Diastereoselective Pinacol Coupling Reaction of Aliphatic and Aromatic Aldehydes Promoted by Low Valent Titanium Iodide in situ Formed by Titanium(IV) Iodide and Copper

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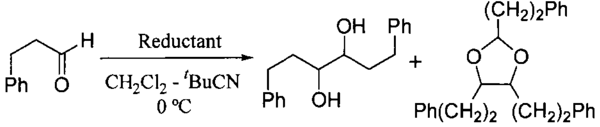
The pinacol coupling reaction of aromatic and aliphatic aldehydes including pivalaldehyde with low valent titanium iodide, in situ formed from titanium iodide(IV) and copper, proceeded smoothly in a mixed solvent of dichloromethane and pivalonitrile to give the corresponding 1,2-diols in good to high yields and *dl*-selectivities.

The reductive coupling of carbonyl compounds known as pinacol coupling reaction is one of the most important tools for synthesizing 1,2-diols. Of various reducing reagents, low valent titanium compounds were quite effective and being studied intensively. It was then revealed that homo-coupling of various carbonyl compounds took place to afford the corresponding pinacols in reasonable yields and diastereoselectivities under mild conditions.[1] Most of the low valent titanium species were originated from titanium(IV) or titanium(III) chloride, and it is known that yields and diastereoselectivities of the pinacol coupling products by using low valent titanium compounds are higher in a homogeneous system compared with a heterogeneous system.[2] It was shown in the previous communication that the use of nitrile solvent increased the solubility of titanium(II) chloride, and caused the reductive coupling to give pinacols in good yields.[3] Matsubara and co-workers then reported that benzaldehyde coupled smoothly to give the corresponding pinacol in a homogeneous reducing system; that is, titanium(II) chloride and tertiary amine in THF.[4] Titanium(II) bromide, a newly utilized soluble low valent titanium compound, afforded various 1,2-diols from aromatic and aliphatic aldehydes in good to high yields and diastereoselectivities when it was combined with copper in a mixed solvent of dichloromethane and pivalonitrile, which was very recently reported from our laboratory.[5] Based on these results, titanium(II) iodide was expected to work as better reductant than titanium(II) chloride and titanium(II) bromide because the negativity of iodine atom was lower than those of chlorine and bromine atoms. In addition, the reactivity of titanium(II) iodide would be enhanced in the coupling reaction because it is hard for titanium(II) iodide having two larger iodine atoms to form clusters and titanium(II) iodide effectively participates in the reduction process.

In the first place, preparation of titanium(II) iodide was tried. Several preparative methods of titanium(II) iodide were already reported where reactions were carried out under extremely severe conditions (high temperature at 800–900 °C) and that sometimes explosive reaction accompanied.[6] Then, similar to the preparative method of titanium(II) chloride,[7] titanium(IV) iodide was treated with hexamethyldisilane aiming to establish a milder preparative procedure. However, pure titanium(II) iodide was not successfully isolated under the similar conditions as of titanium(II) chloride and bromide.[5,7] Next, the in situ formation of low valent titanium iodide species was tried by combining titanium(IV) iodide and several metals as reducing reagents, and its application to pinacol coupling reaction was studied.[8] In this communication, we would like to report an efficient method for the preparation of various pinacols from aromatic and aliphatic aldehydes including pivalaldehyde by using a combination of titanium(IV) iodide and copper.

Table 1. Pinacol coupling reaction of 3-phenylpropionaldehyde by using titanium halides and several metals



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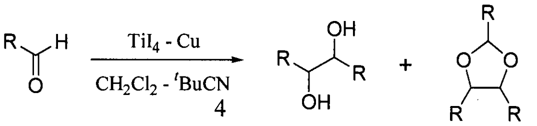
Entry	Reductant[a] (molar ratio of metal / TiX_n)	Time / h	Yield / % 1 [*dl* / *meso*][b]	2
1	TiI_4 + Fe (3.0)	18	0	0
2	TiI_4 + Ni (3.0)	18	0	0
3	TiI_4 + Ti (3.0)	18	0	0
4	TiI_4 + Cu (3.0)	6	80 [80 / 20]	9
5	TiI_4 + Cu (2.0)	6	80 [81 / 19]	11
6	TiI_4 + Cu (1.0)	6	0	0
7	TiI_4	18	0	0
8	Cu[c]	18	0	0
9	CuI[c]	18	0	0
10	$TiBr_4$ + Cu (3.0)	6	61 [78 / 22]	18
11	$TiBr_4$ + Cu (2.0)	6	46 [81 / 19]	21
12[5]	$TiBr_2$ + Cu (1.0)	18	82 [80 / 20]	7

[a]See Ref. 10. $Ph(CH_2)_2CHO$ / TiX_n / ^{t}BuCN = 0.5 / 0.65 / 2.6 mmol in CH_2Cl_2 (4.0 ml). Prescribed amounts of metal were added as shown in Table. [b]Ratios were determined by ^{1}H-NMR analysis of crude product mixture. [c]$Ph(CH_2)_2CHO$ / CuX_n / ^{t}BuCN = 0.5 / 1.3 / 2.6 mmol in CH_2Cl_2 (4.0 ml).

Firstly, 3-phenylpropionaldehyde, an aliphatic aldehyde, was chosen as a substrate. In order to form reactive low valent titanium iodide species, several metals[9] such as copper, iron, nickel and titanium(0) were treated with titanium(IV) iodide at 0 °C in a mixed solvent of dichloromethane and pivalonitrile.[10] In the case when copper was used, the reductive coupling reaction proceeded smoothly to give the corresponding pinacol in high yield with high diastereoselectivity similar to the case of using a combination of titanium(II) bromide and copper shown in the previous communication (Table 1, entries 1–4).[5] On the other hand, the reductive coupling did not proceed at all when each titanium(IV) iodide, copper(0) or copper(I) iodide was independently used (entries 7–9). These results indicated that titanium(IV) iodide was reduced by copper to form low valent titanium iodide species which effectively promoted the homo-coupling of an aldehyde. Then, it was revealed that pinacols were obtained within 6 hours in high yields with high diastereoselectivities when 2 or 3 molar amounts of copper to titanium(IV) iodide were used (entries 4–6). On the other hand, when a combination of titanium(IV) bromide and copper was used, the reaction proceeded slowly and the yield of pinacol was rather low (entries 10,11), though the corresponding pinacol was obtained in high yield when 3-phenylpropionaldehyde was treated with titanium(II) bromide and copper for a longer time (18 hours, entry 12).

Table 2. Pinacol coupling reactions of various aldehydes using low valent titanium iodide reducing system



1 **2**

Entry	R	Conditions[a]	Yield / %	
			1 [*dl* / *meso*][b]	**2**
1	Ph	A	94 [>99 / 1]	0
2	*p*-Cl-Ph	A	93 [>99 / 1]	4
3	*p*-MeO-Ph	A	76 [98 / 2]	9
4	*trans*-PhCH=CH	A	76 [99 / 1]	8
5	$Ph(CH_2)_2$	B	80 [81 / 19]	11
6	*n*-Bu	B	72 [80 / 20]	8
7	*i*-Bu	B	85 [75 / 25]	0
8	*i*-Pr	B	98 [84 / 16]	0
9	*c*-Hex	B	95 [85 / 15]	0
10	*t*-Bu	C	92 [85 / 15]	0

[a] See Ref. 10. Conditions A: aldehyde / TiI_4 / Cu / ^{t}BuCN = 0.5 / 0.5 / 1.0 / 2.0 mmol in CH_2Cl_2 (4.0 ml), -23 °C, 3 h; B: aldehyde / TiI_4 / Cu / ^{t}BuCN = 0.5 / 0.65 / 1.3 / 2.6 mmol in CH_2Cl_2 (4.0 ml), 0 °C, 6 h; C: aldehyde / TiI_4 / Cu / ^{t}BuCN = 0.5 / 0.65 / 1.3 / 2.6 mmol in CH_2Cl_2 (4.0 ml), rt, 6 h. [b] Ratios were determined by ^{1}H-NMR analysis of crude product mixture.

Based on these results, reductive coupling reactions of various aromatic and aliphatic aldehydes using low valent titanium iodide reducing system were tried (summarized in Table 2). Aromatic and α,β-unsaturated aldehydes were converted to the corresponding pinacols at –23 °C in good to high yields and diastereoselectivities along with small amounts of 1,3-dioxolanes (entries 1–4). When aliphatic aldehydes were used as substrates, the reductive coupling proceeded at the temperature ranging from 0 °C to room temperature to give the corresponding pinacols in good to high yields and diastereoselectivities (entries 5–10). Concerning vanadium complex catalyzed pinacol coupling reaction, Hirao and co-workers suggested that the diastereoselection was affected by the bulkiness of the α-position of aldehydes.[11] In the case of using a combination of titanium(IV) iodide and copper, it is interesting to note that the coupling proceeded smoothly to give pinacols in good to high yields and diastereoselectivities, irrespective of the number of substitutuents at α-position of aliphatic aldehydes. Different from the above results, when a bulky α-tri-substituted aliphatic aldehyde, e.g. pivalaldehyde, was treated with a combination of titanium(II) bromide and copper, the coupling product was not obtained at all. Concerning the pinacol coupling reaction of pivalaldehyde by using other metals, niobium,[12] samarium[13] and cerium[14] proceeded to give the corresponding pinacol in fairly good yield with high diastereoselectivity. However, yields of the corresponding pinacols decreased when α-mono- and α-di-substituted aliphatic aldehydes were treated with the above metallic compounds.

As for the reaction mechanism, the reductive coupling proceeded by a similar manner as mentioned in the case of using titanium(II) bromide and copper reducing system shown in the previous communication.[5]

Thus, an efficient method was established for the pinacol coupling reaction of aromatic and α-mono-, di-, tri-substituted aliphatic aldehydes by using a combination of titanium(IV) iodide and copper in a mixed solvent of dichloromethane and pivalonitrile affording the corresponding pinacols in good to high yields and *dl*-diastereoselectivities.

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References and Notes

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10 The typical reaction procedure for the pinacol coupling of 3-phenylpropionaldehyde: To a reddish brown suspension of titanium(IV) iodide (0.65 mmol) and copper powder (1.3 mmol) in dichloromethane (2.5 ml) was added pivalonitrile (2.6 mmol) under argon atmosphere. The color was changed to dark brown and the mixture was stirred for additional 30 minutes at room temperature. Resulted CuI or CuI_2 suspended dark brown solution was cooled to 0 °C and a solution of 3-phenylpropionaldehyde (0.5 mmol) in dichloromethane (1.5 ml) was added. The reaction mixture was stirred for 6 hours, and then the work up was done as shown in Ref. 3. The crude product was purified by TLC to afford the desired pinacol and co-product (80% and 11%, respectively).
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