# *Communications to the Editor*

Atom Economy: Aldol-Type Products by Vanadium-Catalyzed Additions of Propargyl Alcohols and Aldehydes

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The development of synthetic reactions that involve simple additions with anything else needed only catalytically is important to enhance synthetic efficiency.[1] One of the classical atom economic reactions is the aldol condensation; however, rarely is it employed in its original atom economic manner.[2] A number of reasons preclude ready application of the direct aldol condensation—a quite noteworthy one being the chemoselectivity. An alternative strategy that overcomes this deficiency is to generate an appropriate enol derivative by an alternative method but one that retains atom economy. In this paper, we report the development of such a process that created a new bond construction represented by eq 1.

$$R^1{-}\!\equiv\!{-}\underset{\underset{OH}{|}}{C}R^2 \;+\; R^3{-}CHO \xrightarrow{\text{cat}} R^1{-}C(=O){-}C(=R^2)\cdots R^3\text{-}OH \qquad (1)$$
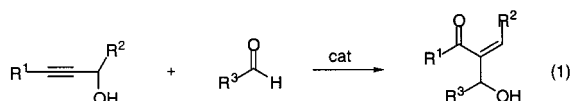
1,3-Transpositions of allylic and propargylic alcohols are catalyzed by a variety of oxo metal complexes including those derived from vanadium,[3] molybdenum,[4] tungsten,[5] and rhenium.[6] The proposed route for the isomerization of propargyl alcohols to enones, as illustrated in Scheme 1, indicates the intermediacy of an allenolate I which is protonated. If this intermediate can be intercepted by an aldehyde faster than protonation, then intermediate II would form which, upon protonation, generates the aldol-type adduct III. Indeed, the Lewis acidity of the metal may promote coordination of the aldehyde to it and thus the aldol-type process.

Initial attempts with triphenylsilyl perrhenate[7] or bis(triphenylsilyl) molybdate[8] were unsuccessful. In the former case, rearrangement occurred but no trapping. In the latter case, a complex mixture resulted. In the case of tris (triphenylsilyl) vanadate (**1**),[3c,9]

Scheme 1. Proposed Addition of Propargyl Alcohols and Aldehydes

the reaction of propargyl alcohol **2** and a stoichiometric amount of benzaldehyde in the presence of 5 mol % **1** in 1,2-dichloroethane (DCE, 1.0 M) at 100 °C gave an 84% yield of the adduct **3**[10] as a 76:24 *Z:E* mixture (see eq 2). Keeping the bath
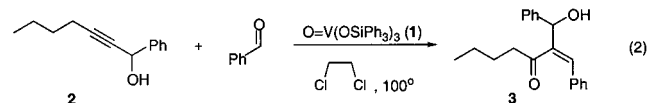
temperature at 100 °C, but changing the solvent to DME gave similar results. On the other hand, in THF at 100 °C (sealed tube), a 71% yield of a 91:9 *Z:E* mixture was obtained. Suspicious that the internal temperature in the last case may not be quite as high, the reaction in DCE was repeated at 80 °C for the same 12 h period. Indeed, the *Z:E* ratio increased to 95:5 with a small loss in yield to 73% due to lower conversion. Performing the reaction at 80° for 20 h increased the yield to 94% with a small loss of *Z:E* selectivity to 91:9.

Using these latter conditions, a range of propargyl alcohols as shown in eq 3 were examined. Table 1, entries 1−4, summarizes the results. Most notably, a sterically hindered substrate as in entry 2 gave an excellent result. Placing an electronegative substituent in R^1 slows the reaction such that a 48 h reaction time was required for better conversion, but still the reaction was incomplete leading to a reduced yield of 42% (entry 4).

If R^2 is different that Ph, then there is the prospect that the allyl alcohol of the product may equilibrate as in eq 3. Indeed, using *p*-anisaldehyde in eq 3 (**4**, $R^1 = n\text{-}C_4H_9$, i.e., **2**), a 2:3 mixture of the unrearranged **6** and rearranged **7** products was obtained in 90% yield. On the other hand, aromatic aldehydes bearing electron-withdrawing groups led to a strong preference for isolation of the kinetic product **6** (Table 1, entries 5−8).[10] As expected based upon eq 3, the amount of rearranged product **7** depends on the reaction time. For example, the reaction time of entry 6 is 10 h. If it is doubled, the **6f:7f** ratio decreases to 89:11 from 95:5 with some loss of *Z:E* selectivity as well (**6f** 98:2, **7f**

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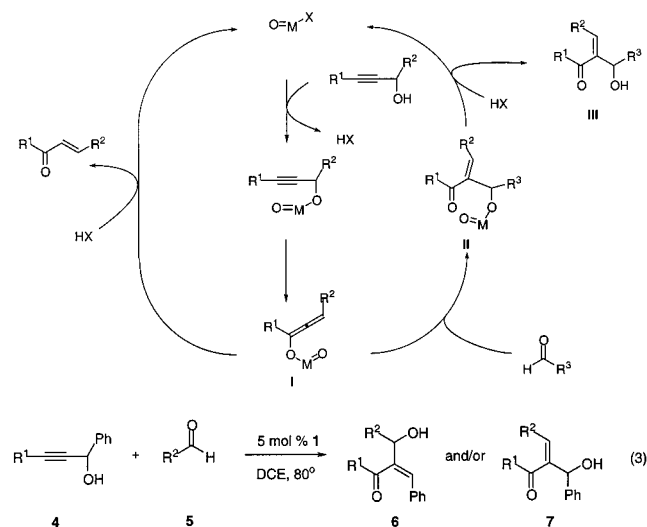
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(7) Schoop, T.; Roesky, H. W.; Noltemeyer, M.; Schmidt, H. G. *Organometallics* **1993**, *12*, 571.

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(10) New compounds have been characterized spectroscopically, and elemental composition has been established by high-resolution mass spectrometry and combustion analysis.

Table 1. Vanadium-Catalyzed Addition of Propargyl Alcohols and Aldehydes[a]

| Entry	R[1]	R[2]	Isolated Yield	Cmpd Suffix	6(Z:E):7(Z:E)
1[b]	n-C$_4$H$_9$	Ph	94%	a	N.A.[g] (91:1)
2[b]	t-C$_4$H$_9$	Ph	95%	b	N.A.[g] (98:2)
3[b,c]	Ph	Ph	73%	c	N.A.[g] (88:12)
4[d]	TDBMSOCH$_2$	Ph	42%	d	N.A.[g] (only Z)
5[b]	n-C$_4$H$_9$	CF$_3$—C$_6$H$_4$—	77%	e	93 (only Z):7 (only Z)
6[e]	n-C$_4$H$_9$	O$_2$N—C$_6$H$_4$—	92%	f	95 (only Z):5 (only Z)
7[b]	n-C$_4$H$_9$	NC—C$_6$H$_4$—	79%	g	95 (96:4):5 (only Z)
8[f]	n-C$_4$H$_9$	C$_6$H$_4$(NO$_2$)—	81%	h	92 (only Z):8 (only Z)
9[b]	n-C$_4$H$_9$	n-CH$_3$CH$_2$CH$_2$	55%	i	Only 6 (89:11)
10[b]	n-C$_4$H$_9$	C$_6$H$_{11}$—	58%	j	90 (96:4):10 (58:42)

[a] Reactions performed using 5 mol % **1**, 1.2 equiv of propargyl alcohol, and 1.0 equiv of aldehyde at 80 °C in DCE at 0.2 M unless noted otherwise. [b] Reaction time of 20 h. [c] Reaction performed at 100 °C. [d] Reaction time of 48 h. [e] Reaction time of 10 h. [f] Reaction time of 12 h. [g] N. A. = not applicable.

86:14). Use of aliphatic aldehydes (entries 9 and 10) also led to good selectivity for the unrearranged product **6**.[10] However, the **Z**:**E** selectivity is not as high as for aromatic aldehydes.

The formation of **6** in preference to **7** can derive either from a thermodynamic effect (i.e., the **6**:**7** ratio represents a thermodynamic ratio) or a slower rate of rearrangement of the kinetic product **6** (see eq 4). That the latter is the case is demonstrated

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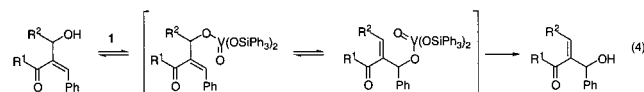
by comparison of entry 5 with eq 5. Thus, the **6e**:[10]**7e** ratio for entry 5 of 93:7 for eq 3 becomes 12:88 in eq 5. In the latter case,

(5)
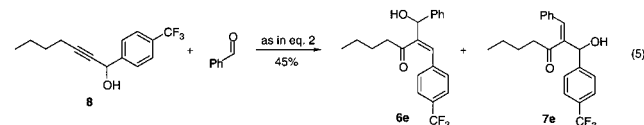
7e is the kinetic product and **6e** the rearranged one. If the **6**:**7** ratio of eq 3 reflected a thermodynamic equilibrium, then the same ratio of products would form regardless of which pair of reactants

were employed. The observed substituent effects on the rearrangements of both the propargyl alcohols and the allyl alcohols indicate that electron-withdrawing groups slow and electron-donating groups speed the reactions. For example, the reaction of entry 5 proceeds twice as fast as the reaction of eq 5. Furthermore, **6e** rearranges significantly faster than **7e** as illustrated by their ratios in entry 5 and eq 5. The existence of the rearrangement in eq 1 was demonstrated by the use of deuterated benzaldehyde as shown in eq 6. After a reaction time of 10 h, a

(6)
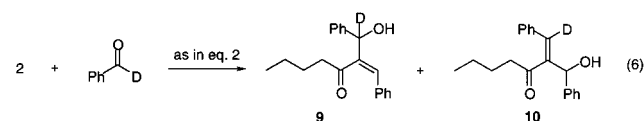
76:24 ratio of **9**:**10** was obtained (62% yield). Increasing the reaction time to 20 h increased the conversion (86% yield) and equilibration to 65:35.

This process represents a new paradigm for formation of aldol-type products which cannot be easily obtained by other methods.[11] Furthermore, the reaction favors formation of the normally less stable *Z*-*β*-arylenones. Direct aldol reactions between enones and aldehydes are prohibited by the difficulty of direct enolization to the allenolate. The products are analogous to Baylis−Hillman adducts.[12] However, the Baylis−Hillman reaction normally requires *β*-unsubstituted acceptors. This vanadium-catalyzed reaction also should lend itself to asymmetric induction, a goal currently under investigation.

Supporting Information Available: Characterization data for **6a**−**j** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) A general procedure follows: In a screw cap reaction vial sealed with a Mininert syringe valve, aldehyde (1.0 mmol) followed by propargyl alcohol (1.2 mmol) was added to a suspension of VO(OSiPh$_3$)$_3$ (5 mol %) in 0.5 mL of DCE. After heating at 80° for the specified time followed by cooling, the reaction mixture was diluted with 20 mL of ether and checked by TLC. The solvent was evaporated in vacuo and the residue purified by flash chromatography eluting with pet. ether−ethyl acetate to give the products.

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