Oxovanadium(IV) Complex-mediated Catalysis in Mukaiyama-type Aldol Additions

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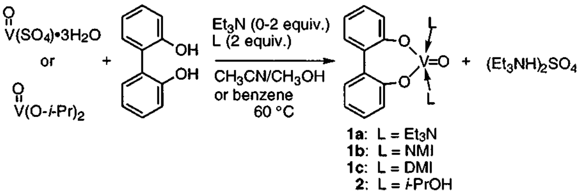
Abstract. Condensation of vanadyl sulfate with 2,2'-biphenol in the presence of *N*-containing ligands provides oxovanadium(IV) complexes which serve as efficient catalysts in Mukaiyama aldol reactions to afford aldol products in 52–100% yields with diastereoselectivities of up to 90/10 (anti/syn)

Key Words: Lewis acids, 2,2'-biphenol, *N*-methylimidazole, diastereoselective, β-hydroxyesters

Mukaiyama-type aldol reactions have constituted one of the most salient tactics in carbon-carbon bond formation. The diversity of Lewis acids,[1] and the great opportunities for the judicious combination of either aldol components have elicited tremendous endeavors toward the stereoselective and asymmetric variants of this type of process.[2] During the search of new functional metal catalysts, chemists have recently switched gears toward the first row transition metals other than d^0–Sc(III),[3] d^0–Ti(IV)[4] and d^{10}–Zn(II),[5] such as Fe(II/III)[5,6] and Cu(II).[7] Among them, the d^9-Cu(II) salts have resurged as extremely mild Lewis acids in various asymmetric aldol-type additions.[8] However, the complimentary, paramagnetic d^1-V(IV) species has received very little attention.[9] Vanadium(IV) complexes are commonly employed as pre-catalysts for sulfide and olefin oxidation when combined with O_2 or peroxide co-oxidants,[10] although the moderately electrophilic nature of oxovanadium complexes toward nitrogen[11] and oxygen[12] functionalities has been well documented in the literature. Spurred by the recent findings on the use of oxotitanium(IV) complexes as Lewis acids in Michael and Mukaiyama aldol reactions,[13] we have initiated a study toward the catalytic profile of the corresponding vanadium(IV) complexes. Herein, we describe our preliminary findings as to their uses in the Mukaiyama aldol reactions.

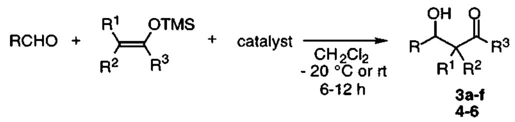
We have selected 2,2'-biphenol as a model template for complex formation in view of its structure and reactivity similarities to the chiral variant, 2,2'-dihydroxy-1,1'-binaphthyl. Although the analogous titanium(IV) complexes have been characterized to be monomeric in nature,[13c] the aggregation behavior of the vanadyl substrates in solution has never been identified. Vanadyl biphenolate complexes with varying ligand attributes were synthesized from two different routes. The first one involves gradual addition of a solution of 2,2'-biphenol (1 equiv.) in CH_3CN (with or without Et_3N) to a solution of vanadyl sulfate trihydrate in warm MeOH by the action of ligands (such as Et_3N, *N*-methylimidazole (NMI), and 1,2-dimethylimidazole (DMI)), Scheme 1.[14] A green solution of the respective vanadyl complex **1** was resulted in 2 hours and may be used directly after concentration. The alternative method, which follows the procedure similar to that of oxotitanium(IV),[13c] requires direct condensation of vanadyl isopropoxide[15] and 2,2'-biphenol in refluxing benzene. A light brown salt **2** obtained after solvent removal was used for the aldol studies. The green color of the vanadyl complexes **1** obtained from the first method is characteristic for many penta-coordinated vanadium(IV) species.[16] Presumably, all these *N*-containing ligands can satisfy the valence requirement around V(IV). All these complexes were subjected to catalysis for the Mukaiyama aldol addition since the varying modes and strengths of ligand coordination around V(IV) may have a decisive influence on the reactivity and stereoselectivity in the aldol process.

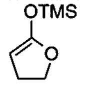
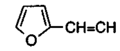
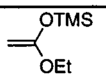
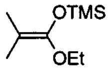
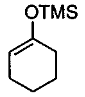


Scheme 1

Aldol additions between benzaldehyde and silyl ketene acetal (SKA) derived from γ-butyrolactone were first examined in the presence of 10-20 mol% of the respective vanadyl catalyst with varying solvent polarity (entry 1–4), Table 1. The reaction was found to proceed more smoothly with **1a** at -20 °C in CH_2Cl_2 or in toluene/CH_2Cl_2, leading to the corresponding β-hydroxylactones-**3a** in 53% yield with moderate anti preference (80/20, anti/syn). When the reaction was conducted at -50 °C, the selectivity was improved to 88/12, albeit with lower conversion (40%). It should be pointed out that vanadyl sulfate alone does not catalyze the reaction due to its poor solubility in aprotic, organic solvents. The reaction proceeded sluggishly in polar coordinating solvents (e.g., CH_3CN, dioxane, and THF). The aldol adducts were produced in less than 15% yield with slightly higher diastereocontrol (84/16, anti/syn).

Table 1. Aldol Reactions between Aldehydes and Enol Silanes Catalyzed by Various Oxovanadium(IV) Complexes



entry	R	enol silane	catalyst	d.r.[a]	yield, %[b]
1	Ph		**1a**	80/20 (40/60)[c]	53 (56)[c]
2			**1a**	80/20	50[d]
3			**1a**	74/26	12[e]
4			**1a**	80/20	10[f]
5			**1b**	90/10	72
6			**1b'**	90/10	93
7			**1c**	87/13	66
8			$SbCl_5$	50/50	57[g]
9			TMSOTf	50/50	91[g]
10	2-Naph		**1b'**	86/14 (35/65)[c]	95 (53)[c]
11	4-$MeOC_6H_4$		**1b'**	80/20 (43/57)[c]	78 (20)[c]
12	4-$NO_2C_6H_4$		**1b'**	76/23 (59/41)[c]	100 (76)[c]
13	Ph—≡		**1b'**	80/20	86
14			**1b'**	90/10	95
15	$Ph(CH_2)_2$		**1b'**	72/28	74
16	*c*-C_6H_{11}		**1b'**	60/40[h]	78
17	4-$NO_2C_6H_4$		**1b'**	---	91
18	Ph		**1b'**	---	62[h]
19	Ph		**1b'**	42/58	73[h]

[a] Anti/syn diastereomeric ratios determined by ^1H NMR analysis. [b] Isolated yields. [c] The values in parenthesis are the resluts from catalyst **2**. [d] Toluene/CH_2Cl_2 (1/1) was used as solvent. [e] Two equivalents of NMI were added. [f] Two equivalents of DMI were added. [g] See refercence 18. [h] Reactions were performed at rt for 48 h.

Significantly better chemical yields (72% and 66%) and diastereocontrols (90/10 and 87/13) were observed when the reactions were carried out with catalyst **1b** and **1c** (entry 5 and 7).[17] It should be noted that roughly equal anti-syn preference was found in this test aldol reaction catalyzed by common Lewis acids (e.g., $SbCl_5$, entry 8) or by silyl-X (e.g., Me_3SiOTf, entry 9).[18] The resulting salt ($(Et_3NH)_2SO_4$) in the catalyst preparation could also interfere with the aldol performance. Best results (93% yield, 90/10) were finally obtained by using catalyst **1b'** where biphenol was not pre-treated with Et_3N (entry 6). Contrasting results were observed when the reactions were catalyzed by **1a** with 2 extra equivalents of NMI or DMI as an additive (*ca.* 10% yield, entry 3 and 4),[19] indicative of the importance of the ligand attributes on the catalytic activity of the vanadyl (IV) complexes in solution.[10b]

In addition to the parent benzaldehyde, 5 different aromatic aldehydes of varying election demands were also examined (entry 10-14). The chemical yields of the resultant β-hydroxylactones were in the range of 86–100% except in the case of **3c** (R = 4-$MeOC_6H_4$), whose yield was decreased by about 15%. In addition, the diastereocontrols were all moderate (76/23–90/10, anti/syn). On the other hand, much poorer conversion yields (20–76%) were observed when the vanadyl catalyst **2** generated from vanadyl isopropoxide was employed. The diastereocontrols of the aldol additions fell within the range of 50/50 to 35/65, but with slight preference of the opposite syn isomer. The oxovanadium(IV) complex-mediated catalysis by **1b'** was also amenable to aliphatic aldehydes (e.g., 3-phenylpropanal and cyclohexylcarbaldehyde,[20] entry 15 and 16). TMS ketene acetals of all three different substitution patterns (un-, mono-, and di-substituted) as well as silyl enol ethers are all capable aldol components, as represented in entry 17-19. A typical reaction procedure is described for benzaldehyde and SKA derived from γ-butyrolactone with catalyst **1b'**: To a solution of vanadyl sulfate trihydrate (1 mmol) and NMI (2 mmol) in hot MeOH (5 mL) was added a solution of 2,2'-biphenol (1 mmol) in warm CH_3CN (2 mL). The reaction mixture which turned dark green gradually was heated at 50 °C for 2 hours. After having been cooled to ambient temperature, the resultant vanadyl complex was concentrated *in vacuo* to give a glassy brownish green solid which was used directly without further purification. The vanadyl catalyst (10 mol%) dissolved in CH_2Cl_2 (5mL) was mixed with benzaldehyde (2 mmol) and the mixture was cooled to -20 °C.[21] Silyl ketene acetal (4–6 mmol, 2–3 equiv.) was added and the reaction mixture was stirred for 6–12 hours. After having been quenched with saturated, aqueous $NaHCO_3$ (5 mL), the reaction mixture was separated and the aqueous layer extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were concentrated and hydrolyzed in 1N HCl/THF solution (5 mL, 0 °C, 2 hours). After usual workup procedure, the aldol products **3a** were isolated by column chromatography on silica gel (1/4, EtOAc/hexane).

In conclusion, we have documented *the first example of the Mukaiyama aldol reaction mediated by oxovanadium(IV) biphenolate complexes*. The complexes can be easily generated from relatively cheap, commercial vanadyl sulfate. More importantly, ease of incorporation of chiral auxiliaries and/or ligands[22] as well as ease of modulation of the metal counterions make oxovanadium(IV) an attractive alternative to other transition metals. Investigations are underway as to the scope of vanadium(IV) in other modes of catalytic reactions as well as in asymmetric modifications of the aldol and related processes.

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