

The Effect of Phase-Transfer Catalysis in the 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides – Synthesis of Substituted Prolines Using AgOAc and Inorganic Base in Substoichiometric Amounts

Jesús Casas,^[a] Ronald Grigg,^[b] Carmen Nájera,^{*[a]} and José M. Sansano^{*[a]}

Dedicated to Pierre and Lucette Duhamel on the occasion of their retirement

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The 1,3-dipolar cycloaddition reaction between imino ester **1a** and ethyl acrylate, employing phase-transfer catalysis (PTC) conditions in the presence of substoichiometric amounts of Lewis acids and inorganic bases, has been studied for the first time. Effects were analysed in the order: solvent, phase transfer agent, inorganic base, metal salt (Lewis acid), quantity of metal salt and the substituents on the 1,3-dipole. The two best methods found in this study [method A: THF, TBAC (10 mol-%), KOH (10 mol-%),

AgOAc (10 mol-%), room temp.; method B: toluene, KOH (10 mol-%), AgOAc (10 mol-%), room temp.] were then applied to the cycloaddition reaction of the imino esters **1a** and **5a** (derived from alanine and glycine) with alkenes. These results were compared to those obtained under thermal 1,3-dipolar cycloaddition reaction conditions and to those previously reported using metallodipoles in the presence of organic bases.

Introduction

Cycloaddition reactions are very important transformations in synthesis, thanks to their simultaneous generation of several stereogenic centres. Control over regioselectivity, facial selectivity and *endo/exo* selectivity is crucial in order to achieve high diastereoselectivities and enantioselectivities.^[1] In this context, the 1,3-dipolar cycloaddition reaction is one of the best and most useful methods for the construction of five-membered rings in a convergent and stereocontrolled manner.^[2] In particular, the [3+2] cycloaddition reaction between azomethine ylides and alkenes is a direct route to substituted prolines^[1–3] – which are valuable substrates in synthetic organic chemistry,^[4] pharmacology,^[5] and biology^[6] – and also to other structures with pyrrolidine nuclei.^[2,7c]

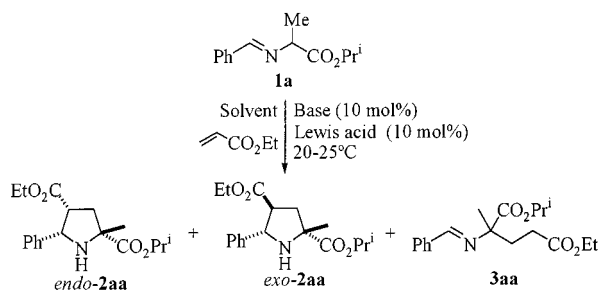
This cycloaddition reaction can be performed by using various different reaction conditions,^[2d,8] the more reliable and elegant procedure being the *in situ* generation of stabilized *N*-metallated azomethine ylides followed by further reaction with alkenes at room temperature.^[2a,2d,8] The reaction with *N*-substituted azomethine ylides exhibits a high degree of *endo* selectivity through a stepwise mechanism, as has been recently reported in the literature.^[9] The main

inconvenience of this process is the generation of Michael adducts in variable proportions, which can occasionally be overcome by modifying certain reaction conditions. While the regiochemistry is clearly dependent on the HOMO–LUMO interaction,^[10] the yield, the diastereoselectivity and the Michael addition product/cycloadduct ratio are strongly influenced by steric^[11] and electronic effects.^[10,12,13] In fact, semiempirical calculations employing *N*-metallated azomethine ylides and nitroalkenes have found that the coordination between metal cation, solvent, dipolarophile and 1,3-dipole is a decisive factor in the reaction course.^[9,12] Silver(I) and lithium azomethine ylides are widely used for this purpose.^[2,7,8] Other metals have been also tested, with variable results.^[14] The common practice is to employ excess or stoichiometric amounts of Ag^I or Li^I salts and excess of Et₃N or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as bases. As well as this, substoichiometric quantities of metal salts have given good results, although little attention has been paid to this fact. 1,3-Dipolar cycloaddition reactions between azomethine ylides and nitroolefins^[12] and chiral enones^[15] using 0.15 equiv. of AgOAc and other examples using substoichiometric amounts of LiBr^[16] have been reported, but all involved an excess of Et₃N or DBU. Additionally, reactions performed in the presence of Ag^I or Li^I salts and triethylamine, all in substoichiometric quantities, gave moderate yields but no improvement in the diastereoselectivity and chemical yields obtained using stoichiometric amounts both of Ag^I salt and of base.^[14e]

Excesses of tetraalkylammonium alkoxides have been used for very clean syntheses of Michael adducts,^[8a] but to the best of our knowledge, phase-transfer catalysis (PTC)

^[a] Department of Organic Chemistry, Faculty of Sciences, University of Alicante, Apdo. 99, 03080 Alicante, Spain
Fax: (internat.) + 34-96/590-3549
E-mail: cnajera@ua.es and jmsansano@ua.es

^[b] Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, Leeds University, Leeds LS2 9JT, United Kingdom
Fax: (internat.) + 44-113/233-6501
E-mail: r.grigg@chem.leeds.ac.uk



Scheme 1

has not been applied to cycloaddition reactions between 1,3-metallodipoles and alkenes. PTC has become a widely used tool for organic chemists and chemical engineers, who recognize the potential profit opportunities likely to result from implementing PTC. Non-asymmetric and asymmetric organic transformations employing PTC conditions are increasing very rapidly, together with discussions about their mechanisms.^[17] Asymmetric synthesis of α -amino acids by C–C bond formation using Schiff base esters and chiral tetraalkylammonium salts constitutes one of the most important achievements in this field.^[18]

In this article we will survey the influence of solid-liquid phase-transfer catalysis in the 1,3-dipolar cycloaddition reactions of stabilized azomethine ylides and alkenes when substoichiometric amounts of both inorganic base and Ag^I salts are used. Substituted proline esters can be obtained regioselectively and diastereoselectively by optimising each component in the title reaction.^[19]

Results and Discussion

The precursors of 1,3-dipoles are Schiff base esters derived from glycine and alanine, and resistant to PTC condi-

tions when using inorganic bases such as NaOH and KOH.^[20] They are easily prepared using known procedures, starting from the corresponding α -amino acids, by transformation into the isopropyl esters, followed by imine formation in water.^{[7][8c]} These imino esters are suitable precursors for obtaining substituted prolines by means of 1,3-dipolar cycloaddition reactions with electrophilic alkenes at room temperature, either by using metal salts or thermally. In search of the best reaction conditions for this kind of cycloaddition reactions, we started with an initial reaction (Scheme 1) and modified it in this order: solvent, PTC catalyst, base, Lewis acid (metal salt), quantity of Lewis acid and the substituents on the dipole.

This initial reaction studied was the 1,3-dipolar cycloaddition between the dipole generated from **1a** and ethyl acrylate (1.1 equiv.), in the presence of AgOAc (10 mol-%) and NaOH (10 mol-%) as base at room temperature (Scheme 1 and Table 1), testing different solvents without using any PTC agent. AgOAc was selected because it is generally the more useful Lewis acid in this type of reaction^[14e] and, on the other hand, an inorganic and economic base like NaOH can be suited to a solid-liquid PTC system. Under these reaction conditions the cycloaddition products **2aa** were mainly obtained, rather than Michael adducts **3aa**. Toluene and dichloromethane afforded almost the same *endo* diastereoselectivity; however, the reaction in toluene was slower (Table 1, Entries 1 and 3). With more polar aprotic solvents, conversion was complete in only 2 h, but in all these cases the diastereoselectivity would be almost identical and the chemoselectivity lower (Table 1, Entries 4–6). The yields of the reaction were quantitative in all the examples shown in Table 1, except in the cases of acetonitrile (70%) and DMF (68%). When acetonitrile was used, the reaction was rapid at the beginning but never reached total conversion, affording a 90:10 ratio of *endo*-**2aa**/*exo*-**2aa** (Table 1, Entry 2). Thus, acetonitrile is unsuitable

Table 1. Solvent and PTC agent effects in the 1,3-dipolar cycloaddition reaction between **1a** and ethyl acrylate in the presence of AgOAc (10 mol-%) and NaOH (10 mol-%) at room temperature

Entry	Solvent	Ammoniumsalt (10 mol-%)	Time [h]	Conversion (%) ^[a]	Product ^{[a][b]} <i>endo</i> - 2aa	<i>exo</i> - 2aa	3aa
1	Toluene	—	85	100	92	8	0
2	MeCN	—	70	70	90	10	0
3	CH ₂ Cl ₂	—	48	100	91	6	3
4	THF	—	2	100	82	4	14
5	Et ₂ O	—	2	100	82	4	14
6	DMF	—	2	68	88	8	4
7	MeOH	—	2	100	33	31	36
8	Toluene	Adogen 464 [®]	5	100	51	8	41
9	Toluene	TBAB	48	63	59	12	29
10	Toluene	TBAC	3	100	73	4	23
11	Toluene	TBAH	24	15	4	72	24
12	THF	TBAC	7	100	94	3	3
13	THF	Adogen 464 [®]	1	100	90	4	6
14	THF	TBAH ^[c]	0.5	100	2	18	80
15	THF	TBAA	9	100	94	5	1
16	THF	TBAA ^[c]	5	100	71	10	19
17	CH ₂ Cl ₂	TBAC	20	100	90	4	6
18	MeCN	TBAC	24	53	59	9	32

^[a] Determined by GC and based on product **1a**. — ^[b] Stereochemistry determined by ¹H NMR (NOESY) experiments. — ^[c] Without NaOH.

for use in the reaction under these conditions, unlike when the reaction is carried out in the presence of an excess both of Ag^I salt and of organic base.^[14c] Polar protic solvents such as methanol (Table 1, Entry 7) inhibited the formation of the metallo-dipole, giving rise to a 1:1 mixture of diastereomers^[8a] and greater quantities of the Michael adduct. The tendency of polar aprotic solvents to increase the reaction rate is in agreement with previously reported semiempirical calculations.^[12] The influence of the temperature was also studied in toluene, THF and acetonitrile; thus, when the reaction was performed at 0 °C it became extremely slow, but gave the same product ratio as the reaction performed at room temperature.

In order to accelerate the reaction in the case of nonpolar solvents we introduced substoichiometric amounts of some PTC agents (10 mol-%) studying the effect of them in the product ratios (Scheme 1 and Table 1). In general, when Adogen 464[®], tetrabutylammonium chloride (TBAC), tetrabutylammonium hydroxide (TBAH), and tetrabutylammonium acetate (TBAA) were used, the reaction rates were increased. However, use of tetrabutylammonium bromide (TBAB) resulted in very low reaction rates because of the insolubility of the AgBr formed during the course of the reaction (Table 1, Entry 9). Very disappointing results were obtained with toluene and acetonitrile under PTC conditions (Table 1, Entries 8–11, and 18). The reaction in dichloromethane was diastereoselective but very slow (Table 1, Entry 7). The best diastereoselectivities and yields, in shorter reaction times, were achieved when using THF as solvent (Table 1, Entries 12 and 15), TBAC and TBAA being the best phase transfer agents. The reactions performed in the presence of Adogen 464[®] and TBAH both took place in 1 h. While Adogen 464[®] provided good *endo* selectivity, TBAH generated a high proportion of Michael adduct, as has been described^[8a] (Table 1, Entries 13 and 14). Surprisingly, when TBAA was used without added base, the process was faster than the analogous procedure using NaOH, but with *exo*-**2aa** and Michael adduct **3aa** unfortunately being detected in significant amounts. TBAC proved beneficial in terms of the reaction rates, but was often detrimental in terms of cycloaddition/Michael addition product ratios. A significant decrease in stereoselectivity was observed, especially in Entries 8, 9, 11, and 14 in Table 1. According to these results, THF proved to be the best solvent in which to carry out cycloaddition reactions between **1a** and ethyl acrylate under typical PTC conditions. Although TBAC or TBAA produced similar results, TBAC afforded prolines in shorter reaction times, and so was used as the PTC agent in subsequent experiments.

The effect of the base (10 mol-%) was also studied, and so different inorganic bases were examined in THF under PTC conditions and in the presence of AgOAc. The results were compared with those obtained using triethylamine and DBU, both in substoichiometric amounts. According to the product ratios and reaction times shown in Table 2, inorganic bases proved to deliver shorter reaction times. Sodium and potassium hydroxides (Table 2, Entries 3 and 4) pro-

Table 2. Base effect in the cycloaddition reaction between **1a** and ethyl acrylate in THF in the presence of AgOAc (10 mol-%) and TBAC (10 mol-%) at room temperature

Entry	Base (10 mol-%)	Time [h]	Conversion (%) ^[a]	Product ^{[a][b]}		
				<i>endo</i> - 2aa	<i>exo</i> - 2aa	3aa
1	K ₂ CO ₃	10	100	91	2	7
2	LiOH·H ₂ O	10	100	89	3	8
3	NaOH	7	100	91	4	5
4	KOH	7	100	94	3	3
5	CsOH·H ₂ O	5	100	73	9	14
6	Et ₃ N ^[c]	24	100	87	1	12
7	DBU ^[c]	10	100	92	8	0

^[a] Determined by GC and based on product **1a**. – ^[b] Stereochemistry determined by ¹H NMR (NOESY) experiments. – ^[c] Reaction run in absence of PTC agent and employing substoichiometric amounts of base (10 mol-%).

vided the best *endo* selectivity, while use of other bases (K₂CO₃, LiOH, and CsOH) resulted in significant quantities of Michael adducts. Reaction conditions using KOH, TBAC and AgOAc in THF (method A) resulted in improvements in the yield and diastereoselectivity of the reaction with respect to those obtained in the presence of organic bases (Table 2, Entries 4, 6, and 7). The good diastereoselectivity achieved when using NaOH in toluene without a PTC agent (Table 1, Entry 1) prompted us to test other bases such as K₂CO₃, LiOH, KOH, and CsOH·H₂O in this solvent. Again, the best diastereoselectivity (*endo*-**2aa**/*exo*-**2aa**, 97:3) and the fastest reaction time (16 h) at room temperature was obtained when using KOH (Method B).

According to the literature, lithium and silver(I) salts are recommended for performing 1,3-dipolar cycloaddition reactions. Nevertheless, the influence of metal salts was also examined. Thus, a 10 mol-% of a metal salt (MgCl₂, ZnCl₂, MnCl₂, LiCl, NiCl₂, and CoCl₂) was suspended in THF in the presence of KOH (10 mol-%) and TBAC (10 mol-%). This resulted in very low diastereoselectivities, providing Michael adducts **3aa** as the major products, with *endo* adducts **2aa** being obtained in negligible quantities. Imidazolidines, generated from cycloaddition reaction between two molecules of imino ester **1a**, were not detected when Mg^{II}, Zn^{II}, and Co^{II} salts were examined,^[8a,14d] again demonstrating the influence of PTC conditions on the course of the reaction. The differences in diastereoselection induced by silver acetate and silver triflate versus that of the other salts under this reaction conditions is impressive, and so for this reason, that cation was used for all the cycloaddition reactions between imino esters **1** and alkenes under solid-liquid PTC conditions. Apparently, the counterion to the metal salt did not affect the product ratios, as seen in the cases of silver acetate and silver triflate.^[8a,14d]

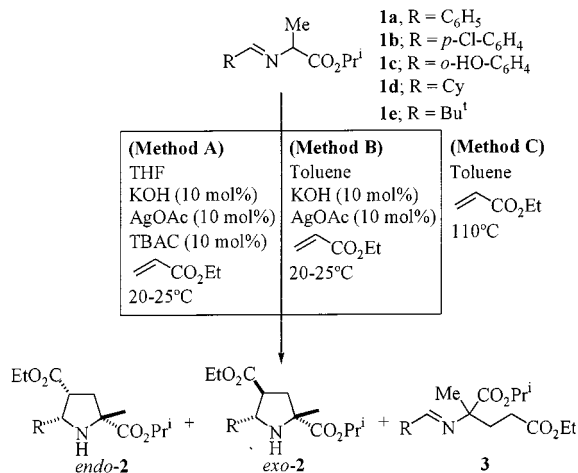
Addition of variable quantities of AgOAc resulted in very significant changes in the cycloaddition reaction between **1a** and ethyl acrylate under PTC conditions (Table 3), in terms of reaction time, conversion and diastereoselectivity. Reaction times became shorter when the quantity of AgOAc was increased (Table 3, Entries 1–4), while larger quantities of Michael adduct **3aa** were formed in the absence of this salt (Table 3, Entry 7). These results, and those

Table 3. 1,3-Dipolar cycloaddition reaction between **1a** and ethyl acrylate in THF under PTC conditions [TBAC (10 mol-%), KOH (10 mol-%)], using variable amounts of AgOAc

Entry	AgOAc (mol-%)	PTC agent (mol-%)	Time [h]	Conversion (%) ^[a]	Product ^{[a][b]}		
					<i>endo</i> - 2aa	<i>exo</i> - 2aa	3aa
1	100	TBAC (10)	2	100	94	3	3
2	15	TBAC (10)	5–6	100	94	3	3
3	10	TBAC (10)	6–7	100	94	3	3
4	5	TBAC (5)	17	100	90	4	6
5	1	TBAC (1)	65	100	89	4	7
6	1	TBAA (1)	16	100	87	5	8
7	0	–	48	73	66	3	31

^[a] Determined by GC and based on product **1a**. – ^[b] Stereochemistry determined by ¹H NMR (NOESY) experiments.

previously obtained, confirmed that silver cation is necessary for achieving good diastereoselectivities in short reaction times. TBAC and TBAA (1 mol-%) were added, together with AgOAc (1 mol-%); both reactions were completed at the same time (Table 3, Entries 5 and 6) and no improvement in the diastereoselection was observed. This result and those in Table 1 confirm that noncolloidal AgCl was formed in the heterogeneous reaction media. In all cases (with TBAC and TBAA), a fine black suspension was observed at the end of the reaction, presumably due to the formation of AgOH. The optimal quantity of Ag^I salt for this reaction was settled as 10 mol-%, since the results obtained were similar when 15 mol-% of Ag^I salt was used (Table 3, Entries 2 and 3).



Scheme 2

Activated aromatic and nonaromatic aldimines of the alanine isopropyl ester were prepared, so as to study the influence of the imine substituent (Scheme 2 and Table 4). Three different reaction conditions were used (Method A: THF, TBAC, KOH, AgOAc; Method B: toluene, KOH and AgOAc; Method C: thermal reaction), on the basis of the best results achieved previously.

The presence of the chloro substituent at the *para* position in the corresponding arylaldimine **1b** accelerated the reaction in all cases, as previously described,^[14c,20d] affording good to excellent diastereoselectivity (Table 4, Ent-

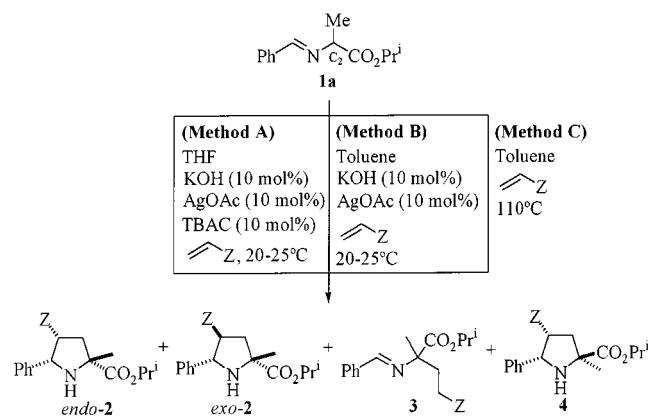
Table 4. 1,3-Dipolar cycloaddition reaction between **1a**–**1e** and ethyl acrylate

Entry	Compound 1	Method	Time [h]	Conversion (%) ^[a]	Product ^{[a][b]}		
					<i>endo</i> - 2aa	<i>exo</i> - 2aa	3aa
1	1a	A	7	100	94	3	3
2	1a	B	10	100	97	3	0
3	1a	C	24	100	84	15	1
4	1b	A	4	100	<i>endo</i> - 2ba	<i>exo</i> - 2ba	3ba
5	1b	B	33	100	93	4	3
6	1b	C	19	100	100	0	0
7	1c	A	1.5	100	87	9	4
8	1c	B ^[d]	24	100	<i>endo</i> - 2ca	<i>exo</i> - 2ca	3ca
9	1c	C	19	0	70	23 ^[c]	0
10	1d	A ^[e]	3	82	0	0	100 ^[f]
11	1d	B ^[e]	8	100	100	0	0
12	1d	C	19	100 ^[g]	–	–	–
13	1e	A ^[e]	4	100	<i>endo</i> - 2ea	<i>exo</i> - 2ea	3ea
14	1e	B ^[e]	72	100	0	0	100
15	1e	C	19	100 ^[g]	–	–	–

^[a] Determined by GC and based on product **1**. – ^[b] Stereochemistry determined by ¹H NMR (NOESY) experiments. – ^[c] Other diastereomer was detected in 7% yield. – ^[d] 1.1 equiv. of KOH was required. – ^[e] 4 equiv. of KOH were required. – ^[f] Amino ester was obtained in 61% yield due to hydrolysis of **1d** under reaction conditions. – ^[g] Only decomposition of the imino ester was observed.

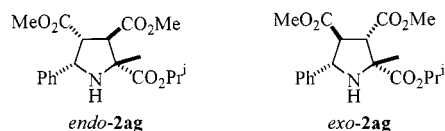
ries 4–6). Under these particular reaction conditions, the *o*-hydroxybenzaldimine **1c** was not a useful substituent because it required stoichiometric amounts of base to produce total conversion (Table 4, Entry 8, Method B) and only decomposition products were obtained, as also occurred in the thermal reaction. In THF, the reaction was very fast, with an improved *exo*-**2ca** ratio, as semiempirical calculations with imino esters and nitroalkenes had predicted.^[12] The reaction between **1d** (R = Cy) and ethyl acrylate illustrated the feasibility of selectively producing either pure cycloadduct *endo*-**2da** or pure Michael adduct **3da** by changing the reaction conditions. Methods A and B, employing an excess of base, afforded *endo*-**2da** in 95% and **3da** in 39% isolated yield, respectively (Table 4, Entries 11 and 10). A bulkier group, such as *tert*-butyl, on the imine function quantitatively afforded the Michael adduct **3ea**, whether method A or method B was employed (Table 4, Entries 13 and 14). This result was in accordance to that previously reported for imino esters, using LiCl as catalyst.^[11,16] Thermal reaction conditions improved neither yield nor diastereoselectivity in any case (Table 4, Entries 3, 6, 9, 12, and 15). All the experiments demonstrated that it was beneficial to apply PTC to 1,3-dipolar cycloaddition reactions using catalytic amounts of AgOAc and KOH. Substituted prolines were accessible by following this methodology, and so the next step was to investigate the reaction between **1a** and several alkenes using the three methods mentioned and to compare the results obtained (Scheme 3 and Table 5).

A bulky, electron-withdrawing group such as *p*-tolylsulfonyl produced a behaviour different to that with ethyl acrylate. Reaction times at room temperature (methods A and



Scheme 3

B) were rather long in the case of *p*-tolyl vinyl sulfone and the diastereoselectivity depended on how stabilized the intermediates of the reaction were. Thus, in a nonpolar solvent (method B), the major product was the cycloadduct *exo*-**2ab**. However, method A, which incorporated higher concentrations of salts, afforded Michael product **3ab** and *endo*-**2ab** as a 5:4 mixture. This vinyl sulfone afforded the best *endo* selectivity when using thermal cycloaddition conditions (method C), whereas *N*-phenylmaleimide (NPM) afforded the best *endo* diastereoselectivity, in almost quantitative yield, in all the examples given in Table 5. In this last case, *endo*-**2ac** was exclusively obtained in high yields after 1 d, independently of the selected method. In the case of acrylonitrile, the best diastereoselectivities were again achieved using method B. The other two procedures furnished mixtures with significant quantities of *exo*-**2ad** product. These results are in agreement with those previously reported, in which the low *endo* selectivity of acrylonitrile was evidenced.^[16b] In the absence of silver acetate, it was possible to obtain the Michael adduct **3ad** as a major product. The reaction between **1a** and dimethyl fumarate at room temperature resulted in similar diastereoselectivities for methods A and B; however, a 58:42 mixture of *endo*-**2ag**/*exo*-**2ag** was isolated from the thermal cycloaddition reaction (method C).



α,β -Unsaturated ketones and aldehydes generated a new diastereomer **4**, which had not been detected previously. According to ¹H NMR experiments (NOESY), product **4** was the stereomutated compound, generated by C²–N bond rotation in the (*E,E*)-metallodipole. This behaviour has been described for 1,3-dipoles with bulky imine substituents when using less reactive dipolarophiles.^[14e] As reported, the yields of the cycloadducts were very poor when using 3-buten-2-one in the presence of LiBr and triethylamine.^[16b]

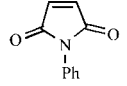
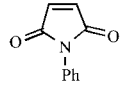
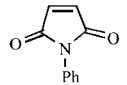
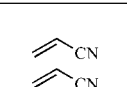
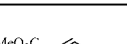
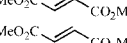
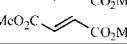
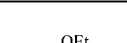
Here, the cycloaddition reaction between **1a** and 3-buten-2-one under PTC conditions (Table 5, method A) proved to be a very valuable route, achieving a good yield (66%) and a high *endo* selectivity. In contrast, complex mixtures of stereoisomers were obtained when using methods B and C. Acrolein, when very long reaction times were employed, afforded significant quantities of stereomutated compound **4af**, together with the *endo*-**2af** adduct (Table 5). Less reactive vinylphosphonate also required 80 °C and very long reaction times (Table 5) to achieve high degrees of conversion. In this case, major compound *exo*-**2ah** was isolated and no traces of stereomutated **4ah** were detected. As shown in Table 5, thermal cycloaddition reactions were only useful when vinyl sulfone was employed as dipolarophile.

Nitrostyrene was used as the dipolarophile in this 1,3-cycloaddition reaction in the presence of an excess of base, furnishing a complex mixture of diastereomeric cycloadducts and Michael addition products, while it has been reported that *exo* products are mainly obtained when using organic bases and silver(I) salts.^[12,21] The cycloaddition reaction under PTC conditions was very sensitive to steric hindrance. For example, *trans*-cinnamaldehyde or methyl crotonate did not give the desired products. Attempts to perform cycloaddition reactions with electron-rich alkenes such as cyclohexene, styrene and ethyl vinyl ether were unsuccessful even when the temperature of the reaction mixture was raised to 110 °C in a sealed tube.

Glycine derivative **5a** was also employed as 1,3-dipole with some representative alkenes in the 1,3-dipolar cycloaddition reactions, using methods A, B and C, (Scheme 4 and Table 6). As expected, the reaction times were shorter than when the alanine derivative had been used. The diastereoselectivity was very high when ethyl acrylate (methods A and B), *N*-phenylmaleimide (method A and B) and acrylonitrile (method B) were employed (see Table 6). Again, the thermal cycloaddition reaction (method C) did not represent any improvement over methods A and B. Stereomutated compounds **8** were detected in all thermal tests, even when using methods A and B, in the reaction with methyl vinyl ketone. In this last example, use of method A afforded compound **8ae** in 58% yield.

Many factors, ions and reaction conditions, are involved in the formation or rupture of the intermediate complexes in the reaction. For glycine and alanine imino esters **1a** and **5a**, respectively, the stereomutation could be promoted by the interaction of a Lewis base (aldehyde or ketone) with the (1,3-dipole)metal complex **I** and **I'**. This interaction would transform the structure of the chelate **I** and **I'** of the imino esters **1a** and **5a**, generating new chelates **II** and **II'** (Scheme 5). The steric hindrance of the intermediate complexes **II** and **II'** would be partially avoided by rotation around N–C² bond, producing the intermediate complexes **III** and **III'**. As illustrated in Scheme 5, the methyl group in **III'** would cause slightly less hindrance than the isopropoxycarbonyl group in **II'**; presumably the stabilization energy gap between them is very small. However, organic complex **III** should experience fewer interactions than the corresponding aggregate **II**, so we would expect larger

Table 5. 1,3-Dipolar cycloaddition reaction of **1a** and dipolarophiles

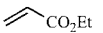
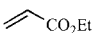
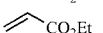
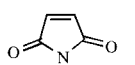
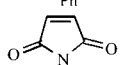
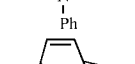
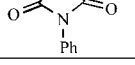
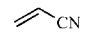
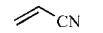
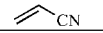
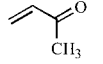
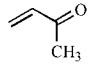
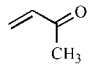
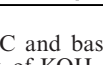
Dipolarophile	Method	Time(h)	Yield (%) ^[a]	Product ^{[a][b]}			
				<i>endo-2</i>	<i>exo-2</i>	3	4
	A	48	73	<i>endo-2ab</i>	<i>exo-2ab</i>	3ab	4ab
	B	48	50	40	10	50	0
	C	17	Quant.	20	70	10	0
				80	10	10	0
	A	24	85	<i>endo-2ac</i>	<i>exo-2ac</i>	3ac	4ac
	B	24	87	100	0	0	0
	C	14	Quant.	100	0	0	0
							
	A	23	94	<i>endo-2ad</i>	<i>exo-2ad</i>	3ad	4ad
	A ^[c]	6	95	57	25	18	0
	B	76	89	0	12	88	0
	C	48	85	96	2	2	0
				23	66	6	5
	A ^[d]	3	66	<i>endo-2ae</i>	<i>exo-2ae</i>	3ae	4ae
	B ^[d]	24	72	87	7	0	6
	C	24	<15	55	39	0	6
				54	10	13	13
	A	48	79	<i>endo-2af</i>	<i>exo-2af</i>	3af	4af
	B	75	81	50	5	0	45
	C	18	Quant.	16	4	0	80
				30	26	17	27
	A	35	95	<i>endo-2ag</i>	<i>exo-2ag</i>	3ag	4ag
	B	24	92	92	8	0	0
	C	18	Quant.	94	6	0	0
				58	42	0	0
	A	24	--	<i>endo-2ah</i>	<i>exo-2ah</i>	3ah	4ah
	B ^[e]	260	30 ^[f]	--	--	--	--
	C	72	90	12	80	8	0
				9	84	7	0

^[a] Determined by GC and based on product **1a**. — ^[b] Stereochemistry determined by ¹H NMR (NOESY) experiments. — ^[c] Without AgOAc. — ^[d] In the presence of 1.5 equiv. of KOH. — ^[e] The reaction was carried out at 80 °C. — ^[f] Decomposition took place after column chromatography (flash silica gel).

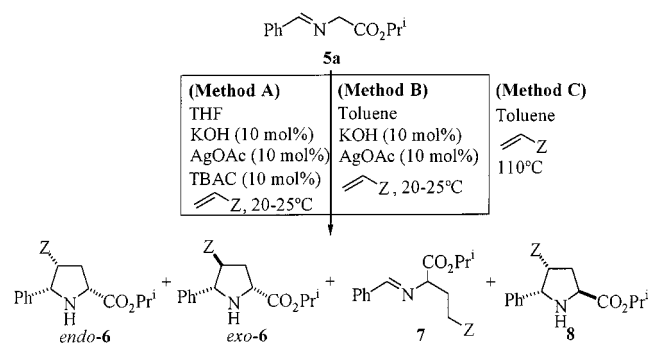
amounts of stereomutated products for glycine than for alanine derivatives (see methyl vinyl ketone examples in Table 5 and Table 6). On the other hand, acrolein has a higher energy LUMO than methyl vinyl ketone,^[22] which justifies its longer reaction times (Table 5). We can also

reckon that complexes **II** and **II'** would act as kinetic *pseudometallo-dipoles*, while **III** and **III'** would work as thermodynamic *pseudometallo-dipoles*. The result obtained with another high energy LUMO alkene such as diethyl vinylphosphonate, heating the reaction at 80 °C, is not con-

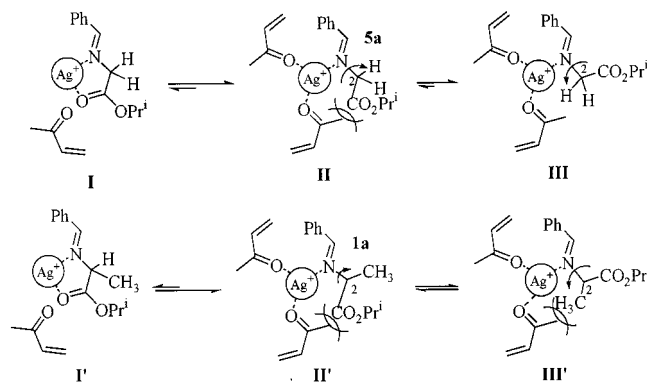
Table 6. 1,3-Dipolar cycloaddition reaction of **5a** and alkenes

Dipolarophile	Method	Time(h)	Yield (%) ^[a]	Product ^{[a][b]}			
				<i>endo</i> - 6	<i>exo</i> - 6	7	8
	A	1	92	<i>endo</i> - 6aa	<i>exo</i> - 6aa	7aa	8aa
	B	5	92	93	7	0	0
	C	19	Quant.	98	2	0	0
	A	30	91	66	6	5	2
	B	20	92	<i>endo</i> - 6ac	<i>exo</i> - 6ac	7ac	8ac
	C	19	Quant.	100	0	0	0
				85	3	8	4
	A	2	93	<i>endo</i> - 6ad	<i>exo</i> - 6ad	7ad	8ad
	B	5	95	57	25	18	0
	C	17	<15	96	2	2	0
				23	66	6	5
	A ^[c]	4	58	<i>endo</i> - 6ae	<i>exo</i> - 6ae	7ae	8ae
	B ^[c]	6	63	5	11	0	84
	C	21	Quant.	55	6	0	39
				54	10	13	13

[a] Determined by GC and based on product **5a**. – [b] Stereochemistry determined by ¹H NMR (NOESY) experiments. – [c] In the presence of 1.5 equiv. of KOH.



Scheme 4



Scheme 5

tradictory with these hypothesis because the kinetic *pseudo*-metallo-dipole **II'** is favoured at this temperature and is more reactive than **III'**. The *exo* adduct is formed preferentially, due to the volume of the electron-withdrawing group, as had occurred with the vinyl sulfone, where significant amounts of *exo* product were detected.

Conclusion

It has been demonstrated that PTC conditions can also be applied to 1,3-dipolar cycloaddition reactions between imino esters of glycine and alanine and electrophilic alkenes. This regioselective and diastereoselective process, carried out in the presence of substoichiometric amounts

of both an inorganic base (KOH) and of silver acetate, is economically more viable than others using excesses of organic bases and metal salts. α,β -Unsaturated aldehydes and ketones react under these conditions, affording good yields of cycloadducts, as does diethyl vinylphosphonate. The reactivity of the imino ester derived from alanine allows this procedure to be applied to imino esters derived from other amino acids, taking into account the sensitivity of this reaction to steric hindrance.

Experimental Section

General: Melting points were determined with a Reichert Thermo-var hot plate apparatus and are uncorrected. – IR spectra were recorded with a Nicolet 510 P-FT and only the structurally most important peaks are listed. – NMR spectra were performed with a Bruker AC 300 and DRX 500 by the NMR Service of the University of Alicante, using CDCl_3 as solvent and TMS as internal standard unless otherwise stated. – Low resolution electron impact (EI) mass spectra were obtained at 70 eV with a Shimadzu QP-5000, and low resolution electrospray ionisation (ESI) mass spectra were obtained with a Finnigan VG platform. HRMS (EI) were recorded with a Finnigan MAT 95S (MS Service of the University of Alicante). – Microanalyses were performed by the Microanalysis Service of the University of Alicante. – Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots visualised with UV light at 254 nm. Flash chromatography used Merck silica gel 60 (0.040–0.063 mm). – Commercially available TBAC hydrate was dehydrated in vacuo (2 Torr) at 60 °C prior to use.

Synthesis of Imino Esters 1. – General Procedure: SOCl_2 (20 mmol, 1.45 mL) was added dropwise to a suspension of amino acid (glycine or alanine, 10 mmol) in 2-propanol (15 mL) at 0 °C. The reaction mixture was refluxed for 16 h and the solvent was evaporated in vacuo (15 Torr). Water (30 mL), Na_2CO_3 (10 mmol, 1.06 g), and the corresponding aldehyde (10 mmol) were added and the mixture was stirred vigorously for 18 h. The aqueous phase was extracted with ethyl acetate (3×20 mL); the organic phase was dried (Na_2SO_4) and concentrated in vacuo (15 Torr) to afford imino esters **1a–f**. Physical and analytical data see below.

Isopropyl 2-[(E)-1-Phenylmethylideneamino]propanoate (1a): Colourless oil, 81%. – TLC: $R_f = 0.71$ (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu} = 1735, 1644 \text{ cm}^{-1}$. – ^1H NMR (300 MHz): $\delta = 1.24, 1.26 [2 \times \text{d}, J = 6.1 \text{ Hz}, 6 \text{ H}, \text{CH}(\text{CH}_3)_2], 1.51 (\text{d}, J = 6.7 \text{ Hz}, 3 \text{ H}, \text{NCHCH}_3), 4.10 (\text{q}, J = 6.7 \text{ Hz}, 1 \text{ H}, \text{NCHCH}_3), 5.06 [\text{sept}, J = 6.1 \text{ Hz}, 1 \text{H } \text{CH}(\text{CH}_3)], 7.41 (\text{m}, 3 \text{ H}, \text{ArH}), 7.78 (\text{m}, 2 \text{ H}, \text{ArH}), 8.31 (\text{s}, 1 \text{ H}, \text{N}=\text{CH})$. – ^{13}C NMR (75 MHz): $\delta = 19.2 (\text{NCHCH}_3), 21.6 [\text{CH}(\text{CH}_3)_2], 67.9, 68.3 [\text{NCHCH}_3 \text{ and } \text{CH}(\text{CH}_3)_2], 128.4, 128.5, 130.9, 135.8 (\text{ArC}), 162.6 (\text{C}=\text{N}), 172.0 (\text{C}=\text{O})$. – MS (EI): m/z (%) = 220 (0.11) [$\text{M}^+ + 1$], 176 (21), 133 (19), 132 (100), 105 (43), 43 (26). – HRMS calcd. for $[\text{C}_{13}\text{H}_{17}\text{NO}_2 - \text{C}_3\text{H}_7]: 176.0711$; found 176.0714.

Isopropyl 2-[(E)-1-(4-Chlorophenyl)methylideneamino]propanoate (1b): Colourless oil, 79%. – TLC: $R_f = 0.73$ (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu} = 1735, 1644 \text{ cm}^{-1}$. – ^1H NMR (300 MHz): $\delta = 1.24, 1.25 [2 \times \text{d}, J = 6.4 \text{ Hz}, 6 \text{ H}, \text{CH}(\text{CH}_3)_2], 1.50 (\text{d}, J = 6.1 \text{ Hz}, 3 \text{ H}, \text{NCHCH}_3), 4.09 (\text{q}, J = 6.8 \text{ Hz}, 1 \text{ H}, \text{NCHCH}_3), 5.05 [\text{sept}, J = 6.4 \text{ Hz}, 1 \text{ H}, \text{CH}(\text{CH}_3)_2], 7.37 (\text{d}, J = 8.3 \text{ Hz}, 2 \text{ H}, \text{ArH}), 7.71 (\text{d}, J = 8.3 \text{ Hz}, 2 \text{ H}, \text{ArH}), 8.26 (\text{s}, 1 \text{ H}, \text{N}=\text{CH})$. – ^{13}C NMR (75 MHz): $\delta = 19.3 (\text{NCCH}_3), 21.7, 21.8$

$[\text{CH}(\text{CH}_3)_2], 67.8, 68.4 [\text{NCHCH}_3, \text{CH}(\text{CH}_3)_2], 128.8, 129.6, 130.9, 137.0 (\text{ArC}), 161.3 (\text{C}=\text{N}), 171.9 (\text{C}=\text{O})$. – MS (EI): m/z (%) = 210 (10) [$\text{M}^+ - 43$], 166 [$\text{M}^+ - 87, 100$], 139 (17), 43 (39). – HRMS calcd. for $[\text{C}_{13}\text{H}_{16}\text{ClNO}_2 - \text{C}_4\text{H}_7\text{O}_2]: 166.0423$; found 166.0420.

Isopropyl 2-[(E)-1-(2-Hydroxyphenyl)methylideneamino]propanoate (1c): Colourless oil, 91%. – TLC: $R_f = 0.75$ (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu} = 1747, 1636 \text{ cm}^{-1}$. – ^1H NMR (300 MHz): $\delta = 1.24, 1.25 [2 \times \text{d}, J = 6.3 \text{ Hz}, 6 \text{ H}, \text{CH}(\text{CH}_3)_2], 1.52 (\text{d}, J = 6.8 \text{ Hz}, 3 \text{ H}, \text{NCHCH}_3), 4.09 (\text{q}, J = 6.8 \text{ Hz}, 1 \text{ H}, \text{NCHCH}_3), 5.03 [\text{sept}, J = 6.3 \text{ Hz}, 1 \text{ H}, \text{CH}(\text{CH}_3)_2], 6.84–6.97 (\text{m}, 2 \text{ H}, \text{ArH}), 7.24–7.34 (\text{m}, 2 \text{ H}, \text{ArH}), 8.37 (\text{s}, 1 \text{ H}, \text{CH}=\text{N}), 13.06 (\text{s}, 1 \text{ H}, \text{OH})$. – ^{13}C NMR (75 MHz): $\delta = 19.4 (\text{NCHCH}_3), 21.6 [\text{C}(\text{CH}_3)_2], 66.1, 68.7 [\text{NCCH}_3, \text{C}(\text{CH}_3)_2], 117.0, 118.5, 118.6, 131.5, 132.5, 160.9 (\text{ArC}), 163.7 (\text{C}=\text{N}), 171.2 (\text{C}=\text{O})$. – MS (EI): m/z (%) = 235 (19) [M^+], 192 (2), 148 (100). – HRMS calcd. for $[\text{C}_{13}\text{H}_{17}\text{NO}_3]: 235.1208$; found 235.1205.

Isopropyl 2-[(E)-1-Cyclohexylmethylideneamino]propanoate (1d): Colourless oil, 73%. – TLC: $R_f = 0.73$ (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu} = 1736, 1665 \text{ cm}^{-1}$. – ^1H NMR (300 MHz): $\delta = 1.20–1.41 [\text{m with } 2 \times \text{d at } 1.23, 1.24, 12 \text{ H}, (\text{CH}_2)_3\text{CH}_2\text{CH}, (\text{CH}_3)_2\text{CH}], 1.39 (\text{d}, J = 6.8 \text{ Hz}, 3 \text{ H}, \text{NCHCH}_3), 1.66–1.90 (\text{m}, 4 \text{ H}, 2 \times \text{CH}_2\text{CH}), 2.24 [\text{m}, 1 \text{ H}, \text{CH}(\text{CH}_3)_2], 3.80 (\text{q}, J = 6.8 \text{ Hz}, 1 \text{ H}, \text{NCHCH}_3), 5.02 [\text{sept}, J = 6.3 \text{ Hz}, 1 \text{ H}, \text{CH}(\text{CH}_3)_2], 7.53 (\text{d}, J = 5.5 \text{ Hz}, 1 \text{ H}, \text{CH}=\text{N})$. – ^{13}C NMR (75 MHz): $\delta = 19.1 (\text{CH}_3\text{CN}), 21.5, 21.6 [\text{CH}(\text{CH}_3)_2], 25.1, 25.8, 29.4, 29.5 [(\text{CH}_2)_5], 43.4, (\text{CHCH}_2), 67.6, 68.0 [\text{CH}(\text{CH}_3)_2, \text{NCHCH}_3], 171.0 (\text{C}=\text{N}), 172.0 (\text{C}=\text{O})$. – MS (EI): m/z (%) = 225 (0.2) [M^+], 138 [$\text{M}^+ - 87$] (47), 55 (20). – HRMS calcd. for $[\text{C}_{13}\text{H}_{23}\text{NO}_2]: 225.1728$; found 225.1721.

Isopropyl 2-[(E)-2,2-Dimethylpropylideneamino]propanoate (1e): Colourless oil, 36%. – TLC: $R_f = 0.55$ (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu} = 1736, 1665 \text{ cm}^{-1}$. – ^1H NMR (300 MHz): $\delta = 1.08 [\text{s}, 9 \text{ H}, \text{CH}(\text{CH}_3)_3], 1.21, 1.23 [2 \times \text{d}, J = 6.3 \text{ Hz}, 6 \text{ H}, \text{CH}(\text{CH}_3)_2], 1.39 (\text{d}, J = 6.8 \text{ Hz}, 3 \text{ H}, \text{NCHCH}_3), 3.82 (\text{q}, J = 6.8 \text{ Hz}, 1 \text{ H}, \text{NCHCH}_3), 5.02 [\text{sept}, J = 6.3 \text{ Hz}, 1 \text{ H}, \text{CH}(\text{CH}_3)_2], 7.56 (\text{s}, 1 \text{ H}, \text{CH}=\text{N})$. – ^{13}C NMR (75 MHz): $\delta = 18.8, (\text{NCCH}_3), 22.6, 22.7 [\text{CH}(\text{CH}_3)_2], 26.7 [\text{C}(\text{CH}_3)_3], 36.1 [\text{C}(\text{CH}_3)_3], 67.4, 67.9 [\text{NCCH}_3, \text{C}(\text{CH}_3)_2], 172.0 (\text{C}=\text{O}), 173.9 (\text{C}=\text{N})$. – MS (EI): m/z (%) = 200 (0.7) [$\text{M}^+ + 1$], 112 (100) [$\text{M}^+ - 87$], 43 (45). – HRMS calcd. for $[\text{C}_{11}\text{H}_{21}\text{NO}_2]: 199.1522$; found 199.1565.

Isopropyl 2-[(E)-1-Phenylmethylideneamino]acetate (5a): Colourless oil, 83%. – TLC: $R_f = 0.70$ (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu} = 1739, 1648 \text{ cm}^{-1}$. – ^1H NMR (300 MHz): $\delta = 1.27 [\text{d}, J = 6.3 \text{ Hz}, 6 \text{ H}, \text{CH}(\text{CH}_3)_2], 4.35 (\text{s}, 2 \text{ H}, \text{NCH}_2), 5.09 [\text{sept}, J = 6.3 \text{ Hz}, 1 \text{ H}, \text{CH}(\text{CH}_3)_2], 7.41 (\text{m}, 3 \text{ H}, \text{ArH}), 7.77 (\text{m}, 2 \text{ H}, \text{ArH}), 8.27 (\text{s}, 1 \text{ H}, \text{CH}=\text{N})$. – ^{13}C NMR (75 MHz): $\delta = 21.6 [\text{C}(\text{CH}_3)_2], 62.0 (\text{NCH}_2), 68.3 [\text{CH}(\text{CH}_3)_2], 128.3, 128.4, 131.0 (\text{ArC}), 135.5 (\text{C}=\text{N}), 169.4 (\text{C}=\text{O})$. – MS (EI): m/z (%) = 162 (37) [$\text{M}^+ - 43$], 118 (81), 91 (100), 43 (37). – HRMS calcd. for $[\text{C}_{12}\text{H}_{15}\text{NO}_2 - \text{C}_3\text{H}_7]: 162.0555$; found 162.0566.

1,3-Dipolar Cycloaddition Reaction between Imino Esters 1 and 5a and Alkenes. – Method A: Potassium hydroxide (0.025 mmol, 2 mg) was added to a suspension of the imino ester **1** (0.25 mmol), alkene (0.3 mmol), silver acetate (0.025 mmol, 4 mg), and previously dehydrated tetrabutylammonium chloride (0.025 mmol, 7 mg) in THF (3 mL), and the resulting mixture was vigorously stirred for the times indicated in the corresponding tables. The solvent was evaporated in vacuo (15 Torr), ethyl acetate added, and the mixture was percolated through silica gel, eluting with ethyl acetate.

The solvent was evaporated (15 Torr) to obtain pyrrolidines or Michael adduct, depending on the reaction (see text and tables).

Method B: Potassium hydroxide (0.025 mmol, 2 mg) was added to a suspension of the imino ester **1** (0.25 mmol), alkene (0.3 mmol), and silver acetate (0.025 mmol, 4 mg) in toluene (3 mL), and the resulting mixture was vigorously stirred for the times shown in the corresponding tables. The solvent was evaporated in vacuo (15 Torr), ethyl acetate was added, and the mixture was percolated through silica gel, eluting with ethyl acetate. The solvent was evaporated (15 Torr) to obtain pyrrolidines or Michael adduct, depending on the reaction (see text and tables).

Method C: A solution of the imino ester **1** (0.25 mmol) and the alkene (0.3 mmol) in toluene (3 mL) was heated in a sealed tube at 110 °C (see tables and text for reaction times). The solvent was evaporated in vacuo (15 Torr) to give the crude products. Physical and analytical data follow.

4-Ethyl 2-Isopropyl (2R*,4R*,5S*)-2-Methyl-5-phenylpyrrolidine-2,4-dicarboxylate (endo-2aa, Method A or B, Table 4): Colourless solid, 95%, m.p. 92–93 °C (ethyl acetate/*n*-hexane). – $C_{18}H_{25}NO_4$ (319.2): calcd. C 67.7, H 7.9, N 4.4; found C 67.6, H 7.9, N 4.2. – TLC: R_f = 0.55 (*n*-hexane/ethyl acetate, 3:2). – IR (KBr): $\tilde{\nu}$ = 1731 cm^{-1} . – 1H NMR (300 MHz): δ = 0.73 (t, J = 7.3 Hz, 3 H, CH_2CH_3), 1.22, 1.23 [2 $\times$ d, J = 6.1 Hz, 6 H, $CH(CH_3)_2$], 1.41 (s, 3 H, $NCCH_3$), 1.97 (dd, J = 13.4, 7.9 Hz, 1 H, $NCCHH$), 2.60 (dd, J = 13.4, 6.0 Hz, 1 H, $NCCHH$), 3.10 (s, 1 H, NH), 3.25 (m, 1 H, $CHCO_2Et$), 3.59 (m, 2 H, CH_2O), 4.57 (d, J = 7.3 Hz, 1 H, PhCH), 5.06 [sept, J = 6.1 Hz, 1 H, $CH(CH_3)_2$], 7.10–7.26 (m, 5 H, ArH). – ^{13}C NMR (75 MHz): δ = 13.5 (CH_3CH_2O), 21.5 [$(CH_3)_2CH$], 27.5 (CH_3CN), 40.3 (CH_2CHCO_2Et), 50.4 ($CHCO_2Et$), 60.0 (CH_2O), 65.0, 65.5 (PhCH, CCO_2iPr), 68.6 [$CH(CH_3)_2$], 126.0, 127.0, 128.0, 139.1 (ArC), 172.5, 175.4 (2 $\times$ C=O). – MS (EI): m/z (%) = 320 (0.1) [M^+ + 1], 232 (100) [M^+ – 87], 158 (27), 42 (23). – HRMS calcd. for [$C_{18}H_{25}NO_4$ – $C_4H_7O_2$]: 232.1337; found 232.1335.

Isopropyl (2R*,4R*,5R*)-2-Methyl-4-(4-methylphenylsulfonyl)-5-phenylpyrrolidine-2-carboxylate (endo-2ab, Method C, Table 5): Colourless solid, 80%, m.p. 92 °C (ethyl acetate/*n*-hexane). – $C_{22}H_{27}NO_4S$ (433.3): calcd. C 63.5, H 6.8, N 3.5; found C 63.4, H 6.9, N 3.4. – TLC: R_f = 0.50 (*n*-hexane/ethyl acetate, 3:2). – IR (KBr): $\tilde{\nu}$ = 1732, 1310, 1150 cm^{-1} . – 1H NMR (300 MHz): δ = 1.22, 1.23 [2 $\times$ d, J = 6.3 Hz, 6 H, $CH(CH_3)_2$], 1.52 (s, 3 H, $NCCH_3$), 2.30 (s, 3 H, CH_3Ar), 2.41 (dd, J = 13.6, 9.5 Hz, 1 H, $NCCHH$), 2.74 (dd, J = 13.6, 8.4 Hz, 1 H, $NCHH$), 3.78–3.87 (m, 1 H, SCH), 4.60 (d, J = 8.4 Hz, 1 H, PhCH), 5.00 [sept, J = 6.3 Hz, 1 H, $CH(CH_3)_2$], 7.15 (m, 7 H, ArH), 7.57 (m, 2 H, ArH). – ^{13}C NMR (75 MHz): δ = 21.4, 21.5 [$CH(CH_3)_2$, $NCCH_3$], 26.1 (CH_3Ph), 38.3 (CH_2CHS), 63.4, 64.9 (PhC, $NCCH_3$), 69.2, 69.9 [SCH, $CH(CH_3)_2$], 127.2, 127.6, 128.2, 128.3, 129.5, 135.3, 139.9, 144.5 (ArC), 175.2 (C=O). – MS (EI): m/z (%) = 314 (11) [M^+ – 87], 158 (100), 42 (25). – HRMS calcd. for [$C_{22}H_{27}NO_4S$ – $C_7H_8O_2S$]: 245.1415; found 244.1418.

Isopropyl (1R*,3S*,3aR*,6aS*)-1-Methyl-4,6-dioxo-3,5-diphenylperhydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (endo-2ac, Method A or B, Table 5): Colourless solid, 87%, m.p. 184–185 °C (ethyl acetate/*n*-hexane). – $C_{23}H_{24}N_2O_4$ (392.1): calcd. C 70.4, H 6.2, N 7.1; found C 70.3, H 6.1, N 7.1. – TLC: R_f = 0.27 (*n*-hexane/ethyl acetate, 3:2). – IR (KBr): $\tilde{\nu}$ = 1723 cm^{-1} . – 1H NMR (300 MHz): δ = 1.31, 1.37 (2 $\times$ d, J = 6.2 Hz, 6 H, $CH(CH_3)_2$), 1.61 (s, 3 H, $NCCH_3$), 2.73 (d, J = 8.3 Hz, 1 H, NH), 3.40 (d, J = 7.5, 1 H, CH_3CCH), 5.65 (dd, J = 9.1, 7.6 Hz, 1 H, PhCCH), 4.83 (dd, J = 9.1, 8.3 Hz, 1 H, PhCH), 5.16 [sept, J = 6.2 Hz, 1 H, $CH(CH_3)_2$],

7.07 (m, 2 H ArH), 7.28–7.39 (m, 8 H, ArH). – ^{13}C NMR (75 MHz): δ = 21.6, 21.8 [$CH(CH_3)_2$], 24.0 ($NCCH_3$), 50.4 ($COCHCPh$), 55.7 ($COCHCN$), 62.1 (PhC), 67.6, 69.7 [CH_3CCO_2iPr , $CH(CH_3)_2$], 126.1, 127.0, 128.1, 128.3, 128.4, 128.9, 131.5, 136.8 (ArC), 171.7, 173.6, 174.4 (3 $\times$ C=O). – MS (EI): m/z (%) = 392 (0.5) [M^+], 306 (16), 305 (100), 219 (17), 131 (17), 43 (14). – HRMS calcd. for [$C_{23}H_{24}N_2O_4$]: 392.1736; found 392.1727.

Isopropyl (2R*,4R*,5S*)-4-Cyano-2-methyl-5-phenylpyrrolidine-2-carboxylate (endo-2ad, Method B, Table 5): Colourless oil, 89%. – $C_{16}H_{20}N_2O_2$ (272.1): calcd. C 70.5, H 7.4, N 10.3; found C 70.2, H 7.5, N 9.9. – TLC: R_f = 0.64 (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu}$ = 2240, 1724 cm^{-1} . – 1H NMR (300 MHz): δ = 1.31, 1.32 [2 $\times$ d, J = 6.3 Hz, 6 H, $CH(CH_3)_2$], 1.48 (s, 3 H, $NCCH_3$), 2.18, (dd, J = 13.6, 7.5 Hz, 1 H, CO_2CCHH), 2.82 (dd, J = 13.6, 3.1 Hz, 1 H, CO_2CCHH), 3.28 (ddd, J = 7.5, 5.9, 3.1 Hz, 1 H, CNCH), 4.50 (d, J = 5.9 Hz, 1 H, PhCH), 5.15 [sept, J = 6.3 Hz, 1 H, $CH(CH_3)_2$], 7.25–7.48 (m, 5 H, ArH). – ^{13}C NMR (75 MHz): δ = 21.5, 21.6 [$CH(CH_3)_2$], 27.0 ($HNCCH_3$), 37.4 ($NCCH$), 41.5 (CH_2CHCN), 64.1, 64.7 (PhC, $HNCCH_3$), 69.4 [$CH(CH_3)_2$], 119.0 (CN), 126.8, 128.3, 128.5, 137.7 (ArC), 174.8 (C=O). – MS (EI): m/z (%) = 185 (100) [M^+ – 87], 43 (13), 42 (18), 41 (12). – HRMS calcd. for [$C_{16}H_{20}N_2O_2$]: 272.1524; found 272.1531.

Isopropyl (2R*,4R*,5S*)-4-Acetyl-2-methyl-5-phenylpyrrolidine-2-carboxylate (endo-2ae, Method A, Table 5): Pale yellow oil, 66%. – $C_{17}H_{23}NO_3$ (289.1): calcd. C 70.6, H 8.0, N 4.8; found C 70.2, H 7.9, N 4.8. – TLC: R_f = 0.69 (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu}$ = 1720 cm^{-1} . – 1H NMR (300 MHz): δ = 1.26, 1.28 [2 $\times$ d, J = 6.3 Hz, 6 H, $CH(CH_3)_2$], 1.46 (s, 3 H, $NCCH_3$), 1.97 (s, 3 H, $COCH_3$), 2.08 (dd, J = 13.1, 10.0 Hz, 1 H, $NCCHH$), 2.60 (dd, J = 13.1, 7.0 Hz, 1 H, $NCCHH$), 3.06 (ddd, J = 10.0, 8.3, 7.0 Hz, 1 H, CH_3COCH), 4.40 (d, J = 8.3 Hz, 1 H, PhCH), 5.04 [sept, J = 6.3 Hz, 1 H, $CH(CH_3)_2$], 7.23–7.43 (m, 5 H, ArH). – ^{13}C NMR (75 MHz): δ = 21.6 [$CH(CH_3)_2$], 27.0 (CH_3CN), 30.0 (CH_3CO), 38.6 (CH_2CHO), 59.7 (CHPh), 63.8 ($CHCOCH_3$), 65.0 (CH_3CCO_2iPr), 68.7 [$CH(CH_3)_2$], 126.9, 127.0, 128.3, 128.4, 143.0 (ArC), 176.5 (OC=O), 207.7 (C=O). – MS (EI): m/z (%) = 289 (0.2) [M^+], 202 (100) [M^+ – 87], 160 (22), 158 (21), 106 (28). – HRMS calcd. for [$C_{17}H_{23}NO_3$ – $C_4H_7O_2$]: 202.1231; found 202.1228.

2-Isopropyl 3,4-Dimethyl (2R*,3R*,4R*,5S*)-2-Methyl-5-phenylpyrrolidine-2,3,4-tricarboxylate (endo-2ag, Method A or B, Table 5): Pale yellow oil, 92%. – $C_{19}H_{25}NO_6$ (363.2): calcd. C 62.8, H 6.9, N 3.9; found C 63.1, H 7.1, N 3.9. – TLC: R_f = 0.60 (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu}$ = 1732 cm^{-1} . – 1H NMR (300 MHz): δ = 1.32, 1.34 [2 $\times$ d, J = 6.7 Hz, 6 H, $CH(CH_3)_2$], 1.37 (s, 3 H, $NCCH_3$), 3.17 (s, 3 H, PhCHCHCO $_2CH_3$), 3.71 (s, 3 H, $NCCHCO_2CH_3$), 3.85–3.94 [m, 2 H, (CH_3O_2CH) $_2$], 4.79 (d, J = 7.9 Hz, 1 H, PhCH), 5.17 (sept, J = 6.7 Hz, 1 H, $CH(CH_3)_2$), 7.23–7.31 (m, 5 H, ArH). – ^{13}C NMR (75 MHz): δ = 21.0 ($NCCH_3$), 21.5, 21.6 [$CH(CH_3)_2$], 51.3, 51.9 (2 $\times$ CO_2CH_3), 52.6, 53.8 ($COCH_2$), 62.8 (PhC), 67.1 ($NCCHCO_2CH_3$), 69.3 [$CH(CH_3)_2$], 127.2, 127.7, 128.1, 139.0 (ArC), 171.1, 171.3, 173.2 (3 $\times$ C=O). – MS (EI): m/z (%) = 363 (0.1) [M^+], 276 (37) [M^+ – 87], 244 (47), 216 (100), 184 (47), 158 (22), 157 (17), 131 (33), 43 (48), 42 (85). – HRMS calcd. for [$C_{19}H_{25}NO_6$]: 363.1681; found 363.1673.

Diethyl (2R*,3S*,5R*)-5-Isopropoxyxycarbonyl-5-methyl-2-phenyltetrahydro-1*H*-pyrrol-3-ylphosphonate (exo-2ah, Method C, Table 5): Pale yellow oil, 90%. – TLC: R_f = 0.81 (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu}$ = 1724, 1247 cm^{-1} . – 1H NMR (300 MHz): δ = 1.05 [t, J = 7.3 Hz, 6 H, (CH_3CH_2O) $_2$], 1.24–1.33

[m, 6 H, CH(CH₃)₂], 1.46 (s, 3 H, NCCH₃), 2.07–2.20 (m, 1 H, NCCHH), 2.39–2.50 (m, 1 H, PCH), 2.63–2.68 (m, 1 H, PhCH), 5.03 [sept, *J* = 6.7 Hz, 1 H, CH(CH₃)₂], 7.22–7.42 (m, 5 H, ArCH). – ¹³C NMR (75 MHz): δ = 15.9, 16.0, 16.1, 16.2, 16.3 (CH₃CH₂O)₂, 21.6 [CH(CH₃)₂], 26.2 (NCCH₃), 39.9 (PCHCH₂), 43.4, 45.3 (PCH), 61.4, 61.5, 61.6, 61.7, 61.8 [(CH₃CH₂O)₂], 64.2 (PhCH), 65.3, 65.5 (NCCH₃), 68.9 [CH(CH₃)₂], 127.5, 127.7, 128.3, 135.3 (ArC), 176.1 (C=O). – MS (EI): *m/z* (%) = 296 (14) [M⁺ – 87], 158 (100), 44 (56), 43 (24), 42 (34), 41 (17), 40 (42). – HRMS calcd. for [C₁₉H₃₀NO₅P – C₄H₇O₂]: 296.1415; found 296.1416.

Isopropyl 4-Cyano-2-methyl-2-[(*E*)-1-phenylmethylideneamino]butanoate (3ad, Table 5): Pale yellow oil, 95%. – TLC: *R*_f = 0.71 (*n*-hexane/ethyl acetate, 3:2). – C₁₆H₂₀N₂O₂ (272.1): calcd. C 70.6, H 7.4, N 10.3; found C 70.2, H 7.3, N 10.7. – IR (film): $\tilde{\nu}$ = 2249, 1725, 1644 cm^{–1}. – ¹H NMR (300 MHz): δ = 1.25 [d, *J* = 6.4 Hz, 6 H, CH(CH₃)₂], 1.50 (s, 3 H, NCHCH₃), 2.07–2.13 (m, 1 H, COCCHH), 2.39–2.45 (m, 1 H, COCCHH), 2.53–2.66 (m, 2 H, CNCH₂), 5.07 [sept, *J* = 6.4 Hz, 1 H, CH(CH₃)₂], 7.44 (m, 3 H, ArH), 7.75 (m, 2 H, ArH), 8.30 (s, 1 H, N=CH). – ¹³C NMR (75 MHz): δ = 12.5 (CH₂CCO), 21.6, 21.7 [CH(CH₃)₂], 23.4 (NCHCH₃), 35.9 (CH₂CN), 66.5 (COCH₃), 69.1 [CH(CH₃)₂], 120.3 (CN), 128.3, 128.5, 131.2, 135.9 (ArC), 160.8 (HC=N), 172.8 (C=O). – MS (EI): *m/z* (%) = 185 (100) [M⁺ – 87], 104 (18), 103 (17), 90 (21), 51 (24), 44 (67), 43 (30), 42 (26), 41 (32). – HRMS calcd. for [C₁₆H₂₀N₂O₂ – C₃H₇]: 229.0977; found 229.0980.

4-Ethyl 2-Isopropyl (2*R,4*R**,5*S**)-5-(4-Chlorophenyl)-2-methylpyrrolidine-2,4-dicarboxylate (endo-2ba, Method B, Table 4):** Colourless needles, 92%, m.p. 93 °C (*n*-hexane/ethyl acetate). – C₁₉H₂₄ClNO₄ (353.6): calcd. C 61.1, H 6.8, N 4.0; found C 61.4, H 6.9, N 4.2. – TLC: *R*_f = 0.77 (*n*-hexane/ethyl acetate, 3:2). – IR (KBr): $\tilde{\nu}$ = 1732 cm^{–1}. – ¹H NMR (300 MHz): δ = 0.86 (t, *J* = 7 Hz, 3 H, COCH₂CH₃), 1.28, 1.29 [2 × d, *J* = 6.3 Hz, 6 H, CH(CH₃)₂], 1.46 (s, 3 H, NCCH₃), 2.02 (dd, *J* = 13.4, 9.5 Hz, 1 H, NCCHH), 2.64 (dd, *J* = 13.4, 5.7 Hz, 1 H, NCCHH), 3.29–3.36 (m, 1 H, CHCO), 3.70 (m, 2 H, CH₂O), 4.60 (d, *J* = 7.5 Hz, 1 H, PhCH), 5.11 [sept, *J* = 6.3 Hz, 1 H, CH(CH₃)₂], 7.24 (s, 4 H, ArH). – ¹³C NMR (75 MHz): δ = 13.6 (CH₃CH₂O), 21.6, 21.7 [(CH₃)₂CH], 27.3 (CH₃CN), 40.1 (CH₂CHCO₂Et), 50.2 (CHCO₂Et), 60.2 (CH₂O), 64.0 (PhC), 65.5 (CH₃CCO₂iPr), 68.7 [CH(CH₃)₂], 128.1, 128.2, 133.1, 137.9 (ArC), 172.2 (CO₂Et), 175.3 (CO₂iPr). – MS (EI): *m/z* (%) = 310 (0.4) [M⁺ – 43], 266 (100) [M⁺ – 87], 165 (16), 57 (15), 43 (45), 42 (71), 41 (26). – HRMS calcd. for [C₁₈H₂₄ClNO₄ – C₄H₇O₂]: 266.0947; found 266.0945.

4-Ethyl 2-Isopropyl (2*R,4*R**,5*S**)-5-(2-Hydroxyphenyl)-2-methylpyrrolidine-2,4-dicarboxylate (endo-2ca, Method A, Table 4):** Pale yellow oil, 85%. – C₁₈H₂₅N₂O₅ (335.2): calcd. C 64.5, H 7.5, N 4.2; found C 64.1, H 7.3, N 4.4. – TLC: *R*_f = 0.71 (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu}$ = 1736 cm^{–1}. – ¹H NMR (300 MHz): δ = 0.88 (t, *J* = 7.2 Hz, 3 H, CH₃CH₂O), 1.29, 1.31 [2 × d, *J* = 6.3 Hz, 6 H, CH(CH₃)₂], 1.52 (s, 3 H, NCCH₃), 2.02, (dd, *J* = 13.4, 7.7 Hz, 1 H, NCCHH), 2.88 (dd, *J* = 13.4, 4.0 Hz, 1 H, NCCHH), 3.75 (m, 1 H, CHCO₂Et), 4.80 (d, *J* = 7.9 Hz, 1 H, PhCH), 5.10 [sept, *J* = 6.3 Hz, 1 H, CH(CH₃)₂], 6.70–7.14 (m, 4 H, ArH). – ¹³C NMR (75 MHz): δ = 13.4 (CH₃CH₂O), 21.4, 21.6 [(CH₃)₂CH], 26.4 (CH₃CN), 39.0 (CH₂CHCO₂Et), 48.9 (CHCO₂Et), 60.7 (CH₂O), 64.1 (PhC), 65.2 (CH₃CCO₂iPr), 68.8 [CH(CH₃)₂], 117.1, 118.4, 118.7, 121.1, 122.6, 128.5, 128.8, 136.5, 158.0 (ArC), 172.4, 174.5, (2 × C=O). – MS (EI): *m/z* (%) = 202 (100) [M⁺ – 133], 77 (17), 51 (16), 44 (30), 43 (39), 42 (66), 41 (46), 40 (25). – HRMS calcd. for [C₁₈H₂₅NO₅ – C₆H₁₃O₃]: 202.0868; found 202.0859.

4-Ethyl 2-Isopropyl (2*R,4*R**,5*R**)-5-Cyclohexyl-2-methylpyrrolidine-2,4-dicarboxylate (endo-2da, Method B, Table 4):** Colourless oil,

60%. – TLC: *R*_f = 0.62 (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu}$ = 1729 cm^{–1}. – ¹H NMR (300 MHz): δ = 1.18–1.23 [m, 15 H, (CH₂)₃CH₂CH, CH₃CH₂O, CH(CH₃)₂], 1.36 (s, 3 H, NCCH₃), 1.52–1.72 [m, 4 H, (CH₂)₂CH], 1.79–1.86 (m, 1 H, NCCHH), 2.02 (m, 1 H, CH₂CH), 2.50 (d, *J* = 13.4 Hz, 1 H, NCCHH), 2.90 (m, 2 H, CyCH, CHCO₂Et), 3.96–4.19 (m, 2 H, CH₃CH₂O), 5.07 [sept, *J* = 6.4 Hz, 1 H, CH(CH₃)₂]. – ¹³C NMR (75 MHz): δ = 14.2 (CH₃CH₂O), 21.6 [CH(CH₃)₂], 25.8, 25.9, 26.3 [(CH₂)₃CH₂], 28.4 (NCCH₃), 30.9, 31.6 [(CH₂)₂CH], 39.7 (CyCH), 42.2 (NCCH₂), 47.4 (CHCO₂Et), 60.0 (CH₃CH₂O), 65.5 (NCCH₃), 68.2, 68.3 [CH(CH₃)₂], 174.1, 175.7 (2 × C=O). – MS (EI): *m/z* (%) = 238 (100) [M⁺ – 87], 82 (69), 67 (17), 55 (33), 44 (15), 43 (35), 42 (31), 41 (47). – HRMS calcd. for [C₁₈H₃₁NO₄ – C₄H₇O₂]: 238.1807; found 238.1801.

5-Ethyl 1-Isopropyl 2-[(*E*)-2,2-Dimethylpropylideneamino]-2-methylpentanedioate (3ea, Method A or B, Table 4): Colourless oil, 67%. – TLC: *R*_f = 0.19 (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu}$ = 1736, 1665 cm^{–1}. – ¹H NMR (300 MHz): δ = 0.96, 1.01 [s, 9 H, C(CH₃)₃], 1.13–1.20 [m, 9 H, CH(CH₃)₂, OCH₂CH₃], 1.24, 1.25 (s, 3 H, NCCH₃), 1.91–1.99 (m, 1 H, NCCHH), 2.06–2.16 (m, 1 H, NCCHH), 2.22–2.35 (m, 2 H, NCCH₂CH₂), 4.04 (q, *J* = 7.2 Hz, 2 H, OCH₂CH₃), 5.01 [sept, *J* = 6.3 Hz, 1 H, CH(CH₃)₂], 7.49 (s, 1 H, CH=N). – ¹³C NMR (75 MHz): δ = 14.1 (CH₃CH₂O), 21.6, 21.7 [CH(CH₃)₂], 23.2, 23.3 (NCCH₃), 26.0, 26.5 [C(CH₃)₃], 29.3, 29.4 (NCCH₂CH₂), 35.2, 36.5 (NCCH₂), 37.6 [C(CH₃)₃], 60.2, 60.3 (OCH₂CH₃), 66.3 (NCCH₃), 68.0, 68.5 [CH(CH₃)₂], 170.3 (C=N), 173.2, 173.3, 173.6, 173.9 (2 × C=O). – MS (EI): *m/z* (%) = 256 (4) [M⁺ – 43], 212 (81) [M⁺ – 87], 98 (21), 96 (22), 82 (41), 69 (16), 57 (19), 55 (49), 44 (37), 43 (71), 42 (48), 41 (100), 40 (37). – HRMS calcd. for [C₁₆H₂₉NO₄ – C₄H₇O₂]: 212.1650; found 212.1660.

Isopropyl (2*R,4*S**,5*R**)-4-Formyl-2-methyl-5-phenylpyrrolidine-2-carboxylate (4af, Method B, Table 5):** Colourless oil, 81%. – C₁₆H₂₁NO₃ (275.1): calcd. C 69.8, H 7.7, N 5.1; found C 70.0, H 7.5, N 5.3. – TLC: *R*_f = 0.58 (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu}$ = 1732 cm^{–1}. – ¹H NMR (300 MHz): δ = 1.26, 1.27 [2 × d, *J* = 6.3 Hz, 6 H, CH(CH₃)₂], 1.52 (s, 3 H, NCCH₃), 2.21 (dd, *J* = 13.6, 5.5 Hz, 1 H, NCCHH), 2.50 (dd, *J* = 13.6, 8.6 Hz, 1 H, NCCHH), 2.98–3.06 (m, 1 H, HCOCH), 4.62 (d, *J* = 7.9 Hz, 1 H, PhCH), 5.00 [sept, *J* = 6.3 Hz, 1 H, CH(CH₃)₂], 7.30 (m, 5 H, ArH), 9.19 (d, *J* = 2.8 Hz, 1 H, CHO). – ¹³C NMR (75 MHz): δ = 21.6, 21.7 [CH(CH₃)₂], 26.1, (NCCH₃), 34.9 (CH₂CHCHO), 62.8 (PhCH), 64.6 (NCCH₃), 68.7 [CH(CH₃)₂], 126.8, 126.9, 128.5, 138.8 (ArC), 176.7 (CO₂iPr), 202.4 (CHO). – MS (EI): *m/z* (%) = 232 (2) [M⁺ – 43], 188 (100) [M⁺ – 87], 158 (15), 106 (41), 91 (17), 44 (24), 43 (38), 42 (60), 41 (36). – HRMS calcd. for [C₁₆H₂₁NO₃ – C₄H₇O₂]: 188.1075; found 188.1078.

4-Ethyl 2-Isopropyl (2*R,4*R**,5*S**)-5-phenylpyrrolidine-2,4-dicarboxylate (endo-6aa, Method A or B, Table 6):** Colourless oil, 92%. – TLC: *R*_f = 0.67 (*n*-hexane/ethyl acetate, 3:2). – IR (film): $\tilde{\nu}$ = 1732 cm^{–1}. – ¹H NMR (300 MHz): δ = 0.82 (t, *J* = 7.2 Hz, 3 H, CH₃CH₂O), 1.30 [d, *J* = 6.3 Hz, 6 H, CH(CH₃)₂], 2.30 (m, 2 H, NCHCH₂), 2.77 (s, 1 H, NH), 3.30 (m, 1 H, CHCO₂Et), 3.57–3.77 (m, 2 H, CH₃CH₂O), 3.92 (dd, *J* = 8.3 Hz, 1 H, CHCO₂iPr), 4.52 (d, *J* = 7.9 Hz, 1 H, PhCH), 5.15 [sept, *J* = 6.3 Hz, 1 H, CH(CH₃)₂], 7.31 (m, 5 H, ArH). – ¹³C NMR (75 MHz): δ = 13.6 (CH₃CH₂O), 21.7, 21.8 [CH(CH₃)₂], 33.6 (NCCH₃), 49.7 (CHCO₂Et), 60.1 (CH₃CH₂O), 65.8 (PhCH), 68.6 [CH(CH₃)₂], 126.8, 127.4, 128.1, 139.1 (ArC), 172.5, 172.7 (2 × C=O). – MS (EI): *m/z* (%) = 305 (0.6) [M⁺], 218 (100) [M⁺ – 87], 172 (17), 145 (16), 144 (49), 117 (36), 43 (42), 41 (28). – HRMS calcd. for [C₁₇H₂₃NO₄]: 305.1627; found 305.1620.

Isopropyl (1R*,3S*,3aR*,6aS*)-4,6-Dioxo-3,5-diphenylperhydropyrrolo[3,4-c]pyrrole-1-carboxylate (endo-6ac, Method A or B, Table 6): Colourless solid, 92%, m.p. 214 °C (*n*-hexane/ethyl acetate). — $C_{22}H_{22}N_2O_4$ (378.3): calcd. C 69.8, H 5.9, N 7.4; found C, 69.5, H 5.8, N 7.5. — TLC: R_f = 0.33 (*n*-hexane/ethyl acetate, 3:2). — IR (KBr): $\tilde{\nu}$ = 1716 cm^{-1} . — 1H NMR (300 MHz): δ = 1.31, 1.37 [2 $\times$ d, J = 6.3 Hz, 6 H, $CH(CH_3)_2$], 2.50 (s, 1 H, NH), 3.52 (dd, J = 8.9, 7.6 Hz, 1 H, PhCHCH), 3.67 (dd, J = 7.6, 6.9 Hz, 1 H, $CHCHCO_2iPr$), 4.04 (d, J = 6.9 Hz, 1 H $CHCO_2iPr$), 4.55 (d, J = 8.9 Hz, 1 H, PhCH), 5.20 [sept, J = 6.3 Hz, 1 H, $CH(CH_3)_2$], 7.12–7.44 (m, 10 H, ArH). — ^{13}C NMR (75 MHz): δ = 21.6, 21.9 [$CH(CH_3)_2$], 48.2 (PhCHCH), 49.5 (NCHCH), 62.2 (NCHCO), 64.1 (PhC), 69.2 [$CH(CH_3)_2$], 125.9, 126.1, 127.0, 128.3, 128.9, 129.0, 131.6, 136.6 (ArC), 168.9, 173.6, 174.7 (3 $\times$ C=O). — MS (EI): m/z (%) = 291 (23) [M^+ – 87], 205 (21), 144 (52), 117 (20), 90 (15), 44 (100), 43 (47), 42 (17), 41 (30), 40 (99).

Isopropyl (2R*,4R*,5S*)-4-Cyano-5-phenylpyrrolidine-2-carboxylate (endo-6ad, Method B, Table 6): Colourless oil, 97%. — $C_{15}H_{18}N_2O_2$ (258.1): calcd. C 69.7, H 7.0, N 10.8; found C 70.0, H 7.2, N 10.9. — TLC: R_f = 0.69 (*n*-hexane/ethyl acetate, 3:2). — IR (film): $\tilde{\nu}$ = 1735, 2243 cm^{-1} . — 1H NMR (300 MHz): δ = 1.30 [d, J = 6.3 Hz, 6 H, $CH(CH_3)_2$], 2.42–2.63 (m, 2 H, $NCCHCH_2$), 2.73 (s, 1 H, NH), 3.25 (m, 1 H, NCCH), 3.10 (dd, J = 8.8, 6.3 Hz, 1 H, $CHCO_2iPr$), 4.40 (d, J = 6.4 Hz, 1 H, PhCH), 5.14 [sept, J = 6.25 Hz, 1 H, $CH(CH_3)_2$], 7.15–7.49 (m, 5 H, ArH). — ^{13}C NMR (75 MHz): δ = 21.6, 21.7 [$CH(CH_3)_2$], 34.4 ($CNCHCH_2$), 35.9 (CNC), 58.5 (CCO_2iPr), 64.8 (PhC), 62.2 [$CH(CH_3)_2$], 119.1 (CN), 126.9, 128.4, 128.5, 137.6 (ArC), 172.0 (C=O). — MS (EI): m/z (%) = 258 (2) [M^+], 171 (100) [M^+ – 87], 154 (27), 117 (27), 43 (30), 41 (21). — HRMS calcd. for [$C_{15}H_{18}N_2O_2$]: 258.1368; found 258.1365.

Isopropyl (2R*,4S*,5R*)-4-Acetyl-5-phenylpyrrolidine-2-carboxylate (8ae, Method A, Table 6): Pale yellow oil, 58%. — $C_{16}H_{21}NO_3$ (275.1): calcd. C 69.8, H 7.7, N 5.1; found C 70.1, H 7.7, N 4.7. — TLC: R_f = 0.75 (*n*-hexane/ethyl acetate, 3:2). — IR (film): $\tilde{\nu}$ = 1716 cm^{-1} . — 1H NMR (300 MHz): δ = 1.29 [d, J = 6.3 Hz, 6 H, $CH(CH_3)_2$], 1.97 (s, 3 H, CH_3CO), 2.28 (m, 1 H, $NCCHH$), 2.48 (m, 1 H, $NCCHH$), 3.12 (m, 1 H, CH_3COCH), 3.94 (dd, J = 9.0, 5.1 Hz, 1 H, NCHCO), 4.27 (d, J = 8.6 Hz, 1 H, PhCH), 5.10 [sept, J = 6.3 Hz, 1 H, $CH(CH_3)_2$], 7.26–7.44 (m, 5 H, ArH). — ^{13}C NMR (75 MHz): δ = 21.7, 21.8 [$CH(CH_3)_2$], 30.6 (CH_3CO), 33.9 (CH_2CHCO_2iPr), 59.2 ($CHCO_2iPr$), 59.4 (CH_3COC), 66.6 (Ph), 68.7 [$CH(CH_3)_2$], 126.8, 127.9, 128.7, 141.4 (ArC), 173.9 (CO_2iPr), 207.1 (C=O). — MS (EI): m/z (%) = 232 (4) [M^+ – 43], 188 (16) [M^+ – 87], 146 (15), 44 (17), 43 (100), 41 (15), 40 (30). — HRMS calcd. for [$C_{16}H_{21}NO_3$ – C_3H_7]: 232.0973; found 232.0970.

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