Aldol Reaction of Enol Esters Catalyzed by Cationic Species Paired with Tetrakis(pentafluorophenyl)borate

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The crossed aldol reaction of enol esters, which are weak carbon nucleophiles, with aldehydes was effectively carried out under mild conditions by using a catalytic amount of several cationic species paired with tetrakis(pentafluorophenyl)borate.

The carbon-carbon bond forming reaction is successfully carried out by treating weakly nucleophilic carbon species with carbonyl compounds using a Lewis acid. For example, the aldol reaction of silyl enol ethers with carbonyl compounds promoted by Lewis acids has been employed in the construction of a wide variety of carbon skeletons.[1] Recently, it was reported[1a] that a catalytic aldol reaction of aldehydes with silyl enol ethers proceeded smoothly to afford aldols using carbocationic species (**1a**) paired with tetrakis(pentafluorophenyl)borate which is known to be a very effective noncoordinating anion of which the countercation exists as a naked one.[2]

1a   **1b**[3]
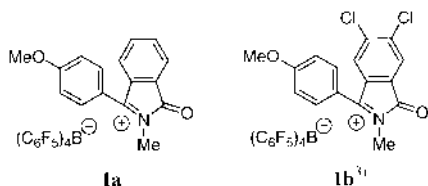
On the other hand, the aldol reaction using enol esters, which are less reactive nucleophiles, is not as common compared with that using silyl enol ethers. One of the most common examples is carried out under basic conditions by generating lithium enolates from enol esters with methyllithium and its subsequent addition to carbonyl compounds.[4] On the other hand, few reports have been published to date concerning the aldol reaction under acidic or neutral conditions using enol esters, which are readily available and act as weak carbon nucleophiles.[5]

It was reported in 1974 that enol acetate reacts with various acetals or benzaldehyde to afford the corresponding aldol-type addition products in good yields using stoichio-

metric amounts of Lewis acids such as $TiCl_4$, $AlCl_3$, $SnCl_4$, $ZnCl_2$, and $BF_3 \cdot OEt_2$ (Chart 1).[5a] In most of the above reactions, a remarkable by-product, β-chloroketone **4**, is formed by subsequent nucleophilic replacement of initially formed aldol acetate **3** with chloride ion originating from the Lewis acids.
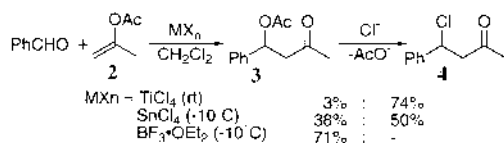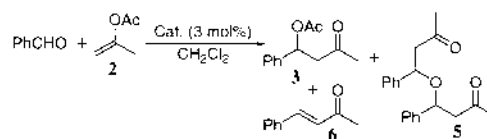
It was thought that if the Lewis acid paired with borate that had no nucleophilicity was employed in the aldol reaction of aldehydes and enol esters, the above-mentioned subsequent nucleophilic substitution by their own anionic species would not take place and the yield of the aldol acylate would thus increase. Therefore the aldol reaction between aldehydes and various enol esters using a catalytic amount of several cationic species paired with tetrakis(pentafluorophenyl)borate was attempted.

First, the catalytic aldol reaction of isopropenyl acetate (**2**) with benzaldehyde was examined using several cationic species paired with the borate mentioned above (see Table 1). A typical experimental procedure is described for the reaction of isopropenyl acetate (**2**) with benzaldehyde: to a suspension of $AgB(C_6F_5)_4$ (0.0075 mmol) in CH_2Cl_2 (0.5 ml) at room temperature TMSCl (0.0075 mmol) was added and the resulting suspension was stirred for 1 h at room temperature and then cooled to 0 °C. To this suspension, a solution of benzaldehyde (0.25 mmol) and **2** (0.75 mmol) in CH_2Cl_2 (1.5 ml) was added dropwise and after the reaction was monitored using thin-layer chromatography, saturated aqueous sodium bicarbonate and CH_2Cl_2 were added at the same temperature, and the organic layer was extracted, washed with

Table 1

Entry	Cat.	Temp./°C	Time/h	Yield/%		
				3	**5**	**6**
1	TMSOTf	−78	1	10	48	0
2	TMSOTf	0	Inst.	73	8	5
3	TMSOTf	r.t.	Inst.	81	2	2
4	$TMSB(C_6F_5)_4$ (**7**)	−78	1	29	32	0
5	$TMSB(C_6F_5)_4$ (**7**)	−45	1	56	25	0
6	$TMSB(C_6F_5)_4$ (**7**)	−28	1	84	4	2
7	$TMSB(C_6F_5)_4$ (**7**)	−15	0.5	85	–	2
8	$TMSB(C_6F_5)_4$ (**7**)	0	Inst.	91	–	0
9	$TMSB(C_6F_5)_4$ (**7**)	r.t.	Inst.	80	–	2
10	$AgB(C_6F_5)_4$	r.t.	0.5	0	0	0
11	TMSCl	r.t.	0.5	0	0	0
12	$SnClB(C_6F_5)_4$	0	1	84	13	1
13	$Sn[B(C_6F_5)_4]_2$	0	0.5	75	12	–
14	$SnCl_3B(C_6F_5)_4$ (**8**)	0	Inst.	94	3	1
15	$TiClB(C_6F_5)_4$	0	1	80	13	2
16	$Ti[B(C_6F_5)_4]_2$	0	0.5	83	10	1
17	$TiCl_3B(C_6F_5)_4$ (**9**)	0	Inst.	92	3	1
18	$(iPrO)_2TiClB(C_6F_5)_4$	0^{a}	2^{a}	71	16	3
19	**1a**[b]	r.t.	1.5	72	9	2
20	**1a**	r.t.	1	91	5	0
21	$TrB(C_6F_5)_4$ (**10**)	r.t.	1	82	–	5

a) The reaction was carried out at 0 °C for 1 h then at room temperature for 1 h. *b)* 1 mol% of catalyst was used.

Chart 1

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brine, and evaporated. The resulting crude product was submitted to silica-gel chromatography to afford the corresponding aldol acetate (91%) as a pale yellow oil (Table 1, Entry 8). Other metal tetrakis(pentafluorophenyl)borates were prepared *in situ* in a manner similar to that described above using the corresponding metal chlorides instead of TMSCl.

It is significant that the ethereal by-product **5** was obtained at lower temperature (below −45 °C, Entries 1, 4, and 5), and thus the yield of the aldol acetate **3** was low. On the other hand, the corresponding aldols were obtained in high yields when the reaction was carried out at 0 °C using 3 mol% of TMS-, Sn(IV)- or Ti(IV) tetrakis(pentafluorophenyl)borate,

or **1a** as a catalyst (Entries 8, 14, 17, and 20, respectively). In the above reactions, neither silver tetrakis(pentafluorophenyl)borate[6] nor chlorotrimethylsilane alone exhibited any catalytic activity (Entries 10 and 11). Next, the scope and limitations of this reaction were investigated using combinations of various enol acetates[7] and aldehydes.

Each cationic species smoothly catalyzed the reaction of the enol ester derived from acetophenone to give the corresponding aldol acetate in high yield (Table 2, Entries 1—5), while the reactions of the α-substituted enol acetates were very weak. The structure of the aldehyde influenced the reactivity of the present reaction: that is, aliphatic aldehydes did not afford any aldol adducts, and even if aromatic aldehyde was used, only the electron-withdrawing group on the aromatic ring afforded the aldol adduct (Table 3). In order to prepare a new catalyst that promotes various aldol reactions, a carbocationic species **1b** was prepared based on the consideration that the carbocationic character would be enhanced by introducing electron-withdrawing atoms onto the aromatic
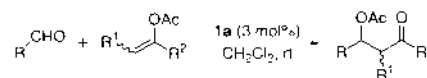
Table 2
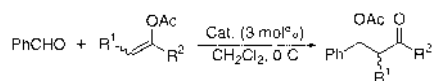
Entry	Enol ester	Cat.	Time/h	Yield/%
1		**7**	Inst.	83
2	OAc / Ph (**11**)	**8**	Inst.	98
3		**9**	Inst.	97
4[a]		**1a**	0.5	92
5[a]		**10**	1	73
6		**7**	1	Trace
7	OAc / Ph (**12**)	**8**	1	Trace
8		**9**	1	Trace
9[a]		**1a**	39	19
10[a]		**1b**	5	48
11		**7**	1	Trace
12	OAc (**13**)	**8**	1	Trace
13		**9**	1	Trace
14[a]		**1a**	48	25
15[a]		**1b**	48	38
16[a]		**10**	5	66

a) The reaction was carried out at room temperature.

Table 3

Entry	R	Enol ester	Time/h	Yield/%
1	4-ClPh	**2**	1.2	72
2[a]		**2**	Inst.	88
3		**11**	1.2	84
4[a]		**11**	Inst.	96
5	4-MeOPh	**2**	15	Trace
6		**11**	15	0
7	PhCH₂CH₂–	**2**	15	0
8		**11**	15	0
9	PhCH=CH–	**11**	22.5	0

a) 3 mol% of **1b** was used as a catalyst instead of **1a**.

Table 4
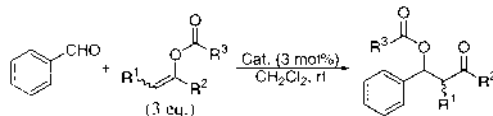
Entry	Enol ester	Cat.	Yield/%[a]				
			1a	**1b**	**7**	**8**	**9**
1		X = OMe	85 (1)	80 (inst.)	91 (inst.)[b]	96 (inst.)[b]	99 (inst.)[b]
2		X = H	84 (1)	94 (inst.)	99 (inst.)[b]	99 (inst.)[b]	97 (inst.)[b]
3		X = CF₃	21 (1)	61 (1)	71 (inst.)[b]	72 (inst.)[b]	79 (inst.)[b]
4		X = OMe	Trace (3)	62 (3)	76 (1)	78 (1)	84 (inst.)
5		X = OMe	93 (5)[c]	95 (1)[c]	36 (1)[b]	32 (1)[b]	71 (1)[b]
6		X = H	41 (48)[c]	82 (3)[c]	Trace (1)[b,d]	Trace (1)[b,d]	Trace (1)[b,d]
7		X = CF₃	0 (48)[c]	0 (48)[c]			

a) The values in parentheses indicate the reaction time (h). b) The reaction was carried out at 0 °C. c) 10 mol% of catalyst was used. d) When the reaction was carried out at room temperature using 10 mol% of each catalyst, the reaction proceeded smoothly to give the corresponding adducts and the yield was 83%, 88%, and 88%, respectively, for catalysts **7**, **8**, and **9**.

ring of the catalyst **1a**. Expectedly, carbocationic species **1b** with two chlorine atoms in its aromatic ring was proved to be a Lewis acid catalyst much stronger than **1a** (Table 2, Entries 10 and 15; Table 3, Entries 2 and 4).

To examine the effect of the acyl moiety on the reactivity of the enol ester, several substituted enol benzoates[7] were employed in the present reaction (Table 4). As shown in Table 4, the yields of the corresponding aldol acylates increased by introducing an electron-donating group into the benzoyl moiety (see Entries 1—3 and 5—7). The more electron-deficient cationic species **1b** gave the adducts in higher yields compared with **1a** (see Entries 1—6).

It is noted that the catalytic crossed-aldol reaction of enol esters, which are weak carbon nucleophiles, with aldehydes was carried out effectively using several cationic species paired with tetrakis(pentafluorophenyl)borate such as $TMSB(C_6F_5)_4$, $SnCl_3B(C_6F_5)_4$, $TiCl_3B(C_6F_5)_4$, **1a**, and **1b**. In addition, the structure-activity relationship of the cationic species was examined using **1a** and **1b**, and it was determined that the more electron-deficient cationic species **1b** had higher catalytic activity than **1a** in the present reaction.

References and Notes

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