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Asymmetric 1,4 Addition of Grignard Reagents to Chiral α,β-Unsaturated Esters in the Presence of Lewis Acids

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Abstract. The synthesis of enantiomerically enriched α-amino acids is described, by means of the diastereoselective conjugate addition of Grignard reagent to (*S*)-2-acetamidoacrylic ethoxycarbonyl-phenyl-methyl ester **1** and its *N*-Boc derivative **5** in the presence of Lewis acids. The addition of magnesium organocuprates has also been analysed. The reaction proceeds with good yields and variable diastereoselectivities, depending on the organometallic reagent and on the Lewis acid utilised.

'Keywords': Amino acids and derivatives, Copper and compounds, Enolates, Michael reactions

Introduction

The asymmetric conjugate addition of an organometallic compound to an activated olefin is an important area in the field of carbon-carbon bond formation [1]. Several diastereoselective Michael additions of organometallic reagents to chiral unsaturated esters [2], oxazolines [3], amides [4] and imides [5] have been successfully reported in the literature. These procedures allow introduction of a new asymmetric centre into a carbon chain of a carboxylic acid derivative under the influence of a chiral auxiliary. As a part of extensive work on asymmetric β-addition, [6] we have been recently become interested in the 1,4-addition of Grignard reagents to unsaturated chiral imides, in the presence of a Lewis acid [7].

On pursuing our investigations on the addition of Grignard reagents in the presence of Lewis acids in comparison with cuprates and since we are also interested in the synthesis of unusual α- and β-amino acids, we report a series of diastereoselective 1,4-addition reactions to chiral esters of acetamidoacrylic acid. Following this route, enantiomerically enriched α-amino acids have been obtained with good yield.

The 1,4-addition of organometallic reagents to 2-aminoacrylic derivatives has been drawing attention, as evidenced by the number of publications describing various aspects of the reaction, including its chemo- regio- and diastereoselectivity. For instance Viallefont described the addition of lithium diorganocuprates to *N*-acylaminoacrylic methyl esters [8]: the results showed that either no addition occurred or mixtures of products were formed, including the 1,4-addition products; nevertheless good results were obtained with the reaction of organocuprates with tosyl and halogeno derivatives of L-serine and L-homoserine. On the other hand, Naso [9] showed an efficient route in the copper (I) catalysed addition of Grignard reagents to methyl 2-acetamidoacrylate for the synthesis of racemic α-amino acids. On the basis of their results, Cativiela [10] studied the behaviour of chiral 2-acetamidoacrylates in the conjugate additions-diastereoselective enolate

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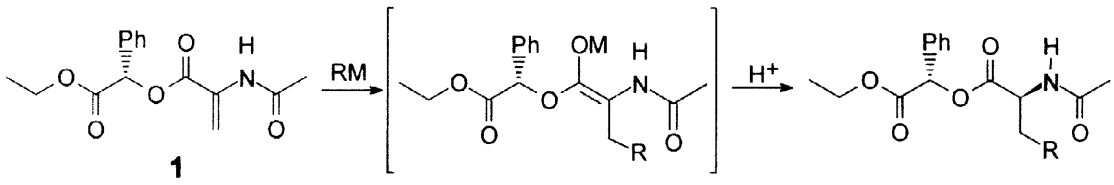
protonation to afford phenylalanine derivatives, and Hegedus [11] reported the asymmetric synthesis of α-amino acids by copper catalysed conjugate addition of Grignard reagents to optically active cyclocarbamatoacrylates. This reaction occurred with high yield and diastereoselectivity, although the chiral auxiliary was not recovered.

In our approach, the synthesis of α-amino acids has been performed by addition of both magnesium organocuprates and Grignard reagents in the presence of Lewis acids to (*S*)-2-acetamidoacrylic ethoxycarbonyl-phenyl-methyl ester **1** (Figure 1). The ester **1** bears three functional groups (i.e. ester, α,β-unsaturated ester and amide) and may therefore be expected to undergo a variety of organic transformations involving chemo-, regio- and stereochemical control. Our synthetic method allows us to obtain the desired adducts **2** with high chemo- and regioselectivity, minimising the products of the 1,2-attack. On the other hand, the stereochemical control is sometimes ineffective.

The chiral auxiliary utilised is the commercially available (*R*)-ethyl mandelate, which has been chosen taking into account that the molecule could assume a preferential conformation with the benzylic hydrogen almost coplanar with the α,β-unsaturated system of the aminoacrylic moiety [12].



1 **2**

Figure 1

Results and Discussion

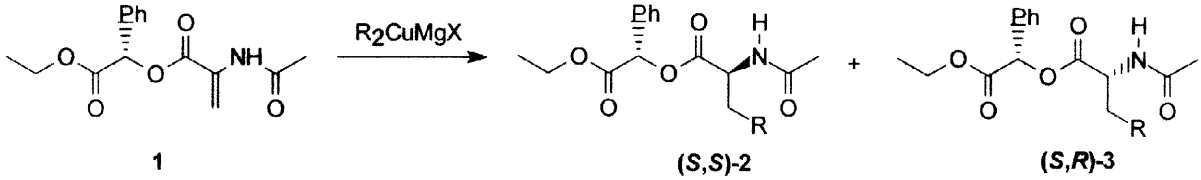
The (*S*)-2-acetamidoacrylic ethoxycarbonyl-phenyl-methyl ester **1** was easily obtained in 98% yield under the Mitsunobu conditions [13], by treatment of *N*-acetamidoacrylic acid and (*R*)-ethyl mandelate with DEAD in THF in the presence of triphenylphosphine. This procedure was utilised because any attempt to obtain the ester **1** by direct esterification of *N*-amidoacryloyl acid failed.

First we studied the 1,4-addition of magnesium organocuprates to **1**. Indeed magnesium organocuprates are good reagents for the conjugate addition on acryloyl esters, since it is well known that the organocuprates add to α,β-unsaturated carbonyl compounds almost exclusively by 1,4-addition [14]. The organometallic reagent was prepared *in situ* as a solutions of R_2MgCuX, by addition of the desired Grignard reagent to $CuBr{\cdot}Me_2S$ in dry THF at low temperature and stirring for 30 minutes under nitrogen (Equation 1).

$$CuBr{\cdot}Me_2S + 2RMgCl \xrightarrow{30\ min} R_2MgCuX{\cdot}Me_2S + MgX_2 \qquad X = Br, Cl$$

Equation 1

Then the cuprate was cooled to the desired temperature and added *via* cannula to a solution of acryloyl mandelate. The reactions were carried out in different solvents, at low temperature and under nitrogen atmosphere and proceeded smoothly affording, in most cases, the adduct and the unreacted starting material **1** exclusively. The results of the 1,4-addition of the organocuprates to the ester **1** are summarized in Table 1.



1 **(*S*,*S*)-2** **(*S*,*R*)-3**

Scheme 1

a: R = *n*-Bu; **b**: R = *i*-Pr; **c**: R = Ph

Table 1. Chemical Yields of **2** and **3** and Diastereomeric Ratios for the addition of Magnesium Organocuprates to **1**

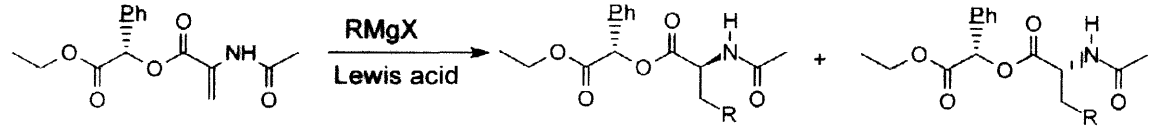
Entry	R_2CuMgX (equiv.)	Solvent	T (°C)	t (h)	Yield of **2+3** (%)	d.r. **2/3**
1	*n*-Bu_2CuMgX (3)	THF	-78	2	>95	64:36
2	*n*-Bu_2CuMgX (3)	CH_2Cl_2/THF	-78	2	80	63:37
3	*n*-Bu_2CuMgX (3)	CH_2Cl_2[a]	-60	4	75	70:30
4	*i*-Pr_2CuMgX (3)	THF	-60	1	>95	78:22
5	*i*-Pr_2CuMgX (3)	CH_2Cl_2/THF	-78	1	>95	81:19
6	Ph_2CuMgX (3)	CH_2Cl_2/THF	-78	5	60	80:20
7	Ph_2CuMgX (3)	THF	-40	4	>95	72:28

[a] The organocuprate was prepared in THF, then the solvent was stripped off and substituted with CH_2Cl_2.

The yields and the diastereomeric ratios were determined by GC, GC-MS and ^1H NMR analysis of the crude reaction mixtures. The addition of copper reagents to **1** proceeded with excellent chemical yields and moderate to good diastereoselectivities. The addition of *n*-Bu_2CuMgX was performed in different solvents (entries 1-3) and the best selectivity was observed when CH_2Cl_2 was used as a solvent for the reaction. In the addition of *i*-$Pr_2CuMgCl$ to the ester **1** (entries 4-5), complete conversion of the starting material was always obtained and the best results of diastereoselectivity were observed when the reaction was performed in a mixture of CH_2Cl_2 and THF. When $Ph_2CuMgCl$ was used at low temperature (-78 °C) (entry 6), a low yield was observed and the presence of a considerable amount of Ph_2 was detected by GC. Complete conversion was obtained when the reaction was performed in THF at -40 °C, although a decreased diastereomeric ratio was observed (entry 7). Furthermore any attempt to perform the 1,4-addition with allyl and vinyl magnesium organocuprates failed, because non-reproducible yields and low diastereomeric ratios were obtained.

To compare these results both in terms of diastereoselectivities and yields, we performed the 1,4-addition of the Grignard reagents in the presence of Lewis acids. Following a previously described protocol [7], **1** was treated with $AlMe_2Cl$, $MgBr_2$, or $TiCl_4$ in CH_2Cl_2 at -30 °C. The organometallic compound was added at the

relevant temperature and stirred for 30 minutes. Then the reaction was quenched with a saturated aqueous solution of NH_4Cl and worked up as usual. The selected results are reported in Table 2.



1 2 3

Scheme 2

a: R = *n*-Bu; **b:** R= *i*-Pr; **c:** R = Ph

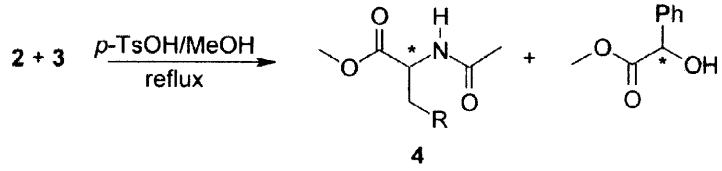
Table 2. Chemical Yields and Diastereomeric Products Ratios for the Addition of Grignard Reagents to ester **1**.

Entry	Reagent (equiv.)	Lewis Acid (equiv.)	T (°C)	Yield of **2**+**3** (%)	d.r. **2**/**3**
1	*n*-BuMgCl (4)	-	-60	57	49:51
2	*n*-BuMgCl (4)	$AlMe_2Cl$ (3)	-60	90	70:30
3	*n*-BuMgCl (4)	$MgBr_2$ (3)	-60	70	53:47
4	*i*-PrMgCl (4)	$AlMe_2Cl$ (3)	-60	90	57:43
5	*i*-PrMgCl (4)	$TiCl_4$ (1.1)	-60	98	49:51
6	PhMgBr (4)	$AlMe_2Cl$ (3)	-20	10	50:50
7	*n*-BuMgCl (3)/CuI (0.15)	$AlMe_2Cl$ (3)	-78	87	57:43
8	*i*-PrMgCl (3)/CuI (0.15)	$AlMe_2Cl$ (3)	-78	87	53:47
9	*i*-PrMgCl (3)/CuI (0.15)	$MgBr_2$ (3)	-78	60	58:42
10	PhMgBr (3)/CuI (0.15)	$AlMe_2Cl$ (3)	-20	-	-

The addition of *n*-BuMgCl in the absence of a Lewis acid proceeded with low yield and diastereoselectivity (entry 1), affording also the product of the 1,2-attack. On the other hand the addition of the same Grignard reagent in the presence of $AlMe_2Cl$ showed a good conversion of the starting material and satisfactory distereomeric ratio (entry 2), while a decreased diastereoselectivity was observed in the presence of $MgBr_2$ (entry 3). When *i*-PrMgCl was used in the presence of $AlMeCl_2$ or $TiCl_4$ (entries 4 and 5), the 1,4-addition products were obtained in high yield, together with traces of the starting material, but the selectivity was unsatisfactory. Furthermore PhMgCl gave only low yield and a large amount of Ph_2 (entry 6) and any attempt to run the addition with allyl organometallic compound failed. When a catalytic amount of CuI was added to the Grignard reagents (entries 7-10) [9], comparable results were obtained. Thus the 1,4-attack is drastically enhanced in the presence of a Lewis acid, while the corresponding 1,2-attack is avoided; unfortunately these Lewis acids are ineffective in enhancing the diastereomeric ratios.

The configuration of the newly created stereogenic centre in the adducts **2c** and **3c** was established by comparison of the ^1H NMR spectrum of the mixture with the spectrum of an authentic sample of **2c** obtained by Mitsunobu reaction between (*S*)-*N*-acetyl-phenylalanine and (*R*)-ethyl mandelate, and was confirmed as (*S,S*) based on the chemical shift of the benzylic hydrogen, that resonates at 5.95 ppm and 5.93 ppm for (*S,S*) and (*S,R*) isomer respectively.

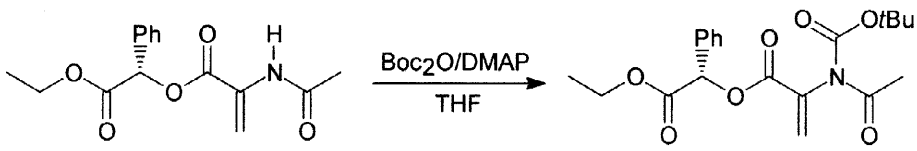
Furthermore mixtures of diastereoisomers **2a,b,c** and **3a,b,c** were transformed to the methyl esters **4a,b,c**, in order to find a general method to establish the configuration of the newly formed asymmetric centres. The mixtures were heated with *p*-toluenesulfonic acid in absolute methanol for 20h. Complete transesterification was observed, and the corresponding methyl esters were purified by flash chromatography (Scheme 3). The absolute configuration of the more abundant enantiomers of the mixtures obtained was determined from comparison of the specific rotations with the values reported in the literature (see experimental).



Scheme 3 **a**: R = *n*-Bu; **b**: R = *i*-Pr; **c**: R = Ph

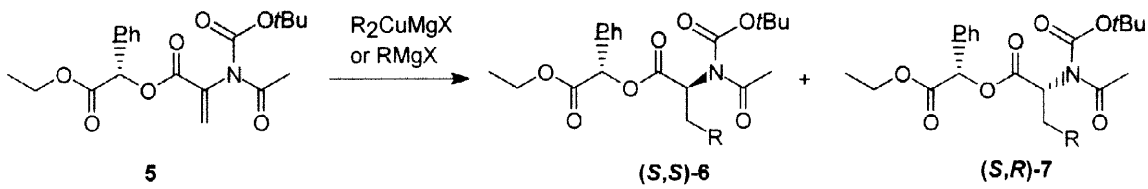
Then the protonation step was investigated under different reaction conditions. For instance we tried to quench the enolate with bulky or optically active protonating agents, such as (1*S*,2*R*)-ephedrine, (*R*)-panctolactone or diethyl malonate. In fact the chiral enolate should interact with a chiral proton source affording the final compound enriched with either the (*S*,*R*) or (*S*,*S*) diastereoisomer [15]. Unfortunately both chiral and bulky quenching agents did not afford a significant improvement in the diastereomeric ratios.

In order to influence the diastereomeric ratio, a set of reactions have been carried out on the *N*-Boc derivative **5**. The ester **1** was treated with Boc anhydride in THF in the presence of a catalytic amount of DMAP. The product **5** was obtained in quantitative yield.



Scheme 4

The conjugate addition to the imide **5** was performed both with magnesium organocuprates and with Grignard reagents (Scheme 5). The reactions have been performed in CH_2Cl_2 or in THF at low temperature following the procedures previously described for the addition to the amide **1**. The results are reported in Table 3.



Scheme 5 **b**: R = *i*-Pr; **c**: R = Ph; **d** = Allyl

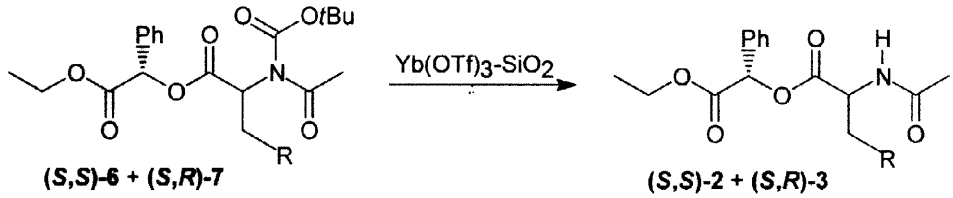
Table 3. Chemical Yields and Diastereomeric Products Ratios for the Addition of Magnesium Organocuprates and Grignard Reagents to **5**.

Entry	Reagent (equiv.)	Lewis Acid (equiv.)	Solvent	T (°C)	Time (min)	Yield of **6** + **7** (%)	d.r. **6**/**7** [b]
1	*i*-Pr_2CuMgX (3)	-	THF/CH_2Cl_2	-78	20	**80**	50:50
2	$Allyl_2CuMgX$ (3)	-	THF/CH_2Cl_2	-50	30	**85**	55:45[a]
3	*i*-PrMgCl (**4**)	$AlMe_2Cl$ (3)	CH_2Cl_2	-50	30	**98**	55:45
4	*i*-PrMgCl (4)	$MgBr_2$ (3)	CH_2Cl_2	-90	30	95	57:43
5	(*i*-Pr)MgCl (3) / CuI (0.15)	$AlMe_2Cl$ (3)	THF	-90	30	90	67:33
6	*i*-PrMgCl (3) / CuI (0.15)	$MgBr_2$ (3)	CH_2Cl_2	-90	30	52	70:30
7	*i*-PrMgCl (3) / CuI (0.15)	$TiCl_4$ (1.1)	CH_2Cl_2	-90	30	40	46:54
8	PhMgCl (3) / CuI (0.15)	$AlMe_2Cl$ (3)	THF	-50	30	60	68:32
9	AllylMgCl (3) / CuI (0.15)	$AlMe_2Cl$ (3)	THF	-60	30	95	60:40[a]
10	AllylMgCl (3) / CuI (0.15)	$MgBr_2$ (3)	CH_2Cl_2	-60	30	58	54:46[a]

[a] The absolute configuration of the more abundant stereoisomer has not been determined. [b] The diastereomeric ratios were determined by ^1H NMR experiments.

Three classes of reagents have been analysed: magnesium organocuprates (entries 1-2), Grignard reagents in the presence of a Lewis acid (entries 3-4) and Grignard reagents/catalytic CuI in the presence of a Lewis acid (entries 5-10). Both cuprates and Grignard reagents in the presence of Lewis acids (entries 1-4) afford the 1,4-adduct in very good yield with no traces of the 1,2 adduct, although no selectivity was observed. It is worth mentioning that all the allyl reagents add to **5** in very satisfactory yields (entries 2, 9 and 10). Moreover when a catalytic amount of CuI was added to the Grignard reagents, good yields and increased diastereomeric ratios were achieved. These results follow different trends and show that a substantial increase of the diastereoselectivity cannot be obtained by protecting the amido group, so probably the diastereofacial protonation is affected by the steric hindrance of the mandelate moiety.

The products **6** and **7** were respectively converted into **2** and **3**, by selective hydrolysis of the *N*-Boc group with $Yb(OTf)_3$-SiO_2 under solvent-free conditions [16] and afforded the desired products in quantitative yield (Scheme 6).



Scheme 6 **(*S*,*S*)-6 + (*S*,*R*)-7** **(*S*,*S*)-2 + (*S*,*R*)-3**

Conclusions

In this paper the addition of several organometallic reagents to amide **1** and imide **5** is studied. Both magnesium organocuprates and Grignard reagents in the presence of CuI and/or Lewis acids afford clean reactions, which proceed in most cases with high yields and complete conversion of the starting material; the presence of the mandelate moiety allows to obtain in some cases good diastereoselectivities.

The products obtained in both cases can be easily transformed into the corresponding α-amino acids, by methanolysis to the corresponding methyl ester, which was performed in quantitative yield and without detectable racemisation. The ethyl mandelate is completely recovered. Obviously, utilising (*S*)-ethyl mandelate enriched amino acids of the D series can be obtained.

Experimental

General: ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively, and chemical shifts are reported in ppm relative to the solvent peak of $CHCl_3$, defined to be δ 7.27. IR spectra were recorded using a FT-IR spectrometer. Melting points are uncorrected and are determined in open capillaries. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). Solvents for flash-chromatography were simply distilled. THF was distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from P_2O_5.

(*S*)-2-acetamidoacrylic ethoxycarbonyl-phenyl-methyl ester (1)

To a stirred solution of (*R*)-mandelic acid (6.66 mmol, 1.013 g) in dry ethanol (10 mL), BF_3-Et_2O (1.33 mmol, 0.17 mL) was added dropwise at room temperature under nitrogen atmosphere. The reaction mixture was refluxed for 1h and then the solvent was removed under reduced pressure to 1-2 mL. EtOAc (40 mL) was then added to the residue and the mixture was washed twice with a saturated aqueous solution of $NaHCO_3$ (10 mL). The organic layers were dried over $MgSO_4$ and concentrated to give (*R*)-ethyl mandelate (1.16 g, 98% yield) which was used in the following step without any further purification. The product was dissolved in dry THF (35 mL) and 2-acetylaminoacrylic acid (7.69 mmol, 0.99 g) and triphenylphosphine (12.8 mmol, 3.35 g) were added at room temperature under nitrogen atmosphere. The solution was then cooled to 0 °C and DEAD (12.8 mmol, 2 mL) was added dropwise. The mixture was stirred for 6 h, THF was removed under reduced pressure and EtOAc (50 mL) was added to the residue. The mixture was washed three times with a saturated solution of $NaHCO_3$ and then the organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Compound **1** was obtained in 80% yield (1.49 g) as an oil, after flash chromatography on silica gel (cyclohexane/EtOAc, 8/2 as eluant).

IR (film): ν = 3375, 1752, 1733, 1696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, *J* = 7.3 Hz, CH_3CH_2), 2.18 (s, 3H, $OCCH_3$), 4.08-4.33 (m, 2H, $COOCH_2$), 5.98 (s, 1H, CHPh), 6.08 (s, 1H, HNCCHH), 6.71 (s, 1H, HNCCHH), 7.41-7.51 (m, 5H, Ph), 7.70 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 13.6, 14.1, 24.0, 61.6, 75.4, 109.8, 128.1, 128.6, 131.8, 134.6, 163.2, 167.8, 169.0; $[\alpha]_D$ +80.0 (*c* 0.6, $CHCl_3$). Anal Calcd. for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.83; H, 5.89; N, 4.80.

General procedure for the conjugate addition of organocuprates to amide (1): To a stirred suspension of CuBr-Me_2S (0.49 mmol, 0.1 g) in dry THF (10 mL), RMgCl (2 equiv., 0.98 mmol, 2M solution in THF, 0.49 mL) was added dropwise under nitrogen atmosphere at -40 °C. After 30 min., the solution was cooled to the temperature listed in Table 1 and added dropwise to a solution of **1** (0.16 mmol, 50 mg) in CH_2Cl_2, previously cooled to the same temperature. After the scheduled time the reaction was quenched by adding 3 mL of an aqueous saturated solution of NH_4Cl at -78 °C. After removing the solvent under reduced pressure, the residue was dissolved in EtOAc (10 mL), washed twice with water (10 mL), filtered on a celite pad, dried on

$MgSO_4$ and concentrated. Compounds **2-3** were purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 1:1 as eluant) and obtained pure as a mixture.

General procedure for the conjugate addition of Grignard reagents to the complex amide (1)/Lewis acid: To a stirred solution of amide **1** (0.16 mmol, 50 mg) in dry CH_2Cl_2 (3 mL), the Lewis acid (3 equiv., 0.48 mmol) was added at –30 °C under nitrogen atmosphere and the mixture was stirred 15 min. Then the mixture was cooled to the desired temperature and RMgCl (4 equiv., 0.64 mmol, 2M solution in THF, 0.32 mL) was added in one portion. The mixture was stirred for 30 min, then an aqueous saturated solution of NH_4Cl (3 mL) was added to the mixture. CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the layers were separated. The organic layer was filtered on a celite pad, dried over $MgSO_4$ and concentrated under reduced pressure. Compounds **2-3** were purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 1:1 as eluant) and obtained pure as a mixture.

General procedure for the copper-(I) catalysed conjugate addition of Grignard reagents to the complex amide (1)/Lewis acid: To a stirred solution of amide **1** (0.16 mmol, 50 mg) in dry CH_2Cl_2 (3 mL), the Lewis acid (3 equiv., 0.48 mmol) was added at –30 °C under nitrogen atmosphere and the mixture was stirred 15 min. In another flask, to a solution of RMgCl (3 equiv., 0.48 mmol, 2M solution in THF, 0.24 mL) in dry CH_2Cl_2, CuI (0.15 equiv., 0.024 mmol, 5 mg) was added at 0 °C and the mixture was stirred 10 min. Then both flasks were cooled at the desired temperature and the amide **1**/Lewis acid complex was added *via* cannula to the CuI/RMgCl mixture. The mixture was stirred for 30 min, then an aqueous saturated solution of NH_4Cl (3 mL) was added to the mixture. CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the layers were separated. The organic layer was filtered on a celite pad, dried over $MgSO_4$ and concentrated under reduced pressure. Compounds **2-3** were purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 1:1 as eluant) and obtained pure as a mixture.

(2a) + (3a): oil; IR (film) ν = 3285, 1750, 1735, 1669 cm^{-1}; **(2a)** ^1H NMR ($CDCl_3$) δ = 0.86 (t, 3H, J = 7.6 Hz, $CH_2CH_2CH_3$), 1.22 (t, 3H, J = 7.1 Hz, $COOCH_2CH_3$), 1.30-1.90 (m, 8H, $CHNCH_2CH_2CH_2CH_2$), 2.02 (s, 3H, $OCCH_3$), 4.08-4.30 (m, 2H, $COOCH_2CH_3$), 4.70-4.88 (m, 1H, CHN), 5.94 (s, 1H, CHPh), 5.98 (d, 1H, J = 7.1 Hz, NH), 7.30-7.55 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.0, 22.4, 23.2, 24.7, 29.7, 31.4, 32.5, 52.2, 61.9, 75.2, 127.6, 128.6, 129.2, 133.5, 168.4, 169.9, 172.3; **(3a)** ^1H NMR ($CDCl_3$) δ = 0.86 (t, 3H, J = 7.6 Hz, $CH_2CH_2CH_3$), 1.25 (t, 3H, J = 7.2 Hz, $COOCH_2CH_3$), 1.30-1.90 (m, 8H, $CHNCH_2CH_2CH_2CH_2$), 2.03 (s, 3H, $OCCH_3$), 4.18 (m, 2H, CH_2OOC), 4.63-4.84 (m, 1H, CHN), 5.91 (s, 1H, CHPh), 5.98 (d, 1H, J = 7.1 Hz, NH), 7.30-7.55 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ = 13.9, 22.4, 23.2, 24.9, 29.7, 31.3, 32.4, 52.1, 61.8, 75.1, 127.5, 128.8, 129.2, 133.5, 168.2, 169.8, 171.9; Anal Calcd. for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.26; H, 7.85; N, 4.07.

(2b) + (3b): oil; IR (film) ν = 3290, 1748, 1733, 1668 cm^{-1}; **(2b)** ^1H NMR ($CDCl_3$) δ = 1.07-1.25 (m, 9H, OCH_2CH_3 + $CH(CH_3)_2$), 1.51-1.99 (m, 3H, $NHCHCH_2CH(CH_3)_2$), 2.03 (s, 3H, $OCCH_3$), 4.06-4.36 (m, 2H, OCH_2CH_3), 4.68-4.86 (m, 1H, CHN), 5.87 (d, 1H, J = 7.5 Hz, NH), 5.93 (s, 1H, CHPh), 7.20-7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ = 13.8, 14.3, 21.7, 22.8, 24.7, 41.3, 50.5, 62.0, 75.0, 127.4, 128.7, 129.2, 133.2, 168.4, 170.1, 172.7; **(3b):** ^1H NMR ($CDCl_3$) δ = 1.07-1.25 (m, 9H, OCH_2CH_3 + $CH(CH_3)_2$), 1.51-1.99 (m,

3H, NHC*H*C*H*$_2$C*H*(CH$_3$)$_2$), 2.02 (s, 3H, OCC*H*$_3$), 4.06-4.36 (m, 2H, OC*H*$_2$CH$_3$),4.68-4.86 (m, 1H, C*H*N), 5.87 (d, 1H, J = 7.5 Hz, NH), 5.93 (s, 1H, C*H*Ph), 7.20-7.50 (m, 5H, Ph); ^{13}C NMR (CDCl$_3$) δ = 13.8, 14.3, 21.8, 22.6, 22.8, 24.7, 41.2, 50.7, 61.7, 75.0, 127.3, 128.7, 129.1, 133.4, 168.2, 169.9, 172.2; **Anal Calcd. for** C$_{18}$H$_{25}$NO$_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.49; H, 7.60; N, 4.26.

(2c) + (3c): oil; IR (film) ν = 3301, 1756, 1670, 1642 cm^{-1}; **(2c):** ^{1}H NMR (CDCl$_3$) δ = 1.24 (t, 3H, J = 7.1 Hz, C*H*$_3$CH$_2$O), 1.94 (s, 3H, OCC*H*$_3$), 3.19 (dd, 1H, J = 6.5, 14.2 Hz, NCC*H*HPh), 3.35 (dd, 1H, J = 6.1, 14.2 Hz, NCCH*H*Ph), 4.12-4.30 (m, 2H, CH$_3$C*H*$_2$O), 5.01 (q, 1H, J = 6.3 Hz, C*H*N), 5.90 (d, 1H, J = 6.3 Hz, N*H*), 5.95 (s, 1H, C*H*Ph), 7.15-7.48 (m, 5H, Ph); ^{13}C NMR (CDCl$_3$) δ = 14.0, 23.0, 37.6, 52.7, 61.9, 74.5, 127.6, 128.5, 129.3, 133.3, 135.8, 168.3, 169.8, 171.2. **(3c):** ^{1}H NMR (CDCl$_3$) δ = 1.22 (t, 3H, J = 7.2 Hz, C*H*$_3$CH$_2$O), 1.98 (s, 3H, OCC*H*$_3$),), 3.11 (dd, 1H, J = 5.7, 14.2 Hz, NCC*H*HPh), 3.17 (dd, 1H, J = 6.0, 14.2 Hz, NCCH*H*Ph), 4.12-4.30 (m, 2H, CH$_3$C*H*$_2$O), 5.10 (dt, 1H, J = 5.7, 6.0 Hz, C*H*N), 5.93 (s, 1H, C*H*Ph), 6.00 (d, 1H, J = 6.0 Hz, NH), 7.15-7.48 (m, 5H, Ph); ^{13}C NMR (CDCl$_3$) δ = 14.4, 23.1, 37.6, 53.0, 62.2, 74.5, 127.6, 128.5, 129.3, 133.3, 135.6, 168.1, 171.0.

Anal Calcd. for C$_{21}$H$_{23}$NO$_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.30; H, 6.25; N, 3.77.

Synthesis of 2c from (*S*)-phenylalanine and (*R*)-ethyl mandelate

The (*S*)-phenylalanine (1 mmol, 165 mg) was added to a stirred solution of NaOH (2 equiv., 2 mmol, 80 mg) in H$_2$O:acetone 3:1 (10 mL) at room temperature. After complete dissolution of the solid, Ac$_2$O (1.1 equiv., 1.1 mmol, 0.1 mL) was added dropwise and the reaction mixture was stirred for an additional hour. The acetone was then removed under reduced pressure and a saturated solution of NaHCO$_3$ was added till pH 9-10, then the mixture was washed three times with EtOAc. The aqueous layers were acidified to pH 3 with 6M HCl and extracted three times with EtOAc. The combined acidic extracts were dried over MgSO$_4$ and evaporated under reduced pressure to give (*S*)-*N*-acetylphenylalanine in 80% yield as a white solid, that was used in the following step without any further purification. The product was added in one portion to a stirred solution of (*R*)-ethyl mandelate (0.66 mmol, 0.12 g) and triphenylphosphine (1.32 mmol, 0.35g.) in dry THF (5 mL) at room temperature under nitrogen atmosphere. A solution of DEAD (1.32 mmol, 0.2 mL) in dry THF (1 mL) was added dropwise to the reaction mixture at 0 °C. After 6 h the solvent was removed under reduced pressure, the residue dissolved in EtOAc and washed with saturated NaHCO$_3$. The organic layers were dried with MgSO$_4$ and concentrated to give **2c** in 98% yield, which was purified by silica gel chromatography (cyclohexane/EtOAc 8:2 as eluant).

Transesterification of compounds 2 and 3 to methyl esters 4

A mixture of compounds **2** and **3** (0.5 mmol) was dissolved in methanol (5 mL) together with a catalytic amount of *p*-TsOH (0.3 equiv., 1.5 mmol, 95 mg). The reaction was heated under reflux for 24h, after which it was cooled and methanol was removed under reduced pressure. The residue was then dissolved in EtOAc and washed twice with a saturated solution of NaHCO$_3$. Compound **4** was obtained as a yellow oil after purification by column chromatography on silica gel (cyclohexane/EtOAc as eluant, 1:1).

A mixture of **2a** and **3a** in 62:38 diastereomeric ratio affords **(4a):** IR (film) ν 3271, 1747. 1654 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ = 0.88 (t, 3H, J = 6.9 Hz, C*H*$_3$CH$_2$CH$_2$CH$_2$), 1.20-1.90 (m, 8H, CH$_3$C*H*$_2$C*H*$_2$C*H*$_2$), 2.04 (s, 3H, COCH$_3$), 3.76 (s, 3H, OCH$_3$), 4.62 (dt, 1H, J = 6.4, 7.2 Hz, CHN), 5.94 (d, 1H, J = 7.8 Hz, NH); ^{13}C

NMR ($CDCl_3$) δ = 14.0, 22.4, 23.3, 24.8, 31.3, 32.5, 52.1 , 52.3, 169.5, 173.1; $[\alpha]_D$ +5.6 (c 0.5, MeOH), corresponding to 24.8 % ee (lit. [17]: $[\alpha]_D$ +22.6, c 2.0, MeOH). Anal Calcd. for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.61; H, 9.55; N, 6.89.

A mixture of **2b** and **3b** in 78:22 diastereomeric ratio affords **(4b):** IR (film) ν 3286, 1748, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.92 (d, 6H, *J* = 6.0 Hz, $(CH_3)_2CHCH_2$), 1.40-1.85 (m, 3H, $(CH_3)_2CHCH_2$), 2.00 (s, 3H, $COCH_3$), 3.71 (s, 3H, OCH_3), 4.63 (dt, 1H, *J* = 5.5, 8.6 Hz, CHN), 6.06 (d, 1H, *J* = 7.0 Hz, NH); ^{13}C NMR ($CDCl_3$) δ = 21.9, 22.7, 23.1, 24.8, 41.6, 50.7, 52.2, 169.9, 173.8; $[\alpha]_D$ –9.4 (c 0.5 H_2O), corresponding to 54.6 % ee; lit. [18]: $[\alpha]_D$ –17.2 (c 2.0, H_2O). Anal Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.81; H, 9.21; N, 7.52.

A mixture of **2c** and **3c** in 72:28 diastereomeric ratio affords **(4c):** IR (film) ν 3280, 1751, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.00 (s, 3H, $OCCH_3$), 3.08 (dd, 1H, *J* = 5.5, 13.5 Hz, CH_2Ph), 3.15 (dd, 1H, *J* = 5.7, 13.5 Hz, CH_2Ph), 3.74 (s, 3H, OCH_3), 4.90 (dt, 1H, *J* = 5.7, 7.7 Hz, CHN), 5.85 (bs, 1H, NH), 7.00-7.30 (m, 5H, Ph);^{13}C NMR ($CDCl_3$) δ = 22.5, 37.8, 51.9, 53.3, 126.7, 128.4, 129.1, 136.2, 170.4, 172.3; $[\alpha]_D$ +44.5 (c 0.5 $CHCl_3$), corresponding to 43.8 % ee; lit. [19]: $[\alpha]_D$ +101.5, (c 1.0, $CHCl_3$). Anal Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.12; H, 6.86; N, 6.34.

(*S*)-*N*-Benzyloxy-*t*butyl-2-acetamidoacrylic ethoxycarbonyl-phenyl-methyl ester (5)

To a stirred solution of amide **1** (4.3 mmol, 1.0 g) in dry THF (30 mL) di-*tert*-butyl dicarbonate (2 equiv., 8.3 mmol, 1.81 g, 1.91 mL) and DMAP (0.05 equiv. 0.2 mmol, 25 mg) were added in one portion, then the mixture was refluxed for 1 h. THF was distilled under reduced pressure and replaced with CH_2Cl_2 and H_2O, the mixture was separated, the organic layer was dried over $MgSO_4$ and concentrated. The product **(5)** was purified by flash chromatography (cyclohexane as eluant) and obtained pure in 95% yield (4.1 mmol, 1.48 g) as an oil.

IR (film) ν = 1747, 1744, 1715, 1647 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.21 (t, 3H, *J* = 7.0 Hz, CH_2CH_3), 1.44 (s, 9H, $C(CH_3)_3$), 2.56 (s, 3H, $COCH_3$), 4.10-4.30 (m, 2H, OCH_2CH_3), 5.78 (s, 1H, CHPh), 5.96 (s, 1H, HNCCHH), 6.62 (s, 1H, HNCCHH), 7.37-47 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.0, 25.9, 27.7, 28.2, 61.7, 75.3, 83.9, 106.5, 127.4, 128.6, 129.1, 133.6, 134.8, 151.4, 162.2, 168.0, 172.3; $[\alpha]_D$ + 64.0 (*c* 2.5, $CHCl_3$). Anal Calcd. For $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.42; H, 6.46; N, 3.63.

General procedure for the conjugate addition of organocuprates to imide (5): For the experimental procedure see the addition to amide **1**. The products were purified by silica gel chromatography (cyclohexane as eluant) and obtained pure as a mixture.

General procedure for the conjugate addition of Grignard reagents to the complex amide (1)/Lewis acid: For the experimental procedure see the addition to amide **1**. The products were purified by silica gel chromatography (cyclohexane as eluant) and obtained pure as a mixture.

General procedure for the copper-(I) catalysed conjugate addition of Grignard reagents to the complex amide (1)/Lewis acid: For the experimental procedure see the addition to amide **1**. The products were purified by silica gel chromatography (cyclohexane as eluant) and obtained pure as a mixture.

(6b) + (7b): IR (film) 1744, 1702 cm^{-1}; **(6b)**: ^1H NMR ($CDCl_3$) δ = 0.92 (d, 6H, *J* = 6.6 Hz, CH_2CH_3), 1.24 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 1.40 (s, 9H, $C(CH_3)_3$), 2.45 (s, 3H, $COCH_3$), 4.02-4.23 (m, 2H, OCH_2CH_3), 5.40-5.50 (m, 1H, CHN), 5.86 (s, 1H, CHPh), 7.30-7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.0, 23.1, 25.8, 26.3, 27.7, 38.5, 54.1, 61.6, 74.7, 84.0, 127.2, 128.6, 129.0, 133.7, 152.2, 168.1, 170.1, 172.5; **(7b)**: ^1H NMR ($CDCl_3$) δ = 0.92 (d, 6H, *J* = 6.6 Hz, CH_2CH_3), 1.20 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 1.46 (s, 9H, $C(CH_3)_3$), 2.53 (s, 3H, $COCH_3$), 4.02-4.23 (m, 2H, OCH_2CH_3), 5.40-5.50 (m, 1H, CHN), 5.94 (s, 1H, CHPh), 7.30-7.50 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ = 14.0, 23.1, 25.9, 26.4, 27.8, 38.5, 54.2, 61.6, 74.8, 84.0, 127.3, 128.6, 129.1, 133.9, 152.2, 168.2, 170.2, 172.6. Anal. Calcd. For $C_{23}H_{33}NO_7$: C, 63.43; H, 7.64; N, 3.22. Found: C, 63.50; H, 7.69; N, 3.28.

(6c) + (7c): IR (film) ν = 1743, 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.23 (t, 3H, *J* = 6.6 Hz, CH_2CH_3), 1.27 (s, 9H, $C(CH_3)_3$), 2.27 and 2.33 (s, 3H, $COCH_3$), 3.16 (dd, 1H, *J* = 10.2, 13.8 Hz, CHHPh) and 3.23 (dd, 1H, *J* = 10.2, 14.0 Hz, CHHPh), 3.44 (dd, 1H, *J* = 5.7, 13.8 Hz, CHHPh) and 3.50 (dd, 1H, *J* = 5.3, 14.0 Hz, CHHPh), 4.08-4.34 (m, 2H, CH_2CH_3), 5.58-5.68 (m, 1H, CHN), 5.93 and 5.99 (s, 1H, CHPh), 7.02-7.70 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ = 13.8 and 13.9, 26.0 and 26.2, 27.5 and 27.9, 53.2, 56.9 and 57.0, 61.5 and 61.7, 74.8, 83.9, 106.4, 126.5, 127.0, 127.1, 128.2, 128.5, 128.9, 133.3 and 133.9, 137.1, 152.1, 168.4 and 169.2, 172.5. Anal. Calcd. For $C_{26}H_{31}NO_7$: C, 66.51; H, 6.65; N, 2.98. Found: C, 66.53; H, 6.59; N, 3.01.

(6d) + (7d): IR (film) ν = 1744, 1702 cm^{-1}; major isomer: ^1H NMR ($CDCl_3$) δ = 1.21 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 1.43 (s, 9H, $C(CH_3)_3$), 1.91-2.38 (m, 4H, CH_2CH_2), 2.54 (s, 3H, $COCH_3$), 4.02-4.36 (m, 2H, CH_2CH_3), 4.92-5.15 (m, 2H, CH_2CH=CHH), 5.38-5.44 (m, 1H, CHN), 5.64-5.88 (m, 1H, CH_2CH=CHH), 5.87 (s, 1H, CHPh), 7.20-7.52 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ = 13.9, 26.3, 27.7, 28.8, 30.3, 55.1, 61.6, 74.8, 84.1, 115.3, 127.2, 128.6, 128.9, 133.8, 137.2, 152.1, 168.0, 169.8, 172.7; minor isomer: ^1H NMR ($CDCl_3$) δ = 1.25 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 1.43 (s, 9H, $C(CH_3)_3$), 1.91-2.38 (m, 4H, CH_2CH_2), 2.46 (s, 3H, $COCH_3$), 4.02-4.36 (m, 2H, OCH_2CH_3), 4.92-5.15 (m, 2H, CH_2CH=CHH), 5.38-5.44 (m, 1H, CHN), 5.64-5.88 (m, 1H, CH_2CH=CHH), 5.96 (s, 1H, CHPh), 7.20-7.52 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ = 13.9, 26.4, 27.8, 28.8, 30.4, 55.2, 61.6, 74.8, 84.1, 115.3, 127.2, 128.6, 128.9, 133.6, 137.2, 152.1, 168.2, 169.7, 172.6. Anal Calcd. For $C_{23}H_{31}NO_7$: C, 63.73; H, 7.21; N, 3.23. Found: C, 63.78; H, 7.26; N, 3.28.

General Procedure for the Hydrolysis of *N*-Boc Derivatives 6 and 7: SiO_2 (72 mg) was added to a solution of $Yb(OTf)_3$ (8 mg) in acetonitrile (10 mL) and the solvent was removed under reduced pressure. Then a solution of products **6** and **7** (0.2 mmol) in CH_2Cl_2 (5 mL) was added and the resulting mixture was concentrated to eliminate the solvent. After 48 h CH_2Cl_2 (20 mL) was added, the mixture was filtered and the liquid was concentrated. After flash chromatography (cyclohexane:EtOAc 8:2 as eluant) a mixture of compounds **2** and **3** was recovered in more then 95% yield.

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