Tetrahedron Letters 50 (2009) 7172–7174

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Chromium-catalyzed pinacol coupling of benzaldehyde in water

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ARTICLE INFO

Article history:
Received 14 September 2009
Revised 5 October 2009
Accepted 6 October 2009
Available online 13 October 2009

Keywords:
Pinacol coupling
Catalysis in water
Chromium catalysis
Benzaldehyde
Stereoselectivity

ABSTRACT

The pinacol coupling of benzaldehyde (0.25 M or 1.25 M) in water was catalyzed by 5–25 mol % $CrCl_2$ in the presence of Zn-dust or Al-dust at 20 °C or 60 °C. In all cases at most 50% of the pinacol coupling product, 1,2-diphenyl-1,2-ethanediol, was obtained with the major product, benzyl alcohol, being formed by a competitive $2e^-$ reduction of the carbonyl. The *dl*- to *meso*-diastereoselectivity of the pinacol products ranged from 0.6:1 to nearly 1:1.

The pinacol coupling reaction of aldehydes to form vicinal diols is developing into a versatile method for carbon–carbon bond formation.[1] Several low valent metals have been employed in stoichiometric amounts to reduce aldehydes to ketyl radicals that can then dimerize to form *meso*- or *dl*-isomers of 1,2-diol products.[1a] More desirable catalytic versions of the pinacol and related reactions are also being developed.[2] Good progress for the catalytic coupling of aldehydes has been achieved using chromium,[3] vanadium,[4] or titanium salts[5] in aprotic solvents by employing stoichiometric reducing metals such as Mn or Zn and chlorosilanes to recycle the catalytic metal. A schematic catalytic cycle for this ternary system is shown in Figure 1. The key aspects of this cycle are the reduction of the vanadium centers in postulated intermediate **A** and the replacement of the alkoxide–vanadium bond with an alkoxide–silicon bond.

Much of the emphasis of studies involving ternary catalyst systems has been on improving catalytic turnovers, controlling the *dl*-/*meso*-diastereomeric ratio of the 1,2-diol products and on inducing enantioselectivity in the coupling reaction.[6] In order to extend the practicality and potentially the scope of the pinacol coupling reaction, recent efforts have started to focus on the development of binary catalyst systems that do not require chlorosilanes to release the catalyst from the diol.[1a] Due to potential advantages in terms of safety, cost, and biocompatibility, development of reactions that proceed efficiently in aqueous media has received increased attention.[7] Hirao has investigated a vanadium-catalyzed pinacol coupling of aromatic aldehydes in water in the presence of Al, Zn, or Mn.[8] Hirao's most effective catalytic system for the coupling of aromatic aldehydes in water was the use of 33 mol % VCl_3 with stoichiometric aluminum at room temperature for 3 days.

In order to extend the scope of reductive couplings in aqueous media, we have initiated an investigation of the use of chromium salts as catalysts for the pinacol reaction. Chromium complexes have been effectively used in ternary catalytic systems for both pinacol and pinacol-type reactions in aprotic solvents.[2,3] Since a good variety of low valent chromium–ligand complexes are known,[9] it is likely that we could attach appropriate chromium species to heterogeneous supports. The use of heterogeneous catalysts in aqueous reactions would facilitate the removal of the catalyst and potentially improve the cost effectiveness and environmental impact of chromium in pinacol coupling reactions. Herein we report preliminary results for the coupling of our initially studied substrate, benzaldehyde.

We initially examined the reductive coupling of benzaldehyde [0.25 M] in water with 10 mol % $CrCl_2$ and excess Zn-dust at

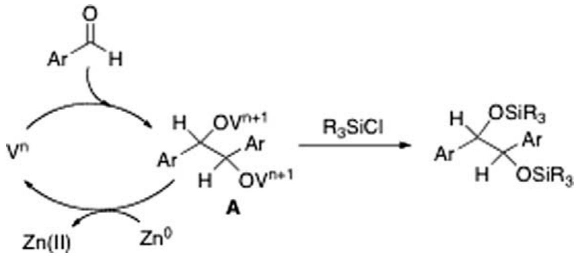

Figure 1. Pinacol coupling by $V^n/Zn(0)/R_3SiCl$-ternary catalyst system.

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0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.027

20 °C.[10] We were gratified to observe the formation of diol **1** in a product ratio of 37% in a *dl*-/*meso*-diastereomeric ratio of 0.7:1 along with the direct reduction product benzyl alcohol **2** in 63% product ratio (Fig. 2). Some unreacted benzaldehyde (ca. 5%) was also observed. An ^{1}H NMR spectrum of a reaction mixture is shown in Figure 3 in which the *dl*-**1** and *meso*-**1** product signals for the benzylic CH groups are well separated, but the benzylic methylene signal of benzyl alcohol **2** is quite near the *meso*-**1** signal. The partial overlap of the latter signals contributes to some uncertainty in determining product ratios.

According to the catalytic scheme depicted in Figure 4,[1b,3,5,8] Cr(II) can initially reduce the aldehyde (step a) to form radical intermediate **B**. The reactive carbon site in **B** can combine with a second aldehyde unit (either before or after its reduction) as in step b to form coupled product **C**. Hydrolysis to release the 1,2-diol and reduction of the chromium species back to a lower valent metal as in step c completes the desired catalytic cycle. However, intermediate **B** can be further reduced by a second electron from coordinated chromium or by an electron from an external metal as in step d. This competitive side reaction can lead to the formation of the undesired reduced benzyl alkoxide **D** that can hydrolyze to form benzyl alcohol **2**.

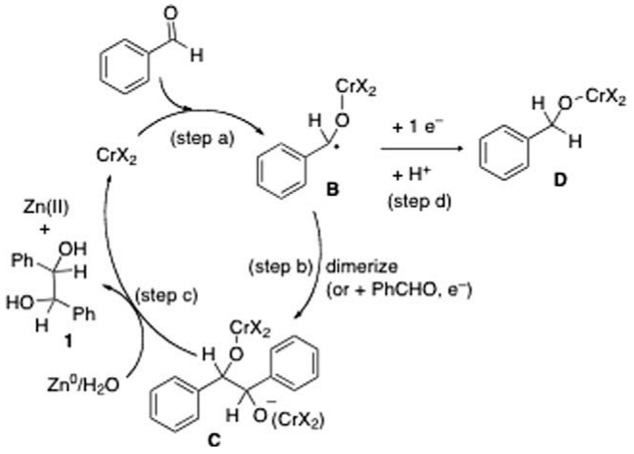

Figure 4. Catalytic cycle for Cr(II)/Zn(0)-catalyzed pinacol reaction with competitive benzaldehyde reduction.

The effects of varying the concentration of the reacting species, the ratio of catalyst, the temperature, and the stoichiometric reductant on the formation of the desired 1,2-diol product were studied. The results are summarized in Table 1 in which product ratios are given. Since the benzyl alcohol product requires only one benzaldehyde per molecule product, but the pinacol diols require 2 equiv of benzaldehyde per product molecule, the actual percent yields of the pinacol products would require doubling the product ratios of **1** and renormalizing them. In control reactions with no chromium catalyst present neither reduction nor pinacol coupling products were observed in the presence of Zn-dust (entries 1 and 2). During the standard reaction time of 20 h the reactions consumed nearly all benzaldehyde at 20 °C or at 60 °C in the presence of Zn-dust (entries 3–8) when the starting benzaldehyde concentration was 0.25 M in water. When the concentration of the reagents and catalyst were increased fivefold, the reactions proceeded to complete consumption of benzaldehyde at 20 °C (compare entries 9–11 with 3–5). In the presence of Al as the stoichiometric reductant, only the reaction at 60 °C was effective (entries 12 and 13). We noted incomplete reactions when the heterogeneous reaction mixtures were not vigorously stirred.

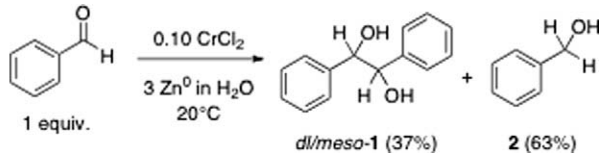

Figure 2. Pinacol coupling of benzaldehyde by Cr(II)/Zn(0) catalyst system in water.

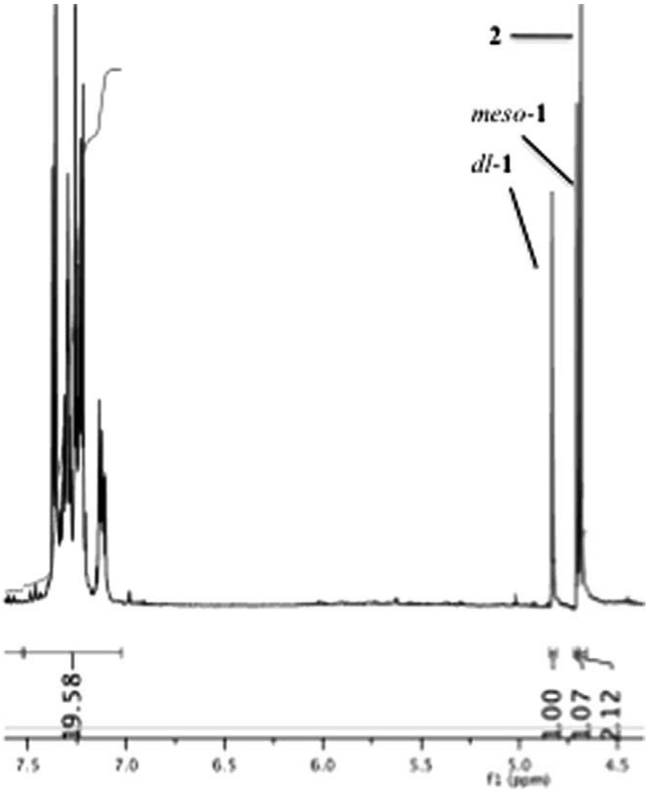

Figure 3. ^{1}H NMR spectrum of pinacol reaction mixture.

In terms of the chemical selectivity for the pinacol coupling versus reduction to form benzyl alcohol, the benzyl alcohol was always the major product under all conditions studied. Under most conditions, the ratio of pinacol to benzyl alcohol varied from 1:1 to 1:2. We noted that at higher temperature with a higher ratio of starting chromium catalyst, a lower selectivity for the pinacol coupling was obtained.

The catalytic reactions produced both diastereomeric pinacol products *dl*-**1** and *meso*-**1** with the *meso*-product favored in ratios from 0.6:1 to nearly 1:1. The stereoselectivity in the presence of aluminum as the stoichiometric reductant was similar to when zinc-dust was used.

In summary, we have shown that chromium salts will catalyze the pinacol coupling of benzaldehyde in water in the presence of zinc or aluminum as terminal reductants. Gratifyingly, the best pinacol/benzyl alcohol ratios were obtained with the lowest chromium catalyst ratios. It was still disappointing that the benzyl alcohol reduction product was in each case the major product of the reaction. Given this promising entry into a catalytic coupling reaction in water, we are next pursuing the reactivity of different ligand systems on chromium to see if the changes in the metal ligation can lead to more selectivity for the coupling reaction. We also plan to extend our investigation to include the coupling of different aromatic as well as aliphatic aldehydes.

Table 1
Pinacol coupling/reduction of benzaldehyde in water

Entry	$CrCl_2$[a]	[PhCHO] (M)	Metal reductant[b]	Temp (°C)	Recovered PhCHO (%)	% *dl*-**1**[c]	%meso-**1**	% **2**	*dl*-/meso-	**1/2**
1	0	0.25	3 equiv Zn	20	100	0	0	0	—	—
2	0	0.25	3 equiv Zn	60	100	0	0	0	—	—
3	5	0.25	3 equiv Zn	20	ca. 5	18	23	59	0.8	0.7
4	10	0.25	3 equiv Zn	20	ca. 5	14	23	63	0.6	0.6
5	25	0.25	3 equiv Zn	20	ca. 5	25	28	47	0.9	0.8
6	5	0.25	3 equiv Zn	60	ca. 5	19	20	61	1.0	0.7
7	10	0.25	3 equiv Zn	60	ca. 5	20	23	57	0.9	0.8
8	25	0.25	3 equiv Zn	60	ca. 5	6	11	83	0.6	0.2
9	5	1.25	3 equiv Zn	20	<1	15	18	67	0.8	0.5
10	10	1.25	3 equiv Zn	20	<1	14	19	67	0.7	0.5
11	25	1.25	3 equiv Zn	20	<1	21	23	56	0.9	0.8
12	10	0.25	3 equiv Al	20	90	n.d.	n.d.	n.d.	n.d.	n.d.
13	10	0.25	3 equiv Al	60	ca. 5	22	25	53	0.9	0.9

[a] Mol % of $CrCl_2$ relative to benzaldehyde.

[b] Equivalents of metal reductant relative to benzaldehyde.

[c] Percentages of products as relative product abundance in ^1H NMR spectrum (unreacted benzaldehyde not included in ratio).

Acknowledgments

Support for this work from the Oklahoma Biofuels Center to R.L. Halterman and K.M. Nicholas and an NSF EPSCOR fellowship to S.M. are gratefully acknowledged.

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10. *General procedure for the catalytic pinacol coupling:* A suspension of zinc powder (3.0 mmol, 196 mg) and $CrCl_2$ (0.10 mmol, 12.3 mg) in water (4 mL) was stirred at 20 °C for about 5 min under a nitrogen atmosphere. Distilled benzaldehyde (1.0 mmol, 100 μL) was added to the mixture which was then stirred vigorously for 20 h. (For the heated reactions, the reaction flask was placed in a silicon oil bath at 60 °C immediately following the addition of the benzaldehyde.) The reactions were quenched with 1 N HCl (5 mL), additional water (4 mL) was added, and the mixture was extracted with ether (3 × 20 mL). The combined organic layers were dried with magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give the crude product mixture (ca. 90% mass recovery) which was analyzed by ^1H NMR spectroscopy in $CDCl_3$. The diagnostic benzylic hydrogen signals for *meso*-**1** at 4.84 ppm, *dl*-**1** at 4.72 ppm, and benzyl alcohol at 4.67 ppm were used in conjunction with the total aromatic region 7.1–7.35 ppm to calculate product ratios.