Titanium(IV) Iodide Promoted Pinacol Coupling

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Pinacol coupling of aromatic aldehydes was efficiently promoted by titanium tetraiodide in propionitrile to give the 1,2-diol derivatives with high *dl*-selectivities in high yields.

The pinacol coupling reaction of carbonyl compound is one of the most useful methods for the preparation of 1,2-diols and 1,2-diamines,[1–3] which are utilized for the synthesis of HIV protease inhibitors and natural products or chiral auxiliaries.[4,5] We have already reported the asymmetric pinacol coupling of imine using Zn and camphorsulfonic acid.[6] A number of methods have been reported for the pinacol coupling. Recently, high diastereoselectivity, catalytic use of active species and cross coupling are achieved.[7–15] Normally, utilizing low valent metal is needed for promoting the pinacol coupling, because the reaction proceeds via a single-electron transfer mechanism.[16]

Herein we report on titanium(IV) iodide promoted pinacol coupling of aldehydes to give the corresponding *dl*-diols. To the best of our knowledge, the pinacol coupling without the use of low valent metal species has not been published.[17]

A typical procedure is as follows: Propionitrile (1.0 mL) was added to TiI_4[18] (1.0 mmol) at ambient temperature under an argon atmosphere. After 10 min stirring, to the solution of TiI_4 was added benzaldehyde (0.5 mmol) in propionitrile (1.0 mL) at −78 °C. After being stirred at −78 °C to room temperature, the reaction was quenched with sat. aq $NaHCO_3$, 5% aq $NaHSO_3$, and triethylamine. The mixture was filtered through a celite pad, and extracted with ethyl acetate (10 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by preparative TLC on silica gel (*n*-hexane : ethyl acetate = 1 : 1 as an eluent) gave 1,2-diphenyl-1,2-ethandiol (90%, *dl* : *meso* = >99: 1).

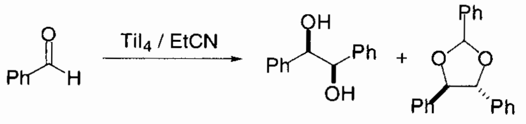

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Table 1. Coupling of benzaldehyde mediated by TiI_4

Entry	TiI_4 (eq.)	Yield of **1** / %[a]	*dl* : *meso*[b]	Yield of **2** / %[a]
1	0.5	-	-	48
2	1.0	22	85 : 15	64
3	1.2	80	99 : 1	9
4	1.5	82	>99 : 1	8
5	2.0	90	>99 : 1	-
6[c]	2.0	6	95 : 5	7
7[d]	2.0	77	97 : 3	-

[a]Isolated yield. [b]Determined by ^{1}H NMR. [c]Dichloromethane was used as a solvent. [d]Acetonitrile was used as a solvent at -45 °C to rt.

The results of investigation of the amount of TiI_4 are summarized in Table 1. The reaction using 0.5 eq of TiI_4 gave the corresponding acetal derivative **2** in 48%. The *dl*-hydrobenzoin was obtained as a major product, when more than 1.0 eq of TiI_4 was used. The relative stereochemistry was determined by the comparison of the spectral data with the reported ones.[19] The moderate *dl*-selectivity was due to selective cyclization of *dl*-diol to acetal **2**, which was obtained as a single isomer when 1.0 eq of TiI_4 was used (Entry 2). The observed high *dl*-selectivity with respect to the acetal **2** is explicable in terms of a steric congestion between two phenyl groups. The best result was obtained using 2.0 eq of TiI_4. Lower yields and selectivities were observed in the reaction using CH_2Cl_2[20] or CH_3CN as a solvent. In contrast to the previous methodologies for the control of diastereoselectivity on the pinacol coupling, e.g., use of TMEDA[21] or a bulky Shiff base,[22] the present procedure uses only 2 eq of TiI_4 for achieving such high selectivities, and hence, is very simple from the standpoint of experimental operation.

Under the optimized conditions, pinacol reactions of various aldehydes were investigated, and the results are summarized in Table 2. The *dl*-diol was obtained in the reaction of *p*-tolualdehyde possessing an electron donating group in moderate yield (Entry 2).[23] The pinacol coupling of aldehydes possessing electron-withdrawing groups such as *p*-bromo- or *p*-chlorobenzaldehyde was efficiently carried out in high yields with high *dl*-selectivities (Entries 3 and 4). The complete *dl*-selectivity was not achieved in the reaction of 2-substituted aldehydes presumably due to the bulkiness of the substituent (Entries 5 and 6). Aliphatic aldehyde such as 3-phenylpropanal did not participate in the present type coupling but was converted to the corresponding acetal derivative in low yield. The reaction mechanism is not obvious at present, whether a single-electron transfer mechanism via in situ generation of low valent titanium species such as Ti(II) or Ti(III) or iodination.[24]

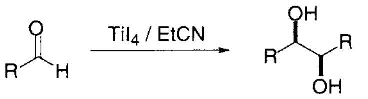

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Table 2. Coupling of aldehydes mediated by TiI_4

Entry	R	Yield / %[a]	*dl* : *meso*[b]
1	Ph	90	>99 : 1
2	*p*-MeC_6H_4	51	>99 : 1
3	*p*-BrC_6H_4	92	>99 : 1
4	*p*-ClC_6H_4	94	>99 : 1
5	2,6-$Cl_2C_6H_3$	68	95 : 5
6	1-Naphthyl	87	97 : 3

[a]Isolated yield. [b]Determined by ^{1}H NMR.

In summary, highly diastereoselective pinacol coupling of aldehydes was achieved using titanium(IV) iodide, a readily available and stable solid. The present method is the first example of pinacol coupling without the use of low valent metal reagents.

References and Notes

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18 Titanium tetraiodide was purified by sublimation (180 °C/0.8 mmHg).
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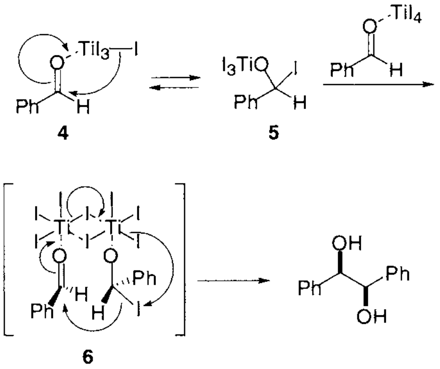
23 A complex mixture was obtained.
24 The latter mechanism involves the initial iodination of the carbonyl group of aldehyde to give iodinated intermediate **5**, which is attacked by the iodide anion from TiI_4 to form an anion species. It has been reported that a similar halogenated intermediate is formed in the reaction of BCl_3 with aromatic aldehydes.[25] This species in turn undergoes addition reaction with another aldehyde to form the pinacol product. The formation of iodinated intermediate **5** appears to be difficult in the cases of electron-rich aldehydes. Therefore, the acetal derivative was obtained in the absence of enough amount of titanium tetraiodide. The slightly lower selectivity in the reaction of 2-substituted aldehydes may be due to the less stability of bimetallic complex **6**.



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