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Pinacol Coupling Reactions Catalyzed by Active Zinc

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Abstract: Pinacol coupling reactions catalyzed by active zinc revealed high activity and extensive suitability. The efficiency of the reaction was improved apparently owing to decreasing reductive potential of zinc. In addition, the results indicated that the zinc activity has a direct relation to the coupling reactivity compared to untreated zinc or other general active zinc.

Keywords: Pinacol coupling reaction, active zinc, carbonyl compounds, electron transfer.

The facile carbon-carbon bond formation is a forever goal and indispensable tool in organic synthesis[1]. Metal-mediated coupling reactions as highly efficient processes are always a major focus of directed synthesis[2]. Pinacol coupling reactions have been recognized to be efficient and selected alternatives for preparing several kinds of compounds[3], not to mention those can be as versatile tools for preparing building blocks or exerted on synthesizing natural products in several key steps[4]. The dimerization of carbonyl compounds using certain active metals[5,6] as catalysts were also reported. However, the procedure by activated metals to diols is still an attractive field, and improvement in the chemoselectivity of the reaction is needed[7]. Herein, we wish to report the pinacol coupling reactions catalyzed by active zinc in THF.

Some methods to clean the surface of zinc have been explored[8], which can be helpful to promote the coupling reactions. There have been some confines to the coupling reactions in the presence of moderate active metal, because the reductive potential of moderate metal is higher than that of ketyl radical formed in reaction, so aliphatic aldehyde or aliphatic ketone with more negative reductive potential is inert in the pinacol coupling reaction under the similar condition (**Table 1**). Compared to the pinacol coupling reactions catalyzed by Zn-cocatalyst[8, 9], merchandise zinc appeared limited suitability in the absence of cocatalysts, such as Lewis acid.

According to the project, we tried to use other catalyst system involving moderate metal to confirm the relation of metal activity and pinacol coupling reactivity. The reductive potential of cadmium is higher and the pinacol coupling reaction can not occur. The same reaction led to satisfactory results when the strong base, such as KOH, was added to the reaction mixture. The yields of diols produced from the starting materials under this condition were 87% for benzophenone and 78% for *p*-methoxyacetophenone, respectively.

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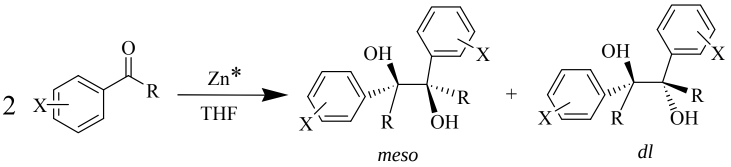
Table 1 Yields of the zinc-mediated pinacol coupling reactions

Substrate	Medium	Yield (%)[a]
o-chlorobenzaldehyde	H_2O-THF	8[b]
benzaldehyde	H_2O	17[b]
acetophenone	H_2O-THF	9[b]
p-methylbenzaldehyde	H_2O-THF	24[b]
p-methylbenzaldehyde	H_2O	12[b]
p-methoxybenzaldehyde	H_2O-THF[d]	84[b](77/23)[c]
p-methoxybenzaldehyde	H_2O	54[b]
p-methoxybenzaldehyde	Solvent free	90[a](57/43)[c]
p-methoxybenzaldehyde	H_2O[e]	91[a] (66/34)[c]
p-methoxybenzaldehyde	H_2O[f]	76[b](65/35)[c]

[a]The yields were determined by ^1H NMR. [b]Isolated yield. [c]*dl/meso* ratio was determined by ^1H NMR. [d]Zinc cleaned by acetic acid. [e]Pinacol coupling reaction mediated by Zn-$AlCl_3$. [f]Pinacol coupling reaction mediated by Zn-$CdCl_2$.

Scheme 1 Zinc-mediated pinacol coupling reactions by active zinc.



X = H, CH_3, CH_3O, Br, Cl; R = H, CH_3

To expand the scope of pinacol coupling reaction, decreasing the reductive potential of zinc to its intrinsic potential is a general alternative to tailor the reactivity. Thus, the active zinc is prepared to mediate the pinacol coupling reaction. Zinc produced by the reaction of sodium with $ZnCl_2$ was tolerant of aromatic aldehydes, aromatic ketones and cyclohexanone and gave diols in high yields (**Scheme 1**).

Based on the results obtained in the Zn-mediated and Cd-mediated pinacol coupling reactions, it speculated that the coupling reactivities were related to the activity of zinc. For the zinc activated by sodium, the zinc cluster reveals more negative reductive potential, and the large cluster can retain high activity in the reaction to minimize the possible monomolecular reductive reaction (**Table 2**).

The sodium used in this work was equivalent to the stoichiometric amount of $ZnCl_2$. After the sodium reacted up and the temperature of the reaction mixture was cooled down to the room temperature, and then the carbonyl compounds were added. The coupling reaction was accomplished more rapidly than that of catalyzed by Zn-$AlCl_3$, and own more general suitability for substrates. Compared to the reaction catalyzed by Zn or Zn-$AlCl_3$, the yields are also elevated to a certain degree. This method is simple and can be exerted on the coupling reaction of aromatic ketones, aromatic aldehydes or cyclohexanone.

Table 2 Pinacol coupling reactions catalyzed by active zinc in THF.

Substrate	Time (h)	Yield[a] (%, *dl/meso*[b])
benzaldehyde	4	89(53/47)
2-chlorobenzaldehyde	3	94(48/52)
2,4-dichlorobenzaldehyde	2	96(48/52)
2-furaldehyde	4	92(65/35)
acetophenone	3	90(56/44)
4-methoxyacetophenone	2	97(43/57)
4-bromoacetophenone	2	93(74/26)
4-methylacetophenone	4	87(43/57)
cyclohexanone	2	90

[a]isolated yield. [b]*dl/meso* ratio was determined by ^{1}H NMR.

The reaction mechanism is involved a single electron transfer process. Active zinc afforded an electron to carbonyl compound and zinc ion coordinated to the carbonyl, then ketyl radical anion occurred coupling reaction to form diols. The coupling reaction gave nearly equivalent amount of diastereoisomer in the absence of conformation controlling factors.

In summary, it demonstrated that the active zinc is beneficial to the pinacol coupling reaction. This study affords a novel approach to vicinal diols by virtue of elevating zinc activity.

General method: Sodium (5 mmol) was treated with anhydrous $ZnCl_2$ (2 mmol) reacted in THF (20 mL) for 5 hour at room temperature, carbonyl compound (1.5 mmol) was then added to the solution. After the reaction was carried out at room temperature for 4-6 hours, 1 mol/L HCl was dropped. The product was extracted with ethyl ether. The ether layer was washed sequentially by saturated aqueous solution of $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$ and removed the ether under vacuum. The raw diol was purified by silica gel chromatography.

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10. Spectra data: **1** ^{1}H NMR (300MHz, CDCl$_3$, δ ppm): 2.27(s, *dl* OH), 2.88 (s, *meso* OH), 4.77 (s, *dl* CH), 4.83 (s, *meso* CH), 7.04-7.32 (m, 10H, Ph). MS (EI, *m/z*): 214, 196, 107. IR (KBr, cm^{-1}): 3100-3350. **3**: ^{1}H NMR (300MHz, CDCl$_3$, δ ppm): 3.03(s, 2H, OH), 5.84 (s, *dl* CH), 5.85 (s, *meso* CH), 7.12-7.37 (m, 8H, Ph). MS (EI, *m/z*): 350, 176, 141, 113, 77. IR (KBr, cm^{-1}): 3200-3500. **4** ^{1}H NMR (300MHz, CDCl$_3$, δ ppm): 2.45 (br, 2H, OH), 4.94 (s, *dl* CH), 5.12 (s, *meso* CH), 6.32 (m, 4H, CH), 7.40 (m, 2H, CH). MS (EI, *m/z*): 194, 181, 97. IR (KBr, cm^{-1}): 3100-3500. **6** ^{1}H NMR (300MHz, CDCl$_3$, δ ppm): 1.41 (s, *dl* CH$_3$), 1.58 (s, *meso* CH$_3$), 2.23 (s, *dl* OH), 2.49 (s, *meso* OH), 3.80 (s, *dl* CH$_3$), 3.83 (s, *meso* CH$_3$), 6.70-7.16 (m, 8H, Ph). MS (EI, *m/z*): 301, 126, 77. IR (KBr, cm^{-1}): 3200-3550. **7** ^{1}H NMR (300MHz, CDCl$_3$ δ ppm): 1.43 (s, *dl* CH$_3$), 1.58 (s, *meso* CH$_3$), 2.30 (s, *dl* OH), 2.59 (s, *meso* OH), 7.10-7.35 (m, 8H, Ph). MS (EI, *m/z*): 291, 199, 120. IR (KBr, cm^{-1}): 3200-3500. **8** ^{1}H NMR (300MHz, CDCl$_3$, δ ppm): 1.52 (s, *dl* CH$_3$), 1.60 (s, *meso* CH$_3$), 2.25 (s, *dl* OH), 2.55 (s, *meso* OH), 7.08-7.27 (m, 8H, Ph). MS (EI, *m/z*): 224, 181, 120, 105, 77. IR (KBr, cm^{-1}): 3200-3400. **9** ^{1}H NMR (300MHz, CDCl$_3$, δ ppm): 1.12-1.96 (m, 20H, CH$_2$), 2.12 (br, 2H, OH). MS (EI, *m/z*): 197, 181, 163, 99. IR (KBr, cm^{-1}): 3100-3600.

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