

A Highly Diastereoselective Pinacol Coupling Reaction of Aldehydes and Ketones Using Low-Valence Niobium Generated from Nb(V)

Shigeru ARAI,* Yukinori SUDO, and Atsushi NISHIDA

Graduate School of Pharmaceutical Sciences, Chiba University; Yayoi-cho, Inage-ku, Chiba 263–8522, Japan.

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A simple method for the diastereoselective synthesis of racemic 1,2-diol mediated by low-valence niobium generated *in situ* is described. A 1,4-dioxane-toluene solvent system was found to be essential to achieve higher selectivities and to prevent other reactions of pinacols, such as deoxygenation and acetal formation. Aromatic aldehydes and ketones were converted to the corresponding pinacols with up to 97 and 85% de, respectively.

Key words carbonyl compound; niobium; pinacol coupling; vicinal diol; zinc

Pinacol coupling is recognized as a powerful method for the synthesis of symmetric 1,2-diols and can be promoted or catalyzed by various metals. In this article, we report an improved methodology for a Nb-mediated highly diastereoselective pinacol coupling reaction.^{1–3)} A NbCl₅ DME complex, which is both commercially available and the most common reductant among niobium agents, has been reported to generate 1,2-dianions from alkynes and imines that react with multiple bonds, and its utility in organic synthesis is well established.^{4,5)} On the other hand, few examples using low-valence Nb prepared from Nb(V) *in situ* have been applied to pinacol coupling.^{1,2)}

We were interested in the reactivity of low-valence Nb and sought to establish a simple and inexpensive protocol.

First, a suitable solvent for the pinacol coupling of **1a** was surveyed with low-valence Nb, which was generated *in situ* by treatment with zinc powder. In general, DME is known to be a useful solvent in Nb(III)-mediated reactions and a Nb complex with DME and an alkyne has been characterized.⁶⁾ Although the reaction proceeded smoothly to give the desired pinacol **2a** in 61% yield, its diastereoselectivity was low, as shown in entry 1. A non-coordinative solvent such as toluene was ineffective and gave **2a** in only 9% yield (entry 2). Moreover, THF, gave **2a** in reasonable yield but with unsatisfactory diastereoselectivity (entry 3). The most critical problem was the rapid polymerization of THF due to the strong Lewis acidity of Nb. 1,4-Dioxane at room temperature (rt) surprisingly increased the ratio to 69:1 (entry 4). This system shows great advantages in that minimize other subsequent reactions of the initially formed pinacols, such as acetal formation and deoxygenation, as observed in Szymoniak's results.¹⁾ To examine this system at a lower temperature, a mixed solvent system was investigated. After optimization, dioxane:toluene (1:4) was revealed to be the best solvent and gave **2a** with a ratio of 79:1 (entry 5). Moreover, 1.1 eq of zinc powder was sufficient for the reaction to proceed with similar results, however a stoichiometric amount of NbCl₅ was essential (entry 6 vs. 7). We assume that 1,4-dioxane plays important roles in both promoting the smooth reduction of Nb(V) by Zn powder and reducing the Lewis acidity of Nb(V) by coordination to prevent the side reaction such as acetal formation of **2a**. These results are summarized in Table 1.

By examining the scope and limitations of this reaction using various aromatic aldehydes, we found that this method-

ology was suitable for a variety of substrates with excellent de values under the optimized conditions. For example, 2-, 3- and 4-chlorobenzaldehydes **1b–d** were smoothly transformed to the corresponding pinacols **2b–d** in 77, 87 and 79% yields and with good diastereoselectivities, respectively (entries 1–3). Electron-donating groups such as 3-Me and 3-MeO substituents, as shown in entries 4 and 5, were also successfully converted into the corresponding diols **2e** and **2f** in 67 and 54% yields with higher selectivity. Surprisingly, electron-donating substituents at the 2- and 4-positions strongly affected the chemical yields. For example, 2-Me, 2-MeO, 4-Me and 4-MeO groups gave complex mixtures and low yields of **2** (less than 28% yield) because these functionalities promote the further deoxygenation of pinacols to give **A** due to the stabilizing effect of benzylic carbocation. On the other hand, the reaction with an electron-withdrawing group such as a 4-CF₃ group, which is thought to prevent further reactions, proceeded smoothly to give **2g** in 66% yield with 24 of diastereo ratio (entry 6). These results are summarized in Table 2.

Having succeeded with aromatic aldehydes, we next sought to confirm the generality of this reaction system using a variety of ketones **3**, and found significantly different results than with aldehydes. For example, treatment of acetophenone **3a** under similar conditions gave the desired pinacol **4a** in 40% yield together with **5a** (46%) (entry 1). The latter rearrangement product seems to be produced from **4a** by the Lewis acidity of Nb(V). To limit further reaction, the addition of excess Zn powder, which rapidly produces low-

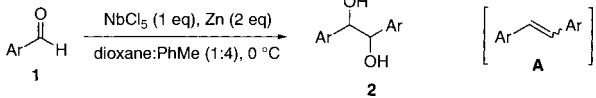
Table 1. Diastereoselective Pinacol Coupling Using **1a**

| Entry | Solvent | Zn (eq) | Conditions | Yield of 2a (%) | <i>dl/meso</i> of 2a ^{a)} |
|-------|--------------------------------------|---------|------------|------------------------|---|
| 1 | DME | 2 | 0 °C, 3 h | 61 | 2.5 |
| 2 | Toluene | 2 | 0 °C, 3 h | 9 | 1.0 |
| 3 | THF | 2 | 0 °C, 3 h | 67 | 2.2 |
| 4 | 1,4-Dioxane | 2 | rt, 3 h | 53 | 69 |
| 5 | 1,4-Dioxane/PhMe (1/4) | 2 | 0 °C, 3 h | 75 | 79 |
| 6 | 1,4-Dioxane/PhMe (1/4) | 1.1 | 0 °C, 3 h | 78 | 71 |
| 7 | 1,4-Dioxane/PhMe (1/4) ^{b)} | 1.1 | 0 °C, 3 h | 53 | 11 |

a) Determined by ¹H-NMR. b) NbCl₅ (0.5 eq) was used.

* To whom correspondence should be addressed. e-mail: arai@p.chiba-u.ac.jp

Table 2. Diastereoselective Pinacol Coupling Using Aromatic Aldehydes



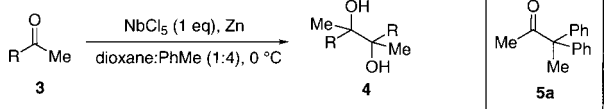
| Entry | 1 | Time (h) | Yield (%) | <i>dl/meso</i> |
|-------|--------------------------------------|----------|----------------|----------------|
| 1 | 1b : Ar=2-Cl-Ph | 1.5 | 2b : 77 | 12 |
| 2 | 1c : Ar=3-Cl-Ph | 1.5 | 2c : 87 | 29 |
| 3 | 1d : Ar=4-Cl-Ph | 2 | 2d : 79 | 43 |
| 4 | 1e : Ar=3-Me-Ph | 2.5 | 2e : 67 | 54 |
| 5 | 1f : Ar=3-MeO-Ph | 2 | 2f : 74 | 77 |
| 6 | 1g : Ar=4-CF ₃ -Ph | 2 | 2g : 66 | 24 |

valence Nb species, was examined. As expected, the rearrangement is sufficiently prevented and the reaction predominantly gave *dl*-**4a** in 70% yield in a reasonable ratio (12 : 1) together with **5a** (8%) (entry 2). While the reason for the significant decrease in *de* is still unclear, we assume that these results are dependent on the kinetic difference between *dl*- and *meso*-**4a** in being transformed into the subsequent rearrangement products. With regard to substituents effect, a methyl group at the 4-position gave **4b** in 35% yield (entry 3) and, as expected, an electron-withdrawing group such as 4-CF₃, prevented such additional reaction to give **4c** in good yield (entry 4). Furthermore, the reaction of aliphatic ketone **3d** proceeded without selectivity in moderate yield (entry 5). These results are summarized in Table 3.

In conclusion, we found that the low-valence Nb which is generated *in situ* promoted the pinacol coupling of aromatic aldehydes and ketones with good to excellent *de*. The stereoselectivities are significantly controlled by a coordinative co-solvent and/or by the substituents on the substrates. However, the generality of the substrate is not still satisfactory, and further studies are needed.

Experimental

The desired compounds are identified by reg. #: **2b** (24133-53-7), **2c** (209900-08-3), **2d** (38152-44-2), **2e** (24133-60-6), **2f** (156091-01-9), **2g** (199166-26-2), **4a** (1636-34-6), **4b** (13145-58-9), **4c** (192198-90-6) and **4d**

Table 3. Diastereoselective Pinacol Coupling Using **3**


| Entry | 2 | Zn (eq) | Time (h) | Yield of 4 (%) | <i>dl/meso</i> ^{a)} |
|-------|---|---------|----------|-----------------------------------|------------------------------|
| 1 | 3a : R=Ph | 1.1 | 2 | 4a : 40 (5a : 46%) | 29 |
| 2 | 3a : R=Ph | 2 | 2 | 4a : 70 (5a : 8%) | 12 |
| 3 | 3b : R=4-Me-Ph | 2 | 3 | 4b : 35 | 46 |
| 4 | 3c : R=4-CF ₃ -Ph | 2 | 2.5 | 4c : 88 | 2.5 |
| 5 | 3d : R=Ph(CH ₂) ₂ | 2 | 2 | 4d : 60 | 1 |

a) Determined by ¹H-NMR.

(40499-44-5).

Representative experimental procedure for pinacol coupling of **1a** (Table 1, entry 5): A suspension of activated Zn powder (77 mg, 1.2 mmol) and NbCl₅ (159 mg, 0.59 mmol) in 1,4-dioxane-toluene (1 : 4, 3.0 ml) was stirred for 1 h at rt under an argon atmosphere. Benzaldehyde **1a** was then added at 0 °C. After the mixture was stirred for an additional 3 h, the reaction was quenched with aqueous 10% aq. K₂CO₃ (2.0 ml) and subjected to ultrasonication for 1 h. The resulting slurry was filtered off by celite and the layers were extracted with AcOEt (5.0 ml×3), washed with brine and dried over Na₂SO₄. After the solvents were removed *in vacuo*, the crude product was purified by flash column chromatography (hexane : AcOEt=5 : 2) to give the desired product **2a** as a white solid (47 mg, 0.22 mmol, 75%, *dl/meso*=79 : 1). The diastereoselectivity was determined by ¹H-NMR analysis with comparison to the literature.²⁾

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