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Vanadium-Catalyzed Addition of Propargyl Alcohols and Imines

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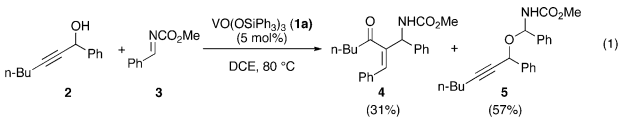
Simple addition reactions and prototropic rearrangements are two major types of atom-economical processes.[1] More powerful and useful transformations are possible when these two classes of reactions are combined. The aldol-type addition reactions of propargylic alcohols and allenic alcohols recently developed in our group are good examples of such transformations.[2]

To extend the scope of the oxovanadium-catalyzed aldol-type reaction, we considered using imines in a Mannich-type addition reaction. The inferior reactivity of imines, compared to that of carbonyl compounds, was an apparent concern we had from the outset because the simple Meyer−Schuster rearrangement product may prevail if the nucleophilic addition to the imines is not efficient.[3] Therefore, we began our study by identifying an appropriate imine substrate for the vanadium catalysis.

The initial screening test results with some readily accessible imines, such as *N*-phenyl, *N*-sulfonyl, *N*-phosphorylimines, and *O*-methyl benzyloxime, were disappointing, producing only the Meyer−Schuster rearrangement product. This result indicates that, although the sigmatropic rearrangement was operative, trapping of the imines was not efficient. Use of the more electrophilic *N*-phenylglyoxaldimine resulted in a complex reaction mixture. On the other hand, the reaction with *N*-methoxycarbonylimine **3** gave the desired Mannich addition product **4** in 31% yield along with an unusual addition product **5** in 57% yield (eq 1).

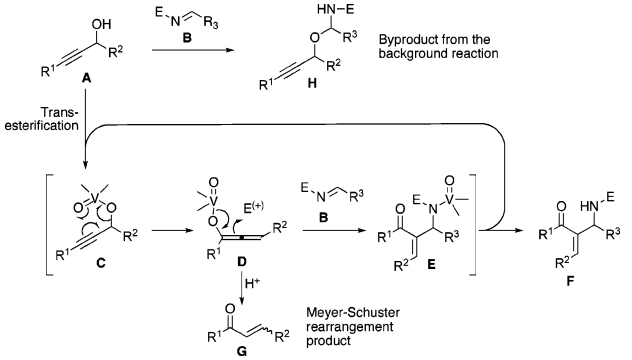


The adduct **5** is likely formed by an uncatalyzed background reaction, as was confirmed by the control experiment run in the absence of the vanadium catalyst, which provided **5** in quantitative yield. Remarkably, this aminal adduct **5** was highly stable and did not revert to **2** and **3** even with prolonged reaction time in the presence or absence of the vanadium catalyst.

Encouraged by the somewhat promising result with *N*-methoxycarbonylimine **3**, a series of optimization studies was conducted to minimize the formation of **5**, varying parameters such as solvent, stoichiometry, and additives. While no other attempts were fruitful, the slow addition of **2** proved beneficial, providing the Mannich addition product **4** in 54% yield and the simple addition product **5** in 20% yield.

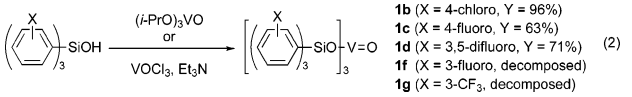
We turned our attention to modifying the vanadium catalyst with electron-withdrawing groups, which we thought would facilitate the desired addition reaction pathway by promoting the transesterification step (Scheme 1, A → C and E → C). Furthermore, the placement of electron-withdrawing groups on the vanadium metal center was expected to increase the Lewis acidity of the catalyst, thereby accelerating the addition step (D → E) through the activation of the imines toward electrophilic attack due to enhanced complexation. Indeed, the transesterification was suggested as the rate-determining step for the oxovanadium-catalyzed Meyer−Schuster

Scheme 1. Proposed Reaction Mechanism



rearrangement.[4] This is consistent with our own results obtained in the previous study of the aldehyde addition reaction in which electron-rich propargyl alcohols provided aldol-type addition product in higher yield than electron-poor propargyl alcohols.

On the basis of this hypothesis, we synthesized a series of oxovanadium catalysts bearing electron-withdrawing groups according to literature procedures (eq 2).[4]



Curiously, vanadates **1f** and **1g** with unsymmetrically substituted arylsilanols failed to give a stable complex. On the other hand, **1b**, **1c**, and **1d** were readily recrystallized and tested in the Mannich-type addition reaction with the propargylic alcohol **2** and *N*-methoxycarbonylimine **3**. The results are summarized in Table 1.

Table 1. Optimization Study

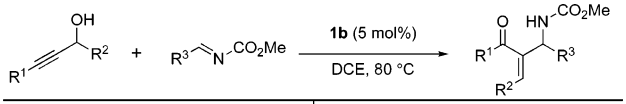
			Yield (%)[c]	
entry	catalyst	conditions[a,b]	**4**	**5**
1	**1a**	A	18	74
2	**1a**	B (20 h)	54	20
3	**1b**	B (20 h)	92	
4	**1b**	B (10 h)	84	
5	**1b**	A	79	
6	**1b**	B (20 h)[d]	74	
7	**1c**	B (20 h)	81	
8	**1d**	B (20 h)	53[e]	

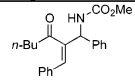
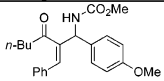
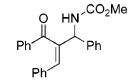
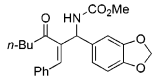
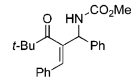
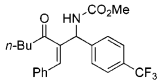
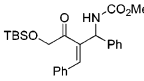
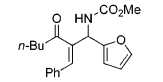
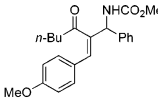
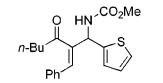
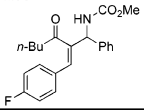
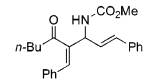
[a] Catalyst (5 mol %) and **2** (1.2 equiv) were employed. [b] Method A: A solution of **2** and **3** and the catalyst in DCE was placed in a reaction vial and allowed to react at 80 °C for 24 h. Method B: A solution of **2** in DCE was added slowly over the given time to a solution of **3** and the catalyst at 80 °C, and stirring was continued such that the total reaction time was 24 h. [c] Isolated yields. [d] **1b** (2.5 mol %) was used. [e] Meyer−Schuster product was isolated in 11% yield.

To our delight, all three new catalysts performed well in suppressing the background reaction compared to the standard catalyst **1a**. Among the vanadium complexes that were examined,

10.1021/ja064011p CCC: $33.50

Table 2. Vanadium-Catalyzed Mannich-type Addition



entry	product	yield	entry	product	yield
1		92%	7		66%
2		71%	8		81%
3		86%	9		76%
4		70%	10		44%
5		71%	11		86%
6		74%	12		50%

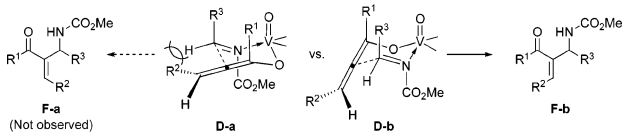
tris[tri(4-chlorophenyl)silyl]vanadate **1b** gave the most desirable result, providing the Mannich-type addition product **4** in 92% yield with no noticeable amount of **5**. Remarkably, **1b** catalyzed the desired addition reaction even without using the slow addition procedure (entry 5). In general, better results were obtained with slower addition of **2** (entries 3−5). The yield eroded when 2.5 mol % of the catalyst was employed instead of 5 mol % (entry 6). The vanadium complex **1c** showed good performance as well, providing the addition product in 81% yield, using a slow addition technique (entry 8). On the other hand, the reaction with the complex **1d** was not as clean as with the other two complexes and produced many byproducts, including the Meyer−Schuster product in 11% yield (entry 7).

Adopting the optimized reaction conditions used in entry 3 of Table 1 as our standard, the variation of the propargylic alcohols and imines was explored (Table 2).[5] All the alcohol substrates bearing an aryl group at the propargylic position participated well in the reaction, providing the Mannich-type addition product in good yield. Unlike the aldehyde addition, the effect of the electronic character of **2** was not pronounced (entries 5 and 6). Imines with both electron-donating groups (entries 7 and 8) and electron-withdrawing groups (entry 9) gave the addition product in moderate to good yield. Imines containing heteroaromatic groups were also examined. The imine derived from furfuraldehyde gave the addition product in somewhat low yield, possibly due to the thermal instability of the imine (entry 10). On the other hand, the thiophene-containing imine gave the adduct in high yield (entry 11). The imine derived from cinnamaldehyde participated moderately well, providing the 1,2-addition product in 50% yield (entry 12).

Notably, the addition reaction produced only *Z*-enones in all examples. The complete stereoselectivity for the *Z*-olefin isomer could be explained by a staggered geometry of the allenoate structure **D** (Scheme 2). The approach from the hydrogen-substituted face (**D-b**), which leads to *Z*-enone product **F-b**, should be favored over the approach from the aryl-substituted face (**D-a**) on steric grounds.

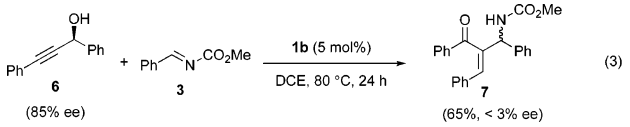
The imine derived from pivaldehyde only led to the formation of the Meyer−Schuster product (44%) and simple adduct (37%).

Scheme 2. Rationale for the *Z*-Selectivity



Attempts to use an enecarbamate as a "masked" imine proved unsuccessful, providing no reaction.[6]

To test whether the chirality of starting material was transferred to the addition product, an enantiomerically enriched propargylic alcohol **6** was prepared.[7] The addition product **7** was obtained in 65% yield, but it showed virtually no enantiomeric excess, indicating that the vanadium-catalyzed addition occurred in a nonstereospecific manner under the given conditions (eq 3).[8]



In summary, the 2-acylallylic carbamates are accessible by an atom-economic strategy from terminal acetylene, aldehyde, and *N*-acylimines by a series of addition reactions by taking advantage of the ability of oxovanadium complex to induce [3.3] sigmatropic rearrangement from propargylic alcohols. The optimized conditions were successfully applied to a range of propargylic alcohols and aromatic imines. The products of the current reaction, the β-aryl-substituted *Z*-enone compounds containing an allylic amino functionality, are not readily accessible with other methods, including the aza-Baylis−Hillman reaction.[9]

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Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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