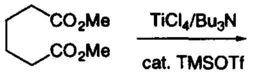
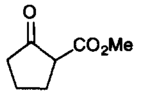
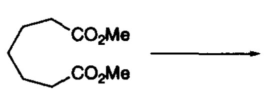
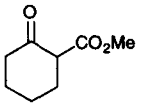
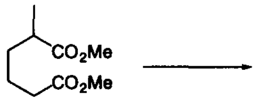
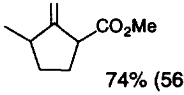
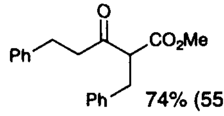
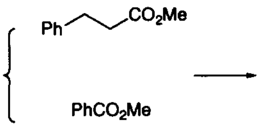
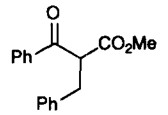
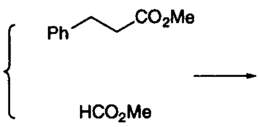
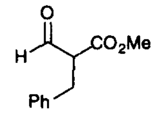
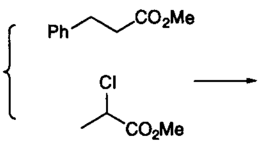
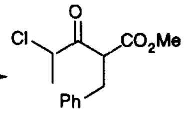
Entry	R^1	R^2	R^3	R^4	Yield/%[b]	*syn*/*anti*[b,c]
1	Ph	H	Ph	Et	61	--
2	Ph	Me	Ph	Me	95 (60)	~100:0 (~0:100)
3	Ph	Me	Et	Et	86 (60)	--
4	Ph	Me	*n*-Pr	*n*-Pr	81	--
5	Ph	Me	Ph	CH_2Cl	91	~100:0
6	Ph	CH_2OCOPh	$-CH_2CH_2CH_2-$		96 (96)	
7	Et	Me	Ph	Me	84 (45)	84:16[d] (13:87)
8	Et	Me	Ph	Et	92	72:28[d]
9	*n*-Pr	Et	Ph	Me	72	~100:0
10[e]	*n*-Pr	Et	*n*-Hept	Me	60	60:40
11	$-CH_2CH_2CH_2-$		Et	Et	71	--
12	Ph	H	*i*-Pr	H	72	--
13	Ph	Me	Ph	H	72 (71)	~100:0 (>95:5)
14	Ph	Me	*n*-Pr	H	96 (74)	~100:0 (86:14)
15	Ph	Me	*i*-Pr	H	95 (80)	~100:0 (91:9)
16	Et	Me	*n*-Hept	H	88 (86)	~100:0
17[f]	Et	Me	*i*-Pr	H	73 (73)	~100:0 (93:7)
18	*n*-Pr	Et	*n*-Pr	H	83	~100:0
19	$-CH_2CH_2CH_2-$		Ph	H	48 (41)	~100:0 (>95:5)

a) These reactions were carried out in CH_2Cl_2 at -78 °C for 2-3 h unless otherwise noted. Molar ratio / ketone : $TiCl_4$: Bu_3N : ketone or aldehyde (acceptor) = 1.0 : 1.2 : 1.4 : 1.2. b) Parentheses indicate the reported data for the case using $Sn(OTf)_2$/*N*-ethylpiperidine.[3] c) These ratios were determined by ^1H NMR (400 MHz) of the crude product unless otherwise noted. d) These ratios were determined by isolated yields. e) This reaction was carried out at -78 °C for 2 h and at room temp. for 2 h. f) Reported data for the case using $TiCl_4$/amine: *i*-Pr_2NEt (95%, 92:8) and Et_3N (73%, 87:13).[2c]

Next, we planned to apply the $TiCl_4/Bu_3N$ reagent to the Claisen condensation between methyl esters. The $TiCl_2(OTf)_2/Et_3N$ reagent mediates the Claisen condensation (intramolecularly, the Dieckmann condensation) between methyl esters, however, a major drawback of this method is the use of an equimolar amount of the metal triflate.[4] Therefore, catalytic use of triflate species should make it more practical and accessible. Thus,

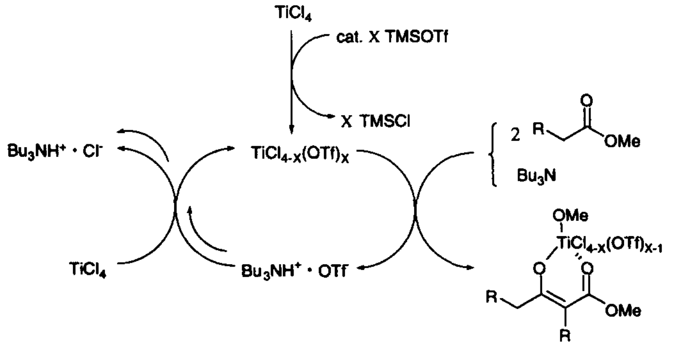
$TiCl_4/Bu_3N$/catalytic TMSOTf (0.05 equiv) was found to be an efficient alternative. These results are listed in Table 2.

Table 2 $TiCl_4/Bu_3N$/catalytic TMSOTf Promoted Direct Claisen Condensation between Methyl Esters.[a)]

Entry	Substrate	Product	Yield/%[b)]
1			91% (80%)
2			60% (51%)
3			74% (56%)
4			74% (55%)
5[c)]			73% (71%)
6[c)]			54% (52%)
7			73%

a) These reactions were carried out in toluene at room temp. for 2-3 h unless otherwise noted. Molar ratio / ester : $TiCl_4$: Bu_3N : TMSOTf : (ester acceptor) = 1.0 : 3.0 : 4.5 : 0.05 : (3.0). b) Parentheses indicate the reported data for the case using $TiCl_2(OTf)_2/Et_3N$. c) These reactions were carried out in toluene at 60 °C for 5-6 h.

Their notable features are described as follows: [1] higher yields were obtained compared to those using $TiCl_2(OTf)_2$ in every example; [2] use of other amines are somewhat inferior in yields in the reaction of dimethyl adipate (entry 1);[9] [3] The yield lowered (50%) by using HOTf in the place of TMSOTf in the reaction for entry 1. This catalytic method is considered to have a practical advantage compared to the original method. We would like to propose the mechanism of the present catalytic reaction in the case of the self-coupling of the methyl esters as illustrated below. Titanium triflate catalyst species, $TiCl_{4-x}(OTf)_x$,[10] would play a major role for the condensation. The reason for the superior action of Bu_3N on both the reactions is not so clear at present.[11]



In conclusion, we performed efficient and general methods for the direct aldol addition reaction and the Claisen condensation. Further extension utilizing $TiCl_4/Bu_3N$ with or without catalytic TMSOTf system is now under way.

Acknowledgment: This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture (Japan). We thank Profs. Masahiko Yamaguchi (Tohoku Univ.) and Nobuharu Iwasawa (Tokyo Univ.) for their helpful discussions.

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5. A typical procedure (Table 1, entry 2): $TiCl_4$ (1M CH_2Cl_2 solution; 1.2 ml) and Bu_3N (185 mg, 1.4 mmol) were successively added to a stirred solution of propiophenone (134 mg, 1.0 mmol) in CH_2Cl_2 (2.0 ml) at -78 °C under an Ar atmosphere. After 30 min, acetophenone (144 mg, 1.2 mmol) was added and the mixture was stirred at -78 °C for 2 h. The reaction mixture was quenched with water. Usual work up and purification by SiO_2 column chromatography (hexane-AcOEt = 9:1) gave 3-hydroxy-2-methyl-1,3-diphenyl-1-butanone (241 mg, 95 %). Colorless oil, ^1H NMR (400 MHz, $CDCl_3$) $\delta = 1.01$ (3H, d, $J = 7.2$ Hz), 1.56 (3H, s), 3.86 (1H, q, $J = 6.8$ Hz), 7.25-7.66 (8H, m), 8.02-8.04 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ=13.84, 30.02, 48.67, 75.36, 124.84, 126.58, 128.12, 128.38, 128.90, 133.90, 145.91. This spectral data shows *syn* (*erythro*) isomer, compared with the reported data of the *anti* (*threo*) isomer.[3]
6. This direct cross coupling between different aliphatic ketones may be the first example.
7. We presently speculate that Ti(IV) forms more a rigid 6-membered chair transition state leading to the *syn*-aldol compared with Sn(II) due to the strong Lewis acidity of Ti(IV). Stereochemical considerations of the titanium enolates with aldehydes is extensively studied. a) Refs. 2a and 2c. b) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343.
8. A typical procedure (Table 2, entry 7): $TiCl_4$ (1M toluene solution; 3.0 ml) was added to a mixture of methyl 3-phenylpropionate (164 mg, 1.0 mmol) and methyl 2-chloropropionate (368 mg, 3.0 mmol) in toluene (2.0 ml) at rt under an Ar atmosphere. Then, TMSOTf (11 mg, 0.05 mmol) and Bu_3N (834 mg, 4.5 mmol) were successively added to the mixture, which was stirred at room temp. for 2.5 h. Usual work up and purification by SiO_2 column chromatography (hexane-AcOEt = 12:1) gave methyl 2-benzyl-4-chloro-3-oxopentanoate (185 mg, 73 %).
9. Under the identical conditions, the yields are as follows: Et_3N (80%), i-Pr_2NEt (78%), and *N*-ethylpiperidine (69%).
10. Titanium triflates are used for useful acylation-type reactions: a) Izumi, J.: Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1995**, 141. b) Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 267. c) Tanabe, Y.; Mukaiyama, T. *Chem. Lett.* **1985**, 673. d) Tanabe, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3309.
11. We presume that Bu_3N more smoothly generate the Ti enolates of ketones compared with i-Pr_2NEt and Et_3N. The following comparable experiments are suggestive. When the order of addition of reagents and substrates was changed ($TiCl_4$, amine, propiophenone, acetophenone), the results were as follows: (i-Pr_2NEt) propiophenone and acetophenone were almost recovered; (Et_3N) self coupling of propiophenone considerably occurred; (Bu_3N) the desired cross coupling mainly proceeded, although the yield was somewhat lower (~50%). These facts implies that (1) i-Pr_2NEt formed an irreversible complex with $TiCl_4$ as Evans pointed out in the case of oxazolidone[2b]; (2) Et_3N slowly dissociates to generate the Ti enolate of propiophenone; and (3) In clear contrast, Bu_3N formed a loose and considerably reversible complex with $TiCl_4$. Useful reactions mediated by $SnCl_4/Bu_3N$ reagent are reported. a) Yamaguchi M.; Hayashi, A.; Hirama, M. *J. Am. Chem. Soc.* **1993**, *115*, 3362. b) Yamaguchi M.; Hayashi, A.; Hirama, M. *Chem. Lett.* **1992**, 2479.

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