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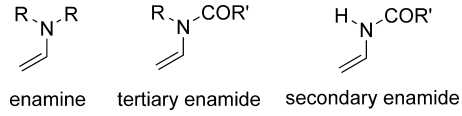
Cr(III)(salen)Cl Catalyzed Enantioselective Intramolecular Addition of Tertiary Enamides to Ketones: A General Access to Enantioenriched 1*H*-Pyrrol-2(3*H*)-one Derivatives Bearing a Hydroxylated Quaternary Carbon Atom

Luo Yang,[†] De-Xian Wang,[†] Zhi-Tang Huang,[†] and Mei-Xiang Wang*[,†,‡]

Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China, and The Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China

Received June 4, 2009; E-mail: mxwang@iccas.ac.cn

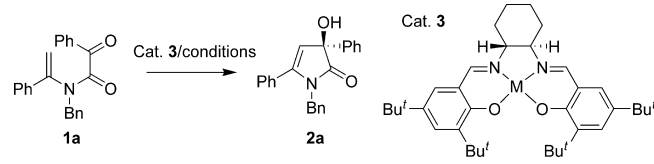
Enamines[1] are useful intermediates in organic synthesis oweing to the pioneering work of Stork in the 1950s.[2] The importance of enamine chemistry is illuminated recently by asymmetric organocatalysis using chiral amine derivatives.[3] As the enamine variant, enamides are, however, stable and show diminished enaminic reactivity because of the electron-withdrawing nature of the *N*-acyl group which alleviates the delocalization of nitrogen lone-pair electrons into a carbon−carbon double bond.[4] The stability of enamides has been exemplified by the observation of enamides as naturally occurring products.[5] The majority of the synthetic application of enamides lies therefore on their catalytic hydrogenation reactions to prepare enantioenriched α-amino acid derivatives.[6] Kobayashi[7] has shown recently that secondary enamides, the enamide species bearing an N−H moiety, are able to react with different electron-deficient reactants in the present of a Lewis acid catalyst. The reactions proceed via the aza-ene addition process, and the secondary enamides behave actually as the aza-ene components.[7,8] The enaminic (nucleophilic) reactions of tertiary enamides are very rare,[4,9] and it has been noted[7a] that tertiary enamides, not like their secondary enamide homologues, are not able to react with electrophiles. In the synthesis of *clausena* alkaloids, however, we[10] found tertiary enamides can act as good nucleophiles to react with epoxide to form homoclausenamide alkaloids. This has encouraged us to explore the enaminic reactions of enamides. We report herein the first catalytic asymmetric intramolecular nucleophilic addition of tertiary enamides to a carbonyl group to give in excellent yield and enantiomeric excess highly functionalized 1*H*-pyrrol-2(3*H*)-one derivatives bearing a hydroxylated quaternary carbon center.



enamine tertiary enamide secondary enamide

We initially examined the reaction of enamide **1a**. Because of easy availability and convenience of handling under atmospheric conditions, Jacobsen's salen metal complexes[11] were chosen as chiral catalysts. The metal species were found crucial in the reaction. In refluxing benzene, for example, the complexes of *R,R*-salen with Al^{III}−Cl **3a**, Fe^{III}−Cl, **3b**, Co^{II} **3c**, and Mn^{III}−Cl **3d** did not show catalytic activity and no reaction was observed (entries 1−4, Table 1). To our delight, the Cr(III)(salen)Cl complex **3e**, however, was an active catalyst to transform enamide **1a** into (*S*)-1-benzyl-3-hydroxy-3,5-diphenyl-1*H*-pyrrol-2(3*H*)-one **2a** in 85% yield with 99% ee at room temperature within 17 h (entry 5, Table 1). Other solvents or mixture solvent systems were not superior to benzene, leading to a long reaction time, low chemical yield, or decreased enantioselectivity (see Supporting Information). It is interesting to note that the presence of a small amount of base gave both high yield and high ee of product **2a** (entries 7−10, Table 1). The combination of catalyst **3e** (5 mol % loading) and Na_2CO_3 (0.2 equiv) in benzene at room temperature was found most efficient for intramolecular enantioselective enamide addition to the carbonyl (entry 10, Table 1).

Table 1. Optimization of Catalytic Enantioselective Reaction of **1a**[a]



entry	cat.	M (mol %)	additive (equiv)	*T* (°C)	*t* (h)	**2** (%)[b]	ee (%)[c]
1	**3a**	Al−Cl (10)	-	80	24	<5	nd[e]
2	**3b**	Fe−Cl (10)	-	80	24	0	-
3	**3c**	Co (10)	-	80	24	<5	nd[e]
4	**3d**	Mn−Cl (10)	-	80	24	<5	nd[e]
5	**3e**	Cr−Cl (10)	-	rt	17	85[d]	99
6	**3e**	Cr−Cl (10)	-	rt	48	77[d]	87
7	**3e**	Cr−Cl (10)	K_2CO_3 (1)	rt	96	93	95
8	**3e**	Cr−Cl (10)	K_2CO_3 (0.2)	rt	54	99	96
9	**3e**	Cr−Cl (10)	Na_2CO_3 (0.2)	rt	24	97	95
10	**3e**	Cr−Cl (5)	Na_2CO_3 (0.2)	rt	16	98	96
11	**3e**	Cr−Cl (2)	Na_2CO_3 (0.2)	rt	136	98	96

[a] A mixture of enamide **1a** (0.3 mmol), catalyst **3** and additive was stirred at room temperature or refluxed in dry benzene (15 mL). The reaction was stopped when reactant was consumed. [b] Isolated yield. [c] Determined by chiral HPLC analysis (see Supporting Information). [d] An uncharacterizable byproduct was obtained. [e] Not determined.

Under the optimized conditions, the scope of the reaction was explored. As indicated by the results in Table 2, almost all amides tested underwent Cr(III)(salen)Cl catalyzed enaminic reaction to afford in excellent yield 3,5-diaryl-3-hydroxy-1*H*-pyrrol-2(3*H*)-one products **2** of high enantiopurity. Notably, the reaction rate was governed strongly by the electronic nature of the substituents on enamides. In the cases of *N*-benzylated enamides **1a**−**1g**, when Ar^1 was a 4-chlorophenyl or 4-bromophenyl group, the reaction proceeded slowly. They took more than 4 days to go to completion (entries 3 and 5, Table 2). In contrast, the replacement of Ar^2 by a 4-chlorophenyl group led to the enhancement of the reaction velocity (entry 8, Table 2). The change of the R substituent on nitrogen from benzyl, *para*-methoxybenzyl, allyl to methyl and phenyl resulted in rate acceleration but with a slight decrease of enantioselectivity (entries 1, 9−12). It is worth noting that the observed electronic effect was consistent with the nucleophilic attack of enamide at the carbonyl moiety. The increased electron density of the enamine double bond and the decreased electron density of the carbonyl led to an enhanced reaction rate. The Cr(III)(salen)Cl

[†] Institute of Chemistry, Chinese Academy of Sciences.
[‡] Department of Chemistry, Tsinghua University.

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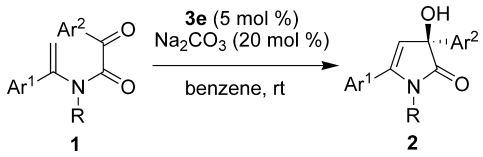
catalyzed reaction was readily scalable. Thus, in a gram-scale reaction, product **2b** was obtained in 99% yield with 99% ee (see Supporting Information). The *S*-configuration of the newly formed stereocenter in products **2**, which was determined unambiguously by X-ray crystallography of an *O*-methylated derivative of **2d** (see Supporting Information), indicated the nucleophilic attack of enamide at the *re*-face of the carbonyl in the presence of *R*,*R*-Cr(III)(salen)Cl complex **3e**.

Table 2. Catalytic Enantioselective Reaction of Enamides **1**[a]



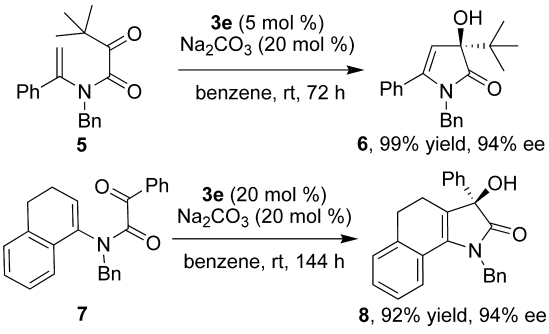
1 **2**

entry	1	R	Ar[1]	Ar[2]	*t* (h)	2 (%)[b]	ee (%)[c]
1	**1a**	Bn	Ph	Ph	16	**2a** (98)	96
2	**1b**	Bn	4-Me-C_6H_4	Ph	4	**2b** (99)	98
3	**1c**	Bn	4-Cl-C_6H_4	Ph	114	**2c** (99)	96
4	**1c**	Bn	4-Cl-C_6H_4	Ph	17[d]	**2c** (93)	97
5	**1d**	Bn	4-Br-C_6H_4	Ph	96	**2d** (97)	99
6	**1e**	Bn	Ph	4-Me-C_6H_4	68	**2e** (98)	97
7	**1f**	Bn	Ph	4-F-C_6H_4	72	**2f** (99)	97
8	**1g**	Bn	Ph	4-Cl-C_6H_4	16	**2g** (98)	97
9	**1h**	PMB	Ph	Ph	11	**2h** (99)	98
10	**1i**	Allyl	Ph	Ph	15	**2i** (99)	94
11	**1j**	Me	Ph	Ph	4	**2j** (99)	89
12	**1k**	Ph	Ph	Ph	4	**2k** (97)	88

[a] Substrate **1** (0.5 mmol) was reacted in benzene (25 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis (see Supporting Information). [d] 10 mol % of **3e** were used.

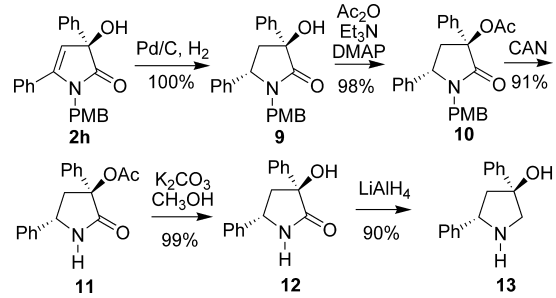
The Cr(III)(salen)Cl-catalyzed enantioselective reaction was also applicable to other substrates (Scheme 1). Enamide **5**, which contains a *t*-Bu group, underwent an equally efficient reaction to afford highly enantiopure product **6** (94% ee) in 99% yield. The reaction of tetralone-derived enamide **7** was slow due to probably the steric effect of 1,2-dihydronaphthalene moiety. Use of 20 mmol % of catalyst loading led to a complete transformation of **7** within 144 h into a fused heterocyclic product **8** with an ee of 94%.

Scheme 1. Catalytic Enantioselective Addition Reaction of **5** and **7**



The resulting (*S*)-3-hydroxy-3,5-diaryl-1*H*-pyrrol-2(3*H*)-one compounds **2** are valuable compounds. The highly functionalized quaternary carbon center in 1*H*-pyrrol-2(3*H*)-one is hardly accessible by other methods. In a closely related system, for example, catalytic asymmetric addition of arylboronic acids to *N*-benzylisatin gave 1-benzyl-3-aryl-3-hydroxyindolin-2-ones in only moderate yield and enantioselectivity (ee <73%).[12] To demonstrate the synthetic utility of products **2**, we undertook the practical synthesis of (3*S*,5*S*)-3,5-diphenyl-3-pyrrolidinol, its racemic form found to possess various useful pharmacological properties.[13] As illustrated in Scheme 2, catalytic hydrogenation of **2h** gave a single diastereoisomer **9** in which two phenyl group are cis-orientated (see Supporting Information). The diastereoselectivity is probably due to the directing effect of the 3-hydroxy group of **2h**. *O*-Acetylation of **9** with Ac_2O followed by deprotection of *para*-methoxybenzyl (PMB) with ceric ammonium nitrate (CAN) afforded product **11**. Deacetylation of **11** with K_2CO_3 in methanol and reduction of the resulting lactam **12** with $LiAlH_4$ gave the desired (3*S*,5*S*)-3,5-diphenyl-3-pyrrolidinol **13** (Scheme 2).

Scheme 2. Synthesis of (3*S*,5*S*)-3,5-Diphenyl-3-pyrrolidinol **13**



In summary, we have provided a general and powerful approach to highly enantiopure functionalized γ-lactams that bear a hydroxylated quaternary carbon center from *R*,*R*-Cr(III)(salen)Cl complex-catalyzed intramolecular addition of tertiary enamide to a carbonyl moiety. Exploration of intramolecular and intermolecular enaminic reactions of tertiary enamides with other electrophiles is underway.

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Supporting Information Available: Experimental procedures, compound characterization, ^1H and ^{13}C NMR spectra, X-ray structure of *O*-methylated derivative of **2d** and **6** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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