Catalytic Addition of Homoenolates to Imines – The Homo-Mannich Reaction

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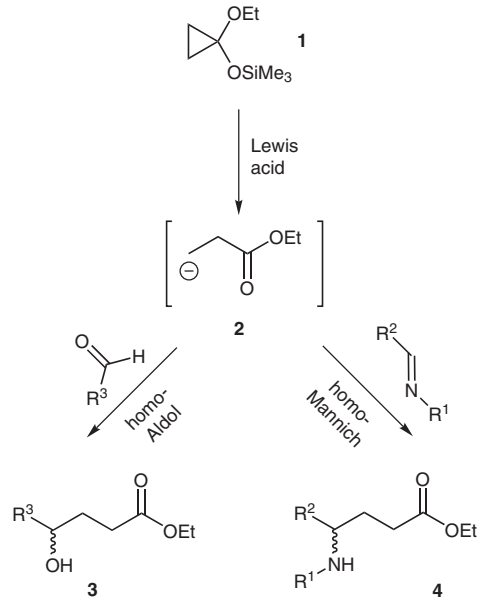
Dedicated to Prof. Dr. Frank Seela on the occasion of his 65th birthday.

Abstract: For the first time, homo-Mannich reactions with unmasked homoenolates have been achieved by adding homoenolate precursor **1** and imines **5**. The key to this reaction is the right choice of the Lewis acids – $Cu(OTf)_2$ proved to be most suitable for preparing the homoenolate and activation of the imine. An asymmetric catalytic version of this reaction is provided by using chiral, non-racemic phenyl-derived bisoxazolidine as ligand for the Lewis acid.

Key words: asymmetric catalysis, amino acids, Lewis acids, homoenolates, Mannich reaction

The Mannich reaction is one of the basic reactions in organic synthesis which has served in numerous sequences as the key reaction.[1] If one considers the closely related aldol reaction as one of the cornerstones of stereoselective synthesis, it is most striking that the development of asymmetric, especially catalytic versions of Mannich reactions, have been successfully accomplished only recently.[2] Amongst others, the use of chiral, non-racemic Lewis acids has played an important role. To stay in comparison of aldol- and Mannich reactions, the corresponding homoaldol reactions have been studied in detail and have been employed in various natural product syntheses.[3] However, homo-Mannich reactions (addition of homoenolates to imines or iminium anions) have not been reported in the literature (Scheme 1). In connection with our work on cyclopropanone hemiacetals **1**[4] we became very intrigued by the idea of employing homoenolates **2** generated from **1** in addition reactions to imines to achieve the synthesis of γ-amino acids **4**.[5] In this communication we are presenting results to demonstrate for the first time that, in fact, homoenolates can be added to imines.[6,7] These results may be considered as entering points towards the development of homo-Mannich reactions. In addition, we will provide a catalytic asymmetric version of this reaction and demonstrate that diastereoselective homo-Mannich reactions can be achieved by using chiral imines.

Since the pioneering work of Kuwajima and Nakamura cyclopropanone hemiacetals **1** have been used to provide direct access to ester homoenolates **2**. They showed that this can be achieved by various Lewis acids such as $TiCl_4$ or $ZnCl_2$. Homoenolates **2** can be added to aldehydes to provide homoaldol products **3** (Scheme 1). Imines, which tend to have a lower electrophilicity than their corresponding aldehydes, can be activated efficiently by Lewis acids. Therefore, one can assume that cleavage of cyclopropanone hemiacetals **1** and activation of imines can be achieved by the same Lewis acid in one pot. For the nature of the Lewis acids, we hoped that $Cu(OTf)_2$ currently used very successfully in Mannich reactions would serve as valuable catalysts to enforce the homo-Mannich reaction.[2e,8]



Scheme 1

In our initial studies, we have chosen N-protected α-imino esters **5**. As the N-protecting group we used the electron rich *p*-methoxyphenyl (PMP) group, which additionally permits easy removal under oxidative conditions.[9] *N*-Tosyl- and *N*-phenyl-derived imines proved to be of no use for this reaction type, no reaction could be observed. Therefore, PMP-protected imines have been used throughout these studies (Scheme 2).

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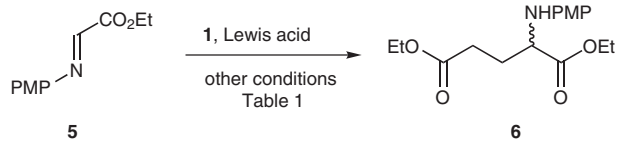

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Scheme 2

Table 1 Results for the Reaction of Imine **5**[11] with Cyclopropanone Hemiacetals **1** in the Presence of Various Lewis Acids

Entry	Lewis acid	Catalyst (mol%)	Solvent	Time (h)	Yield (%)
1	$Cu(OTf)_2$	100	THF	48	72[a]
2	$Cu(OTf)_2$	20	Toluene	18	85[a]
3	$Cu(OTf)_2$	20	CH_2Cl_2	18	73[a]
4	$Cu(OTf)_2$	10	THF	18	86[a]
5	$Cu(OTf)_2$	5	THF	48	60[a]
6	$Cu(OTf)_2$	50	Et_2O	72	28[a]
7	$CuBr_2$	100	CH_2Cl_2	72	10
8	$CuBr_2$	100	Et_2O	72	Traces[b]
9	$CuBr_2$	100	THF	72	Traces[b]
10	$Zn(OTf)_2$	100	CH_2Cl_2	72	Traces[b]
11	$Zn(OTf)_2$	100	THF	72	Traces[b]
12	$Zn(OTf)_2$	100	Et_2O	72	N.r.[c]
13	$In(OTf)_3$	100	CH_2Cl_2	72	27
14	$In(OTf)_3$	100	THF	72	Traces[b]
15	$In(OTf)_3$	100	Et_2O	72	Traces[b]
16	BF_3	100	CH_2Cl_2	18	26
17	BF_3	100	THF	72	Traces[b]
18	BF_3	100	Et_2O	72	Traces[b]
19	CsF	100	CH_2Cl_2	72	N.r.[c]
20	CsF	100	THF	72	N.r.[c]
21	CsF	100	Et_2O	72	N.r.[c]
22	$BiCl_3$	100	CH_2Cl_2	18	21
23	$BiCl_3$	100	THF	72	23
24	$BiCl_3$	100	Et_2O	72	N.r.[c]
25	$TiCl_4$	100	Et_2O	24	N.r.[c]
26	TMSOTf	100	THF	24	N.r.[c]

[a] Yield of isolated products, otherwise yields determined by GLC of the crude reaction mixture after passing through a plug of silica gel.
[b] Traces: yields < 10%.
[c] N.r.: no reaction.

Kuwajima and Nakamura explored a great variety of Lewis acids suitable for cleavage of **1**. It seemed appropriate to use these for the activation of imines, too. Although homoenolate formation proceeded successfully in all cases, most of these Lewis acids failed to activate the imine to form homo-Mannich products in reasonable yields (Table 1, run 7–25). TMSOTf failed to form the homoenolate, instead it activated the imine (run 26). This could be proven in experiments using 1 equivalent $TiCl_4$ and 1 equivalent TMSOTf. In this case, the product could be observed in high yields indicating the formation of the homoenolate with $TiCl_4$ and the activation of the imine with TMSOTf. A similar pattern has been observed in homoaldol reactions.[3g]

Turning to $Cu(OTf)_2$, which has been shown to be a very suitable imine-activating Lewis acid, we have been able to achieve the formation of N-protected γ-amino esters. In all experiments employing $Cu(OTf)_2$ only substoichiometric amounts had to be used. In CH_2Cl_2 20 mol% had to be used to obtain **6** in 73% yield. Better results could be obtained by carrying out the reaction in THF (86% yield, 10 mol% Lewis acid), but the yield decreased by lowering the amount of $Cu(OTf)_2$ (59% yield, 5 mol% Lewis acid). Diethyl ether was not suitable as solvent. Even with a very high amount of catalyst the yield dropped to 26%. Interestingly, toluene as solvent gave also very good results. In the presence of 20 mol% of the catalyst, 85% of the product could be obtained.

These very encouraging results gave rise to believe that this reaction can be carried out in an asymmetric catalytic version. Recently, it was demonstrated very successfully that chiral, non-racemic bisoxazoline–copper(II) complexes **7** and **8** act as effective catalysts in aldol- and Mannich reactions, amongst others.[2e,8]

We employed **7** and **8** (20 mol%) in the presence of $Cu(OTf)_2$ (20 mol%). The chemical yields with complex **8** were comparable to the ones reported in Table 1 (78%), however, the enantiomeric excess obtained was only 44% (as determined by chiral HPLC). To our surprise, complex **7** did not lead to any product formation. In this case the formation of a homoenolate, which is catalyzed also by the Lewis acid, could not be observed. However, heating the reaction solution up to 50 °C, homoenolate formation and subsequent product formation could be observed, but without any stereoselectivity.

Assuming the chelating model previously proposed for imides and glyoxylates, notable differences have been observed while using *tert*-butyl **7** or phenyl-derived ligands **8** (Figure 1).[8b] In hetero-Diels–Alder reactions and glyoxylate-ene reactions, an opposite diastereoselectivity was observed, which was explained by a change in metal center geometry. Here, it can be concluded to some extend that distortion at the metal center leads to productive binding of the imine to complex **8**, whereas non-productive binding of the imine to **7** can be accounted for the failure of the reaction. Interestingly, the same negative outcome can be observed in the case of isopropyl- (from valine)

and benzyl-derived (from phenylalanine) ligands. Further studies have to be done to gain a reliable mechanistic insight into this reaction.

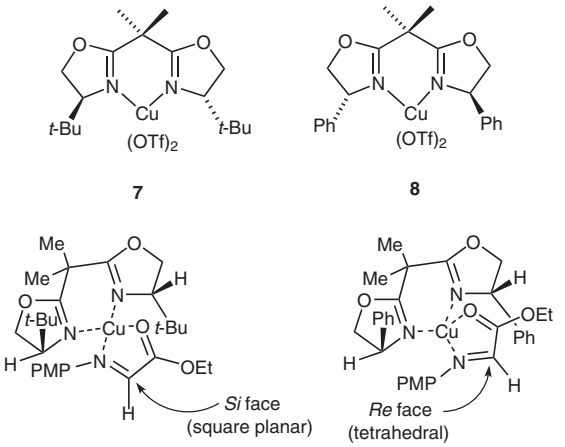
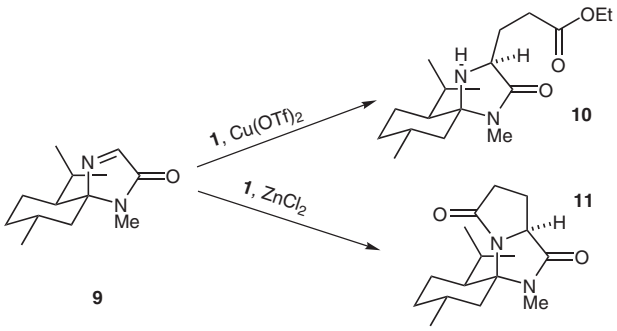


Figure 1 Transition states for the Mannich reaction and the homo-Mannich reaction

To show the potential of this new reaction, we employed menthone-derived chiral glycine equivalent **9** as the imine (Scheme 3).[10] It can certainly be assumed that the addition of homoenolate **2** is governed by the chiral, non-racemic auxiliary, and therefore, leading to products in high diastereoselectivities. Compound **9** can be easily synthesized by forming the *N*,*N*-acetal (menthone and *N*-methyl glycinamide) first and subsequent oxidation with PDC.



Scheme 3

Indeed, by adding **1** to the chiral imine **9** in the presence of $Cu(OTf)_2$ only one addition product could be observed in 41% yield. As revealed by NMR spectroscopy, product **10** was diastereomerically pure. In the presence of $ZnCl_2$, however, lactam formation can be observed exclusively (yield 19%). The structure of cyclized **11** could be determined by NMR- and by X-ray spectroscopy. The products obtained in these reactions clearly revealed that the nucleophilic attack of the homoenolate **1** was controlled by the isopropyl moiety of the chiral auxiliary, which is efficiently shielding the back of the imine moiety. The formation of the non-cyclized **10** can be explained by the formation of TMSOTf, which is silylating the amide ion formed as an intermediate from the homoenolate addition and thus preventing further cyclization. In the case of $ZnCl_2$, no silylation is possible, therefore, the formation of the lactam can be achieved.

After clarifying some chemoselectivity aspects of this new reaction, problems concerning regioselectivity while using substituted cyclopropyl hemiacetals have to be addressed. Future plans also include the utilization of other chiral, non-racemic Lewis acids to achieve the asymmetric synthesis of non-natural γ-amino acids.

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(11) **Experimental Procedures;**
Procedure for the Cu(OTf)$_2$-Catalyzed Homoenolate Addition to Imine 5.
In an inert atmosphere [(1-ethoxycyclopropyl)oxy]trimethylsilane (**1**, 250 μL, 1.21 mmol, 1.3 equiv) was added to a stirred mixture of Cu(OTf)$_2$ (37 mg, 0.7 mmol) in THF (3 mL) at –78 °C. Imine **5** (207 mg, 1.0 mmol) was dissolved in 1.0 mL of THF and added to the reaction mixture. Stirring was continued for 18 h at r.t. The reaction was quenched with EtOH (1–2 mL), concentrated, the residue dissolved in CH_2Cl_2 (2 mL) and filtered over a small bed of silica gel using CH_2Cl_2 (20 mL) as eluent. Evaporation of the solvent under reduced pressure afforded the crude reaction product **6**, which was purified by column chromatography. R_f = 0.6 (silica gel, petrol ether–EtOAc, 1:1, TLC developed twice). The separation of the enantiomers was carried out with a Daicel Chiralcel OD-H column (hexane–*i*-PrOH, 8:2; c_{analyt} 0.1 mg/mL; flow rate 0.5 mL/min, λ 254 nm); t_{R1} = 14.87 min; t_{R2} = 16.28 min.
Procedure of the BOX-Catalyzed Reaction.
In an oven dried 50 mL flask equipped with a magnetic stirring bar, Cu(OTf)$_2$ (35.5 mg, 0.1 mmol) and (*S*,*S*)-2,2-isopropylidene-bis-(4-phenyl-2-oxazoline) (**8**, 38 mg, 0.11 mmol) were added. The mixture was stirred under high vacuum for 2 h and then filled with dry argon. Dry THF (5 mL, distilled over Na and $LiAlH_4$) was added and the solution was stirred for 4 h. Imine **5** (207 mg, 1.0 mmol) was dissolved in 1–2 mL of dry THF and added dropwise followed by hemiacetal **1** (250 μL, 1.21 mmol) at –78 °C. Stirring was continued for 72 h at r.t. and then the reaction was quenched with EtOH (1–2 mL), concentrated and the residue dissolved in CH_2Cl_2 (2 mL), filtered over a small pad of silica gel using CH_2Cl_2 (20 mL) as eluent. Evaporation of the solvent under reduced pressure afforded the crude product **6**, which was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 1:1).