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α-Amino acid synthesis via a Cu(II) chiral Lewis acid mediated addition of soft carbon nucleophiles to glycine cation equivalents

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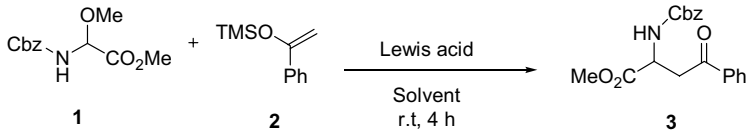
Abstract—A new method for the formation of α-amino acid derivatives via Lewis acid mediated additions of soft carbon nucleophiles to carbamate protected glycine cation equivalents is described. A number of derivatives have been prepared in moderate yields and up to 85% ee using a Cu(II)-diamine catalyst combination.

1. Introduction

Recently there have been many examples of Lewis acid catalysed/mediated additions of nucleophiles to imines in the context of chiral auxiliary chemistry.[1–7] However there have only been a few reported chiral Lewis acid catalysed variants of this Mannich-type reaction.[8–12] The use of α-imino esters as substrates in Mannich-type reactions leads to the formation of α-amino acids. More specifically the use of silyl enol ethers as nucleophiles in such reactions gives us access to γ-oxo-α-amino acids (aspartic acid analogues), which are an interesting and useful class of biologically active α-amino acids.[13–22] Although Lectka[9–11] and Kobayashi[12] have successfully achieved the formation of α-amino acids by the addition of soft carbon nucleophiles to imines using chiral Lewis acids, both methods employ protecting groups that require aggressive deprotection conditions. Herein we report an asymmetric Lewis acid mediated addition of soft carbon nucleophiles to imines bearing carbamate-type protecting groups that can be removed under mild conditions. Furthermore, the reactive imine is formed in situ and has the ability to control the stereoselectivity of the addition of the nucleophile by forming a stable five-membered chelate with the chiral Lewis acid by binding through both the imine N and the carbonyl O. With this in mind *N*-benzyloxycarbonyl-α-methoxy glycinate **1** was chosen as a suitable substrate to begin the investigation.

2. Results and discussion

In order to ascertain effective Lewis acid and solvent combinations for catalysing/mediating the addition, an initial screen was conducted (Scheme 1). Lewis acids and solvents were chosen using score plots, resulting from principal components analyses,[23] so as to enable an investigation of a range of chemical behaviours. Encouragingly, six 'hits' were identified from this screen using LC–MS analysis of the crude reaction mixtures (Table 1). These six 'hits' were investigated further and the ratios of the starting material to target molecule were calculated from the crude ^{1}H NMR spectrum. The



1 **2** **3**

Scheme 1. Lewis acid and solvent screen.

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Table 1. Lewis acid and solvent screen

	$ZnCl_2$	$CuBr_2$	$AlCl_3$	$SnCl_4$	$Cu(OTf)_2$	$Yb(OTf)_3$
MeCN					✓	✓
DCM	✓		✓		✓	
THF						
Toluene					✓	

✓ = Product identified by LC–MS.

best Lewis acid and solvent combinations were found to be $Cu(OTf)_2$ in DCM or MeCN.

The next step was to introduce the asymmetry-inducing element in the form of an enantiopure chiral ligand. The introduction of a ligand into the system could have profound effects on the catalytic system and so it was important to screen a variety of ligands. From the literature, ligands for copper **4**–**11** (Fig. 1) were examined first, with a view to designing new ligands if necessary at a later stage. Again nucleophile **2** and substrate **1** were used in the reaction with stoichiometric amounts of copper(II) triflate and ligands **4**–**11** in both DCM and MeCN (Scheme 2 and Table 2)[27].

The results show that certain ligands **7**–**11** influenced the stereochemical outcome of the reaction to some extent. The effect of using different solvents was also very noticeable, not only in modulating the enantioselectivity but also in altering the yield of the product obtained. It is interesting to note that in the reactions performed with no ligand, using acetonitrile as the solvent gave the best yield (29%). However with some ligands (entries 4, 5 and 8) the reactivity was reversed and DCM became the preferred solvent for obtaining a significant amount of the product. This difference is likely to be due to the fact that acetonitrile is a coordinating solvent and can therefore behave as a ligand, whereas DCM is noncoordinating. The best ligand and solvent combination was clearly cyclohexyl diamine **10** in DCM. When the reaction was performed with ligand **10** in MeCN, the yield increased; however this combination gave very little to no enantioselectivity. Since the use of cyclohexyl

Table 2. Ligand screen

Entry[a]	Ligand	Solvent	Yield/%	Ee[b]/%	Major isomer[c]
1	None	DCM	8	0	—
2	None	MeCN	29	0	—
3	**7**	MeCN	26	23	Faster
4	**8**	DCM	14	0	—
5	**9**	DCM	18	0	—
6	**10**	MeCN	40	4	Slower
7	**10**	DCM	7	44	Slower
8	**11**	DCM	8	21	Faster

[a] For the ligand/solvent combinations not represented in the table, there was no reaction.

[b] Enantioselectivities were obtained by use of chiral HPLC after removal of the N-protecting group using TMSI in MeCN.

[c] Refers to the slower (retention time 21.90 min) or faster (retention time 17.53 min) running enantiomer when analysed by HPLC using a Chiralcel OD column.

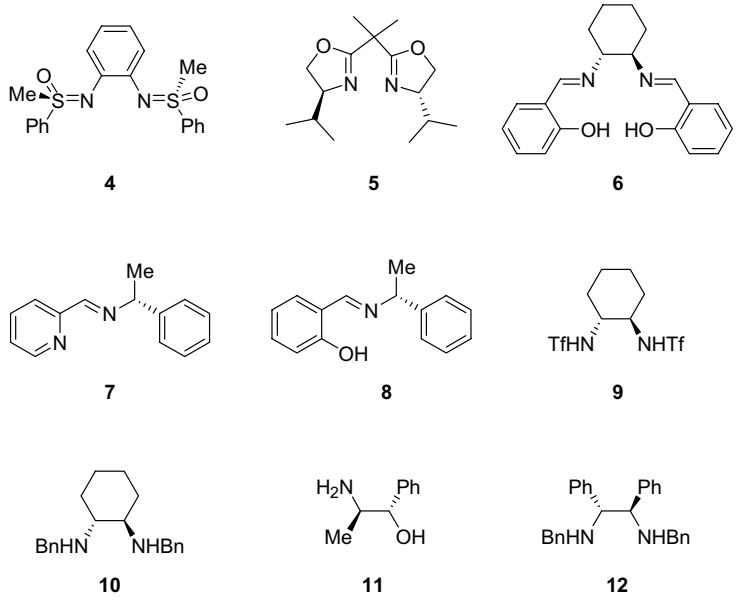
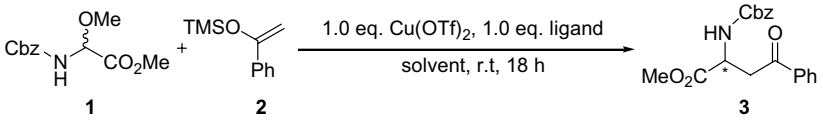


Figure 1. Ligands which can form copper(II) complexes.



Scheme 2. Chiral ligand screen.

diamine **10** in DCM gave the highest ee, we decided to investigate the use of the related ligand (1*R*,2*R*)-*N*,*N*′-dibenzyl-1,2-diphenylethane-1,2-diamine **12** with DCM. Kobayashi et al.[24,25] and Kanemasa et al.[26] have already demonstrated the use of this diphenyl backbone to great effect in asymmetric Lewis acid catalysis.

Ligand **12** was synthesised via pinacol coupling (Fig. 2) followed by successive recrystallisations of the tartaric acid salt. Use of **12** as the ligand in DCM solvent gave a yield of 13% and a corresponding ee of 52%, which was marginally better than the result obtained when using ligand **10** in this solvent.

Investigations into the effect on yield and enantioselectivity of the reaction by changing the leaving group and then the protecting group on the substrate using the preferred $Cu(OTf)_2$/DCM/**12** combination were subsequently conducted (Scheme 3 and Table 3).

Of all the leaving groups studied, the best results were obtained when the superior acetate leaving group was employed. By comparing the last two entries in Table 3 it would appear that the steric properties of the protecting group also play an important role in the selectivity of the reaction. An increase of 11% in the enantioselectivity in going from the Cbz to the Boc protecting group shows that the bulky *tert*-butyl group led to higher selectivity in the reaction when compared to the benzyl group. The electronic properties of these groups are very similar and there is no apparent reason for the 27% increase in yield in going from the Cbz to the Boc protecting group.

To demonstrate the generality of the reaction, six other soft carbon nucleophiles were employed using the optimal reaction conditions and substrate **19** (Scheme 4 and Table 4). There appears to be good nucleophilic compatibility over the range of nucleophiles investigated. It is interesting to note that the use of enamine **20** led to a product ee of 85% compared to 73% when using silyl enol ether **2**, where the use of both nucleophiles gives the same product.

Table 3. Effect of changing the leaving group and protecting group

Ligand	R	P	Yield/%	Ee[a]/%
10	Me	Cbz	7	44
12	Me	Cbz	13	52
12	H	Cbz	8	45
12	Ac	Cbz	31	62
12	Ac	Boc	58	73

[a] Enantioselectivities were obtained by chiral HPLC after removal of the N-protecting group (Cbz using TMSI in MeCN, Boc using TFA in DCM).

The use of silyl enol ether **21** would be expected to give a lower yield due to the electron-withdrawing properties of the *para*-nitro group thus decreasing the reactivity with respect to silyl enol ether **2**. This was indeed the case with the yield being 32% with the use of nucleophile **21** and 58% with the use of **2**. Unfortunately it was not possible to develop chiral HPLC assays for the deprotected products resulting from the use of nucleophiles **21**, **23** and **24** and so the enantioselectivity of these reactions could not be determined.

3. Conclusion

In summary, a new general methodology for forming α-amino acids by the Lewis acid mediated addition of soft carbon nucleophiles to a carbamate-protected glycine

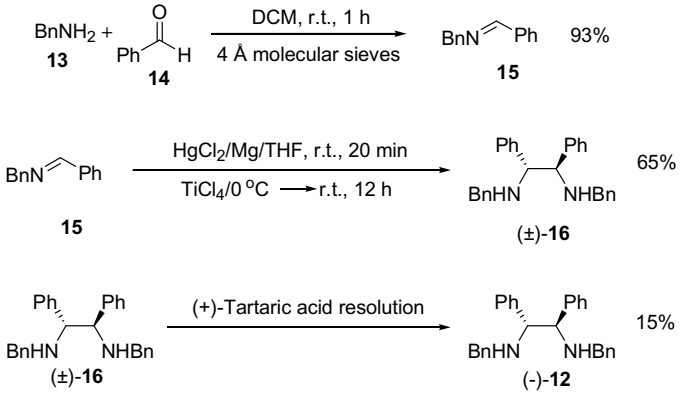
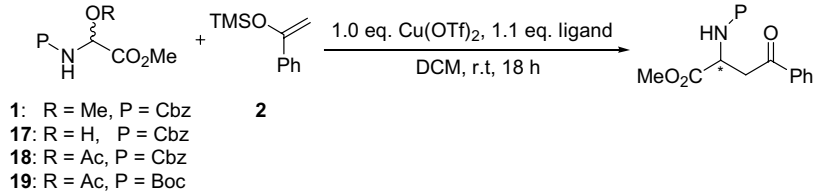
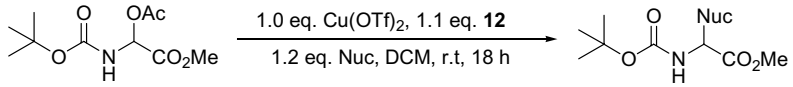


Figure 2. Synthesis of (1*R*,2*R*)-*N*,*N*′-dibenzyl-1,2-diphenyl-ethane-1,2-diamine **12**.



Scheme 3. Assessment of leaving group and protecting group effects.



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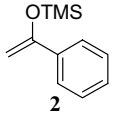
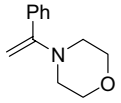
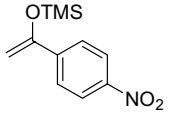
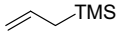
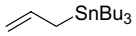
Scheme 4. Test of nucleophile compatibility.

Table 4. Test for nucleophile compatibility

Entry	Nucleophile	Yield/%	Ee[a]/%
1	 **2**	58	73
2	 **20**	52	85
3	 **21**	32	Not determined
4	 **22**	27	28
5	 **23**	25	Not determined
6	 **24**	28	Not determined

[a] Enantioselectivities were obtained by chiral HPLC after removal of the N-protecting group using TFA in DCM.

cation equivalent has been developed. Initial results show that moderate yields and good levels of enantioselectivity can be obtained. Along with improving the yield and selectivity of the reaction, studies are currently being conducted towards lowering the catalyst loading while further investigating the versatility of this reaction.

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27. Data for 2-amino-4-oxo-4-phenyl butyric acid methyl ester: $\nu_{max}(CHCl_3)/cm^{-1}$ 3393 (NH), 3031, 2955, 1739, 1685; δ_H (300 MHz; $CDCl_3$) 2.08 (2H, br s, NH_2), 3.40 (1H, A of ABX, J_{AB} 17.9, J_{AX} 6.6, $CHCH_2$), 3.49 (1H, B of ABX, J_{AB} 17.9, J_{BX} 4.4, $CHCH_2$), 3.72 (3H, s, CH_3), 3.97 (1H, X of ABX, J_{AX} 6.3, J_{BX} 4.4, CH), 7.38–7.49 (2H, m, Ph), 7.51–7.61 (1H, m, Ph) 7.87–7.96 (2H, m, Ph); δ_C (100 MHz; $CDCl_3$) 42.9, 50.7, 52.3, 128.0, 128.6, 133.4, 136.5, 175.2, 197.8; *m/z* (ES) 230 ($[M+Na]^+$, 100%), 246 ($[M+K]^+$, 28%); HRMS: (ES) Found: $[M+Na]^+$ 230.0786, $C_{11}H_{13}NO_3Na$ requires: 230.0793; HPLC (20% water/MeCN, 1 mL/min, C18) 2.96 min; chiral HPLC (10% *i*PrOH/hexane, 1.0 mL/min) 17.53, 21.90 min.