J|A|C|S COMMUNICATIONS

Published on Web 03/01/2010

# Direct Catalytic Asymmetric Vinylogous Mannich-Type and Michael Reactions of an α,β-Unsaturated γ-Butyrolactam under Dinuclear Nickel Catalysis

Nicholas E. Shepherd, Hirooki Tanabe, Yingjie Xu, Shigeki Matsunaga,* and Masakatsu Shibasaki*

*Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

Received January 12, 2010; E-mail: mshibasa@mol.f.u-tokyo.ac.jp; smatsuna@mol.f.u-tokyo.ac.jp

Catalytic asymmetric vinylogous reactions of γ-butenolides and related compounds have been intensively studied, giving versatile functionalized chiral γ-butenolide skeletons.[1−3] In contrast, the use of their aza-analogues, α,β-unsaturated γ-butyrolactams, as donors in catalytic asymmetric reactions is rare, despite their synthetic utility.[1a,4] For example, a vinylogous Mukaiyama Mannich-type adduct of a siloxypyrrole was utilized as a key building block for the synthesis of anti-influenza agent A-315675.[4] Lewis acid catalyzed asymmetric vinylogous Michael reaction of an acryloyloxazolidinone[5] and Lewis base catalyzed asymmetric vinylogous aldol reaction[6] using the siloxypyrrole have been recently reported. There are, however, no reports on catalytic asymmetric Mannich-type reactions of siloxypyrroles. Moreover, there is no example of direct catalytic asymmetric reactions of α,β-unsaturated γ-butyrolactams under proton transfer conditions,[7] which are more favorable in terms of atom economy. Thus, the development of direct catalytic asymmetric reactions of α,β-unsaturated γ-butyrolactams is highly desirable. Herein, we describe our efforts to address these issues. A homodinuclear $Ni_2$-Schiff base **1** complex (Figure 1) promoted the direct catalytic asymmetric vinylogous Mannich-type reaction of an α,β-unsaturated γ-butyrolactam with *N*-Boc imines and vinylogous Michael reaction to nitroalkenes, giving products in up to 99% ee in both reactions.

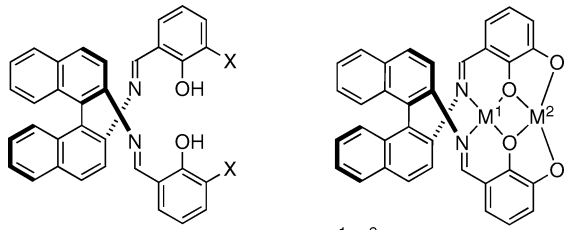
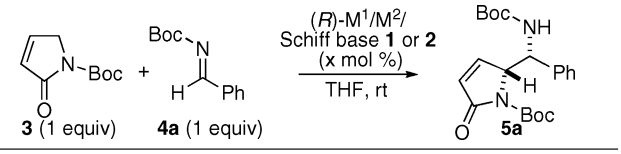



***Figure 1.*** Structures of dinucleating Schiff base **1**-$H_4$, bimetallic $Ni_2$-Schiff base **1** complex, and Schiff bases **2**-$H_2$.

To realize the direct vinylogous reaction with α,β-unsaturated γ-butyrolactam **3**, the chemoselective activation of **3** as a donor and imine **4** as an electrophile is required. However, undesirable electrophilic activation of the α,β-unsaturated γ-butyrolactam unit in both **3** and the vinylogous Mannich product must be avoided, as this may lead to side reactions, such as polymerization. In addition, the enantioselectivity, diastereoselectivity, and α/γ-selectivity of the metal dienolate should be controlled. Among acid/base bifunctional catalysts developed in our group,[8] bimetallic Schiff base **1** catalysts,[9−11] which were previously used for catalytic deprotonation of the α-proton in carbonyl donors, showed promising results in the present vinylogous reactions. The optimization studies using α,β-unsaturated γ-butyrolactam **3** and *N*-Boc imine **4a** are summarized in Table 1. Initial trials using dinuclear $Mn_2$,[9c] $Co_2$,[9b] $Cu_2$, and $Pd_2$-**1** complexes resulted in poor reactivity (entries 1−4). In contrast, a dinuclear $Ni_2$-**1** complex[10] smoothly promoted the vinylogous reaction at room temperature. The α-adduct was not detected at all, and the desired γ-adduct **5a** was obtained as a single isomer in 85% NMR conversion yield with 99% ee (entry 5). The yield was improved by the addition of DRIERITE ($CaSO_4$) as a desiccant to give **5a** with >95% yield and 99% ee (entry 6). Molecular sieves also had beneficial effects to improve yield, but there was a reproducibility problem in terms of diastereoselectivity using molecular sieves. Thus, DRIERITE was utilized for further studies. Catalyst loading was successfully reduced to 5 mol % without loss of reactivity or stereoselectivity (entry 7). Control experiments using monometallic Ni-Schiff base **2a**−**2c** complexes did not afford the desired Mannich adduct **5a** but gave only byproducts (entries 8−10). In entries 11−12, heterobimetallic Pd/Ni-**1** and Cu/Ni-**1** complexes also did not give **5a**. The results in entries 8−12 suggested that two Ni metal centers are essential for the chemoselective 1:1 reaction of **3** with imine **4a**. We assume that a bimetallic Lewis acid/Brønsted base bifunctional mechanism would be operative in the present reaction, as we previously observed in other reactions.[9,10]

***Table 1.*** Optimization of Reaction Conditions




| entry | $M^1$ | $M^2$ | Schiff base | *x* | additive | time (h) | % yield[a] | dr[a] | % ee[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Mn-OAc | Mn-OAc | **1** | 10 | none | 17 | 0 | − | − |
| 2 | Co-OAc | Co-OAc | **1** | 10 | none | 17 | 15 | − | − |
| 3 | Cu | Cu | **1** | 10 | none | 17 | trace | − | − |
| 4 | Pd | Pd | **1** | 10 | none | 17 | 3 | − | − |
| 5 | Ni | Ni | **1** | 10 | none | 17 | 85 | >30:1 | 99 |
| 6 | Ni | Ni | **1** | 10 | DRIERITE | 24 | >95 | >30:1 | 99 |
| 7 | Ni | Ni | **1** | 5 | DRIERITE | 24 | 95 | >30:1 | 99 |
| 8 | Ni | none | **2a** | 5 | DRIERITE | 24 | 0 | − | − |
| 9 | Ni | none | **2b** | 5 | DRIERITE | 24 | 0 | − | − |
| 10 | Ni | none | **2c** | 5 | DRIERITE | 24 | 0 | − | − |
| 11 | Pd | Ni | **1** | 5 | DRIERITE | 24 | 0 | − | − |
| 12 | Cu | Ni | **1** | 5 | DRIERITE | 24 | 0 | − | − |

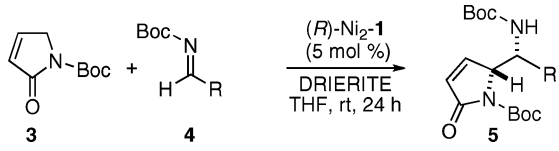
[a] Determined by $^1$H NMR analysis of crude mixture. [b] Determined by HPLC analysis using chiral column IA.

The substrate scope of the reaction is summarized in Table 2.[12] The $Ni_2$-**1** catalyst was applicable to nonisomerizable aryl and heteroaryl imines. High enantio- and diastereoselectivity were achieved for aryl imines with either an electron-withdrawing or electron-donating substituent at the *ortho*-, *meta*-, or *para*-position (entries 2−7, 23:1→30:1 dr, 99% ee). With heteroaryl imines, the reactivity somewhat decreased. Thus, the reaction was performed



10.1021/ja1002636 

***Table 2.*** Direct Catalytic Asymmetric Vinylogous Mannich-Type Reaction of an α,β-Unsaturated γ-Butyrolactam and *N*-Boc Imines[a]

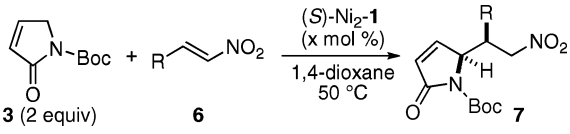



**3** **4** **5**

| entry | R: **4** | | product **5** | % yield[b] | dr[c] | % ee[d] |
|---|---|---|---|---|---|---|
| 1 | Ph- | **4a** | **5a** | 95 | >30:1 | 99 |
| 2 | 2-naphthyl | **4b** | **5b** | 76 | 30:1 | 99 |
| 3 | 1-naphthyl | **4c** | **5c** | 93 | 26:1 | 99 |
| 4 | 2-Cl-$C_6H_4$- | **4d** | **5d** | 95 | >30:1 | 99 |
| 5 | 3-Me-$C_6H_4$- | **4e** | **5e** | 87 | >30:1 | 99 |
| 6 | 4-Cl-$C_6H_4$- | **4f** | **5f** | 87 | >30:1 | 99 |
| 7 | 4-MeO-$C_6H_4$- | **4g** | **5g** | 85 | 23:1 | 99 |
| 8[e] | 2-furyl | **4h** | **5h** | 61 | 5:1 | 99 |
| 9[e] | 3-thienyl | **4i** | **5i** | 83 | 21:1 | 99 |

[a] Reaction was run using 1 equiv of **3**, 1.2 equiv of **4**, in THF (0.3 M) in the presence of DRIERITE unless otherwise noted. [b] Isolated yield after purification by column chromatography. [c] Determined by $^1$H NMR analysis of crude mixture. [d] Determined by HPLC using chiral column IA or AD-H. [e] Reaction was run using 2 equiv of **3** and 1 equiv of **4**.

***Table 3.*** Direct Catalytic Asymmetric Vinylogous Michael Reaction of an α,β-Unsaturated γ-Butyrolactam to Nitroalkenes[a]




**3** (2 equiv) **6** **7**

| entry | R: **6** | | cat. (*x* mol %) | time (h) | **7** | % yield[b] | dr[c] | % ee[d] |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph- | **6a** | 2.5 | 13 | **7a** | 98 | >30:1 | 97 |
| 2 | 4-Br-$C_6H_4$- | **6b** | 2.5 | 12 | **7b** | 96 | 29:1 | 99 |
| 3 | 2-Br-$C_6H_4$- | **6c** | 2.5 | 11 | **7c** | 98 | 16:1 | 98 |
| 4 | 4-MeO-$C_6H_4$- | **6d** | 2.5 | 25 | **7d** | 98 | >30:1 | 98 |
| 5 | 2-furyl | **6e** | 2.5 | 11 | **7e** | 98 | >30:1 | 98 |
| 6 | 2-thienyl | **6f** | 2.5 | 15 | **7f** | 99 | >30:1 | 98 |
| 7 | $PhCH_2CH_2$- | **6g** | 2.5 | 24 | **7g** | 89 | 26:1 | 96 |
| 8 | *i*-propyl | **6h** | 2.5 | 24 | **7h** | 97 | >30:1 | 99 |
| 9 | (*E*)-Ph-CH=CH- | **6i** | 2.5 | 16 | **7i** | 83 | 25:1 | 99 |
| 10 | Ph- | **6a** | 1 | 36 | **7a** | 84 | 29:1 | 93 |

[a] (*S*)-$Ni_2$-**1** catalyst was used in Table 3. Reaction was run using 2 equiv of **3** in 1,4-dioxane (0.15 M) at 50 °C. [b] Isolated yield after purification by column chromatography. [c] Determined by $^1$H NMR analysis of crude mixture. [d] Determined by HPLC using chiral column IC, IB, or AD-H.

with 2 equiv of **3**, and products **4h**−**4i** were obtained in 99% ee (entries 8−9). Unfortunately, isomerizable aliphatic imines resulted in low yield (<20%) due to competitive isomerization to enamides over nucleophilic activation of **3**.

Trials to further expand the vinylogous nucleophilicity of **3** under bimetallic Schiff base catalysis revealed that vinylogous Michael reaction to nitroalkenes[3b] proceeded nicely in 1,4-dioxane at 50 °C using the same $Ni_2$-**1** catalyst. As summarized in Table 3, the reaction of aryl, heteroaryl, and alkyl substituted nitroalkenes **6a**−**6h** proceeded smoothly with 2.5 mol % catalyst loading, and products were obtained in 89−99% yield, 16:1→30:1 dr, and 96−99% ee after 11−25 h (entries 1−8).[12] Nitrodiene **6i** was also applicable, and the 1,4-adduct was predominantly obtained in 83% yield, 25:1 dr, and 99% ee (entry 9). Catalyst loading was successfully reduced to 1 mol %, although enantioselectivity decreased to 93% ee (entry 10).

In summary, we developed direct catalytic asymmetric vinylogous Mannich-type and Michael reactions of α,β-unsaturated γ-butyrolactam. Negative control experiments clearly suggested the importance of a dinuclear Ni system. The dinuclear Ni-catalyzed reactions proceeded selectively at the γ-position, giving vinylogous Mannich adducts in 5:1→30:1 dr and 99% ee and vinylogous Michael adducts in 16:1→30:1 dr and 93−99% ee. Further studies to expand the vinylogous nucleophilicity under dinuclear Schiff base catalysis, including trials to improve the yield with enolizable aliphatic imines, are ongoing.

**Acknowledgment.** This work was supported by the Takeda Science Foundation (for S.M.), Grant-in-Aid for Scientific Research (S), for Young Scientist (A), and for Scientific Research on Priority Areas (No. 20037010, Chemistry of Concerto Catalysis). N.E.S. is thankful for a JSPS postdoctoral fellowship. We thank Mr. Z. Chen for fruitful discussions and Dr. M. Shiro at RIGAKU for his assistance in X-ray crystallographic analysis of **7b**.

**Supporting Information Available:** Experimental procedures, spectral data of new compounds, and cif files. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) Reviews: (a) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, 1525. (b) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929.

(2) For selected examples of asymmetric vinylogous Mannich-type reactions of siloxyfurans, see: (a) Martin, S. F.; Lopez, O. D. *Tetrahedron Lett.* **1999**, *40*, 8949. (b) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230. (c) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399. (d) Mandai, H.; Mandai, K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 17961. (e) Salvador González, A.; Gómez Arrayás, R.; Rodríguez Rivero, M.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335. (f) Yuan, Z.-L.; Jiang, J.-J.; Shi, M. *Tetrahedron* **2009**, *65*, 6001. For other examples, see ref 1.

(3) For direct catalytic asymmetric vinylogous reaction of γ-butenolides, Mannich-type reaction: (a) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2319. 1,4-Addition to nitroalkenes: (b) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572.

(4) (a) DeGoey, D. A.; Chen, H.-J.; Flosi, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. *J. Org. Chem.* **2002**, *67*, 5445. (b) Barnes, D. M.; Bhagavatula, L.; DeMattei, J.; Gupta, A.; Hill, D. R.; Manna, S.; McLaughlin, M. A.; Nichols, P.; Premchandran, R.; Rasmussen, M. W.; Tian, Z.; Wittenberger, S. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3541. For other synthetic applications and stereoselective transformation of α,β-unsaturated γ-butyrolactam unit, see ref 1a.

(5) Suga, H.; Takemoto, H.; Kakehi, A. *Heterocycles* **2007**, *71*, 361.

(6) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Zanardi, F.; Casiraghi, G. *Tetrahedron Lett.* **2009**, *50*, 3428.

(7) For racemic direct-type vinylogous reactions of α,β-unsaturated γ-butyrolactam and related donors, see: (a) Sartori, A.; Curti, C.; Battistini, L.; Burreddu, P.; Rassu, G.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Tetrahedron* **2008**, *64*, 11697. (b) Curti, C.; Sartori, A.; Battistini, L.; Rassu, G.; Burreddu, P.; Zanardi, F.; Casiraghi, G. *J. Org. Chem.* **2008**, *73*, 5446. For related racemic transformations of isoindolinones, see: (c) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Biomol. Chem.* **2007**, *5*, 1466, and references therein.

(8) Review: (a) Shibasaki, M.; Matsunaga, S.; Kumagai, N. *Synlett* **2008**, 1583. For a catalyst developed for α-selective addition of dienolates in direct aldol process, see: (b) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 10842.

(9) For selected examples, see Cu-Sm catalyst: (a) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900. $Co_2$-**1**: (b) Chen, Z.; Furutachi, M.; Kato, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2218. $Mn_2$-**1**: (c) Kato, Y.; Furutachi, M.; Chen, Z.; Mitsunuma, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9168.

(10) $Ni_2$-**1**: (a) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (b) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255.

(11) For selected examples of related bifunctional bimetallic Schiff base complexes in asymmetric catalysis, see: (a) Annamalai, V.; DiMauro, E. F.; Carroll, P. J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 1973, and references therein. (b) Yang, M.; Zhu, C.; Yuan, F.; Huang, Y.; Pan, Y. *Org. Lett.* **2005**, *7*, 1927. (c) Hirahata, W.; Thomas, R. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2008**, *130*, 17658. (d) Mazet, C.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1762. (e) Wu, B.; Gallucci, J. C.; Parquette, J. R.; RajanBabu, T. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 1126.

(12) The relative and absolute configurations of **5a** and **7b** were unequivocally determined by X-ray crystallographic analysis. See Supporting Information.

JA1002636