Diastereoselective Aldol Reaction of α-Bromo Ketones with Aliphatic Aldehydes by Using Titanium(II) Chloride and Copper

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(Received July 21, 1999; CL-990645)

Highly diastereoselective aldol reaction of α-bromo ketones with aliphatic aldehydes was successfully carried out by using titanium(II) chloride and copper in dichloromethane at low temperature. Similarly, Reformatsky-type reaction of α-bromo thioester with aliphatic aldehydes was promoted under mild conditions to afford β-hydroxy thioesters in good to moderate yields.

Aldol reaction is frequently employed in organic synthesis as one of the most important and useful tools for carbon-carbon bond formation. In general, the reaction is achieved under either basic or acidic conditions by generating active enolates from donor carbonyl compounds or by activating acceptor carbonyl compounds as electrophiles, respectively.

The oxidative metallation of α-halo carbonyl compounds with low-valent metals generates the corresponding metal enolates under nearly neutral conditions as is represented by the Reformatsky reaction.[1] Using a variety of metals or low-valent metals, the Reformatsky and aldol reactions of α-halo carbonyl compounds, i.e. donors, with such metals as Sn,[2] Co,[3] Cr,[4] or Sm[5] were developed and high diastereoselectivities were achieved on treatment with acceptor carbonyl compounds. In these cases, however, there are some limitations known in the preparation of key reducing reagent or in the generality of substrates. Recently, Saigo and co-workers reported that the Reformatsky and aldol reactions of α-halo carbonyl compounds gave the corresponding products with high diastereoselectivities when low-valent germanium reagent, prepared from GeI_2 or $GeCl_4$ with potassium metal, was used.[6]

It was then considered that highly diastereoselective aldol reaction would be achieved if low-valent titanium species were used for the generation of nucleophiles since the reaction of titanium(IV) enolates with aldehydes proceeded to form the corresponding aldols with high diastereoselectivities.[7] Although the aldol reaction of α-halo ketones with aldehydes was already reported to have been promoted by low-valent titanium species generated from catalytic amount of $TiCl_4$ and zinc,[8a] no satisfactory results were obtained concerning the generality of substrates. It was also reported that α,β-unsaturated ketones were produced *via* aldol and successive dehydration reactions of 2-bromoacetophenone with various aldehydes using $TiCl_4$ and KI.[8b] In this reaction, the intermediates were supposed to be titanium enolates, but the reaction conditions were rather severe and the diastereoselectivities were not studied.

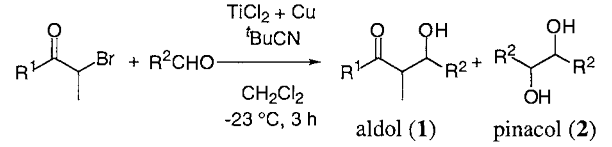
Recently, it was reported from our laboratory that $TiCl_2$ and zinc were efficient reducing reagents for pinacol coupling reaction in dichloromethane with pivalonitrile as an additive.[9] In this communication, we would like to describe a diastereoselective aldol reaction of α-halo ketones with several aliphatic aldehydes by the combined use of $TiCl_2$ and copper.

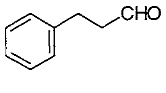
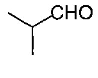
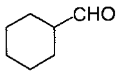
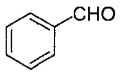
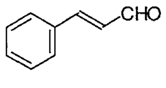
In the first place, aldol reaction of 2-bromoacetophenone with benzaldehyde was tried in the presence of $TiCl_2$ in dichloromethane / pivalonitrile (ca. 10 / 1) at room temperature. The desired aldol was obtained in 26% yield along with two kinds of pinacol coupling products originated from benzaldehyde (8%) and 2-bromoacetophenone (6%). In the above reaction, respective generations of the titanium enolate from 2-bromoacetophenone and of the ketyl radicals from benzaldehyde and 2-bromoacetophenone with low-valent titanium species would proceed at the same time; therefore, formations of aldol and the undesirable pinacols took place competitively. When 2-iodoacetophenone was used, the desired aldol was produced in 55% yield along with 1% of the pinacol originated from benzaldehyde, and the pinacol originated from 2-iodoacetophenone was not detected. In order to promote the reduction of 2-bromoacetophenone, a combination of $TiCl_2$ and Cu powder was used at -23 °C in the above experiment,[10] and the aldol was then obtained in 79% yield along with a small amount of the pinacol originated from benzaldehyde (5%) without forming the pinacol originated from 2-bromoacetophenone. It was assumed that Cu powder would effectively promote the generation of titanium enolate from 2-bromoacetophenone in comparison with that of ketyl radical.

The yields and diastereoselectivities of aldol products as well as the yields of side products, i.e. pinacols originated from the aldehydes, are summarized in Table 1. Both aromatic and aliphatic α-bromo ketones reacted smoothly with acceptor aliphatic aldehydes to give the corresponding *syn*-aldol products preferentially in good yields without forming pinacols originated from α-bromo ketones and the aldehydes (Entries 1-6). When benzaldehyde or cinnamaldehyde was used as an acceptor in the above reaction, the corresponding aldol was similarly obtained as a main product with high diastereoselectivity along with a small amount of the pinacol coupling product originated from the aldehyde (Entries 7-10).

A typical procedure is described for the reaction of 2-bromopropiophenone with 3-phenylpropanal: to a suspension of $TiCl_2$ (0.4 mmol) and Cu powder (0.5 mmol)[11] in CH_2Cl_2 (0.8 mL) at room temperature was added ^{t}BuCN (1.6 mmol)[12] under argon atmosphere. After the resulting suspension was cooled down to -78 °C, a solution of 2-bromopropiophenone (0.3 mmol) in CH_2Cl_2 (0.5 mL) and a solution of 3-phenylpropanal (0.3 mmol) in CH_2Cl_2 (0.5 mL) were successively added dropwise. The mixture was warmed up to -23 °C and stirred for 3 h. Phosphate buffer (pH=7) was added and the precipitate was removed by filtration, and then filtrate was separated. The aqueous layer was extracted with ether (3 mL x 3), and the combined organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was

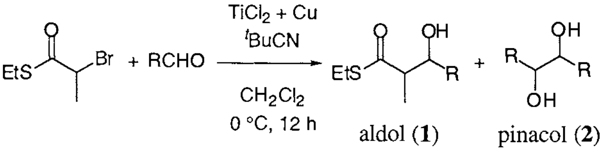
Table 1. Aldol reaction of α-bromo ketones with aldehydes using $TiCl_2$ and Cu powder

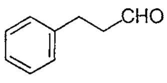
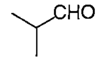
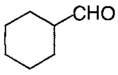
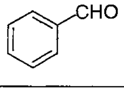


Entry	R^1	R^2CHO	Yield of **1** / % [*syn* / *anti*]^a	Yield of **2** / % [*dl* / *meso*]^a
1	Ph		94 [91/ 9]	N.D.
2	Et		89 [83/17]	N.D.
3	Ph		84 [84/16]	N.D.
4	Et		76 [73/17]	N.D.
5	Ph		92 [85/15]	N.D.
6	Et		90 [75/25]	N.D.
7	Ph		96 [96/ 4]	3 [92/ 8]
8	Et		89 [89/11]	10 [86/14]
9	Ph		89 [91/ 9]	11 [70/30]
10	Et		70 [85/15]	22 [77/23]

^{a}Determined by ^1H NMR.

Table 2. Reformatsky-type reaction of α-bromo thioester with aldehydes using $TiCl_2$ and Cu powder



Entry	RCHO	Yield of **1** / % [*syn* / *anti*]^a	Yield of **2** / % [*dl* / *meso*]^a
1		69 [74/26]	2 [88/12]
2		74 [64/36]	N.D.
3		81 [63/37]	N.D.
4		21 [82/16]	76 [76/24]

^{a}Determined by ^1H NMR.

purified by TLC to afford the *syn*- and *anti*-4-hydroxy-3-methyl-1,6-diphenyl-2-hexanone (94%, *syn* / *anti* = 91 / 9).

Though Reformatsky-type reaction of ethyl iodoacetate with 3-phenylpropanal under the same reaction conditions did not proceed at all and a 1,3-dioxolane was obtained in 59% yield by acetalization of the undesirable pinacol with 3-phenylpropanal, it was found that the reaction of *S*-ethyl 2-bromopropanethioate with aliphatic aldehydes gave the corresponding β-hydroxy thioesters in good to moderate yields (Table 2).

Thus, the highly diastereoselective aldol reaction of α-bromo ketones with aliphatic aldehydes was effectively achieved by using a combination of $TiCl_2$ and copper. It is noteworthy that this reaction can be carried out by just mixing substrates and above reagents without pre-treatment. Reformatsky-type reaction of α-bromo thioester with aliphatic aldehydes took place under the same conditions to afford β-hydroxy thioesters in good to moderate yields. Further studies on the optimization of Reformatsky-type reaction are now in progress.

This work was supported by Grant-in-Aids for Scientific Research from the Ministry of Education, Science and Culture.

References and Notes

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10 The reductive coupling reaction of benzaldehyde using a combination of $TiCl_2$ and zinc at -23 °C afforded the corresponding pinacol in 91% yield within 1 h, however, the pinacol was obtained in 32% yield after 6 h when $TiCl_2$ and copper were used as promoters at -23 °C.

11 Copper powder was purchased from Soekawa Chemical Co., Ltd. and used as received. The aldol reaction of 2-bromoacetophenone with benzaldehyde did not proceed at all by use of the copper powder without $TiCl_2$.

12 In the absence of pivalonitrile, the reaction shown in entry 7 (Table 1) gave the desired aldol in 20% yield along with 6% of the pinacol originated from benzaldehyde.