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

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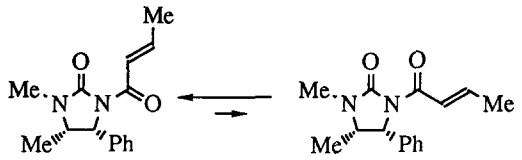
Abstract: The asymmetric 1,4 addition of PhMgCl, MeMgBr and allylMgBr to chiral imides **1** has been studied under various conditions. The presence of a Lewis acid, as $AlMe_2Cl$, affords an enhanced diastereoselectivity favouring the formation of the product derived from the attack on the *re* face. The 1,4 addition of allyl diisopropoxyborate to imides **1** has also been analysed.

Numerous asymmetric syntheses have been made in an attempt to introduce a new asymmetric centre into a carbon chain of a carboxylic acid derivative under the influence of a chiral auxiliary. The enantioselective Michael addition [1] of organometallic reagents to chiral unsaturated esters,[2] oxazolines,[3] amides [4] and imides [5] has attracted much interest in the past years. For instance, the 1,4 addition of alkyl magnesium chlorides [6] and Gilman reagents [6] to conjugated *N*-enoyl sultams occurred with excellent face differentiation while Michael addition of Grignard reagents to cinnamamides derived from (1*R*,2*S*)-(-)-ephedrine [5] afforded the corresponding β-methyl and β-phenyl alkanoic acids having high enantiomeric purities. As a part of an extensive work on asymmetric β-addition, we showed that α,β-unsaturated chiral imides bearing an imidazolidin-2-one group, easily prepared by Helmchen [7] from ephedrine and urea, undergoes stereoselective conjugate addition reactions with hydroxylamine [8] or phthalimido salts [9] promoted by Lewis acids. Recently Cresson and al. [5,10] reported the total regio- and stereoselectivity observed in the carbon-carbon bond formation in addition of cuprates on the same unsaturated chiral imides.

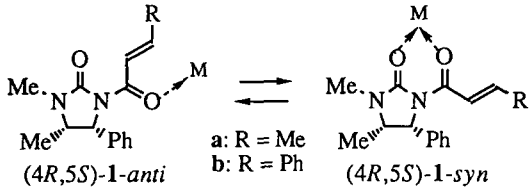
It is well known that Grignard reagents add preferentially to the carbonyl function by 1,2-addition while organocuprates preferentially add to α,β-unsaturated carbonyl compounds almost exclusively by 1,4 addition.[11] Furthermore in our case the 1,2 addition would be certainly favoured, owing to the nature of the carbon-nitrogen bond of the imide system. Indeed the bond order is about 0.98, to be compared with the stronger amide bond (bond order 1.13).

In order to clarify some aspects of 1,4- or 1,2-additions in the presence of a Lewis acids, we describe here the reaction of Grignard reagents in comparison with cuprate addition. MM+ calculations conducted on the ground state conformation of **1a** reveals that the *anti* arrangement of the imide carbonyl group is more stable than the *syn* conformation by ca. 5 Kcal.[12]



(4*R*,5*S*)-**1a**-*anti* E = 4.98 Kcal (4*R*,5*S*)-**1a**-*syn* E = 9.97 Kcal (eq. 1)

Nevertheless the diastereofacial selectivity relationship depends on the conformational changes of **1** in the presence of coordinating metals. Due to the presence of the stereogenic centres at carbons 4 and 5 of the imidazolidin-2-one ring, a preferential attack on the *re* face of **1**-*anti* conformation and *si* face of **1**-*syn* conformation can be predicted depending on the metal selected and on the number of Lewis acid equivalents used.



(4*R*,5*S*)-**1**-*anti* **a**: R = Me **b**: R = Ph (4*R*,5*S*)-**1**-*syn* (eq. 2)

The results of the addition of phenyl magnesium chloride to crotonyl imide **1a** are summarised in Table 1. All the reactions were carried out several times. The products obtained from 1,2-attack are a mixture of the corresponding ketone and tertiary alcohol. The total amount of 1,2-attack is calculated on the basis of the percentage of the recovered (4*R*,5*S*)-3,4-dimethyl-5-phenylimidazolidin-4-one. The diastereomeric excesses of the alkylated products were determined by ^{1}H NMR and GC-MS of the crude reaction mixture and the absolute configuration was assigned by comparison with authentic samples prepared by additions of Gilman reagents. The ratio of diastereoisomers was determined by integration of the protons at carbon 4 of the imidazolidinone ring, the value at higher field corresponding to the product obtained from the addition of the reagents on the *re* face of the α,β-unsaturated substrate.[5,10]

Entries 1, 2 and 3 are very significative in respect to our investigation. Indeed the 1,4 attack occurred in low yield and low diastereoselectivity when 3 or 5 equivalents of Grignard reagent were used. Furthermore although low conversion is observed when the reaction is carried out in ether, the major isomer is the one derived from the 1,4 attack on the *re* face of the substrate thus showing that the attack occurs on the preferential

1-*anti* conformation of the substrate with the carbonyl groups in the opposite direction. With 5 equivalents (entry 2) the diastereomeric ratio decreases and with 9 equivalents (entry 3) complete inversion of selectivity is obtained thus showing that the Grignard reagent acts both as nucleophile and as chelating agent of carbonyl groups as in **1**-*syn* conformation. Moreover 2 equivalents of TMSCl [13] were added to reduce the 1,2-attack due to the large excess of Grignard reagent.

The conjugate addition of Grignard reagents to α,β-unsaturated imides under the action of ytterbium triflate [14] gave very disappointing results (entry 4). When $AlMe_2Cl$ [15] was used as Lewis acid in CH_2Cl_2, the diastereomeric ratio increased together with a reduction of 1,2 attack was observed confirming the strong compatibility of aluminium derivatives with Grignard reagents and with the chiral substrate. Furthermore in the presence of TMSCl (entries 6 and 7) the 1,2 attack was practically avoided. The best results in terms of yields and diastereoselectivity were obtained with 2 equivalents of $AlMe_2Cl$ in THF (entry 9). The results obtained with 2 equivalents of $AlMe_2Cl$ (entries 8 and 9) are in agreement with the intermediary formation of a chelated salt, firstly proposed by Evans, then confirmed by us [8] and Castellino [16] through ^1H NMR analysis.

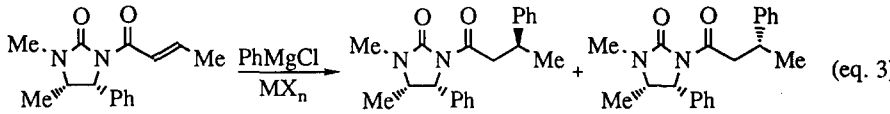
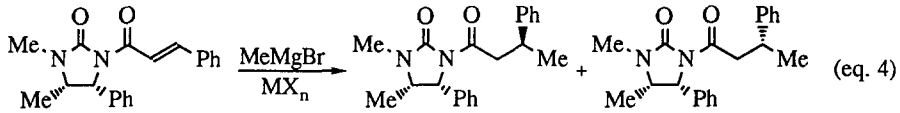


Table 1. Diastereomeric Products Ratios and Chemical Yields for the Addition of Phenyl Magnesium Chloride to Imide **1a**.

Entry	Reagent (equiv.)	Lewis Acid (equiv.)	T (°C)	Solvent	Yield [a] of 2+3 (%)	Ratio 2/3	Yield [a] of 1,2-attack (%)
1	PhMgCl (3)	/	-40	Et_2O	41	31:69	37
2	PhMgCl (5)	/	-40	Et_2O	25	40:60	75
3	PhMgCl (5)	$MgBr_2$ (1.5)	-40	Et_2O	28	45:55	72
4	PhMgCl (9)	TMSCl (2)	-80	CH_2Cl_2	62	87:13	38
5	PhMgCl (3)	$Yb(OTf)_3$ (1)	-50	CH_2Cl_2	20	41:59	11
6	PhMgCl (3)	$AlMe_2Cl$ (1.5)	-80	CH_2Cl_2	43	93:7	39
7	PhMgCl (3)	$AlMe_2Cl$ (1.3) TMSCl (1.5)	-80	CH_2Cl_2	32	92:8	/
8	PhMgCl (6)	$AlMe_2Cl$ (1.3) TMSCl (1.5)	-60	CH_2Cl_2	83	91:9	17
9	PhMgCl (5)	$AlMe_2Cl$ (2)	-60	CH_2Cl_2	62	90:10	38
10	PhMgCl (5)	$AlMe_2Cl$ (2)	-60	THF	89	90:10	3

[a] The remaining fraction to 100% yield is starting material.

The addition of MeMgBr to the cinnamoyl imide **1b** are reported in Table 2. Entry 1 shows the results obtained in our hands for the addition of cuprates.[5] When 5 equivalents of MeMgBr were added, the formation of (4*R*,5*S*,3'*S*)-**2** as major isomer was observed, derived from the 1,4 attack on **1b**-*anti* conformation, although in the presence of abundant amounts of compounds derived from 1,2 attack. On the basis of this result it appears clear that an excess of Grignard reagent acts both as nucleophile and as Lewis acid and comparable although inverted diastereoselectivity with the cuprate was observed (entry 2). Surprisingly on decreasing the reaction temperature the diastereomeric ratio decreased too probably owing to a slower equilibration from **1b**-*anti* to **1b**-*syn* conformation of the substrate (entry 3). In the presence of $AlMe_2Cl$ and TMSCl a diastereoselectivity comparable with what obtained with cuprates was achieved (entry 4). Unfortunately in all the reported cases a competitive considerable 1,2 attack was detected.



(eq. 4)

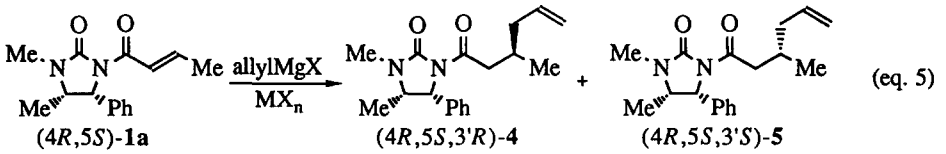
Table 2. Diastereomeric Products Ratios and Chemical Yields for the Addition of Methyl Magnesium Bromide to Imide **1b**.

Entry	Reagent (equiv.)	Lewis Acid (equiv.)	Temp. (°C)	Solvent	Yield [a] of 2+3 (%)	Ratio 2/3	Yield [a] of 1,2-attack (%)
1	MeCuMgBr. Me_2S (1.5)	/	-78/rt..	THF	100	30:70	/
2	MeMgBr (5)	/	0	Et_2O	30	70:30	70
3	MeMgBr (5)	/	-40	Et_2O	52	56:44	48
4	MeMgBr (3)	$AlMe_2Cl$ (1.3) TMSCl (1.5)	-80	CH_2Cl_2	63	30:70	34

[a] The remaining fraction to 100% yield is starting material.

Tables 3 and 4 show the results of the addition of allylMgCl [17] on **1a** and **1b** under different conditions and with different Lewis acids. The data reported in Table 3 show that in the presence of $SnCl_4$ a low conversion is obtained, while when 1 equivalents of $Yb(OTf)_3$ is used as Lewis acid, better results are observed (entry 3). A complete conversion is achieved with 2 equivalents of $AlMe_2Cl$ in THF or CH_2Cl_2 (entries 6 and 7). Under these conditions the 1,2 attack is practically avoided.

On the other hand, as reported in Table 4, high diastereomeric ratios have been obtained when the bulky phenyl group of cinnamoyl derivative **1b** is present as the substituent on the double bond. The best conditions are reported in entry 5, when $AlMe_2Cl$ is used as Lewis acid, while $Yb(OTf)_3$ is less selective than $AlMe_2Cl$ (entry 6).

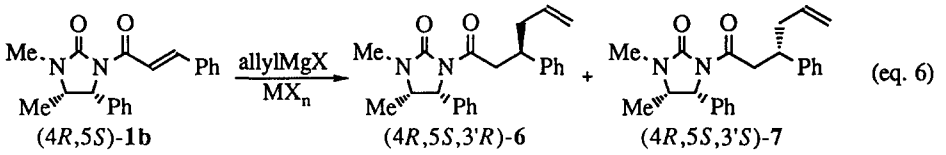


(eq. 5)

Table 3. Diastereomeric Products Ratios and Chemical Yields for the Addition of Allyl Magnesium Halides to Imide **1a**.

Entry	Reagent (equiv.)	Lewis Acid (equiv.)	Temp. (°C)	Solvent	Yield [a] of 4+5 (%)	Ratio 4/5	Yield [a] of 1,2-attack (%)
1	$Allyl_2CuMgBr.$ Me_2S (1.5)	/	-78/rt.	THF	97	>99:1	3
2	AllylMgCl (2)	$SnCl_4$ (1.3)	-80	CH_2Cl_2	33	85:15	28
3	AllylMgCl (3)	$Yb(OTf)_3$ (1)	-70/-20	CH_2Cl_2	93	75:25	7
4	AllylMgCl (2)	$AlMe_2Cl$ (1.3)	-80/-60	CH_2Cl_2	68	75:25	/
5	AllylMgCl (3)	$AlMe_2Cl$ (1.5)	-80	CH_2Cl_2	92	76:24	7
6	AllylMgBr(3)	$AlMe_2Cl$ (2)	-80	CH_2Cl_2	94	63:37	5
7	AllylMgCl (3)	$AlMe_2Cl$ (2)	-78	THF	100	95:5	/

[a] The remaining fraction to 100% yield is starting material.



(eq. 6)

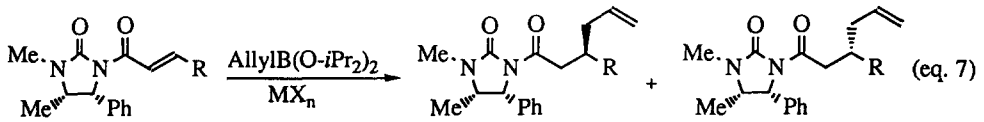
Table 4. Diastereomeric Products Ratios and Chemical Yields for the Addition of Allyl Magnesium Halides to Imide **1b**.

Entry	Reagent (equiv.)	Lewis Acid (equiv.)	Temp. (°C)	Solvent	Yield [a] of 6+7 (%)	Ratio 6/7	Yield [a] of 1,2-attack (%)
1	$Allyl_2CuMgBr.$ Me_2S (1.5)	/	-78	THF	97	>99:1	3
2	AllylMgCl (9)	/	0	Et_2O	92	91:9	8
3	AllylMgCl (2)	$AlMe_2Cl$ (1.3)	-40	Et_2O	36	93:7	10
4	AllylMgCl (3)	$AlMe_2Cl$ (1.5)	-80	CH_2Cl_2	73	82:18	12
5	AllylMgCl (3)	$AlMe_2Cl$ (2)	-80	CH_2Cl_2	92	93:7	5
6	AllylMgBr (3)	$Yb(OTf)_3$ (1)	-70/-20	CH_2Cl_2	92	82:18	8
7	$AllylSnBu_3$ (1.5)	$AlMe_2Cl$ (2)	-78/-20	CH_2Cl_2	65	64:36	29

[a] The remaining fraction to 100% yield is starting material.

These data show that in the presence of small Grignard reagents (compared with the larger cuprates) the substituent on the double bond assumes great importance for control by the diastereomeric ratios and the yields. In order to compare these results with those obtained by reaction of **1a** and **1b** with different allylating agents, allyldiisopropoxyborane was tested. It is known that highly diastereoselective products are generally obtained with the use of allyl boron reagents. Furthermore the selective formation of allyl boronic esters [18] *via* the allylation of trialkylborates using allyl magnesium bromide have been recently described. Indeed at -78 °C allyl magnesium bromide reacts cleanly with triisopropyl borate to provide allyldiisopropoxyborane in high yield.

The results of the addition of allyldiisopropoxyborane on crotonyl and cinnamoyl imides **1a** and **1b** are summarised in Table 5. Due to the high reactivity of boron reagents the reactions were carried out at -78 °C and -80 °C. Under these conditions, the reactions proceeded extremely fast and with high stereoselectivity. When 1.5 equivalents of reagent were utilised (entry 1) low conversion was obtained accompanied by a considerable amount of 1,2 attack. Yields of 1,4 adducts increased when 3 equivalents of allyl boronic ester where used (entries 2 and 3). Repetition of the same protocol on **1b**, gave low conversion, the rest being starting material. However a very high conversion and good stereoselectivity accompanied only by traces of 1,2 attack were obtained when the allyl boronic ester was added to the starting **1b** in the presence of 2 equivalents of $AlMe_2Cl$ (entry 5). Under these conditions the ^1H NMR and mass spectra of the raw material appeared identical to that recorded when the cuprates were used (Table 4, entry 1).



R = Me: (4*R*,5*S*)-**1a**
R = Ph: (4*R*,5*S*)-**1b**

R = Me: (4*R*,5*S*,3'*R*)-**4**
R = Ph: (4*R*,5*S*,3'*R*)-**6**

R = Me (4*R*,5*S*,3'*S*)-**5**
R = Ph (4*R*,5*S*,3'*S*)-**7**

Table 5. Diastereomeric Products Ratios and Chemical Yields for the Addition of Allyl Boronic Esters to Imides **1a** and **1b**.

Entry	R	Products	Reagent (equiv.) [a]	Time (h)	Temp. (°C)	Yield [b] of 1,4-attack (%)	Ratio **4/5** or **6/7**	Yield [b] of 1,2-attack (%)
1	Me	**4+5**	AllylB(O-*i*Pr)$_2$ (1.5)	3	-78	33	98:2	29
2	Me	**4+5**	AllylB(O-*i*Pr)$_2$ (3)	1.5	-80	53	92:8	24
3	Me	**4+5**	AllylB(O-*i*Pr)$_2$ (3)	2	-80	70	96:4	26
4	Ph	**6+7**	AllylB(O-*i*Pr)$_2$ (3)	2	-80	26	99:1	15
5	Ph	**6+7**	AllylB(O-*i*Pr)$_2$ (3) $AlMe_2Cl$ (2)	2	-80	91	80:20	5

[a] All the reactions were carried out in ether. [b] The remaining fraction to 100% yield is starting material.

In conclusion we have shown that β-alkyl carboxylic acids derivatives can be prepared through carbon-carbon bond formation by reacting α,β-unsaturated imides with Grignard reagents. With these substrates, the presence of a Lewis acid (as $AlMe_2Cl$) in the reaction mixture affords best results in terms of yields and diastereomeric ratios, owing to the chelating effect of the metal. The presence of the Lewis acid also reduces the 1,2 attack.

EXPERIMENTAL SECTION

General Methods. ^1H and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz respectively. Chemical shifts are reported in ppm relative to the solvent peak of $CHCl_3$. IR spectra were recorded with a FT-IR spectrometer. Melting points were determined in open capillaries and are uncorrected. Flash cromathography was performed with Merck silica gel 60 (230-400 mesh). THF was distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from P_2O_5. Et_2O was distilled from sodium and $LiAlH_4$. MeMgCl, PhMgCl, allylMgCl are commercially available. $AlMe_2Cl$, $SnCl_4$, $Yb(OTf)_3$ and TMSCl are commercially available.

General procedure for the synthesis of 1a and 1b.

To a stirring solution of (4*R*,5*S*)-1,5-dimethyl-4-phenilimidazolidin-2-one [7] (6.84 mmol, 1.3 g) in anhydrous THF (30 mL), MeMgBr (3M in THF, 8.21 mmol, 2.74 mL), dry THF (20 mL) was added dropwise at 0 °C under inert atmosphere. After 30 minutes acyl chloride (1.5 equiv.) was added dropwise to the solution. After 3 additional hours the reaction was quenched with MeOH (20 mL) and the solvent was concentrated under reduced pressure. Water (10 mL) was added to the residue and extracted three times with CH_2Cl_2 (3 x 20 mL). The collected organic layers, dried over Na_2SO_4 and concentrated, were purified by silica gel cromathography (eluant: cyclohexane/ethyl acetate 7:3) and afforded the product in 85% yield.

(4*R*,5*S*)-1a: For all the spectroscopic and analytical data see ref. 8.
(4*R*,5*S*)-1b: For all the spectroscopic and analytical data see ref. 19.

Preparation of (4*R*,5*S*,3'*S*)-2 and (4*R*,5*S*,3'*R*)-3 according to Table 1 entry 4

To a stirring solution of **1a** (0.78 mmol, 200 mg) in anhydrous THF (20 mL) $AlMe_2Cl$ (1M in hexane, 1.56 mmol, 1.56 mL) was added dropwise at 0 °C under inert atmosphere. After 40 minutes PhMgCl (2M in THF, 3.9 mmol, 1.95 mL) was added dropwise at -60 °C. After 2 additional hours the reaction was quenched with water (10 mL) and THF was evaporated under reduced pressure. The mixture was extracted three times with EtOAc (3 x 25 mL) and the collected organic layers were filtrated over celite, dried over Na_2SO_4 and concentrated. The purification of the residue by silica gel chromathography (eluant cyclohexane/ethyl acetate 8:2) afforded the product as a mixture of two diastereoisomers.

General procedure for the synthesis of (4*R*,5*S*)-1,5-dimethyl-3-alkanoyl-4-phenyl-imidazolidin-2-ones 2, 3, 4, 5, 6, and 7. The above reported protocol should be modified according to the reaction conditions reported in Tables 1, 2, 3 and 4.

Synthesis of allyl derivatives 4, 5, 6, and 7 by reaction with allyl boronic esters

To a stirring solution of triisopropylborate (0.96 mmol, 0.22 mL) in anhydrous ether (10 mL), precooled allylMgCl (1M in Et_2O, 0.96 mmol, 0.96 mL) was added dropwise at -78 °C under inert atmosphere. After 1h a solution of **1a** (0.32 mmol, 100 mg) in Et_2O (10 mL) was added dropwise at -78 °C. The reaction was quenched after 3 h with water (10 mL) at -78 °C and extracted three times with Et_2O (3 x 20 mL). The collected organic layers were filtrated over celite, dried over Na_2SO_4 and concentrated under reduced pressure. The purification of the residue by silica gel cromathography (eluant cyclohexane/ethyl acetate 7:3) afforded the product as a mixture of two diastereoisomers.

(4*R*,5*S*,3'*S*)-2: IR (film) ν 2980, 1735, 1370, 1245, 1050 cm^{-1}; MS (m/z) 336 (46) M^+, 321 (17), 189 (100), 132 (25), 105 (43), 91 (12), 77 (17), 58 (53); ^1H NMR ($CDCl_3$) δ (ppm) 0.80 (d, 3H, J=6.6Hz, *CH*$_3$-CH-CH-Ph), 1.26 (d, 3H, J=6.9Hz, *CH*$_3$-CH-CH_2-CO), 2.85 (s, 3H, *CH*$_3$-N), 3.10 (dd, 1H, J=8.5Hz, J=15.4Hz, C*H*H-CH-Ph), 3.32-3.42 (m, 1H, CH_2-*CH*-Ph), 3.52 (dd, 1H, J=15.4Hz, J=6.1Hz, CH*H*-CH-Ph), 3.91 (dq, 1H, J=6.6Hz, J=8.5Hz, Ph-CH-*CH*-CH_3), 5.30 (d, 1H, J=8.5Hz, CH_3-CH-*CH*-Ph), 7.10-7.90 (m, 10H, 2*Ph*); $[\alpha]_D$ -35.9 (5.1, $CHCl_3$). HRMS calcd for (M^+) $C_{21}H_{24}N_2O_2$ 336.1838, found 336.1833.

(4*R*,5*S*,3'*R*)-3: IR (film) ν 2980, 1735, 1370, 1245, 1050 cm^{-1}; MS (m/z) 336 (39) M^+, 321 (17), 189 (100), 132 (22), 105 (45), 91 (15), 77 (15), 58 (47); ^1H NMR ($CDCl_3$) δ (ppm) 0.78 (d, 3H, J=6.6Hz, *CH*$_3$-CH-CH-Ph), 1.30 (d, 3H, J=6.9Hz, *CH*$_3$-CH-CH_2-CO), 2.83 (s, 3H, *CH*$_3$-N), 3.25 (dd, 1H, J=8.5Hz, J=15.4Hz, C*H*H-CH-Ph), 3.32-3.42 (m, 1H, CH_2-*CH*-Ph), 3.50 (dd, 1H, J=15.4Hz, J=6.1Hz, CH*H*-CH-Ph), 3.78 (dq,1H, J=6.6Hz, J=8.5Hz, Ph-CH-*CH*-CH_3), 5.20 (d, 1H, J=8.5Hz, CH_3-CH-*CH*-Ph), 7.11-7.88 (m, 10H, 2*Ph*); $[\alpha]_D$ -63.2 (1.6, $CHCl_3$). HRMS calcd for (M^+) $C_{21}H_{24}N_2O_2$ 336.1838, found 336.1836.

(4*R*,5*S*,3'*R*)-4: IR (film) ν 3080, 3040, 2980, 2940, 1740, 1725, 1685, 1430, 1330, 1200 cm^{-1}; MS (m/z) 300 (59) M^+, 285 (16), 259 (33), 232 (76), 217 (25), 189 (57), 175 (21), 132 (61), 113 (100), 77 (20), 58 (95); ^1H NMR ($CDCl_3$) δ (ppm) 0.80 (d, 3H, J=6.6Hz, *CH*$_3$-CH-CH-Ph), 0.87 (d, 3H, J=6.6Hz, *CH*$_3$-CH-CH_2-CO), 1.95-2.20 (m, 3H, *CH*$_2$-CH=CH_2 and CH_2-*CH*-CH_3), 2.73 (dd, 1H, J=8.1Hz, J=15.6Hz, CO-C*H*H), 2.80 (s, 3H, N-*CH*$_3$), 3.03 (dd, 1H, J=5.3Hz, J=15.6Hz, CO-CH*H*), 3.88 (dq, 1H, J=8.5Hz, J=6.6Hz, CH_3-*CH*-CH-Ph), 4.90-5.02 (m, 2H, C*H*$_2$=CH), 5.31 (d, 1H, J=8.5Hz, CH_3-CH-*CH*-Ph), 5.75 (m, 1H, CH_2-*CH*=CH_2), 7.10-7.41 (m, 5H, *Ph*); $[\alpha]_D$ -26.0 (1.6, $CHCl_3$). HRMS calcd for (M^+) $C_{18}H_{24}N_2O_2$ 300.1838, found 300.1835.

(4*R*,5*S*,3'*S*)-5: IR (film) ν 3080, 3040, 2980, 2940, 1740, 1725, 1685, 1430, 1330, 1200 cm^{-1}; MS (m/z) 300 (45) M^+, 285 (13), 259 (25), 232 (55), 217 (18), 189 (40), 175 (16), 132 (53), 113 (87), 77 (30), 58 (100); ^1H NMR ($CDCl_3$) δ (ppm) 0.80 (d, 3H,J=6.7Hz, *CH*$_3$-CH-CH-Ph), 0.90 (d, 3H, J=6.5Hz, *CH*$_3$-CH-CH_2-CO), 1.95-2.20 (m, 3H, *CH*$_2$-CH=CH_2 and CH_2-*CH*-CH_3), 2.83 (s, 3H, N-*CH*$_3$), 2.88 (dd, 1H, J=6.1Hz, J=15.6Hz, CO-C*H*H), 2.94 (dd, 1H, J=8.1Hz, J=15.6Hz, CO-CH*H*), 3.88 (dq, 1H, J=8.5Hz, J=6.7Hz, CH_3-*CH*-CH-Ph), 4.90-5.02 (m, 2H, C*H*$_2$=CH), 5.31 (d, 1H, J=8.5Hz, CH_3-CH-*CH*-Ph), 5.75

(m, 1H, CH_2-*CH*=CH_2), 7.10-7.41 (m, 5H, *Ph*); $[\alpha]_D$ -38.0 (1.5, $CHCl_3$). HRMS calcd for (M^+) $C_{18}H_{24}N_2O_2$ 300.1838, found 300.1833.

(4*R*,5*S*,3'*R*)-6: IR (film) ν 3060, 3030, 2980, 2970, 1730, 1685, 1425, 1385, 1260, 1240 cm^{-1}, MS (m/z) 362 (54) M^+, 321 (85), 232 (38), 189 (51), 131 (100), 113 (31), 103 (27), 91 (31), 77 (20), 58 (28); ^1H NMR ($CDCl_3$) δ (ppm) 0.78 (d, 3H, J=6.6Hz, *CH*$_3$-CH-CH-Ph), 2.3-2.42 (m, 2H, *CH*$_2$-CH=CH_2), 2.78 (s, 3H, N-*CH*$_3$), 3.18-3.36 (m, 2H, CO-CH*H* and CO-CH_2-*CH*-Ph), 3.54 (dd, 1H, J=8.4Hz, J=15.8Hz, CO-C*H*H), 3.70 (dq, 1H, J=8.5Hz, J=6.6Hz, CH_3-*CH*-CH-Ph), 4.86-5.0 (m, 2H, *CH*$_2$=CH-CH_2), 5.12 (d, 1H, J=8.5Hz, CH_3-CH-*CH*-Ph), 5.54-5.70 (m,1H, *CH*=CH_2), 7.10-7.60 (m, 10H, 2*Ph*); $[\alpha]_D$ -68.1 (4.0, $CHCl_3$). HRMS calcd for (M^+) $C_{23}H_{26}N_2O_2$ 362.1994, found 362.1997.

(4*R*,5*S*,3'*S*)-7: IR (film) ν 3060, 3030, 2980, 2970, 1730, 1685, 1425, 1385, 1260, 1240 cm^{-1}, MS (m/z) 362 (23) M^+, 321 (33), 246 (19), 232 (16), 189 (25), 148 (28), 131 (100), 116 (37), 103 (24), 91 (31), 77 (28), 58 (22); ^1H NMR ($CDCl_3$) δ (ppm) 0.80 (d, 3H, J=6.6Hz, *CH*$_3$-CH-CH-Ph), 2.3-2.42 (m, 2H, *CH*$_2$-CH=CH_2), 2.78 (s, 3H, N-*CH*$_3$), 3.18-3.36 (m, 2H, CO-CH*H* and CO-CH_2-*CH*-Ph), 3.48 (dd, 1H, J=8.4Hz, J=15.8Hz, CO-C*H*H), 3.70 (dq, 1H, J=8.5Hz, J=6.6Hz, CH_3-*CH*-CH-Ph), 4.86-5.0 (m, 2H, *CH*$_2$=CH-CH_2), 5.25 (d, 1H, J=8.5Hz, CH_3-CH-*CH*-Ph), 5.54-5.70 (m,1H, *CH*=CH_2), 7.10-7.60 (m, 10H, 2*Ph*); $[\alpha]_D$ -8.9 (1.1, $CHCl_3$). HRMS calcd for (M^+) $C_{23}H_{26}N_2O_2$ 362.1994, found 362.1992.

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References and Notes

1. a) P. Pelmutter, "Conjugate Addition Reactions in Organic Synthesis", Pergamon Press, Oxford (1992); for an excellent review see: b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.*, **1992**, *92*, 771.
2. a) Kawana, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1966**, *39*,9 10; b) Fang, C.; Ogawa, T.; Suemune, H.; Sakai, K. *Tetrahedron: Asymmetry*, **1991**,*2*,389; c) Inouye, Y.; Walborsky, H.M., *J. Org. Chem.*, **1962**, *27*, 2706; d) Fuji, K.; Tanaka, K.; Mizuchi, M.; Hosoi S., *Tetrahedron Lett.* **1991**, *32*, 7277.
3. a) Meyers, A. I.; Whitten, C. E. *J. Am. Chem. Soc.*, **1975**, *97*, 6266; b) Meyers, A. I; Smith, R. K.; Whitten, C. E., *J. Org. Chem.* **1979**, *44*, 2250; c) Meyers, A. I.; Shipman, M. S., *J.Org.Chem.* **1991**, *56*, 7098.
4. a) Mukaiyama,T.; Iwasawa, N., *Chem. Lett.* **1981**, 913; b) Soai, K.; Ookawa, A.; Nohara Y., *Syn. Commun.*, **1983**, *13*, 27; c) Soai, K.; Ookawa, A., *J. Chem. Soc. Perkin Trans.I.*, **1986**, 759; d) Touet, J.; Baudouin, S.; Brown, E., *Tetrahedron:Asymmetry*, **1992**, *3*, 587. For the 1,4 addition of RLi and RMgX reagents to α,β-unsaturated amides, see (e) Mpango, G. B.; Mahalanabis, K. K.; Mahdavi-Damghani, Z.; Snieckus, V., *Tetrahedron Lett.*, **1980**, 4823.
5. Melnyk, O.; Stephan, E.; Pourcelot, G.; Cresson, P., *Tetrahedron*, **1992**,*48*, 841.
6. a) Posner, G. H.; Frye, L. L.; Hulce, M., *Tetrahedron*, **1984**, *40*, 1401; b) Oppolzer, W.; Kingma, A. J., *Helv.Chim.Acta*, **1989**, *72*, 1337; c) Oppolzer, W.; Poli, G.; Kingma, A. J.; Starkemann, C.; Bernardinelli, G., *Helv. Chim. Acta*, **1987**, *70*, 2201; d) Oppolzer, W.; Mills, R. J.; Pachinger, W.;

Stevenson, T., *Helv. Chim. Acta*, **1986**, *69*, 1542; e) Oppolzer, W.; Kingma, A. J.; Poli, G., *Tetrahedron*, **1989**, *45*, 479; f) Palomo, C.; Berrée, F.; Linden, A.; Villalgordo, J. M., *J. Chem. Soc., Chem. Comm.*, **1994**, 1861.

7. Roder, H.; Helmchen, G.; Peters, E. M.; Schnering, H. G. V.; *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 898.
8. Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trerè, A., *J. Org. Chem.*, **1993**, *58*, 5615.
9. Cardillo, G.; De Simone; A.; Gentilucci, L.; Sabatino, P.; Tomasini, C. *Tetrahedron Lett.*, **1994**, *35*, 5051.
10. a) Pourcelot, G.; Melnyk, O.; Besace, Y.; Stephan, E.; Cresson, P., *J. Organomet. Chem.*. **1990**, *388*, C5.
11. a) House, H. O.; Fischer, W. F., *J. Org. Chem.*, **1968**, *33*, 949; b) Normant, J. F., *Lab. Chim. Org.*, **1971**, *11*, 44; c) Kharasch, M. S.; Reinmuth, O., *Gringnard Reactions of Nonmetallic Substances*; Prentice Hall: New York, 1954; d) Dewar, M. J. S., *Bull. Soc. Chim. Fr.*, **1951**, C79.
12. Both s-*trans* conformations are higher energy than the s-*cis* conformations. For spectroscopic evidences see ref. 8.
13. a) Lipshutz, B. H.; Dimock, S. H.; James, B., *J. Am. Chem. Soc.*, **1993**, *115*, 2983; b) Lipshutz, B. H.; James, B., *Tetrahedron Lett.* **1993**, *34*, 6689.
14. a) Matsubara, S.; Yoshioka, M.; Utimoto, K., *Chemistry Lett.*, **1994**, 827; b) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M., *Synlett*, **1993**, 472.
15. Evans, D. A.; Chapman, K. T.; Bisaha, J., *J. Am. Chem. Soc.* **1984**, *106*, 4261.
16. a) Castellino, S.; Dwight, W. J., *J. Am. Chem. Soc.*, **1993**, *115*, 2986; b) Lou, B.; Li, G.; Lung, F.; Hruby, V. J., *J. Org. Chem.*, **1995**, *60*, 5509.
17. Yamamoto, Y.; Asao, N., *Chem. Rev.*, **1993**, *93*, 2207.
18. Kabalka, G. W.; Pace, R. D., *Tetrahedron Lett.*, **1993**, *34*, 783.
19. Cardillo, G.; Gentilucci, L.; Tomasini, C.; Visa Castejon-Bordas, M. P., *Tetrahedron:Asymmetry*, **1996**, *7*, 000.

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