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

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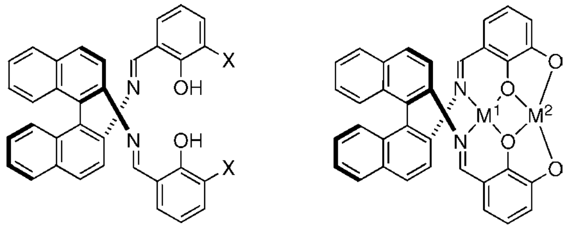
Catalytic asymmetric vinylogous reactions of *γ*-butenolides and related compounds have been intensively studied, giving versatile functionalized chiral *γ*-butenolide skeletons.[1−3] In contrast, the use of their aza-analogues, α,*β*-unsaturated *γ*-butyrolactams, as donors in catalytic asymmetric reactions 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.



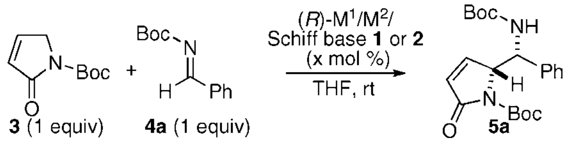
X = OH: Schiff base **1**-H_4
X = H: Schiff base **2a**-H_2
X = *t*Bu: Schiff base **2b**-H_2
X = OMe: Schiff base **2c**-H_2

(*R*)-M^1/M^2/**1** complex
M^1= M^2= Ni: (*R*)-Ni_2-**1** cat.

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 ^1H 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

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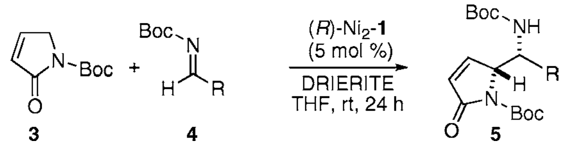
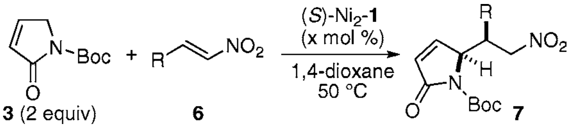
Table 2. Direct Catalytic Asymmetric Vinylogous Mannich-Type Reaction of an α,β-Unsaturated γ-Butyrolactam and *N*-Boc Imines[a]



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]



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.

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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.

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