Asymmetric Synthesis

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Cinchona Alkaloid Amide/Copper(II) Catalyzed Diastereo- and Enantioselective Vinylogous Mannich Reaction of Ketimines with Siloxyfurans**

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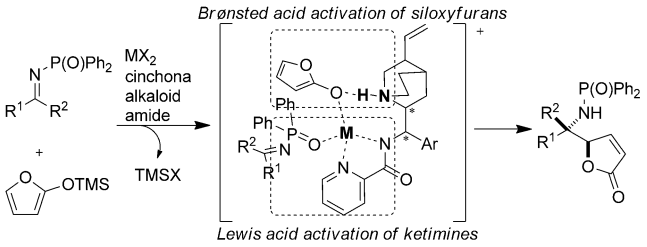
Optically active δ-amino-α,β-unsaturated carbonyl compounds are receiving considerable attention due to their broad application in the synthesis of biologically active compounds and their synthetic importance.[1] Their utility has prompted considerable interest in developing asymmetric methods for the preparation of δ-amino-α,β-unsaturated carbonyl compounds. One of the most efficient methods for the synthesis of chiral δ-amino-α,β-unsaturated carbonyl compounds is the enantioselective vinylogous Mannich reaction of imines.[2] However, the catalytic enantioselective vinylogous Mannich reaction of imines derived from ketones (ketimines) is still not fruitful, in comparison with imines derived from aldehydes.[3] To the best of our knowledge, only one example of an enantioselective vinylogous Mannich reaction of ketimines was reported by Snapper, Hoveyda, and co-workers. They reported that the reaction of siloxyfurans with various activated ketimines derived from ketoesters using a chiral phosphine catalyst and AgOAc gave chiral γ-butenolides in high yield with high selectivity.[4] Although a pioneering study has been made, there are no reports challenging the difficulty of the enantioselective vinylogous Mannich reaction of ketimines derived from unactivated ketones. Therefore, the development of novel catalyst systems with wide substrate tolerance and acceptable catalytic activity for the vinylogous Mannich reaction still remains a major challenge. Recently, we reported the enantioselective reaction of some nucleophiles with various ketimines,[5] and we also developed novel catalysts derived from cinchona alkaloids.[6] We herein report the enantioselective vinylogous Mannich reaction of siloxyfurans with various ketimines using our original chiral catalysts derived from cinchona alkaloids (Scheme 1).



Scheme 1. Cinchona alkaloid amide/metal catalyzed asymmetric vinylogous Mannich reaction of ketimines with siloxyfurans.

The enantioselective reaction of ketimine **1a** with 2-trimethylsiloxyfuran **2a** (2.0 equiv) was carried out at room temperature in the presence of chiral catalysts **3** (10 mol%), which are derived from cinchona alkaloids and metal species (Table 1). The reaction of **1a** with **2a** using *N*-picolynoyl-9-amino-9-deoxy-*epi*-cinchonine **3a** and Et_2Zn in the presence of isopropyl alcohol afforded product **4a** in high yield with moderate diastereoselectivity and low enantioselectivity (entry 1). Optimization experiments for the metal acetates, such as $Zn(OAc)_2$, $Mg(OAc)_2$, and $Cu(OAc)_2$, were carried out to improve the yield and stereoselectivity of the product, $Cu(OAc)_2$ emerged as the most suitable Lewis acid in this reaction (entries 2–4).[7] To improve the enantioselectivity, we next optimized the structure of cinchona alkaloid ligands. The picolinamide ligand **3b**, which is derived from quinine, gave the opposite enantiomer of **4a** with good selectivity, but in low yield (entry 5). Cinchonine **3c** and *N*-benzoylamide **3d** did not afford the product (entries 6 and 7). To improve the reactivity and selectivity, we added a substituent in the 4 position of the pyridine ring in the ligand. Although the enantioselectivity decreased slightly in the reaction when using picolinamide ligand **3e**, which has an electron-donating methoxy group, catalysts **3f** and **3h**, which have an electron-withdrawing chloro group, afforded **4a** with high enantioselectivity (entries 8,9, and 11). On the other hand, a reaction using 4-nitro-substituted ligand **3g** did not afford product **4a** (entry 10). Finally, switching the additive from *i*PrOH to trimethylsilyl alcohol (TMSOH) provided product **4a** in moderate yield with high selectivity (entry 12).[8] The opposite enantiomer of **4a** could be obtained in high yield with high selectivity by a reaction using **3h**, which is derived from 9-amino-9-deoxy-*epi*-cinchonidine (entry 13).

Having established the reaction conditions, the vinylogous Mannich reaction of a series of ketimines with siloxyfuran **2a**

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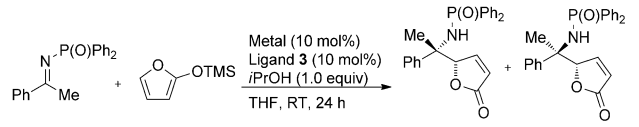
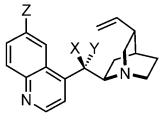
Table 1: Diastereo- and enantioselective vinylogous Mannich reaction of ketimine **1a** with 2-trimethylsiloxyfuran **2a**.[a]



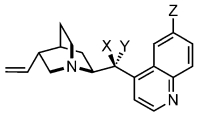
1a **2a**

Entry	Metal	3	Conv. [%][b]	*Syn*/*Anti*[b]	*ee* (*anti*) [%]
1	Et_2Zn	**3a**	93	11:89	44
2	$Zn(OAc)_2$	**3a**	96	14:86	15
3	$Mg(OAc)_2$	**3a**	70	10:90	3[c]
4	$Cu(OAc)_2$	**3a**	53	3:97	78
5	$Cu(OAc)_2$	**3b**	32	3:97	81[c]
6	$Cu(OAc)_2$	**3c**	–	–	–
7	$Cu(OAc)_2$	**3d**	–	–	–
8	$Cu(OAc)_2$	**3e**	29	3:97	74
9	$Cu(OAc)_2$	**3f**	32	2:98	82
10	$Cu(OAc)_2$	**3g**	–	–	–
11	$Cu(OAc)_2$	**3h**	56	2:98	89[c]
12[d]	$Cu(OAc)_2$	**3f**	70	1:99	92
13[d]	$Cu(OAc)_2$	**3h**	89	1:99	97[c]

[a] Reaction conditions: ketimine **1a** (0.1 mmol), **2a** (2.0 equiv), metal species (10 mol%), **3** (10 mol%), *i*PrOH (1.0 equiv), and THF (0.2 M) were used. [b] Conversions and diastereomeric ratios were determined by NMR analysis of the crude product. [c] The opposite enantiomer was obtained. [d] The reaction was carried out using **2a** (4.0 equiv) and TMSOH (1.2 equiv) in THF (0.5 M) at −20 °C.

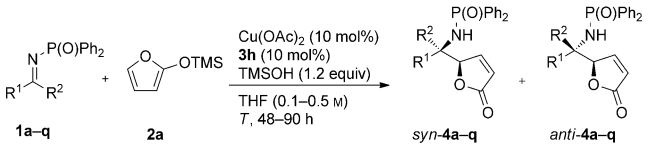


3a: X=NHCOPy, Y=H, Z=H
3c: X=H, Y=OH, Z=H
3d: X=NHBz, Y=H, Z=H
3e: X=NHCO(4-MeO)Py, Y=H, Z=H
3f: X=NHCO(4-Cl)Py, Y=H, Z=H
3g: X=NHCO(4-NO_2)Py, Y=H, Z=H



3b: X=NHCOPy, Y=H, Z=OMe
3h: X=NH(4-Cl)COPy, Y=H, Z=H

Table 2: Asymmetric vinylogous Mannich reaction of various ketimines **1a–q** with 2-trimethylsiloxyfuran **2a** using **3h**/$Cu(OAc)_2$.[a]

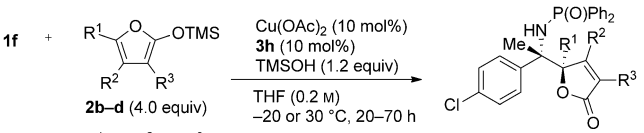


1a–q **2a**

Entry	R^1	R^2	1	*T* [°C]	Yield [%][b]	*Syn*/*Anti*[c]	*ee* (*anti*) [%]
1	Ph	Me	**1a**	−20	85	1:99	97
2[d]	Ph	Me	**1a**	−20	64	1:99	92
3	*p*-MeC_6H_4	Me	**1b**	−20	82	1:99	96
4	*p*-$OMeC_6H_4$	Me	**1c**	−10	51	2:98	96
5	*p*-FC_6H_4	Me	**1d**	0	86	1:99	96
6	*m*-ClC_6H_4	Me	**1e**	−20	99	1:99	95
7	*p*-ClC_6H_4	Me	**1f**	0	95	1:99	96
8	*m*-BrC_6H_4	Me	**1g**	−10	95	1:99	96
9	*p*-BrC_6H_4	Me	**1h**	−20	94	1:99	97
10[d]	*p*-BrC_6H_4	Me	**1h**	−20	88	1:99	91
11[e]	*p*-$NO_2C_6H_4$	Me	**1i**	−10	99	1:99	94
12[e]	2-naphthyl	Me	**1j**	0	93	1:99	95
13[e]	2-thienyl	Me	**1k**	−10	81	1:99	95
14	3-thienyl	Me	**1l**	−10	72	1:99	97
15[e]	2-furyl	Me	**1m**	0	88	4:96	94
16	Ph	Et	**1n**	−20	31	12:88	95
17[f]	$PhCH_2CH_2$	Me	**1o**	−10	73	4:96	95
18[f]	*n*-pentyl	Me	**1p**	0	63	6:94	95
19[f]	Et	Me	**1q**	0	60	6:94	93

[a] Reaction conditions: ketimine **1** (0.1 mmol), **2a** (4.0 equiv), $Cu(OAc)_2$ (10 mol%), **3h** (10 mol%), TMSOH (1.2 equiv), and THF (0.5 M) were used. [b] Yield of isolated product. [c] Diastereomeric ratio was determined by NMR analysis of the crude product. [d] Reaction was carried out using **3f** instead of **3h**, and the opposite enantiomer was obtained. [e] In 1:1 THF and CH_2Cl_2 (0.2 M). [f] Reaction was carried out without TMSOH.

was examined using **3h**/$Cu(OAc)_2$ as catalyst (Table 2). The reaction of ketimines **1b** and **1c**, which bear electron-donating groups such as methyl or methoxy in the *para* position, gave the corresponding products **4b** and **4c** in high to moderate yield (82 and 51%) with excellent diastereoselectivity (*syn*/*anti* 2:98 and 1:99) and enantioselectivity (96% *ee*; entries 3 and 4), respectively. The reaction of electron-deficient ketimines **1d–i**, which bear fluoro, chloro, bromo, or nitro groups, were tolerated under these reaction conditions, giving products **4d–i** with excellent yield and selectivity (entries 5–11). Ketimines **1j–m**, which have a 2-naphthyl or heteroaryl group, such as 2 or 3-thienyl, or 2-furyl groups, also afforded products **4j–m** in 72–93% yield with 94–97% *ee* (entries 12–15). On the other hand, the reaction of more sterically hindered ketimine **1n**, which is derived from propiophenone, gave **4n** in low yield, but with high selectivity (entry 16). Ketimines derived from dialkyl ketones **1o–q** were also activated in the reaction, and products **4o–q** were obtained with excellent yield and selectivity (entries 17–19). To the best of our knowledge, there are only a few reports of catalytic enantioselective nucleophilic reactions of ketimines derived from dialkyl ketones with good enantioselectivity.[9] The reaction using cinchonine derivative **3f** instead of **3h** afforded the opposite enantiomer of products **4a** and **4h** with high enantioselectivity (entries 2 and 10). These results are the first successful application of the vinylogous Mannich reaction of siloxyfuran with ketimines derived from unactivated ketones.

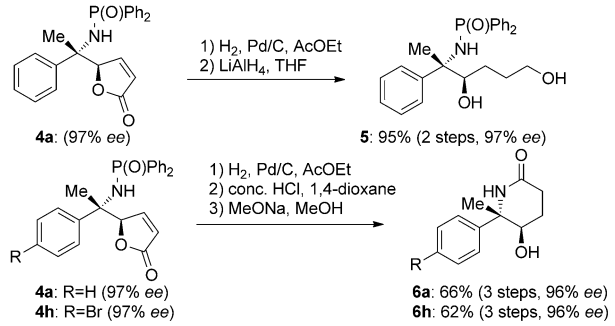


2b: R^1=H, R^2=H, R^3=Me
2c: R^1=H, R^2=Me, R^3=H
2d: R^1=Me, R^2=H, R^3=H

4r: 97%, d.r. 1:99, 86% *ee*
4s: 99%, d.r. 1:99, 95% *ee*
4t: 0%

Scheme 2. The vinylogous Mannich reaction of ketimine **1f** with methyl-substituted siloxyfurans **2b–d**.

We next examined the reaction of methyl-substituted siloxyfurans **2b–d** with **1f** using **3h**/$Cu(OAc)_2$ as catalyst (Scheme 2). The reaction of 3-methyl-2-siloxyfuran **2b** with **1f** gave product **4r** in 97% yield with excellent diastereoselectivity (*syn*/*anti* 1:99) and high enantioselectivity (86% *ee*). The reaction of 4-methyl-2-siloxyfuran **2c** also afforded product **4s** with excellent selectivity (99% yield, *syn*/*anti* 1:99,



Scheme 3. Synthetic applications of **4a** and **4h**.

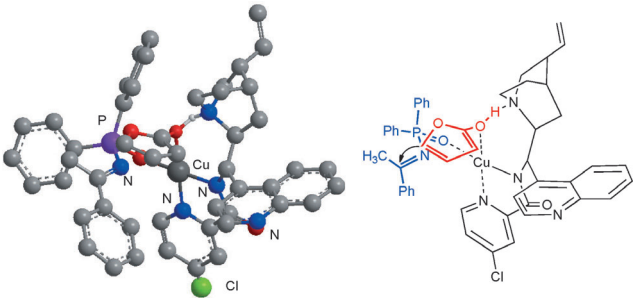
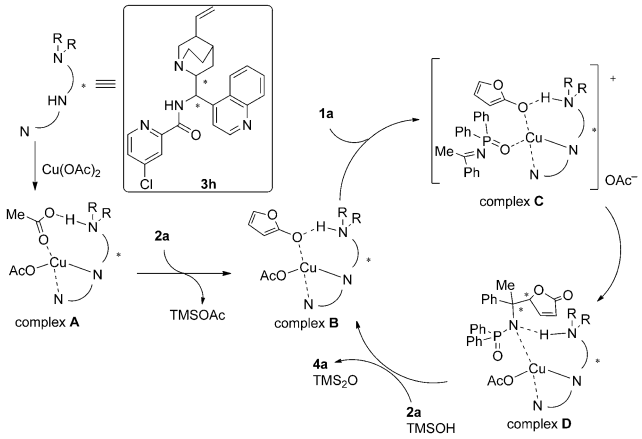


Figure 1. Proposed transition state for the asymmetric vinylogous Mannich reaction of ketimine with **2a** using **3h**.

95% *ee*), although 5-methyl-2-siloxyfuran **2d** did not give **4t**, probably owing to the steric bulk of siloxyfuran.

We next examined a synthetic application of the vinylogous Mannich product (Scheme 3). Product **4a** could be converted into 5-aminohexane-1,4-diol derivative **5** after the reduction of alkene and lactone using H_2 Pd/C and $LiAlH_4$. On the other hand, hydrogenation, deprotection of the diphenylphosphinoyl group under acidic condition, and cyclization of **4a** and **4h** using sodium methoxide afforded cyclic amides **6a** and **6h** without loss of enantiopurity. The absolute configuration of **6h** was assigned as (5*R*,6*S*) by X-ray crystallographic analysis (see the Supporting Information).



Scheme 4. Proposed reaction mechanism for the asymmetric vinylogous Mannich reaction of ketimine with siloxyfuran.

The proposed catalytic cycle for the vinylogous Mannich reaction is shown in Scheme 4. The picolinamide ligand **3h** reacts with $Cu(OAc)_2$ to afford complex **A**, which is protonated by acetate. Then, the acetate reacts with 2-siloxyfurane **2a** to give TMSOAc and dienolate-containing complex **B**.[10] Ligand exchange of acetate to ketimine **1a** on copper(II) gives complex **C**.[11] A C–C bond-forming reaction between dienolate and ketimine proceeds in the coordination sphere of copper(II) in complex **C** to give complex **D**. Then, complex **B** is regenerated by a proton-exchange reaction of complex **D** with TMSOH and **2a**.

From the above proposal and the absolute stereochemistry of the product, the assumed transition state for the vinylogous Mannich reaction is shown in Figure 1. Two nitrogens from **3h** and two oxygens coordinate to copper (II) in a square planer manner, and the dienolate attacks the ketimines in the coordination sphere of the copper cation. The dienolate approaches the *Re* face of the ketimines, thus avoiding steric repulsion from the diphenylphosphinoyl group. Further studies are required to fully elucidate the mechanistic details of the reaction.

In conclusion, we have developed the first asymmetric vinylogous Mannich reaction of unactivated ketimines with siloxyfurans using a new class of catalyst, which consists readily accessible cinchona alkaloid amide and $Cu(OAc)_2$. The asymmetric vinylogous Mannich reaction was screened for a broad range of ketimines and substituted siloxyfurans. Products containing contiguous tetra- and trisubstituted stereocenters were produced with high selectivity. This approach provides both enantiomers of optically active δ-amino-δ,δ-disubstituted-α,β-unsaturated carbonyl compounds in high yield and with excellent selectivity. Further research is in progress to study the potential of these catalytic systems for other reactions.

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