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INTERMOLECULAR PINACOL CROSS COUPLING OF ARYL ALDEHYDES OR THEIR DIMETHYL ACETALS WITH NON-ARYL ALDEHYDES.

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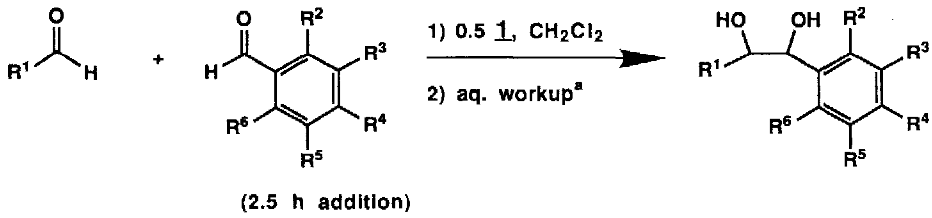
Abstract. 1-Aryl-2-alkyl-1,2-ethanediols have been synthesized via intermolecular pinacol cross coupling of aryl with non-aryl aldehydes. Dimethyl acetals of aryl aldehydes can also be cross coupled with non aryl aldehydes to yield 2-aryl-2-methoxy-1-alkyl-1-ethanols. The reaction is accomplished employing the vanadium(II) reagent $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ which is prepared *in situ* from $VCl_3(THF)_3$.

Recently we reported the first practical intermolecular pinacol cross coupling reaction between two electronically similar aldehydes promoted by the vanadium(II) reagent $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ (**1**).[1] The coupling of electronically activated ketones with other carbonyls has been accomplished with several low valent metal reagents.[2] However, an efficient synthesis of 1-aryl-2-alkyl-1,2-ethanediols via dimerization of an aryl aldehyde with a non-aryl aldehyde has not been reported. Herein, we describe such a reaction. A method for coupling dimethyl acetals of certain aryl aldehydes with non-aryl aldehydes that complements the pinacol cross coupling reaction is also discussed.

In general, we have found that slow addition (ca. 2 h) of an aryl aldehyde to a dichloromethane solution of **1** (generated *in situ* from $VCl_3(THF)_3$[3] and zinc dust; see Table 1) and a non-aryl aldehyde is necessary to obtain good yields of cross coupled products. Rapid addition (1-10 min) results in approximately 1:1 mixtures of cross and homo coupled products.[4] Cross coupling reactions work best when the aryl aldehyde has an *ortho* or *para* electron withdrawing group or when it is capable of forming a chelate with the metal. These trends are related to the increased rate of coupling exhibited by these two classes of aldehydes. We have already noted the results of chelation on the rate of aldehyde coupling.[1] The effect imparted by electron withdrawing substituents is most likely a result of the lowered reduction potential of these aldehydes. However, the exact mechanism of homo or cross pinacol coupling reactions remains to be answered.

Although the results presented in Table 1 represent the first efficient synthesis of 1-aryl-2-alkyl-1,2-ethanediols via pinacol cross coupling, the method clearly suffers in complete generality. An alternative cross coupling reaction was sought that would allow us to access products derived from slow reacting aryl aldehydes. Our initial studies on

Table 1[a]



Entry	R^1	R^2	R^3	R^4	R^5	R^6	Yield[b,c](ds)
1	$Ph(CH_2)_2$	OMe	H	H	H	H	65(1:1)
2	n-C_5H_{11}	Br	H	H	H	H	82(1:1)
3.	n-C_5H_{11}	H	H	Br	H	H	25(1:1)
4.	n-C_5H_{11}	H	H	H	H	H	49(1:1)
5.	n-C_5H_{11}	CF_3	H	H	H	H	79(1:1)
6.	n-C_5H_{11}	H	H	CF_3	H	H	77(1:1)
7.	$Ph(CH_2)_2$	Cl	H	H	H	Cl	82(2:1)
8.	i-Pr	CF_3	H	H	H	H	72(4:1)[d]

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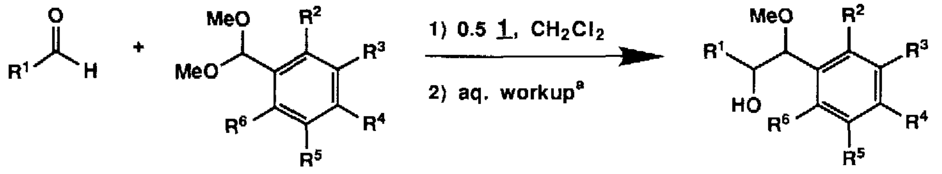
[a] A dry 50 mL flask was charged with $VCl_3(THF)_3$ (0.82 g, 2.2 mmol), zinc dust (80 mg, 1.2 mmol) and dichloromethane (15 mL) (all manipulations performed under nitrogen). The red suspension was stirred and within 10-20 min the solution color became green. The non-aryl aldehyde (2.0mmol) in dichloromethane (5 mL) was then added via syringe (solution turns red-brown). The aryl aldehyde (2.0 mmol) in dichloromethane (5 mL) was added to the reaction solution over 2.5 h using a syringe pump. After stirring an additional 30 min., the reaction was quenched with sodium tartrate (10% w:v, 50 mL) (the mixture should be shaken vigorously) and extracted with dichloromethane (3 x 50 mL). The combined organics were washed with saturated $NaHCO_3$ (50 mL) and dried ($MgSO_4$). Crude products were purified by flash chromatography on silca gel (hexane/ethyl acetate). [b] All yields (isolated) are for ca. 1:1 mixtures of *threo* and *erythro* diols. [c] All new compounds have been completely characterized by combustion and spectroscopic analysis. [d] The major isomer was the *threo* diol.

Table 2[a]



Entry	R^1	R^2	R^3	R^4	R^5	R^6	Yield[b,c](ds)
1	$Ph(CH_2)_2$	H	H	H	H	H	75(1:1)
2	$Ph(CH_2)_2$	H	H	OMe	H	H	78(1:1)
3.	$Ph(CH_2)_2$	H	CH_2OCH_2		H	H	52(1:1)

[a] The reaction conditions are the same as described in footnote a of Table 1 except that the acetal was added dropwise over a 10 min. period and was left to stir for an additional 15 h. [b] All yields are for isolated products. [c] All new compounds have been completely characterized by combustion and spectroscopic analysis.

the reactivity of **1** indicated that the dimethyl acetal of benzaldehyde self coupled to give a 1:1 mixture of (*d,l*:*meso*)-1,2-diphenyl-1,2-dimethoxyethane.[5] One could postulate that this reaction proceeds via the dimerization of two α-alkoxy radicals. However, an alternative mechanism could involve trapping such a radical by a vanadium(II) center to give an organometallic intermediate.[6,7] Reaction of this species with a second equivalent of a coordinated acetal could then lead to the observed products. If the latter mechanism is operative, then substitution of the second equivalent of acetal with a non-aryl aldehyde should lead to cross coupled products. Furthermore, it was expected that reaction of such an organometallic intermediate with an aldehyde would be faster than with more of its precursor acetal. The results of these reactions are provided in Table 2.[8] Hindered dimethyl acetals do not work well in this reaction and cyclic acetals do not react with **1** at all. From a synthetic standpoint, the reaction is potentially useful in that it provides difunctional products where the vicinal oxygens have been selectively discriminated.

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3. Manzer, L. E. *Inorganic Syntheses* **1982**, *21*, 135.

4. The predominant homo coupled products are derived from aryl aldehyde coupling.

5. Coupling of acetals derived from aromatic ketones and aldehydes has been previously observed: (a) Ishikawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Japan* **1978**, *51*, 2059.

6. For examples of the trapping of organic free radicals by transition metal radicals see: (a) Nugent, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1989**, *111*, 4525. (b) Nugent, W. A.; RajanBabu, T. V. *ibid.* **1988**, *110*, 8561. (c) Cooper, T. A. *ibid.* **1973**, *95*, 4158.

7. For examples of group IV α-alkoxy organometallic intermediates see: (a) Buchwald, S. L.; Nielsen, R. B.; Dewan, J. C. *Organometallics* **1989**, *8*, 1593. (b) Erker, G.; Dorf, U.; Atwood, J. L.; Hunter, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 2251 and references therein.

8. Kagan and coworkers have found that ketones can be coupled with "α-alkoxy radicals" generated from reaction of SmI_2 with α-alkoxyacid chlorides. Our reaction does not work with dialkyl ketones. Sasaki, M.; Collin, J.; Kagan, H. B. *Tetrahedron Lett.* **1988**, *29*, 4847.

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