Asymmetric Alkynyl Additions to Aldehydes Catalyzed by Tunable Oxovanadium(V) Complexes of Schiff Bases of β-Amino Alcohols

Sheng-Hsiang Hsieh, Han-Mou Gau*

Department of Chemistry, National Chung-Hsing University, Taichung 402, Taiwan
Fax +886(4)22862547; E-mail: hmgau@dragon.nchu.edu.tw

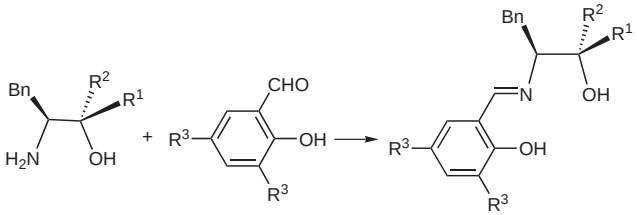
Received 16 March 2006

Abstract: The first example of asymmetric alkynyl additions to aldehydes catalyzed by oxovanadium(V) catalysts of tridentate Schiff bases of β-amino alcohols **3a**–**h** is reported. Catalytic reactions employing the best-performing catalyst **3g** furnish chiral propargyl alcohols in good to excellent enantioselectivities from 73% to 99% ee.

Key words: oxovanadium complex, alkynylation, Schiff bases, β-amino alcohols, aromatic aldehydes, aliphatic aldehydes, propargyl alcohols

Chiral secondary propargyl alcohols are important building blocks for many important biological compounds[1] and considerable efforts were devoted in recent years to developing catalytic systems for synthesis of chiral propargyl alcohols. The first effective asymmetric alkynyl addition to aldehydes for the synthesis of chiral propargyl alcohols was demonstrated by Corey and coworker using chiral oxazaborolidines.[2] Recent studies of asymmetric alkynylations to aldehydes employed zinc reagents[1,3] exclusively, and both aromatic and aliphatic aldedydes were reported to furnish chiral propargyl alcohols in high yields and high enantioselectivities with the use of either zinc or titanium catalysts. For zinc systems, catalytic alkynyl additions to aliphatic aldehydes were first developed by Carreira and coworkers using $Zn(OTf)_2$ and an ephedrine ligand.[4] Following the paper, BINOLs[5] and chiral nitrogen-containing alcohols[6] were reported as ligands to induce high stereoselectivities, and in a recent paper, alkynyl additions to unsaturated aldehydes were reported by Trost and coworkers.[7] For titanium-catalyzed alkynylation reactions, BINOLs or H_8-BINOLs were demonstrated to be excellent ligands by Chan et al.,[8] Pu et al.,[9] and Gong and coworkers.[10] For those catalytic systems, alkynylzinc reagents were generated from reactions of diethylzinc with terminal alkynes in general at elevated temperatures or from dimethylzinc with alkynes. Wang and coworkers developed a titanium-sulfonamide alcohol system to achieve excellent enantioselectivities of chiral propargyl alcohols with alkynylzinc reagents prepared at room temperature from diethylzinc.[11] Recently, Pu and coworkers found that an addition of hexamethylphosphoramide (HMPA) greatly accelerates the formation of alkynylzinc reagent from $ZnEt_2$ and terminal alkynes at room temperature.[12]

To our knowledge, there are only a couple examples of asymmetric alkynyl additions to aldehydes catalyzed by systems other than zinc and titanium metals. One is the above-mentioned boron system by Corey and coworker and another one is an In/BINOLate system by Shibasaki and coworkers.[13] Yet, there is no report of vanadium catalysts for asymmetric alkynylation reactions. We here report the first example of asymmetric alkynylation reactions employing chiral oxovanadium(V) complexes of tridentate Schiff bases of β-amino alcohols. Like the titanium(IV) metal center, the vanadium(V) metal behaves as a Lewis acidic center. In this study, a series of amino alcohols **1a**–**d** with one or two stereogenic centers were prepared starting from L-phenylalanine according to standard procedures. Treatment of **1a**–**d** with 2-hydroxy benzaldehyde or 2-hydroxy-3,5-di-*tert*-butylbenzaldehyde afforded quantitative yields of Schiff bases **2a**–**e** (Equation 1). These Schiff bases reacted with 1 mol equivalent $VO(O\textit{i}\text{-}Pr)_3$ in absolute ethanol at room temperature for one hour to give quantitative yields of oxovanadium(V) complexes **3a**–**e** (Equation 2).[14] Those complexes were confirmed by elemental analyses and by ^1H NMR and ^{13}C NMR spectroscopy and square pyramidal structures are suggested for the complexes based on the known related structures.[15]



1a: $R^1 = R^2 = H$
1b: $R^1 = R^2 = Ph$
1c: $R^1 = Ph$, $R^2 = H$
1d: $R^1 = t\text{-Bu}$, $R^2 = H$

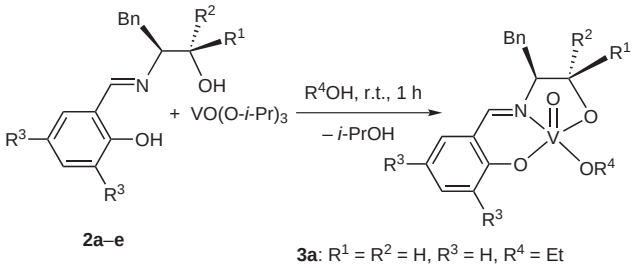
R^3 = H or *t*-Bu

2a: $R^1 = R^2 = H$, $R^3 = H$
2b: $R^1 = R^2 = Ph$, $R^3 = H$
2c: $R^1 = Ph$, $R^2 = H$, $R^3 = H$
2d: $R^1 = t\text{-Bu}$, $R^2 = H$, $R^3 = H$
2e: $R^1 = t\text{-Bu}$, $R^2 = H$, $R^3 = t\text{-Bu}$

Equation 1

The asymmetric alkynylation was first examined on benzaldehyde employing 10 mol% catalysts **3a**–**e** at –20 °C for 24 hours (Equation 3) and results are listed in Table 1. For catalyst **3a** of $R^1 = R^2 = R^3 = H$, the propargyl alcohol was obtained in 100% yield with a low enantioselectivity of 12% ee in *R*-configuration (entry 1). When **3b** of $R^1 = R^2 = Ph$ was used, the propargyl alcohol was ob-

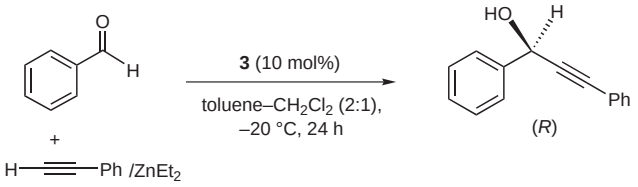
SYNLETT 2006, No. 12, pp 1871–1874
Advanced online publication: 24.07.2006
DOI: 10.1055/s-2006-948195; Art ID: W05606ST



3a: $R^1 = R^2 = H$, $R^3 = H$, $R^4 = Et$
3b: $R^1 = R^2 = Ph$, $R^3 = H$, $R^4 = Et$
3c: $R^1 = Ph$, $R^2 = H$, $R^3 = H$, $R^4 = Et$
3d: $R^1 = t$-Bu, $R^2 = H$, $R^3 = H$, $R^4 = Et$
3e: $R^1 = t$-Bu, $R^2 = H$, $R^3 = t$-Bu, $R^4 = Et$
3f: $R^1 = t$-Bu, $R^2 = H$, $R^3 = H$, $R^4 = i$-Pr
3g: $R^1 = t$-Bu, $R^2 = H$, $R^3 = H$, $R^4 = i$-Bu
3h: $R^1 = t$-Bu, $R^2 = H$, $R^3 = H$, $R^4 = t$-Bu

Equation 2

tained as a racemic mixture in 100% yield (entry 2). When the reaction was conducted using catalyst **3**c having a Schiff base containing two stereogenic centers with R^1 = Ph and R^2 = H, the enantioselectivity of the product increases to 43% ee (entry 3). When R^1 of Ph is replaced with a bulkier *t*-Bu group as in catalyst **3d**, the reaction furnished the product in a dramatic increase of the enantioselectivity up to 75% ee (entry 4). The steric effect of R^3 group on the phenolate ring was then examined. For **3e** with R^3 of bulky *t*-Bu groups, the yield of the product decreases to 78% and the enantioselectivity drops substantially to 32% ee (entry 5).



Equation 3

The above results demonstrate that catalysts with Schiff bases containing two stereogenic centers are superior in stereocontrol to catalysts having Schiff bases with one stereogenic center. In catalytic reactions, the benzaldehyde accesses the vanadium metal center from the open site *trans* to the strong oxo ligand and, thus, the size of the OR^4 alkoxide group on the vanadium metal is expected to affect the stereoselectivity of chiral propargyl alcohols as well. To study the steric effect of the R^4 group, the Schiff base **2d** was reacted with 1 mol equivalent $VO(Oi\text{-}Pr)_3$ in 2-propanol, isobutanol, or *tert*-butanol to furnish quantitative yields of complexes **3f**–**h** in one hour after removing volatile materials completely (Equation 2). Asymmetric alkynylation reactions using catalysts **3f**–**h** were then conducted and enantioselectivities improve to 84% ee for catalyst **3f** having a bulkier 2-propoxide ligand (entry 6) and to 96% for **3g** with the isobutoxide ligand (entry 7). However, the enantioselectivity of the chiral propargyl alcohol drops significantly to 69% ee with the catalyst **3h** having OR^4 of the bulkiest *tert*-butoxide ligand (entry 8).

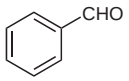
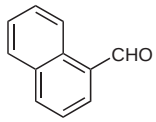
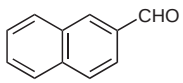
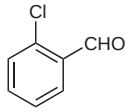
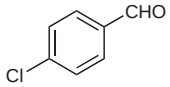
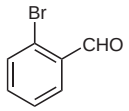
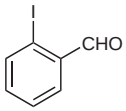
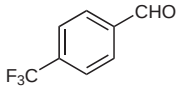
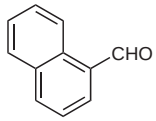
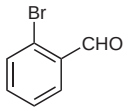
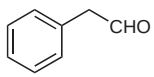
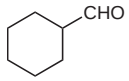
Table 1 Alkynylation of Benzaldehyde Catalyzed by Oxovanadium(V) Complexes of Schiff Bases of Amino Alcohols[a,b]

Entry	Catalyst	R^1	R^2	R^3	R^4	Yield (%)[c]	ee (%)[d]
1	3a	H	H	H	Et	100	12
2	3b	Ph	Ph	H	Et	100	*rac*
3	3c	Ph	H	H	Et	100	43
4	3d	*t*-Bu	H	H	Et	95	75
5	3e	*t*-Bu	H	*t*-Bu	Et	78	32
6	3f	*t*-Bu	H	H	*i*-Pr	100	84
7	3g	*t*-Bu	H	H	*i*-Bu	98	96
8	3h	*t*-Bu	H	H	*t*-Bu	100	69

[a] Benzaldehyde:$ZnEt_2$:phenylacetylene:catalyst = 0.5:1.5:1.5:0.05 mmol; toluene, 5 mL; CH_2Cl_2, 2.5 mL.
[b] $ZnEt_2$ and phenylacetylene were refluxed in toluene for 6 h and the resulted solution cooled to r.t. The resulted mixture was transferred to the solution of the catalyst in CH_2Cl_2 at –20 °C followed by the addition of benzaldehyde.
[c] Yields were calculated based on ^1H NMR spectra.
[d] The ee values were determined by HPLC using an OD column from Daicel.

Alkynyl additions to various aldehydes were then conducted employing the best performed oxovanadium(V) catalyst **3g**. The desired chiral propargyl alcohols were obtained in excellent isolated yields (Table 2). It is found that positions of the substituted group on aromatic aldehydes play a key role in stereoselectivities with higher enantioselectivities obtained for substrates having an *ortho*-substituted group. For example, the enantioselectivity of the propargyl alcohol obtained from 1-naphthaldehyde at 96% ee (entry 2) is much higher than the enantioselectivity for 2-naphthaldehyde at 78% ee (entry 3). Similarly, a higher enantioselectivity was observed for 2-chlorobenzaldehyde at 90% ee (entry 4) than the enantioselectivity at 75% ee for 4-chlorobenzaldehyde (entry 5). For 2-bromobenzaldehyde, the product was obtained in a superb 99% ee (entry 6). For 2-iodobenzaldehyde, the propargyl alcohol was obtained in an excellent enantioselectivity of 92% ee (entry 7). For the aromatic aldehyde containing a strong electron-withdrawing CF_3 at the *para*-position, the product in a slightly lower enantioselectivity of 85% ee was obtained (entry 8). In this study, two examples of 1-hexynyl additions to aromatic aldehydes were examined and a reaction time of 48 hours is required to afford products in satisfactory yields. For 1-naphthaldehyde, the addition reaction gave the product in a moderate 66% yield but with an excellent enantioselectivity of 93% ee (entry 9). For 2-bromobenzaldehyde, the product was obtained in 84% yield with 80% ee (entry 10). For aliphatic aldehydes, the product in a moderate 73% ee was obtained for the phenylacetylenyl addition to benzylaldehyde (entry 11) and a good 88% ee was obtained for cyclohexylaldehyde as the substrate (entry 12).

Table 2 Asymmetric Alkynylation of Aldehydes Catalyzed by Oxovanadium Catalyst **3g**[a,b]

Entry	Substrate	Alkyne	Isolated yield (%)	ee (%)
1		Ph—C≡CH	95	96
2		Ph—C≡CH	94	96
3		Ph—C≡CH	92	78
4		Ph—C≡CH	96	90
5		Ph—C≡CH	91	75
6		Ph—C≡CH	95	99
7		Ph—C≡CH	96	92
8		Ph—C≡CH	96	85
9[c]		^{n}Bu—C≡CH	66	93
10[c]		^{n}Bu—C≡CH	84	80
11		Ph—C≡CH	85	73
12		Ph—C≡CH	96	88

[a] Reaction conditions are the same as those described in footnote of Table 1.
[b] The ee values were determined by HPLC using an OD column from Daicel and compared with literature values.
[c] 48 h.

In summary, the first example of oxovanadium(V) catalysts catalyzed asymmetric alkynylation reactions is reported. The chiral propargyl alcohols are obtained in high isolated yields with good to excellent enantioselectivities up to 99% ee. Several important features are demonstrated in this study. First, isolated oxovanadium(V) complexes of Schiff bases are used as effective catalysts. Second, the catalysts are stable and can be easily prepared from reactions of $VO(O\textit{i}\text{-}Pr)_3$ with Schiff bases of amino alcohols in alcohol. Third, stereoselectivities of propargyl alcohols are tunable through adjustments of steric sizes of substituents on Schiff base ligands and of the alkoxide ligand on the vanadium metal. Further investigations of oxovanadium(V) complexes in asymmetric catalysis are currently underway.

Acknowledgment

Financial support from National Science Council of Taiwan, Republic of China (Grant Number NSC-93-2113-M-005-021) is appreciated.

References and Notes

(1) For references, please see: Pu, L. *Tetrahedron* **2003**, *59*, 9873.
(2) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151.
(3) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Jiang, B.; Chen, Z.; Xiong, W. *Chem. Commun.* **2002**, 1524. (c) Braga, A. L.; Appelt, H. R.; Silveira, C. C.; Wessjohann, L. A.; Schneider, P. H. *Tetrahedron* **2002**, *58*, 10413. (d) Kamble, R. M.; Singh, V. K. *Tetrahedron Lett.* **2003**, *44*, 5347. (e) Makita, N.; Hoshino, Y.; Yamamoto, H. *Org. Biomol. Chem.* **2004**, *2*, 3312. (f) Xu, Z.; Chen, C.; Xu, J.; Miao, M.; Yan, W.; Wang, R. *Org. Lett.* **2004**, *6*, 1193. (g) Fang, T.; Du, D.-M.; Lu, S.-F.; Xu, J. *Org. Lett.* **2005**, *7*, 2081. (h) Emmerson, D. P. G.; Hems, W. P.; Davis, B. G. *Org. Lett.* **2006**, *8*, 207.
(4) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.
(5) Xu, M.-H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555.
(6) (a) Lu, G.; Li, X.; Zhou, Z.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2147. (b) Dahmen, S. *Org. Lett.* **2004**, *6*, 2113. (c) Zhu, M.; Li, X.-Z.; Yuan, K.; Cao, B.-X.; Hou, X.-L. *Tetrahedron: Asymmetry* **2004**, *15*, 219. (d) Kang, Y.-F.; Liu, L.; Wang, R.; Yan, W.-J.; Zhou, Y.-F. *Tetrahedron: Asymmetry* **2004**, *15*, 3155. (e) Yamashita, M.; Yamada, K.-I.; Tomioka, K. *Adv. Synth. Catal.* **2005**, *347*, 1649. (f) Mao, J.; Wan, B.; Wu, F.; Lu, S. *Chirality* **2005**, *17*, 243. (g) Thoniyot, C. C. P.; Hirayama, L. C.; Romano, T.; Singaram, B. *Tetrahedron: Asymmetry* **2005**, *16*, 1829. (h) Pizzuti, M. G.; Superchi, S. *Tetrahedron: Asymmetry* **2005**, *16*, 2263.
(7) Trost, B. M.; Weiss, A. H.; Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8.
(8) (a) Liu, G.; Li, X.; Chan, W. L.; Chan, A. S. C. *Chem. Commun.* **2002**, 172. (b) Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636.
(9) (a) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855. (b) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143. (c) Liu, L.; Pu, L. *Tetrahedron* **2004**, *60*, 7427.
(10) Liu, Q.-Z.; Xie, N.-S.; Luo, Z.-B.; Cui, X.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-C. *J. Org. Chem.* **2003**, *68*, 7921.
(11) Xu, Z.; Wang, R.; Xu, J.; Da, C.-S.; Yan, W.-J.; Chen, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5747.
(12) Gao, G.; Wang, Q.; Yu, X.-Q.; Xie, R.-G.; Pu, L. *Angew. Chem. Int. Ed.* **2006**, *45*, 122.
(13) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760.

(14) **General Procedures for Synthesis of Oxovanadium(V) Complexes 3a–h.**
To a solution of a Schiff base (1.00 mmol) in 10 mL appropriate alcohol, $VO(O\textit{i}\text{-}Pr)_3$ (0.24 mL, 1.0 mmol) was added at r.t. The mixture was stirred for 1 h and the solvent was removed under reduced pressure to give a quantitative yield of the product. All compounds were characterized by ^1H NMR and ^{13}C NMR spectroscopy and by elemental analyses. Two sets of NMR resonances are observed for each complex due to the presence of two isomers in solution. Spectroscopic data of complexes **3c** and **3g** as examples are listed in the following. The two isomers are designated as major and minor based on relative intensities of resonances. ^1H NMR spectra for the two isomers in the phenyl region are overlapped and resonances of the minor are included in data of the major.
Complex **3c**: dark green solid. ^1H NMR (400 MHz, $CDCl_3$): δ (major, 69%) = 7.56 (s, 1 H, CH=N), 7.50–6.76 (m, Ph), 6.43 (d, *J* = 3.2 Hz, 1 H, C*H*O), 5.34–5.26 (m, 2 H, OCH_2), 4.20 (d, *J* = 6.0 Hz, 1 H, C*H*N), 3.61 (dd, *J* = 7.6, 9.2 Hz, 1 H, CH_AH_BPh), 2.62 (dd, *J* = 2.0, 9.0 Hz, 1 H, CH_AH_BPh), 1.59 (t, *J* = 5.2 Hz, 3 H, CH_3) ppm; δ (minor, 31%) = 7.57 (s, 1 H, CH=N), 6.65 (d, *J* = 3.6 Hz, 1 H, C*H*O), 5.40–5.36 (m, 2 H, OCH_2), 4.53 (d, *J* = 7.2 Hz, 1 H, C*H*N), 2.57 (dd, *J* = 2.4, 9.2 Hz, 1 H, CH_AH_BPh), 2.47 (dd, *J* = 7.6, 9.2 Hz, 1 H, CH_AH_BPh), 1.69 (t, *J* = 4.8 Hz, 3 H, CH_3) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 163.26, 162.86, 162.71, 140.50, 137.86, 137.11, 135.82, 135.57, 132.45, 132.35, 130.19, 130.14, 128.70, 128.60, 128.55, 128.47, 127.62, 127.43, 127.01, 126.77, 126.67, 126.05, 125.95, 124.98, 119.78, 119.51, 118.84, 93.35, 90.92, 87.19, 86.39, 84.50, 79.54, 79.07, 78.62, 42.02, 36.23, 36.11, 25.58, 19.13, 17.97, 17.74. Anal. Calcd for $C_{24}H_{24}NO_4V$ (%): C, 65.31; H, 5.48; N, 3.17. Found: C, 65.66; H, 5.08; N, 3.57.
Complex **3g**: brown solid. ^1H NMR (400 MHz, $CDCl_3$): δ (major, 71%) = 7.45–6.77 (m, CH=N, Ph), 4.89 (d, *J* = 4.0 Hz, 1 H, *CH*N), 4.85 (ddd, *J* = 6.8, 11.4, 28.0 Hz, 2 H, OCH_2), 4.05 (d, *J* = 12.0 Hz, 1 H, *CH*O), 3.83 (dd, *J* = 12.4, 12.4 Hz, 1 H, CH_AH_BPh), 3.43 (d, *J* = 13.2 Hz, 1 H, CH_AH_BPh), 2.16–2.06 (m, 1 H, CH_2CH), 1.18 (s, 9 H, *t*-Bu), 1.03 [d, *J* = 6.8 Hz, 6H, $CH(CH_3)_2$] ppm; δ (minor, 29%) = 5.24 (d, *J* = 4.0 Hz, 1 H, C*H*N), 5.05 (ddd, *J* = 6.8, 11.0, 30.8 Hz, 2 H, OCH_2), 4.32 (d, *J* = 11.6 Hz, 1 H, C*H*O), 3.28 (d, *J* = 14.0 Hz, 1 H, CH_AH_BPh), 2.62 (dd, *J* = 12.4, 12.4 Hz, 1 H, CH_AH_BPh), 2.40–2.22 (m, 1 H, CH_2CH), 1.21 (s, 9 H, *t*-Bu), 1.12 [d, *J* = 6.8 Hz, 6 H, $CH(CH_3)_2$] ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.18, 163.73, 161.93, 161.78, 137.98, 137.17, 135.37, 135.08, 132.25, 132.15, 130.20, 130.03, 128.44, 128.38, 126.67, 126.60, 120.01, 119.34, 119.04, 118.97, 118.64, 118.57, 98.05, 94.60, 89.84, 88.71, 83.31, 78.13, 36.77, 36.31, 35.81, 31.91, 31.60, 27.55, 27.12, 19.47, 19.41, 18.79. Anal. Calcd for $C_{24}H_{32}NO_4V$ (%): C, 64.13; H, 7.18; N, 3.12. Found: C, 63.72; H, 7.42; N, 3.59.

(15) (a) Hartung, J.; Drees, S.; Greb, M.; Schimdt, P.; Svoboda, I.; Fuess, B.; Murso, A.; Stalke, D. *Eur. J. Org. Chem.* **2003**, 2388. (b) Blum, S. A.; Bergman, R. C.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 150.