Efficient Method for Pinacol Coupling of Aromatic and Aliphatic Ketones by Using Titanium(II) Chloride and Zinc in the Presence of Pivalonitrile

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The reductive coupling reaction of aromatic and aliphatic ketones including acyclic aliphatic ketones proceeded smoothly to give the corresponding pinacols in good to high yields below room temperature by the combined use of titanium(II) chloride and zinc in the presence of pivalonitrile. *Meso*-selective formation of the coupling products was observed in the cases with some acyclic aliphatic ketones.

The reductive coupling of carbonyl compounds using low-valent early transition metal species is known as pinacol coupling reaction, and various reducing reagents have been developed extensively over these three decades.[1] Recently, several intramolecular versions of the above reaction were effectively employed as key steps in the total synthesis of complex natural and unnatural products.

Concerning the intermolecular version of the above reaction, recent topics are directed to investigate the formation of the C_2 or S_2 symmetric homocoupling products under mild reaction conditions in high diastereoselectivity (*dl* or *meso*). For this purpose, a variety of reductants including low-valent titanium species generated *in situ* from $TiCl_4$ or $TiCl_3$ were employed as effective reagents for the diastereoselective coupling reaction.[2,3] In cases of aromatic aldehydes, for example, the corresponding homocoupling products were afforded with high *dl*-selectivity under the following conditions: $TiCl_4$ / Te in DME, Cp_2TiCl_2 / ^{s}BuMgCl in THF, $TiCl_3$(THF solution) in dichloromethane or $(Cp_2TiCl)_2$ in THF.[4a-d] Further, it was reported recently that *dl*-homocoupling product was preferentially formed from acetophenone by the combined use of $TiCl_3$ / Mg / catechol system in THF.[4e] However, there were few reports which discussed diastereoselectivity of the coupling reaction of *aliphatic ketones* because of the low reactivity of these ketones. The reaction did not actually proceed under mild conditions, which were generally required for controlling selectivity. Further, formation of coupling products from aliphatic ketones is limited since accompanying deoxygenation gives the corresponding olefin or rearranged product under rather severe reaction conditions. Therefore, homocoupling product was obtained in 13% yield (*dl* / *meso* = 45 / 55) when the coupling reaction of 3-methyl-2-butanone was tried by using $TiCl_4$ / Zn combined system which was firstly reported from our laboratory in 1973 (in reflux THF for 14 h).[2b] It was also revealed that the corresponding pinacol was obtained in only ca. 2% yield (*dl* / *meso* ≈ 53 / 47) when coupling of 3-methyl-2-butanone was carried out using $TiCl_3$ / Zn combined system at room temperature. In the case of treating 4-phenyl-2-butanone with $TiCl_3$ / Zn in reflux THF for 12 h, the desired pinacol, the corresponding deoxygenated olefin and 4-phenyl-2-butanol were formed in 58% (*dl* / *meso* ≈ 51 / 49), 2% and 11% yields, respectively. Then, an efficient pinacol coupling reaction which proceeds under mild conditions and also a systematic approach to the correlation between diastereoselectivity and structure of aliphatic ketones were studied.

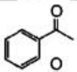
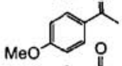
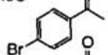
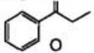
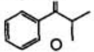
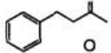
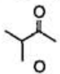
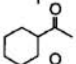
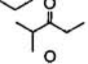
In our total synthesis of antitumor agent Taxol, construction of A ring on to the BC ring system was performed by intramolecular pinacol coupling reaction using low-valent titanium species prepared *in situ* from $TiCl_2$ and $LiAlH_4$.[5] Though similar reaction was carried out by combined use of $TiCl_3$ / $LiAlH_4$, the above mentioned reaction was completed under milder conditions because of decreased acidity of the reducing reagent prepared in advance. The titanium(II) reagent, $TiCl_2$, is facilely prepared from $TiCl_4$ and hexamethyldisilane according to the reported procedure,[6] and it can be stored under argon atmosphere for a long time. Then, in order to find a more efficient method, application of $TiCl_2$ to the synthesis of various pinacols was further studied.

In the first place, reductive coupling reaction of acetophenone was tried in the presence of $TiCl_2$ / Zn combined system in THF. In this case, the desired pinacol was produced in 93% yield (*dl* / *meso* = 76 / 24) at room temperature without accompanying rearranged products. However, the corresponding homocoupling product was not obtained in THF at room temperature when 4-phenyl-2-butanone, an example of acyclic aliphatic ketones, was employed. After searching various reaction conditions, it was found that the coupling proceeded when dichloromethane was used as a solvent. In dichloromethane, the coupling reaction of 4-phenyl-2-butanone gave the desired pinacol in 23% yield (*dl* / *meso* = 50 / 50) by using 1 molar equivalent of $TiCl_2$ / Zn combined system at room temperature. This phenomenon is similar to that of Porta's result which demonstrated that THF complex of $TiCl_3$ in dichloromethane[4c] was effective to the pinacol coupling of benzaldehyde while $TiCl_3$ in THF did not give a favorable result.[2b]

Next, several additives such as pyridine[7] and HMPA[8] which have been effectively utilized in the reductive coupling reaction using low-valent metallic reagent were examined in order to increase the chemical yield. Though pyridine, HMPA or 2-methyloxazoline was not effective for accelerating this low-valent titanium-mediated reaction (0%, 0% or 13% yield, respectively), the coupling reaction proceeded to give the pinacol in 44% yield with 1 molar equivalent of $TiCl_2$ / Zn system in the coexistence of pivalonitrile.[9] After screening several reaction conditions, it was found that the yield was dramatically improved to 87% yield when 2 molar equivalents of $TiCl_2$ were added gradually to the reaction mixture in the presence of zinc and pivalonitrile at room temperature.[10] When acetonitrile or methoxybenzonitrile was used as an additive in the above reaction, the corresponding pinacol was obtained in 78% or 52% yield, respectively.

It is assumed that nitriles moderately coordinate to the low-valent titanium species to form the coordinated complex, which helps both solvation of the titanium particles and electron donation of the titanium complex to the carbonyl compounds.[11] On the other hand, other additives (pyridine, HMPA and 2-methyloxazoline) coordinate too strongly to the titanium reagent, which would resist the reductive interaction to carbonyl compounds. Furthermore, it is noted that nitrile is known as one of the most popular solvents for the electrochemical analysis because of the smooth electron-transfer reactions in nitriles.

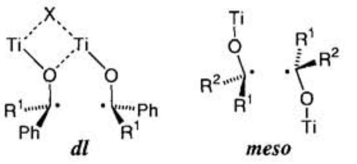
Table 1. Synthesis of pinacols from ketones

Entry	Ketone	Method[a]	Yield /%	*dl* / *meso*[b]
1		A	93 (98)[c]	71 / 29 (72 / 28)[c]
2		A	93	79 / 21
3		A	90	66 / 34
4		A	94	68 / 32
5		A	83	>98 / 2[d]
6		B	87	50 / 50
7		B	97	50 / 50
8		B	90	39 / 61
9		B	87	35 / 65
10		B	61	23 / 77
11		B	98	-

[a] Ref. 9 and 10. [b] Determined by ^{1}H NMR. [c] Method B. 1.2 molar equivalent of $TiCl_2$ was used. [d] Determined by HPLC (CHIRALCEL OD).

The yields and diastereoselectivities of the pinacol coupling reaction starting from several ketones are summarized in Table 1. Aromatic ketones were transformed to the corresponding pinacols in high yields though the diastereoselectivities were rather low compared to the reported values (entries 1-3).[4e] However, it was found that the coupling reaction of isobutyrophenone proceeded smoothly to gave the desired pinacol in 83% yield with almost perfect *dl*-selectivity (entry 5). As generally discussed, the present result of *dl*-selection may also be explained by assuming the intermediates (Figure 1) in which the titanium atoms were placed side by side on solid surface, or by bridging with chlorine[4c] and/or additives.[3b] It is supposed that more stable titanium-bridged complex giving *dl*-product is determined by both electronic effect and steric difference between the aromatic and aliphatic groups at 2- and 2'-positions of carbonyl groups.

In the cases of acyclic and cyclic aliphatic ketones (entries 6-11), the corresponding pinacol coupling products were obtained in good to high yields. The diastereoselectivity was not observed when 4-phenyl-2-butanone or 2-octanone was used as a substrate in which a set of methyl and methylene groups existed at the 2- and 2'-positions of carbonyl (entries 6 and 7). On the other hand, the *meso*-selectivity was attained when two substituents connecting to carbonyl are dimensionally different as in the combination of methyl and methyne (entries 8 and 9), and of methylene and methyne (entry 10). These results indicate that the diastereoselectivity of the products depends on the difference of the bulkiness of two 2- and 2'-substituents. In addition, *dl*- or *meso*-selectivity corresponding to the aromatic or aliphatic ketones may attribute to the respective characteristic properties. In the cases of aromatic ketones, generated ketyl radical species might keep the titanium complex relatively stable and lead to the formation of *dl*-products (Figure 1).



R^1 and R^2 = H or Alkyl

Figure 1. Supposed reaction mechanism.

Thus, the *dl*- and *meso*-selective reductive coupling reaction of aromatic and aliphatic ketones in dichloromethane was effectively achieved by the combined use of $TiCl_2$ and Zn in the coexistence of pivalonitrile under extremely mild reaction conditions.

References and Notes

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9 (Method A) To a suspension of $TiCl_2$ (0.5 mmol) and activated Zn powder (0.5 mmol) in CH_2Cl_2 (2.5 mL) was added ^{t}BuCN (2 mmol) under argon atmosphere. After the resulting dark brown and gray suspension was cooled to 0 °C, a solution of acetophenone (0.5 mmol) in CH_2Cl_2 (1.3 mL) was added. The reaction mixture was stirred for 16 h at room temperature and then saturated aqueous NH_4Cl was added. The mixture was filtered and extracted with CH_2Cl_2, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4. After filtration and concentration of the mixture, the crude product was purified by TLC to afforded the desired pinacol (93%).

10 (Method B) To a gray suspension of activated Zn powder (1 mmol) and ^{t}BuCN (4 mmol) in CH_2Cl_2 (2.5 mL) was added a solution of 4-phenyl-2-butanone (0.5 mmol) in CH_2Cl_2 (1.3 mL) under argon atmosphere. After the reaction mixture was stirred for 30 min, $TiCl_2$ (1 mmol) was added gradually (divided in 6 times at interval of 1 h) under argon by powder inlet equipped to the reaction apparatus. The resulting mixture was stirred for additional 1 h, and then saturated aqueous NH_4Cl was added. The same work up as shown in Ref. 7 gave the desired pinacol (87%).

11 Actually, on ^{13}C NMR spectra, signals of pivalonitrile (δ 125.3, 27.8 and 27.5 ppm) shifted and broadened (δ 131.0, 31.0 and 24.8 ppm) by addition of 1/3 molar equivalent of $TiCl_2$ in chloroform-*d* at room temperature. This result indicates the formation of coordinated complex.