Chiral 3,6-Dihydro-2*H*-1,4-oxazin-2-ones as Alanine Equivalents for the Asymmetric Synthesis of α-Methyl α-Amino Acids (AMAAs) under Mild Reaction Conditions

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Abstract: 3,6-Dihydro-2*H*-1,4-oxazin-2-ones **1** act as very reactive chiral cyclic alanine equivalents and can be diastereoselectively alkylated or allylated using mild reaction conditions: potassium carbonate under phase-transfer catalysis (PTC) conditions when using activated alkyl halides, organic bases such as *tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) when using unactivated alkyl halides, and neutral Pd(0)-catalysis when allylic carbonates are used. In most cases, the diastereoselectivity under all these different reaction conditions is excellent although the reactions are always carried out at room temperature. Hydrolysis of the obtained alkylated or allylated oxazinones allows the preparation of enantiomerically enriched (*S*)-α-methyl α-amino acids (*S*)-AMAAs. The PTC and organic base methodologies have also been applied to the synthesis of (*R*)-α-methyl α-amino acids starting from (*R*)-alanine. When dihalides are used as electrophiles under PTC or BEMP conditions, a spontaneous *N*-alkylation also takes place giving bicyclic oxazinones, which can be hydrolyzed to enantiomerically pure cyclic (*S*)-AMAAs.

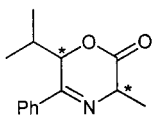
Key words: amino acids, asymmetric synthesis, oxazinones, phase-transfer catalysis, palladium catalysis

Introduction

The development of versatile and new methodologies for the synthesis of natural and non-natural α-amino acids in optically pure form is an important and challenging synthetic endeavour for organic chemists nowadays due to their central role in chemistry and biology.[1] Among them, α-alkyl- and especially α-methyl α-amino acids (AMAAs) are valuable tools for restricting the conformational mobility of a peptide backbone and promote particular structures in the *de novo* design of peptides and proteins.[2] Moreover, they can make peptides resistant to degradation,[3] an example being the α-methylphenylalanine analogue of aspartame which was found to possess the same sweetness and superior stability.[3c] Also, they are present in natural antibiotics,[4] and can act as enzyme inhibitors,[5] possessing important therapeutic activity such as (*S*)-α-methyl-DOPA (Aldomet) which is a very well-known commercial antihypertensive.[5b] In spite of this array of interesting features, there is a lack of commercially available enantiomerically pure α-methyl α-amino acids, which is in part probably due to the nonexistence of a general and economical large-scale synthesis for these compounds.

The most direct synthetic approach to scalemic AMAAs is the diastereoselective α-alkylation of an enolate obtained from an alanine equivalent. This has been achieved by phase-transfer catalytic (PTC) alkylation of alanine-aromatic aldehydes Schiff bases, using cinchoninium and cinchonidinium salts as chiral catalysts (up to 50% ee)[6a,b] or TADDOL (up to 82% ee),[6c] which is a very attractive and promising method[7] because of the experimental simplicity and the potential for scaleup. Also, several chiral cyclic alanine-derived systems such as bis-lactim ethers,[8a] imidazolidinones,[8b] oxazolidinones,[8c] oxazinones[8d] and nickel complexes,[8e] together with acyclic chiral systems[9] have been developed, some of them with impressive diastereofacial enolate bias. However, when using these templates the key alkylation step requires in most cases the use of strong bases (BuLi, LDA, LHMDS, *t*-BuOK, etc.), very anhydrous conditions, and low reaction temperatures in order to achieve a high degree of asymmetric induction. Such strict reaction conditions, together with a troublesome hydrolysis of α,α-dialkylated α-amino acid derivatives,[8b] made the development of an economical industrial process for the preparation of these amino acids difficult. The development of new chiral alanine equivalents able to asymmetrically induce the quaternary stereogenic carbon using simpler and milder reaction conditions then seems desirable.

In this context, we envisaged the usefulness of compounds of the type 3,6-dihydro-2*H*-1,4-oxazin-2-ones,[10] for instance as chiral alanine templates **1**[10a,b] by considering its structural features: a presumably highly acidic Cα-hydrogen and then easy enolate formation due to the strong stabilizing effect of the conjugated phenylimine moiety, and a cyclic structure with a bulky substituent able to block one of the diastereomeric faces of the formed enolate. In addition, we have recently prepared the chiral glycine equivalent **2**[10c] which condenses readily with aldehydes under mild PTC reaction conditions, proving the high reactivity of these type of heterocycles.[11]



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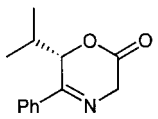

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Results and Discussion

The desired oxazinone **1** was obtained according to a modification of the procedure described by Sunjic et al.,[12] which is outlined in Scheme 1. The starting material α-bromoisovalerophenone (**3**) was prepared by $AlCl_3$-catalyzed bromination of the corresponding ketone following a standard method.[13] Subsequent reaction of the potassium salt of the *N*-Boc-protected (*S*)-alanine (**4**) with α-bromo ketone **3**, afforded a ca. 1/1 mixture of diastereomeric esters **5** which were separated by flash chromatography and crystallization into pure isomers (*R*,*S*)-**5** and (*S*,*S*)-**5** in 31% yield each. Isomer (*R*,*S*)-**5** was then Boc-deprotected in acid conditions and cyclized after treatment with triethylamine to afford 3,6-dihydro-2*H*-1,4-oxazin-2-one (6*R*)-**1** in 70% yield after column chromatography through Florisil. This purification was later overcome by considering that the crude oxazinone was suitable for further use after a simple filtration through a plug of Florisil (>90% pure by GLC). Analysis of the final reaction crude by ^{1}H NMR (300 MHz) revealed the presence of a mixture of *cis/trans* diastereomers in a ca. 1/20 ratio. It seemed that C3 had a certain tendency to epimerization, but as this carbon will become part of the enolate after deprotonation, this configurational instability is irrelevant. An analytical sample of the major isomer (3*S*,6*R*)-**1** was obtained after chromatography/recrystallization and its configuration fully confirmed by NOE experiments and X-ray diffraction analysis.[14] In this way we had a system with an isopropyl group at the C6 stereogenic (*R*)-carbon which presumably would create the appropriate diastereofacial bias for the attack of an electrophile after the base-induced proton abstraction on C3. Semiempirical calculations were carried out on a model lithium enolate of (6*R*)-**1**[15] with an optimized geometry showing the shielding effect of the isopropyl group lying at C6 on the planar enolate (Figure).

Obviously, if the cyclization reaction could be carried out from the ester (*S*,*S*)-**5**, the final oxazinone would have a stereogenic (*S*)-carbon at C6 and then we could get the opposite sense of induction at C3. In other words, it would be possible to obtain both new configurations on C3 after proton abstraction and alkylation with the corresponding

Biographical Sketches

Rafael Chinchilla was born in Alicante in 1959. He studied chemistry at the University of Alicante where he also obtained his Ph.D. in 1990. After doing postdoctoral research with Professor J.-E. Bäckvall at the University of Uppsala, Sweden, he joined the group of Professor C. Nájera at the University of Alicante where he was appointed Associate Professor in 1997. His current research interest include sulfone chemistry, asymmetric synthesis, amino acids and peptide coupling reagents.

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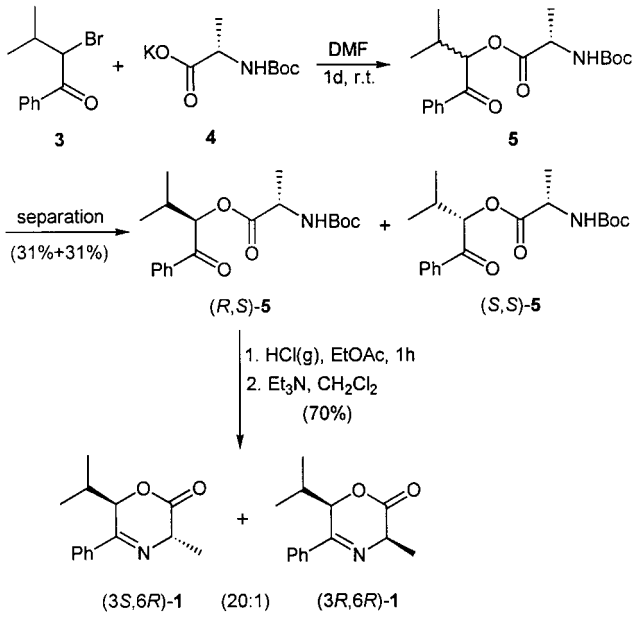
Carmen Nájera was born in Nájera (La Rioja), Spain, in 1951 and graduated in chemistry from the University of Zaragoza in 1973. She obtained her Ph.D. from the University of Oviedo in 1979 and spent postdoctoral stays with Prof. D. Seebach at the ETH (Zürich), Prof. J. E. Baldwin at the Dyson Perrins Laboratory (Oxford), Prof. E. J. Corey at Harvard University and Prof. J.-E. Bäckvall at Uppsala University. She became Associate Professor in 1985 at the University of Oviedo and full Professor in 1993 at the University of Alicante. Her current research interests are focused on organometallic chemistry, sulfones, amino acids, asymmetric synthesis and peptide coupling reagents.



Scheme 1

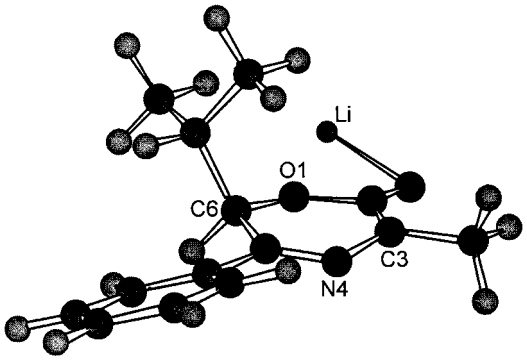
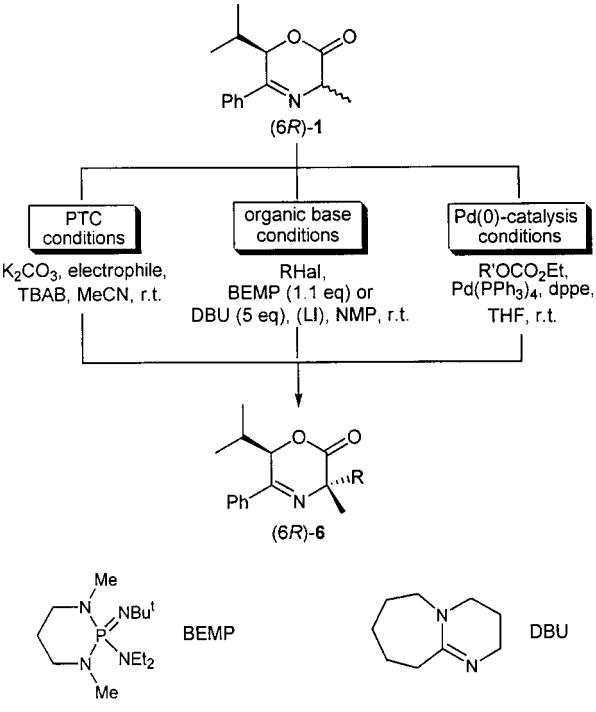


Figure. AM1-optimized geometry of a lithium enolate of (6R)-1

electrophile. Thus, it was possible to obtain supposed (6*S*)-**1** in a 1/2.5 *cis/trans* ratio following the same procedure as with (6*R*)-**1** but, surprisingly, isolation of a pure analytical sample of the apparent enantiomer of (3*S*,6*R*)-**1**, which showed identical ^{1}H and ^{13}C NMR spectra, revealed a totally different and much lower optical rotation absolute value for this compound. Moreover, this value proved to be erratic when the cyclization was repeated, showing the strong tendency towards racemization of this isomer (3*S*,6*S*)-**1** which blocked the possibility of its further synthetic use.

The ease of enolate formation on oxazinones **1** was demonstrated when the ca. 1/20 *cis/trans* diastereomeric mixture of (6*R*)-**1** was diastereoselectively alkylated with activated halides such as allyl, propargyl and benzyl halides as well as ethyl iodoacetate, under solid-liquid PTC reaction conditions using potassium carbonate as base and tetrabutylammonium bromide (TBAB) as phase-transfer catalyst (Scheme 2, Table 1, entries 1–6). The cyclic structure of the alanine-ketone Schiff base derivative (6*R*)-**1** allowed this PTC-induced alkylation, which previously only has been achieved in the case of alanine-aldehyde Schiff base derivatives.[6] Oxazinones (6*R*)-**6**, such as a precursor of (*S*)-α-methyl-DOPA (Table 1, entry 6), were thus obtained generally with excellent diastereoselectivities even working at room temperature, proving the effectiveness of the predicted blocking effect of the isopropyl group towards one face of the planar enolate. Under these reaction conditions also an aldol reaction with paraformaldehyde and a conjugate addition with methyl acrylate took place, affording the corresponding oxazinones (6*R*)-**6g** and (6*R*)-**6h**, respectively (Table 1, entries 7 and 8). Yields of isolated oxazinones **6** were in most cases moderate due to partial decomposition observed during the chromatographic purification. The proposed configuration was confirmed by NOE experiments and, in the case of (6*R*)-**6b**, also by X-ray diffraction analysis.[14] In order to check if the use of strong bases and low reaction temperatures could improve yields or diastereoselectivities, oxazinone (6*R*)-**1** was deprotonated with LDA at -78°C and alkylated with allyl iodide or benzyl bromide as electrophiles, but compound (6*R*)-**6a** and **6b** were obtained with the same yield and de as when PTC conditions were used.

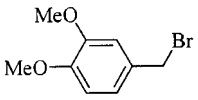
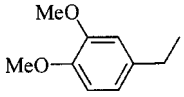
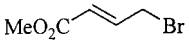
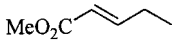


Scheme 2

Although the highly diastereoselective alkylation of oxazinone (6*R*)-**1** under such simple and mild reaction conditions seemed promising due to the particularly attractive use of PTC, when these methodologies were used with unactivated electrophiles, such as ethyl or butyl iodide, the reaction failed and only partial decomposition of the start-

ing material was observed. Strong bases (LDA, LHMDS, *t*-BuOK and NaH) at low temperatures even in the presence of co-solvents (HMPA, DMPU) were also attempted, but no alkylation was observed. We then pay attention to strong organic bases, particularly to Schwesinger's[16] 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP), which has been recently used in the alkylation of the resin-bound benzophenone

Table 1 Diastereoselective Alkylation of (6*R*)–**1** under PTC Conditions

Entry	Electrophile	R	*t* (h)[a]	Product **6**, % yield[b]	% de[c]
1	CH_2=$CHCH_2I$	CH_2=$CHCH_2$	24	(6*R*)–**6a**, 62	92
2	HC≡CCH_2Br	HC≡CCH_2	12	(6*R*)–**6b**, 70	>96
3	$PhCH_2Br$	$PhCH_2$	8	(6*R*)–**6c**, 75	>96
4			12	(6*R*)–**6d**, 75	90
5			12	(6*R*)–**6e**, 68	84
6	EtO_2CCH_2I	EtO_2CCH_2	24	(6*R*)–**6f**, 60	90
7	$(CH_2O)_n$	$HOCH_2$	12	(6*R*)–**6g**, 63	60
8	CH_2=$CHCO_2Me$	$MeO_2CCH_2CH_2$	12	(6*R*)–**6h**, 60	90

[a] Monitored by GLC.
[b] Isolated yield for the pure major diastereomer after flash chromatography.
[c] Determined by ^{1}H NMR (300 MHz) and/or GLC for the reaction crude.

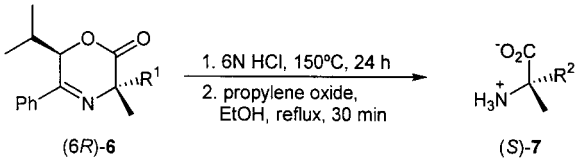
Table 2 Diastereoselective Alkylation of Oxazinones (6*R*)-**1** under Organic Base Conditions

Entry	RHal	Base, LiI (eq)	Solvent	*t* (h)[a]	*C*/*O*-Alkylation ratio[b]	Product (6*R*)–**6**,[c] % yield[d]
1	EtI	BEMP, LiI (1.2)	NMP	1	25/1	(6*R*)–**6i**, 55
2	i-PrI	BEMP, LiI (1.2)	NMP	1	24/1	(6*R*)–**6j**, 48
3	BuI	BEMP	THF	12	5/3	(6*R*)–**6k**, 38
4	BuI	BEMP	DMF	1	9/1	(6*R*)–**6k**, 56
5	BuI	BEMP	MeCN	1	10/1	(6*R*)–**6k**, 58
6	BuI	BEMP	NMP	1	17/1	(6*R*)–**6k**, 64
7	BuI	BEMP, LiI (1.1)	NMP	1	50/1	(6*R*)–**6k**, 65
8	BuBr	BEMP, LiI (2)	NMP	1	1/0	(6*R*)–**6k**, 38
9	i-BuI	BEMP, LiI (1.5)	NMP	1	1/0	(6*R*)–**6l**, 45
10	$Ph(CH_2)_2I$	BEMP, LiI (1.5)	NMP	1	1/0	(6*R*)–**6m**, 52
11	$ClCH_2I$	BEMP	NMP	1	1/0	(6*R*)–**6n**, 57[e]
12	CH_2=$CHCH_2Cl$	BEMP	NMP	1	1/0	(6*R*)–**6a**, 38
13	$PhCH_2Cl$	BEMP	NMP	1	5/1	(6*R*)–**6c**, 44
14	EtI	DBU	NMP	1	50/1	(6*R*)–**6i**, 53
15	i-PrI	DBU	NMP	1.75	5/1	(6*R*)–**6j**, 46
16	i-PrI	DBU, LiI (1.2)	NMP	1.25	100/1	(6*R*)–**6j**, 33
17	BuI	DBU	NMP	1	25/1	(6*R*)–**6k**, 53
18	i-BuI	DBU	NMP	2.5	10/1	(6*R*)–**6l**, 28
19	$ClCH_2I$	DBU	NMP	1.25	1/0	(6*R*)–**6n**, 52[e]
20	CH_2=$CHCH_2Cl$	DBU	NMP	1	1/0	(6*R*)–**6a**, 37
21	$PhCH_2Cl$	DBU	NMP	1	5/1	(6*R*)–**6c**, 43
22	$PhCH_2Cl$	DBU, LiI (1.2)	NMP	1	1/0	(6*R*)–**6c**, 45

[a] Monitored by GLC.
[b] Determined by ^{1}H NMR (300 MHz) and/or GLC.
[c] Diastereomeric ratio >98:2: ^{1}H NMR (300 MHz) and/or GLC of the reaction crude.
[d] Isolated yield of the major diastereomer (6*R*)–**6** after flash chromatography.
[e] Neutral silica gel was used.

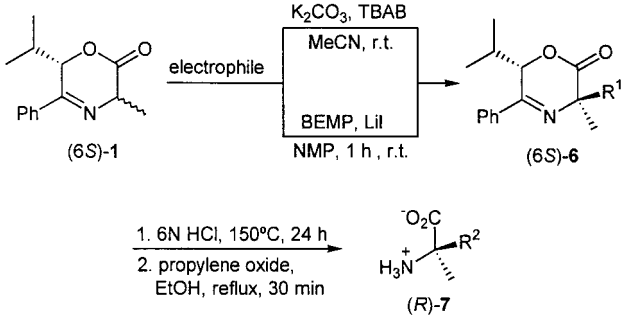
imine of glycine with unactivated alkyl halides,[17] and also to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Thus, the reaction of (6*R*)-**1** with a series of unactivated alkyl iodides in the presence of BEMP or DBU and also at room temperature afforded the alkylated oxazinones (6*R*)-**7** with diastereoselectivities higher than 96% (^{1}H NMR, 300 MHz) in moderate yields and in shorter reaction times than when using PTC conditions (Scheme 2 and Table 2). In all cases, the presence of a certain amount of the corresponding *O*-alkylation product in the reaction crude was detected. When the reaction was carried out with butyl iodide as electrophile and different solvents (Table 2, entries 3–6), 1-methyl-2-pyrrolidinone (NMP) was more appropriate due to improvement in the *C/O*-alkylation ratio and isolated yield of the desired oxazinone (Table 2, entry 6). A significant increment of the *C/O*-alkylation ratio was observed if a certain amount of LiI was added to the reaction mixture when using this alkyl iodide (from 17/1 to 50/1, Table 2, entries 6 and 7). A strong hard-hard coordination between the lithium cation and the enolate oxygen could explain the improving of the *C/O*-alkylation ratio.[18] Thus, other alkyl iodides were used as alkylating agents always in the presence of LiI (Table 2, entries 1, 2, 9 and 10). Moreover, the presence of 2 equiv of LiI even allowed the use of an alkyl bromide as alkylating agent (Table 2, entry 8). In general, higher yields of (6*R*)-**6** were obtained when using 1.1 equiv of BEMP as base than when using DBU. In this last case, an excess of base (5 equiv) was always necessary and the addition of LiI also showed improvements in the *C/O*-alkylation ratio (compare entries 15 and 16, and entries 21 and 22). With some electrophiles, and using both bases, only the *C*-alkylation product was detected even in the absence of LiI (entries 11, 12, 19 and 20). These reaction conditions with organic bases also allowed employing allyl and benzyl chlorides as alkylating agents (Table 2, entries 12, 13, 20, 21 and 22), or even chloroiodomethane (Table 2, entries 11 and 19), whereas the reaction with all these electrophiles under PTC conditions failed. Polymer-bound BEMP was also attempted as base, but the reaction needed much longer reaction times and was rather sluggish.

Representative oxazinones (6*R*)-**6** were submitted to acidic hydrolysis (Scheme 3 and Table 3). Thus, they were treated with 6M hydrochloric acid at 150 ºC in a pressure tube, and the resulting hydrochlorides were refluxed with propylene oxide in ethanol allowing the isolation of the biochemically interesting free (*S*)-AMAAs (*S*)-α-methylphenylalanine (**7c**),[3c] (*S*)-α-methylaspartic acid (**7f**),[2c,d] (*S*)-α-methylserine (**7g**),[2e] (*S*)-α-methylglutamic acid (**7h**)[2d] and (*S*)-α-methylleucine (**7l**)[2g] in general with high ee, also confirming the proposed stereochemistry for the alkylated starting oxazinones (6*R*)-**6**. Attempts at recovering the chiral auxiliary, in the form of hydroxy ketone, after the hydrolysis was unfruitful due to decomposition/racemization.



Scheme 3

It was then logical that both of these methodologies (PTC and organic base conditions) could be applied to the synthesis of the corresponding enantiomeric (*R*)-AMAAs. The only change should be then the use of the potassium salt of the Boc-protected (*R*)-alanine as starting material in the procedure illustrated in Scheme 1. Oxazinones (6*S*)-**1** were thus obtained following this synthetic route again as a ca. 1/20 *cis/trans* diastereomeric mixture, and also diastereoselectively alkylated under PTC reaction conditions to afford alkylated oxazinones (6*S*)-**6** which were hydrolyzed as above to the corresponding enantiomeric free (*R*)-AMAAs (Scheme 4 and Table 4, entries 1–3). In addition, (*R*)-α-ethylalanine (*R*)-**7i** (D-isovaline: D-Iva)[19] was prepared following the organic base methodology (BEMP) (Scheme 4 and Table 4, entry 4).



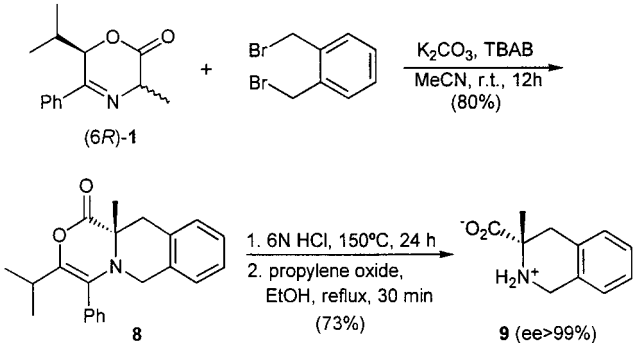
Scheme 4

Table 3 Hydrolysis of Oxazinones (6*R*)–**7**. Synthesis of (*S*)-α-Methyl α-Amino Acids **7**

Entry	R^1	Substrate (6*R*)–**6**	R^2	Product **7**, % yield[a]	% ee[b]
1	$PhCH_2$	(6*R*)–**6c**	$PhCH_2$	(*S*)–**7c**, 80	98
2	EtO_2CCH_2	(6*R*)–**6f**	HO_2CCH_2	(*S*)–**7f**, 78	92
3	$HOCH_2$	(6*R*)–**6g**	$HOCH_2$	(*S*)–**7g**, 75	58
4	$MeO_2C(CH_2)_2$	(6*R*)–**6h**	$HO_2C(CH_2)_2$	(*S*)–**7h**, 70	90
5	i-Bu	(6*R*)–**6l**	i-Bu	(*S*)–**7l**, 72	99

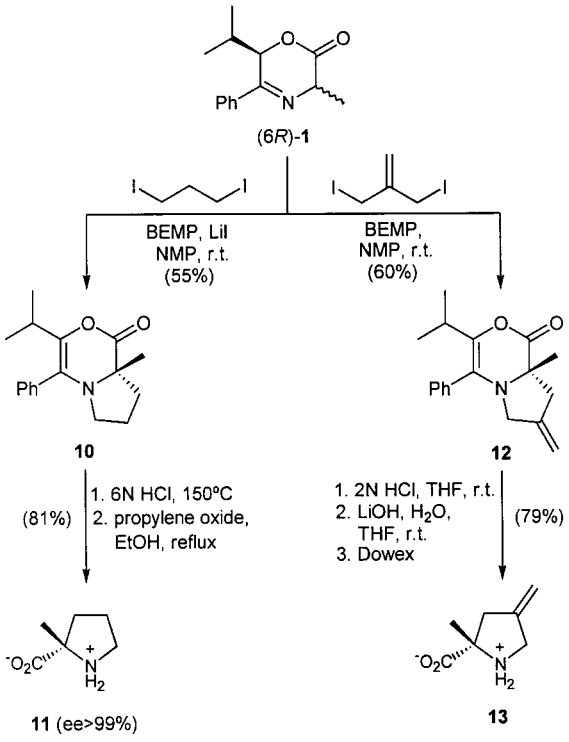
[a] Referred to oxazinone (6*R*)–**6**.
[b] Determined by comparison with [α] values in the literature.

When an activated dihalide such as *o*-dibromomethylbenzene was used as alkylating agent of (6*R*)-**1** following the PTC procedure, the expected *C*-alkylation took place, but interestingly also further *N*-alkylation and isomerization of the iminic double bond, affording the tricylic system **8** in 80% isolated yield after flash chromatography (Scheme 5). Hydrolysis of this compound under the previously described acid conditions afforded the cyclic (*S*)-AMAA **9** with ee>99%, deduced from its optical rotation sign and value,[20a] thus confirming the supposed stereochemistry of **8** and the high asymmetric induction achieved in the *C*-alkylation step, respectively. This interesting spontaneous cyclization could allow the preparation of other cyclic amino acids following a more simple and direct experimental procedure than when using other chiral templates.[20,21]



Scheme 5

This cyclization reaction was also observed using an unactivated dihalide such as 1,3-diiodopropane and using BEMP as base in the presence of LiI and at room temperature (Scheme 6). Under these reaction conditions bicyclic oxazinone **10** was obtained in 55% isolated yield, and further acid hydrolysis yielded (*S*)-α-methylproline (**11**) in ee>99%. If DBU was used as base, the necessary large excess (5 equiv) produced competing dehydroiodination before the *N*-alkylation step, affording variable amounts of the allylic derivative (6*R*)-**6a** together with the desired compound **10**. The reaction was also carried out using 3-iodo-2-iodomethylprop-1-ene[22] as electrophile, affording



Scheme 6

the bicyclic system **12** in 60% isolated yield, which was now hydrolyzed under milder reaction conditions, thus preventing a possible addition reaction of HCl to the double bond when using more concentrated acid and higher temperatures (Scheme 6). Thus, the enamine moiety in **12** was hydrolyzed with diluted acid and the ester function with LiOH. Final treatment with a Dowex column allowed the isolation of the new AMAA (*S*)-2-methyl-4-methyleneproline (**13**) in 79% yield. Its final ee could not be determined, but taking into account the ee obtained in the synthesis of (*S*)-α-methylproline and the de obtained in the alkylation reaction of (6*R*)-**1** using an allyl halide and BEMP (Table 2, entry 12), it seems reasonable to suppose an ee higher than 96% for this new obtained AMAA. The non-methylated analogue of **13**, (*S*)-4-methyleneproline, is a potent proline dehydrogenase inhibitor.[23] Sur-

Table 4 Synthesis of (*R*)-α-Methyl α-Amino Acids from (6*S*)–**1**

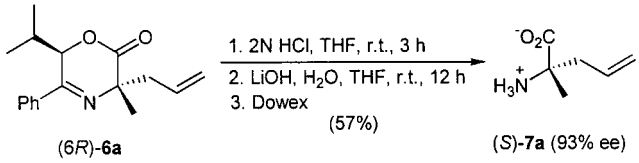
Entry	Electrophile	R^1	Product **6**, % yield[a] (% de)[b]	R^2	Product **7**, % yield[c] (% ee)[d]
1[e]	$PhCH_2Br$	CH_2Ph	(6*S*)–**6c**, 75 (>96)	CH_2Ph	(*R*)–**7c**, 76 (98)
2[e]	ICH_2CO_2Et	CH_2CO_2Et	(6*S*)–**6f**, 65 (90)	CH_2CO_2H	(*R*)–**7f**, 80 (93)
3[e]	CH_2=$CHCO_2Me$	$CH_2CH_2CO_2Me$	(6*S*)–**6h**, 59 (90)	$CH_2CH_2CO_2H$	(*R*)–**7h**, 66 (92)
4[f]	EtI	Et	(6*S*)–**6i**, 60 (96)	Et	(*R*)–**7i**, 89 (97)

[a] Isolated yield of pure major diastereomer after flash chromatography.
[b] Determined by ^{1}H NMR (300 MHz) and/or GLC on the reaction crude.
[c] Referred to oxazinone **6**.
[d] Determined by comparison with [α] values in the literature.
[e] PTC Conditions.
[f] Organic base conditions (BEMP).

prisingly, the use of 1,4-diiodobutane as dielectrophile failed to allow the cyclization reaction. Also, attempts at achieving a *C*-dialkylation reaction using activated or unactivated dihalides together with 2 equivalents of (6*R*)-**1** under different reaction conditions, as a possible route to bis-α-methyl α-amino acids, failed.

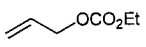
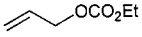
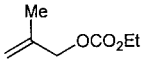
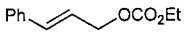
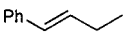
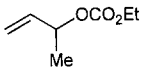
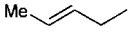
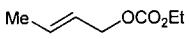
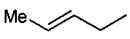
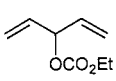
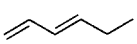
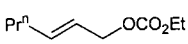
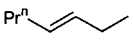
We then realized the possibility that substrate (6*R*)-**1** could be diastereoselectively allylated using allylic carbonates under mild neutral Pd(0) catalysis, taking into account that chemically similar O'Donnell's benzophenone imines of glycine and alanine ester derivatives have been previously allylated under these reaction conditions.[24] The final enantiomerically enriched analogs of allylglycine would be useful chirons for the synthesis of pharmacologically important molecules,[25] as well as of natural products.[26] Following this methodology, oxazinones (6*R*)-**1** were smoothly allylated with different allylic carbonates in the presence of catalytic amounts of $Pd(PPh_3)_4$ (5 mol%) and 1,2-bis(diphenylphosphino)ethane (dppe) (14 mol%) at room temperature with good diastereoselectivities (Scheme 2 and Table 5). In some cases a certain lack of regioselectivity was observed (Table 5, entries 4–7), although the major regioisomer was easily purified by flash chromatography. However, when LiI, which has recently been used to improve the regioselectivity of Pd(0)-catalyzed allylation reactions,[27] was added to the reaction mixture only the starting oxazinone was recovered. The reaction, although slower, could also be performed with in situ generation of the Pd(0) catalyst. Thus, reaction of (6*R*)-**1** with allyl ethyl carbonate in the presence of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) for 12h afforded (6*R*)-**6a** in 69% isolated yield (Table 5, entry 2).

Hydrolysis of one of these allylated oxazinones (6*R*)-**6a** was carried out using similar reaction conditions as with bicyclic system **12** (see above), yielding (*S*)-α-allylalanine (**7a**) in 57% isolated yield and 93% ee (Scheme 7).



Scheme 7

Table 5 Diastereoselective Allylation of (6*R*)–**1** under Pd(0)-Catalysis

Entry	R'OCO_2Et	*t* (h)	R	Product (6*R*)–**6**, % yield[a]	% de[b]
1		2		(6*R*)–**6a**, 60	>96
2[c]		12		(6*R*)–**6a**, 69	>96
3		2		(6*R*)–**6o**, 65	>96
4		2		(6*R*)–**6p**, 53[d]	82
5		3		(6*R*)–**6q**, 65[e]	84
6		3		(6*R*)–**6q**, 60[e]	84
7		3		(6*R*)–**6r**, 56[f]	70
8		3		(6*R*)–**6s**, 53	88

[a] Isolated yield of the major regio- and diastereoisomer after flash chromatography.
[b] Determined by ^1H NMR (300 MHz) and/or GLC on the reaction crude.
[c] A mixture of $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%) was used as catalyst.
[d] 28% of the other regioisomer was also detected (^1H NMR).
[e] 13% of the other regioisomer was also detected (^1H NMR).
[f] 21% of the other regioisomer was also detected (^1H NMR).

Conclusion

As a summary, we have shown the potential interest of oxazinones **1** as chiral alanine equivalents, which can be used for the asymmetric synthesis of interesting enantiomerically enriched acyclic and cyclic (*S*)- and (*R*)-AMAAs. The most remarkable characteristic of these systems is their ability to achieve a high degree of asymmetric induction working under very simple and mild reaction conditions and always at room temperature. In this way, PTC or organic bases, and also neutral Pd(0)-catalysis conditions have been used for alkylation or allylation reactions, in most cases with excellent diastereoselectivities. These experimental procedures are easy to scale up, a reason that could make these heterocycles promising starting materials for the industrial preparation of nowadays important AMAAs.

Melting points are uncorrected. IR were recorded on a Nicolet 510 P-FT and only the structurally most important peaks are listed. NMR spectra were determined on a Bruker AC-300 at 300 MHz for ^{1}H and 75 MHz for ^{13}C using $CDCl_3$ as solvent and TMS as internal standard unless otherwise stated. Optical rotations were measured on a Jasco DIP-1000 polarimeter. GLC analyses were performed on a HP-5890 instrument (HP-1, 12 m x 0.22 mm column) equipped with a flame ionization detector, using nitrogen as the carrier gas (1.5 mL/min); T_{column}=60ºC (3 min) and 15ºC/min. Low resolution electron impact (EI) mass spectra were obtained at 70 eV on a Shimadzu QP-5000. HRMS (EI) were recorded on VG-Micromass ZAB-ZF, Kratos MS 80 RFA, and Finnigan MAT 95 S. Microanalyses were performed by the Microanalyses Service of the University of Alicante. Analytical TLC was performed on Schleicher & Schuell F1400/LS silica gel plates and the spots visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040–0.063 mm).

α-Bromoisovalerophenone (3)
To a solution of isovalerophenone (8.4 mL, 50 mmol) and $AlCl_3$ (133 mg, 1 mmol) in Et_2O (40 mL) was added Br_2 (2.57 mL, 50 mmol) dropwise at r.t. The resulting mixture was refluxed for 4 h and filtered through a pad of silica gel (hexane/EtOAc: 1/1) yielding, after evaporation (15 Torr), compound **3** (11.8 g, 98%) as a white solid; mp 53ºC (hexane/EtOAc); TLC: R_f 0.62 (hexane/EtOAc = 4/1).

IR (KBr): ν = 1686 cm^{-1}.

^{1}H NMR ($CDCl_3$):[28] δ = 1.02 (d, 3 H, *J* = 6.7 Hz), 1.21 (d, 3 H, *J* = 6.7 Hz), 2.49 (m, 1 H), 4.96 (d, 1 H, *J* = 8.5 Hz), 7.47 (m, 2 H), 7.50 (m, 1 H), 7.99 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 20.3, 20.6, 31.0, 55.8, 128.6, 128.7, 133.5, 134.9, 193.5.

MS: *m/z* (%) = 198 (M^+–Pr^i, 2), 161 (22), 106 (24), 105 (100), 77 (54), 51 (38), 41 (26).

Esters 5
To a mixture of (*S*)- or (*R*)-*N*-Boc-alanine (6.65 g, 35 mmol) in MeOH (35 mL) was added 1M KOH in MeOH (35 mL). The solvent was evaporated (15 Torr) and the residue was dissolved in DMF (70 mL). To this solution was added α-bromoisovalerophenone **3** (8.44 g, 35 mmol) and the resulting mixture was stirred for 24 h at r.t. The mixture was diluted with EtOAc (90 mL) and washed with H_2O (4 x 50 mL). Evaporation of the solvent (15 Torr) yielded a ca. 1/1 diastereomeric mixture of esters (^{1}H NMR) which were separated by flash chromatography (silica gel, hexane→hexane/EtOAc 8/2) and crystallization (hexane/EtOAc) affording 3.75 g (31%) of each pure diastereomer. The pure (*R*,*S*)- or (*S*,*R*)-**5** isomers also can be isolated in 27% yield directly by crystallization (hexane/EtOAc) from the reaction crude.

(1*R*)- and (1*S*)-1-Benzoyl-2-methylpropyl (2*S*)- and (2*R*)-2-(*tert*-Butoxycarbonylamino) propanoate ((*R*,*S*)-5 and (*S*,*R*)-5)
White needles; mp 129ºC (hexane/EtOAc); TLC: R_f 0.51 (hexane/EtOAc = 7/3).

(*R*,*S*)-Isomer: $[\alpha]_D^{24}$ -52.9 (*c* = 1.2; CH_2Cl_2); (*S*,*R*)-isomer: $[\alpha]_D^{25}$ +55.1 (*c* = 1.2; CH_2Cl_2).

IR (KBr): ν = 1686, 1737, 3376 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.93 (d, 3 H, *J* = 6.7 Hz), 1.05 (d, 3 H, *J* = 7.0 Hz), 1.45 (s, 9 H) 1.46 (d, 3 H, *J* = 7.3 Hz), 2.33 (m, 1 H), 4.46 (t, 1 H, *J* = 7.3 Hz), 5.11 (d, 1 H, *J* = 6.4 Hz), 5.77 (d, 1 H, *J* = 4.5 Hz), 7.48 (m, 2 H), 7.60 (m, 1 H), 7.93 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 16.7, 18.6, 19.5, 28.3, 30.2, 49.4, 79.7, 79.9, 128.3, 128.8, 133.5, 135.3, 155.0, 172.8, 196.0.

MS: *m/z* (%) = 233 (M^+–NHBoc, 0.5), 105 (100), 77 (25), 59 (22), 57 (38), 56 (23), 44 (80), 41 (63).

Anal. Calcd for $C_{19}H_{25}NO_7$: C 65.31, H 7.79, N 4.01. Found: C 65.38, H 7.92, N 4.00.

(1*S*)- and (1*R*)-1-Benzoyl-2-methylpropyl (2*S*)- and (2*R*)-2-(*tert*-Butoxycarbonylamino) propanoate ((*S*,*S*)-5 and (*R*,*R*)-5)
White crystals; mp 99ºC (hexane/EtOAc); TLC: R_f 0.55 (hexane/EtOAc: 7/3); $[\alpha]_D^{29}$ -0.3 (*c* = 2; CH_2Cl_2).

IR (KBr): ν = 1698, 1749, 3377 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.92 (d, 3 H, *J* = 7.0), 1.07 (d, 3 H, *J* = 6.7), 1.44 (s, 9 H), 1.46 (d, 3 H, *J* = 7.3), 2.32 (m, 1 H), 4.47 (q, 1 H, *J* = 7.6), 5.04 (d, 1 H, *J* = 7.0), 7.47 (m, 2 H), 7.58 (m, 1 H), 7.92 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 16.6, 18.6, 19.5, 28.3, 30.8, 48.9, 79.7, 79.9, 128.2, 128.7, 133.5, 135.3, 155.1, 173.2, 196.0.

MS: *m/z* (%) = 233 (M^+–NHBoc, 0.7), 105 (100), 77 (30), 57 (32), 44 (85), 41 (44).

Oxazinones (6*R*)- and (6*S*)-1
The ester (*R*,*S*)-**5** or (*S*,*R*)-**5** (3.49 g, 10 mmol) was dissolved in sat. HCl(g) in EtOAc (30 mL) and the mixture was stirred for 1 h at r.t. The solvent was removed (15 Torr) and the obtained solid hydrochloride was suspended in CH_2Cl_2 (20 mL). Et_3N (2.79 mL, 20 mmol) was added and the resulting mixture was stirred for 1 h at r.t. and filtered through a pad of Florisil (EtOAc) affording oxazinones (6*R*)- or (6*S*)-**1** (2.2 g) as ca. 1/20 *cis/trans* mixtures which were >90% pure by GLC (82% based on this purity) and used without further purification. Analytical samples of (3*S*,6*R*)- and (3*R*,6*S*)-**1** were obtained after further column chromatography on Florisil (hexane/EtOAc gradients) and recrystallization in hexane/EtOAc.

(3*S*,6*R*)- and (3*R*,6*S*)-6-Isopropyl-3-methyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one ((3*S*,6*R*)-1 and (3*R*,6*S*)-1)
White solid; mp 100 ºC (hexane/EtOAc); TLC: R_f 0.56 (hexane/EtOAc = 7/3); (3*S*,6*R*)-isomer: $[\alpha]_D^{25}$ -201.4 (*c* = 1; CH_2Cl_2); (3*R*,6*S*)-isomer: $[\alpha]_D^{25}$ +208.4 (*c* = 1; CH_2Cl_2).

IR (KBr): ν = 1633, 1744 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.94 (d, 3 H, *J* = 6.7 Hz), 1.04 (d, 3 H, *J* = 7.0 Hz), 1.74 (d, 3 H, *J* = 7.2 Hz), 2.22 (m, 1 H), 4.28 (m, 1 H), 5.47 (m, 1 H), 7.42 (m, 3 H), 7.71 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 16.9, 19.3, 19.8, 32.5, 54.3, 84.4, 126.7, 128.8, 130.9, 135.8, 165.1, 170.5.

MS: *m/z* (%) = 231 (M^+, 4), 172 (32), 131 (61), 104 (48), 56 (100).

Anal. Calcd for $C_{14}H_{17}NO_2$: C 72.70, H 7.41, N 6.06. Found: C 72.70, H 7.42, N, 6.12.

Alkylation of Oxazinone 1 under Solid–Liquid PTC Conditions; General Procedure

A heterogeneous mixture of crude (6*R*)-**1** or (6*S*)-**1** (257 mg of crude of ca. 90% purity, equivalent to 231 mg of pure compound, 1 mmol), tetrabutylammonium bromide (TBAB, 33 mg, 0.1 mmol), K_2CO_3 (400 mg, 3 mmol), and the corresponding electrophile (1.5 mmol) in MeCN (3 mL) was stirred at r.t. until total consumption of the starting material (GLC). The resulting mixture was filtered through a pad of silica gel, the solvent was evaporated (15 Torr) and the crude was analyzed by ^{1}H NMR and/or GLC for the determination of the de. Purification by flash chromatography (silica gel, hexane/EtOAc gradients) afforded pure major diastereoisomers (6*R*)-**6** or (6*S*)-**6** (see Tables 1 and 4) or compound **8**.

***(3S,6R)*-3-Allyl-6-isopropyl-3-methyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6a]**

Colorless oil; TLC: R_f 0.68 (hexane/EtOAc = 7/3); $[\alpha]_D^{23}$ +63.5 (*c* = 1.3; CH_2Cl_2).

IR (film): ν = 1659, 1741 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.77 (d, 3 H, *J* = 6.9 Hz), 1.11 (d, 3 H, *J* = 6.9 Hz), 1.65 (s, 3H), 2.09 (dsept, 1 H, *J* = 6.9, 2.4 Hz), 2.59 (dd, 1 H, *J* = 13.3, 6.7 Hz), 2.79 (dd, 1 H, *J* = 13.3, 7.9 Hz), 5.10 (m, 2 H), 5.48 (d, 1 H, *J* = 2.4 Hz), 5.62 (m, 1 H), 7.44 (m, 3 H), 7.58 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.1, 19.0, 27.4, 31.8, 46.7, 61.2, 84.5, 119.9, 126.6, 128.7, 130.4, 132.3, 136.4, 162.3, 170.9.

MS: *m/z* (%) = 271 (M^+, 24), 230 (42), 157 (79), 145 (57), 91 (46), 43 (52), 41 (100).

HRMS for $C_{17}H_{21}NO_2$ calcd 271.1572, found 271.1569.

(3S,6R)-6-Isopropyl-3-methyl-5-phenyl-3-propargyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6b]

White crystals; mp 132 ºC (hexane/EtOAc); TLC: R_f 0.56 (hexane/EtOAc = 7/3); $[\alpha]_D^{30}$ +93.4 (*c* = 1.1; CH_2Cl_2).

IR (KBr): ν = 1662, 1741, 3292 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.78 (d, 3 H, *J* = 6.9 Hz), 1.14 (d, 3 H, *J* = 6.9 Hz), 1.66 (s, 3 H), 2.00 (t, 1 H, *J* = 2.4 Hz), 2.11 (dsept, 1 H, *J* = 6.9, 2.6 Hz), 2.70 (dd, 1 H, *J* = 16.4, 2.7 Hz), 2.97 (dd, 1 H, *J* = 16.4, 2.7 Hz), 5.6 (d, 1 H, *J* = 2.6 Hz), 7.43 (m, 3 H), 7.61 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.1, 19.0, 27.0, 31.8, 33.0, 60.5, 71.4, 79.5, 84.8, 126.7, 128.7, 130.5, 136.3, 163.4, 170.1.

MS: *m/z* (%) = 269 (M^+, 29), 268 (49), 230 (100), 182 (77), 128 (78), 77 (55), 43 (95).

Anal. Calcd for $C_{17}H_{19}NO_2$: C 75.81, H 7.11, N 5.20. Found: C 75.45, H 7.08, N 5.04.

(3S,6R)- and (3R,6S)-3-Benzyl-6-isopropyl-3-methyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6c and (6*S*)-6c]

Colorless oil; TLC: R_f 0.58 (hexane/EtOAc = 7/3); (3*S*,6*R*)-isomer: $[\alpha]_D^{25}$ +153.4 (*c* = 1.8; CH_2Cl_2), (3*R*,6*S*)-isomer: $[\alpha]_D^{25}$ -153.5 (*c* = 2; CH_2Cl_2).

IR (film): ν = 1660, 1739 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.64 (d, 3 H, *J* = 6.9 Hz), 0.92 (d, 3 H, *J* = 6.9 Hz), 1.78 (s, 3 H), 1.83 (dsept, 1 H, *J* = 6.9, 2.4 Hz), 3.07 (d, 1 H, *J* = 12.8 Hz), 3.35 (d, 1 H, *J* = 12.8 Hz), 4.38 (d, 1 H, *J* = 2.4 Hz), 7.0 (m, 2 H), 7.2 (m, 3 H), 7.4 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 14.5, 18.8, 27.7, 31.2, 48.4, 62.8, 84.0, 126.3, 127.0, 128.0, 128.6, 130.0, 130.6, 135.8, 136.9, 163.4, 170.7.

MS: *m/z* (%) = 321 (M^+, 11), 145 (71), 105 (40), 91 (100), 43 (47).

HRMS for $C_{21}H_{23}NO$ calcd 321.1729, found: 321.1729.

(3S,6R)-3-(3,4-Dimethoxybenzyl)-6-isopropyl-3-methyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6d]

Colorless oil; TLC: R_f 0.29 (hexane/EtOAc = 7/3); $[\alpha]_D^{25}$ +140.5 (*c* = 1.82; CH_2Cl_2).

IR (film): ν = 1660, 1739 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.67 (d, 3 H, *J* = 6.9 Hz), 0.96 (d, 3 H, *J* = 6.9 Hz), 1.78 (s, 3H), 1.90 (dsept, 1 H, *J* = 6.9, 2.1 Hz), 3.01 (d, 1 H, *J* = 13.1 Hz), 3.31 (d, 1 H, *J* = 13.1 Hz), 3.43 (s, 3 H), 3.85 (s, 3 H), 4.56 (d, 1 H, *J* = 2.1 Hz), 6.46 (d, 1 H, *J* = 1.8 Hz), 6.64 (dd, 1 H, *J* = 8.2, 1.8 Hz), 6.74 (d, 1 H, *J* = 8.2 Hz), 7.43 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 14.5, 18.7, 27.4, 31.2, 47.9, 55.1, 55.6, 62.8, 83.8, 110.6, 113.5, 122.2, 126.2, 128.2, 128.5, 130.1, 136.6, 147.7, 147.8, 162.8, 170.4.

MS: *m/z* (%) = 381 (M^+, 2), 151 (100).

HRMS for $C_{15}H_{18}NO_4$ calcd 381.1940, found 381.1929.

Methyl (*E*)-4-[(3*S*,6*R*)-6-Isopropyl-3-methyl-2-oxo-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-3-yl]but-2-enoate [(6*R*)-6e]

Colorless oil; TLC: R_f 0.54 (hexane/EtOAc = 7/3); $[\alpha]_D^{24}$ +56.4 (*c* = 1.5; CH_2Cl_2).

IR (film): ν = 1659, 1727 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.79 (d, 3 H, *J* = 6.9 Hz), 1.10 (d, 3 H, *J* = 6.9 Hz), 1.66 (s, 3 H), 2.10 (dsept, 1 H, *J* = 6.9, 2.9 Hz), 2.76 (ddd, 1 H, *J* = 13.6, 7.3, 1.5 Hz), 2.92 (ddd, 1 H, *J* = 13.6, 7.9, 1.2 Hz), 3.70 (s, 3H), 5.50 (d, 1 H, *J* = 2.9 Hz), 5.88 (d, 1 H, *J* = 15.6 Hz), 6.77 (m, 1 H), 7.44 (m, 3 H), 7.60 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.4, 19.0, 27.6, 32.0, 44.8, 54.4, 60.6, 84.7, 125.1, 126.7, 128.7, 130.6, 136.0, 142.5, 162.9, 166.4, 170.5.

MS: *m/z* (%) = 329 (M^+, 4), 270 (43), 230 (65), 186 (44), 145 (73), 43 (100).

HRMS for $C_{19}H_{23}NO_4$ calcd 329.1627, found: 329.1621.

Ethyl 2-[(3*S*,6*R*)- and (3*R*,6*S*)-6-Isopropyl-3-methyl-2-oxo-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-3-yl]acetate [(6*R*)-6f and (6*S*)-6f]

Colorless oil; TLC: R_f 0.57 (hexane/EtOAc = 7/3); (3*S*,6*R*)-isomer: $[\alpha]_D^{30}$ +73.8 (*c* = 1.6; CH_2Cl_2), (3*R*,6*S*)-isomer: $[\alpha]_D^{25}$ -69.8 (*c* = 1.6; CH_2Cl_2).

IR (film): ν = 1663, 1739 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.81 (d, 3 H, *J* = 6.9 Hz), 1.16 (m, 6 H), 1.62 (s, 3 H), 2.12 (dsept, 1 H, *J* = 6.9, 2.4 Hz), 2.88 (d, 1 H, *J* = 17.1 Hz), 3.31 (d, 1 H, *J*=17.1Hz), 4.00 (m, 2 H), 5.66 (d, 1 H, *J* = 2.4 Hz), 7.41 (m, 3 H), 7.55 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.0, 15.2, 19.0, 27.8, 31.3, 46.1, 57.8, 60.7, 84.8, 126.6, 128.7, 130.2, 136.8, 163.8, 170.8, 171.1.

MS: *m/z* (%) = 317 (M^+, 15), 258 (46), 202 (88), 144 (52), 104 (100), 43 (64).

HRMS for $C_{18}H_{23}NO_4$ calcd 317.2627, found: 317.2627.

(3S,6R)-3-Hydroxymethyl-6-isopropyl-3-methyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6g]

Colorless oil; TLC: R_f 0.47 (hexane/EtOAc = 1/1); $[\alpha]_D^{26}$ -13.1 (*c* = 1.2; CH_2Cl_2).

IR (film): ν = 1662, 1739, 3418 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.81 (d, 3 H, *J* = 6.9 Hz), 1.11 (d, 3 H, *J* = 6.9 Hz), 1.55 (s, 3 H), 2.11 (dsept, 1 H, *J* = 6.9, 3.0 Hz), 2.39 (br s, 1 H), 3.76 (d, 1 H, *J* = 10.6 Hz), 3.98 (d, 1 H, *J* = 10.6 Hz), 5.57 (d, 1 H, *J* = 3.0 Hz), 7.45 (m, 3 H), 7.62 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.6, 19.1, 23.2, 32.1, 62.1, 70.6, 84.5, 126.8, 128.8, 130.8, 136.2, 164.6, 170.9.

MS: *m/z* (%) = 261 (M^+, 8), 231 (54), 230 (70), 202 (69), 186 (96), 160 (72), 105 (66), 104 (67), 91 (53), 86 (62), 77 (65), 43 (100), 42 (58).

HRMS for $C_{15}H_{19}NO_3$ calcd 261.1365, found 261.1363.

Methyl 3-[(3*S*,6*R*)- and (3*R*,6*S*)-6-Isopropyl-3-methyl-2-oxo-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-3-yl]propanoate [(6*R*)-6h and (6*S*)-6h]

Colorless oil; TLC: R_f 0.47 (hexane/EtOAc = 7/3); (3*S*,6*R*)-isomer: $[\alpha]_D^{26}$ +12.5 (*c* = 1.5; CH_2Cl_2), (3*R*,6*S*)-isomer: $[\alpha]_D^{25}$ -10.9 (*c* = 1.5; CH_2Cl_2)

IR (film): ν = 1658, 1739 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.80 (d, 3 H, *J* = 7.0 Hz), 1.12 (d, 3 H, *J* = 7.0 Hz), 1.63 (s, 3 H), 2.07–2.48 (m, 5 H), 3.46 (s, 3 H), 5.56 (d, 1 H, *J* = 3.1 Hz), 7.45 (m, 3 H), 7.62 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.5, 19.1, 27.7, 29.8, 32.0, 37.5, 51.5, 59.8, 84.6, 126.7, 128.7, 130.6, 136.1, 162.7, 171.1, 173.0.

MS: *m/z* (%) = 317 (M^+, 7), 258 (80), 202 (62), 144 (52), 115 (47), 104 (100), 55 (79), 43 (88), 42 (43).

HRMS for $C_{18}H_{23}NO_4$ calcd 317.1627, found: 317.1638.

(11a*S*)-3-Isopropyl-11a-methyl-4-phenyl-1,6-dihydro[1,4]oxazino[4,3-*b*]isoquinolin-1-one (8)

White solid; yield: 80%; mp 101ºC (hexane/EtOAc); TLC: R_f 0.73 (hexane/EtOAc = 7/3); $[\alpha]_D^{25}$ -117.0 (*c* = 1; CH_2Cl_2).

IR (KBr): ν = 1742 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.99 (d, 3 H, *J* = 6.9 Hz), 1.25 (d, 3 H, *J* = 6.9 Hz), 1.32 (s, 3 H), 2.69 (sept, 1 H, *J* = 6.9 Hz), 3.02 (d, 1 H, *J* = 15.4 Hz), 3.26 (d, 1 H, *J* = 15.4 Hz), 3.70 (d, 1 H, *J* = 14.8 Hz), 3.89 (d, 1 H, *J* = 14.8 Hz), 6.87 (d, 1 H, *J* = 7.0 Hz), 7.12–7.42 (m, 8 H).

^{13}C NMR ($CDCl_3$): δ = 19.5, 21.0, 21.9, 28.0, 36.8, 48.0, 56.0, 122.9, 124.7, 126.4, 127.2, 128.3, 128.4, 128.5, 129.6, 134.1, 134.3, 136.2, 138.1, 168.5.

MS: *m/z* (%) = 333 (M^+, 32), 290 (100), 104 (34).

Anal. Calcd for $C_{22}H_{23}NO_2$: C 79.25, H 6.95, N 4.20. Found: C 79.56, H 6.93, N, 4.19.

Alkylation of Oxazinone (6*R*)-1 under Organic Base Conditions; General Procedure

To a solution of the oxazinone **1** (257 mg of crude of ca. 90% purity, equivalent to 231 mg of pure compound, 1 mmol) LiI if necessary (see Table 2) in the appropriate solvent (2 mL) was added the corresponding base (BEMP: 1.1 mmol, 318 μL; DBU: 5 mmol, 748 μL) at 0ºC. The alkyl halide (2 mmol) was added in one portion and the temperature was allowed to rise to r.t. until total consumption of the starting material (GLC). The mixture was diluted with EtOAc (25 mL), washed with H_2O (3 x 15 mL), dried (Na_2SO_4) and evaporated (15 Torr). The residue was analyzed by ^1H NMR to determine the de. Further purification by flash chromatography (silica gel, hexane/EtOAc gradients) afforded pure major diastereomer **6** (see Table 2), and compounds **10** or **12**.

(3*S*,6*R*)- and (3*R*,6*S*)-3-Ethyl-6-isopropyl-3-methyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6i and (6*S*)-6i]

Colorless oil; TLC: R_f 0.60 (hexane/EtOAc = 7/3); (3*S*,6*R*)-isomer: $[\alpha]_D^{25}$ +26.5 (*c* = 1.6; CH_2Cl_2), (3*R*,6*S*)-isomer: $[\alpha]_D^{25}$ -25.1 (*c* = 1.6; CH_2Cl_2).

IR (film): ν = 1659, 1743 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.79 (m, 6 H), 1.13 (d, 3 H, *J* = 7.0 Hz), 1.62 (s, 3 H), 1.86 (m, 1 H), 2.13 (m, 2H), 5.53 (d, 1 H, *J* = 2.4 Hz), 7.44 (m, 3 H), 7.60 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 8.9, 15.2, 19.0, 27.6, 31.9, 35.9, 61.3, 84.5, 126.6, 128.8, 130.4, 136.4, 162.4, 171.5.

MS: *m/z* (%) = 259 (M^+, 2), 200 (84), 104 (100).

HRMS for $C_{16}H_{21}NO_2$ calcd 259.1572, found 259.1577.

(3*S*,6*R*)-3,6-Diisopropyl-3-methyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6j]

Colorless oil; TLC: R_f 0.61 (hexane/EtOAc = 7/3); $[\alpha]_D^{25}$ +42.8 (*c* = 2; CH_2Cl_2).

IR (film): ν = 1660, 1736 cm^{-1}

^1H NMR ($CDCl_3$): δ = 0.77 (d, 3 H, *J* = 6.9 Hz), 0.88 (d, 3 H, *J* = 6.7 Hz), 1.00 (d, 3 H, *J* = 6.7 Hz), 1.13 (d, 3 H, *J* = 6.9 Hz), 1.58 (s, 3 H), 2.13 (dsept, 1 H, *J* = 6.9, 2.6 Hz), 2.28 (sept, 1 H, *J* = 6.7 Hz), 5.50 (d, 1 H, *J* = 2.6 Hz), 7.44 (m, 3 H), 7.63 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.2, 16.0, 18.0, 19.1, 25.5, 31.9, 38.7, 63.0, 84.2, 126.6, 128.6, 130.3, 136.5, 161.4, 171.7.

MS: *m/z* (%) = 273 (M^+, 1), 214 (47), 104 (48), 71 (46), 55 (61), 43 (94), 41 (100).

HRMS for $C_{17}H_{23}NO_2$ calcd 273.1729, found 273.1726.

(3*S*,6*R*)-3-Butyl-6-isopropyl-3-methyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6k]

Colorless oil; TLC: R_f 0.67 (hexane/EtOAc = 7/3); $[\alpha]_D^{25}$ +28.5 (*c* = 1.1; CH_2Cl_2).

IR (film): ν = 1659, 1739 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.78 (d, 3 H, *J* = 7.0 Hz), 0.83 (t, 3 H, *J* = 7.2 Hz), 1.12 (d, 3 H, *J* = 7.0 Hz), 1.12 (m, 2 H), 1.25 (m, 2 H), 1.62 (s, 3 H), 1.82 (m, 1 H), 2.09 (m, 2 H), 5.52 (d, 3 H, *J* = 2.5 Hz), 7.43 (m, 3 H), 7.60 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 13.9, 15.3, 19.1, 22.5, 26.8, 28.0, 31.9, 42.8, 60.8, 84.5, 126.7, 128.8, 130.4, 136.5, 161.9, 171.7.

MS: *m/z* (%) = 287 (M^+, 3), 187 (55), 186 (52), 104 (100), 43 (77).

HRMS for $C_{18}H_{25}NO_2$ calcd 287.1885, found 287.1883.

(3*S*,6*R*)-3-Isobutyl-6-isopropyl-3-methyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one ((6*R*)-6l)

Colorless oil; TLC: R_f 0.65 (hexane/EtOAc = 7/3); $[\alpha]_D^{25}$ +72.7 (*c* = 1.4; CH_2Cl_2).

IR (film): ν = 1659, 1742 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.80 (d, 3 H, *J* = 7.0 Hz), 0.81 (d, 3 H, *J* = 6.7 Hz), 0.84 (d, 3 H, *J* = 6.7 Hz), 1.13 (d, 3 H, *J* = 7.0 Hz), 1.57 (m, 1 H), 1.86 (dd, 1 H, *J* = 13.6, 5.4 Hz), 2.1 (m, 2 H), 5.53 (d, 1 H, *J* = 2.4 Hz), 7.44 (m, 3 H), 7.59 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.4, 19.1, 22.6, 23.8, 25.1, 29.5, 31.8, 50.9, 60.0, 84.5, 126.6, 128.7, 130.3, 136.5, 161.5, 172.0.

MS: *m/z* (%) = 287 (M^+, 2), (43), 43 (87), 41 (100).

HRMS for $C_{18}H_{25}NO_2$ calcd 287.1885, found: 287.1893.

(3*S*,6*R*)-6-Isopropyl-3-methyl-5-phenyl-3-phenylethyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6m]

Colorless oil; TLC: R_f 0.60 (hexane/EtOAc = 7/3); $[\alpha]_D^{25}$ +20.7 (*c* = 1.3; CH_2Cl_2).

IR (film): ν = 1658, 1739 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.81 (d, 3 H, *J* = 6.7 Hz), 1.13 (d, 3 H, *J* = 6.7 Hz), 1.65 (s, 3 H), 2.04–2.25 (m, 2 H), 2.36–2.51 (m, 3 H), 5.52 (d, 1 H, *J* = 2.8 Hz), 7.10–7.24 (m, 5 H), 7.46 (m, 3 H), 7.62 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.4, 19.1, 28.0, 31.1, 32.0, 44.5, 60.7, 84.7, 125.9, 126.7, 128.3, 128.4, 128.8, 130.5, 136.4, 141.0, 162.3, 171.4.

MS: *m/z* (%) = 335 (M^+, 4), 202 (42), 188 (48), 104 (58), 91 (100), 69 (56), 41 (76).

HRMS for $C_{22}H_{25}NO_2$ calcd 335.1885, found 335.1874.

(3*S*,6*R*)-3-Chloromethyl-6-isopropyl-3-methyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6n]
Colorless oil; TLC: R_f 0.53 (hexane/EtOAc = 7/3); $[\alpha]_D^{25}$ +31.1 (*c* = 1.5; CH_2Cl_2).

IR (film): ν = 1661, 1743 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.78 (d, 3 H, *J* = 7.0 Hz), 1.14 (d, 3 H, *J* = 7.0 Hz), 1.68 (s, 3 H), 2.13 (dsept, 1 H, *J* = 7.0, 2.7 Hz), 3.73 (d, 1 H, *J* = 10.2 Hz), 4.11 (d, 1 H, *J* = 10.2 Hz), 5.62 (d, 1 H, *J* = 2.7 Hz), 7.44 (m, 3 H), 7.62 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.0, 18.9, 25.6, 31.7, 52.8, 61.8, 84.7, 126.6, 128.7, 130.6, 135.9, 164.5, 168.8.

MS: *m/z* (%) = 279 (M^+, 1), 144 (42), 104 (100), 77 (45), 69 (68), 41 (79).

HRMS for $C_{15}H_{18}ClNO_2$ calcd 279.1026, found 278.0956.

(8a*S*)-3-Isopropyl-8a-methyl-4-phenyl-6,7,8,8a-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (10)
White solid; yield: 81%; mp 115 ºC (hexane/EtOAc); TLC: R_f 0.80 (hexane/EtOAc = 7/3); $[\alpha]_D^{25}$ -317.8 (*c* = 1; CH_2Cl_2).

IR (KBr): ν = 1743 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.01 (d, 3 H, *J* = 6.7 Hz); 1.30 (d, 3 H, *J* = 7.0 Hz), 1.31 (s, 3 H), 1.66–1.86 (m, 2 H), 1.94 (m, 1 H), 2.67–2.84 (m, 3 H), 3.16 (m, 1 H), 7.34 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 19.8, 21.1, 21.8, 22.9, 27.8, 35.5, 50.8, 61.2, 122.4, 128.1, 128.3, 129.2, 134.8, 139.3, 169.1.

MS: *m/z* (%) = 271 (M^+, 2), 104 (46), 41 (100).

HRMS for $C_{17}H_{21}NO_2$ calcd 271.1572, found 271.1572.

(8a*S*)-3-Isopropyl-8a-methyl-7-methylene-4-phenyl-6,7,8,8a-tetrahydro-1*H*-pirrolo[2,1-*c*][1,4]oxazin-1-one (12)
Colorless oil; TLC: R_f 0.79 (hexane EtOAc = 7/3); $[\alpha]_D^{25}$ -221.4 (*c* = 1; CH_2Cl_2).

IR (film): 1755 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.02 (d, 3 H, *J* = 6.9 Hz), 1.31 (d, 3 H, *J* = 6.9 Hz), 1.35 (s, 3 H), 2.62 (d, 1 H, *J* = 16.5 Hz), 2.81 (sept, 1 H, *J* = 6.9 Hz), 3.29 (d, 1 H, *J* = 13.7 Hz), 3.50 (d, 1 H, *J* = 16.5 Hz), 3.78 (d, 1 H, *J* = 13.7 Hz), 4.80 (s, 1 H), 4.97 (s, 1 H), 7.36 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 19.6, 21.0, 21.7, 27.8, 41.3, 55.7, 61.9, 107.0, 122.3, 128.2, 128.3, 129.2, 134.4, 141.3, 142.6, 168.6.

MS: *m/z* (%) = 283 (M^+, 9), 43 (58), 41 (100).

HRMS for $C_{18}H_{21}NO_2$ calcd 283.1572, found 283.1576.

Hydrolysis of Oxazinones 6; Synthesis of AMAAs 7, 9 and 11; General Procedure

A mixture of the corresponding oxazinone **6** (0.5 mmol) in 6M HCl (1 mL) was heated at 150 ºC (bath temperature) in a pressure tube for 24 h. H_2O (10 mL) was added and the mixture was extracted with EtOAc (10 mL). The aqueous layer was evaporated (15 Torr), and the resulting solid hydrochloride was dissolved in EtOH (2 mL) and refluxed with propylene oxide (1 mL) for 30 min. The formed precipitate was filtered off yielding the corresponding free amino acids (see Tables 3 and 4).

(*S*)- and (*R*)-α-Methylphenylalanine [(*S*)- and (*R*)-7c]
(*S*)-Isomer: white solid; $[\alpha]_D^{25}$ -21.5 (*c* = 1; H_2O), lit.[29] $[\alpha]_D$ -22.0 (*c* = 1; H_2O). (*R*)-Isomer: white solid; $[\alpha]_D$ +21.6 (*c* = 1; H_2O).

^1H NMR (D_2O): δ = 1.52 (s, 3 H), 2.95 (d, 1 H, *J* = 14.7 Hz), 3.27 (d, 1 H, *J* = 14.7 Hz), 7.24 (m, 2 H), 7.36 (m, 3 H).

(*S*)- and (*R*)-α-Methylaspartic acid [(*S*)- and (*R*)-7f]
(*S*)-Isomer: white solid; $[\alpha]_D^{25}$ +48.9 (*c* = 1; H_2O). (*R*)-Isomer: white solid; $[\alpha]_D^{25}$ -49.5 (*c* = 1; H_2O), lit.[30] $[\alpha]_D$ -52.9 (*c* = 1; H_2O).

^1H NMR (D_2O): δ = 1.48 (s, 3 H), 2.76 (d, 1 H, *J* = 17.7 Hz), 3.01 (d, 1 H, *J* = 17.7 Hz).

(S)-α-Methylserine [(*S*)-7g]
White solid; $[\alpha]_D^{25}$ +3.6 (*c* = 1; H_2O), lit.[31] $[\alpha]_D$ +6.3 (*c* = 1; H_2O).

^1H NMR (D_2O): δ = 1.37 (s, 3 H), 3.61 (d, 1 H, *J* = 12.2 Hz), 3.85 (d, 1 H, *J* = 12.2 Hz).

(*S*)- and (*R*)-α-Methylglutamic acid [(*S*)- and (*R*)-7h]
(*S*)-Isomer: white solid; $[\alpha]_{436}^{25}$ +22.0 (*c* = 2.7; 6M HCl), lit.[31] $[\alpha]_{436}$ +23.7 (*c* = 4; 6M HCl) for ≥97% ee. (*R*)-isomer: white solid; $[\alpha]_{436}^{25}$ -22.4 (*c* = 2.8; 6M HCl).

^1H NMR (D_2O): δ = 1.47 (s, 3 H), 2.06 (m, 2 H), 2.34 (m, 2 H).

(*R*)-α-Ethylalanine [(*R*)-7i]

White solid; $[\alpha]_D^{25}$ -10.0 (*c* = 1; H_2O), lit.[32] $[\alpha]_D^{20}$ -10.3 (*c* = 1; H_2O).

^1H NMR (D_2O): δ = 0.90 (t, 3 H, *J* = 7.6 Hz), 1.44 (s, 3 H), 1.73 (dq, 1 H, *J* = 14.7, 7.6 Hz), 1.89 (dq, 1 H, *J* = 14.7, 7.6 Hz).

(*S*)-α-Methylleucine [(*S*)-7l]
White solid; $[\alpha]_D^{25}$ +38.2 (*c* = 2; H_2O), lit.[33] $[\alpha]_D^{20}$ +34.2 (*c* = 3; H_2O).

^1H NMR (D_2O): δ = 0.87 (d, 3 H, *J* = 6.1 Hz), 0.92 (d, 3 H, *J* = 6.1 Hz), 1.43 (s, 3 H), 1.62 (m, 2 H), 1.82 (m, 1 H).

(*S*)-3-Methyl-1,2,3,4-tetrahydro-3-isoquinolinocarboxylic Acid (9)
White solid; yield: 73%; $[\alpha]_D^{25}$ -31.9 (*c* = 1; 6N HCl), lit.[20a] (*R*)-isomer $[\alpha]_D^{20}$ +31.6 (*c* = 1; 6N HCl).

^1H NMR (D_2O): δ = 1.52 (s, 3 H), 3.03 (d, 1 H, *J* = 17.1 Hz), 3.28 (d, 1 H, *J* = 17.1 Hz), 4.32 (d, 1 H, *J* = 16.2 Hz), 4.45 (d, 1 H, *J* = 16.2 Hz), 7.27 (m, 4 H).

(*S*)-α-Methylproline (11)
White solid; yield: 81%; $[\alpha]_D^{25}$ -71.9 (*c* = 1; MeOH), lit.[20a] $[\alpha]_D$ -72.1 (*c* = 1; MeOH).

^1H NMR (D_2O): δ = 1.53 (s, 3 H), 3.59, 2.03 (2m, 3 H), 2.28 (m, 1 H), 3.22–3.39 (m, 2 H).

Palladium(0)-Catalyzed Allylation of Oxazinones (6*R*)-1; General Procedure

To a solution of the oxazinone (6*R*)-**1** (116 mg, 0.5 mmol) and the corresponding allylic carbonate (0.5 mmol) in anhyd THF (1 mL) was added a solution of $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and dppe (28 mg, 0.07 mmol) [or $Pd(OAc)_2$ (6 mg, 0.025 mmol) and PPh_3 (13 mg, 0.05 mmol), see Table 5 entry 2] in anhyd THF (0.5 mL). The reaction was stirred at r.t. until completion (GLC), the solvent was evaporated (15 Torr) and the residue analyzed by ^1H NMR and/or GLC to determine the de. Further purification by flash chromatography (silica gel, hexane/EtOAc gradients) afforded the corresponding major pure regio- and diastereoisomers (6*R*)-**6** (see Table 5).

(3*S*,6*R*)-6-Isopropyl-3-methyl-3-(2-methylprop-2-enyl)-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6o]
Colorless oil; TLC: R_f 0.68 (hexane/EtOAc = 7/3); $[\alpha]_D^{27}$ +80.0 (*c* = 1.4; CH_2Cl_2).

IR (film): ν = 1645, 1660, 1745 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.76 (d, 3 H, *J* = 6.9 Hz), 1.12 (d, 3 H, *J* = 6.9 Hz), 1.63 (s, 3 H), 1.65 (s, 3 H), 2.07 (dsept, 1 H, *J* = 6.9, 2.4 Hz), 2.55 (d, 1 H, *J* = 13.1 Hz), 2.83 (d, 1 H, *J* = 13.1 Hz), 4.69 (s, 1 H), 4.83 (t, 1 H, *J* = 1.7 Hz), 5.46 (d, 1 H, *J* = 2.4 Hz), 7.43 (m, 3 H), 7.57 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.1, 19.0, 24.2, 28.3, 31.8, 49.6, 61.7, 84.6, 115.4, 126.5, 128.7, 130.3, 136.6, 141.1, 161.9, 171.0.

MS: *m/z* (%) = 285 (M^+, 25), 230 (100), 185 (44), 145 (63), 105 (56), 91 (56), 43 (80).

HRMS for $C_{18}H_{23}NO_2$ calcd 285.1729, found 285.1711.

(3*S*,6*R*)-6-Isopropyl-3-methyl-5-phenyl-3-[(*E*)-3-phenylprop-2-enyl]-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6p]
Colorless oil; TLC: R_f 0.60 (hexane/EtOAc = 7/3); $[\alpha]_D^{29}$ +92.6 (*c* = 1.3; CH_2Cl_2).

IR (film): ν =1659, 1740 cm^{-1}.

^1H NMR ($CDCl)_3$: δ = 0.75 (d, 3 H, *J* = 6.9 Hz), 1.06 (d, 3 H, *J* = 6.9 Hz), 1.70 (s, 3 H), 2.02 (dsept, 1 H, *J* = 6.9, 2.4 Hz), 2.71 (dd, 1 H, *J* = 13.4, 7.6 Hz), 2.94 (dd, 1 H, *J* = 13.4, 7.6 Hz), 5.35 (d, 1 H, *J* = 2.4 Hz), 6.03 (m, 1 H), 6.39 (d, 1 H, *J* = 15.9 Hz), 7.23 (m, 5 H), 7.41–7.52 (m, 5 H).

^{13}C NMR ($CDCl)_3$: δ = 15.1, 18.9, 27.3, 31.7, 45.9, 61.5, 84.5, 123.5, 126.2, 126.5, 127.4, 128.5, 128.7, 130.3, 134.9, 136.5, 137.1, 162.7, 170.9.

MS: *m/z* (%) = 347 (M^+, 2), 117 (100).

HRMS for $C_{23}H_{25}NO_2$ calcd 347.1885, found 347.1871.

(3*S*,6*R*)-3-[(*E*)-But-2-enyl]-6-isopropyl-3-methyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6q]
Colorless oil; TLC: R_f 0.68 (hexane/EtOAc = 7/3); $[\alpha]_D^{25}$ +66 (*c* = 1; CH_2Cl_2) (for a 96:4 diast. ratio).

IR (film): ν = 1659, 1742 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.76 (d, 3 H, *J* = 7.0), 1.11 (d, 3 H, *J* = 7.0 Hz), 1.62 (d, 3 H, *J* = 6.4 Hz), 1.63 (s, 3 H), 2.06 (dsept, 1 H, *J* = 7.0, 2.4 Hz), 2.49 (dd, 1 H, *J* = 13.4, 7.0 Hz), 2.71 (dd, 1 H, *J* = 13.4, 8.2 Hz), 5.27 (m, 1 H), 5.42 (d, 1 H, *J* = 2.4 Hz), 5.50 (m, 1 H), 7.44 (m, 3 H), 7.57 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.1, 18.2, 19.0, 27.2, 31.8, 45.7, 61.5, 84.5, 124.5, 126.5, 128.8, 130.3, 130.7, 136.6, 162.2, 171.12.

MS: *m/z* (%) = 285 (M^+, 12), 231 (51), 230 (63), 188 (61), 145 (89), 105 (70), 91 (59), 55 (80), 43 (100).

HRMS for $C_{18}H_{23}NO_2$ calcd 285.1729, found 285.1725.

(3*S*,6*R*)-6-Isopropyl-3-methyl-3-[(2*E*)-penta-2,4-dienyl]-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6r]
Colorless oil; TLC: R_f 0.66 (hexane/EtOAc = 7/3); $[\alpha]_D^{25}$ +97.7 (*c* = 1.2; CH_2Cl_2).

IR (film): ν = 1658, 1741 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.76 (d, 3 H, *J* = 6.9 Hz), 1.10 (d, 3 H, *J* = 6.9 Hz), 1.65 (s, 3 H), 2.05 (dsept, 1 H, *J* = 6.9, 2.4 Hz), 2.59 (dd, 1 H, *J* = 13.4, 7.6 Hz), 2.81 (dd, 1 H, *J* = 13.4, 7.9 Hz), 5.01 (d, 1 H, *J* = 10.4 Hz), 5.08 (d, 1 H, *J* = 16.8 Hz), 5.40 (d, 1 H, *J* = 2.4 Hz), 5.51 (m, 1 H), 6.05 (dd, 1 H, *J* = 15.2, 10.7 Hz), 6.25 (m, 1 H), 7.43 (m, 3 H), 7.56 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 15.1, 19.0, 27.3, 31.7, 45.5, 61.3, 84.6, 116.9, 126.6, 127.6, 128.7, 130.3, 135.9, 136.5, 136.6, 162.6, 170.9.

MS: *m/z* (%) = 297 (M^+, 20), 230 (81), 188 (63), 161 (50), 105 (75), 91 (62), 67 (52), 43 (100).

HRMS for $C_{19}H_{23}NO_2$ calcd 297.1729, found 297.1719.

(3*S*,6*R*)-3-[(*E*)-Hex-2-enyl]-6-isopropyl-3-methyl-5-phenyl-3,6-dihydro-2*H*-1,4-oxazin-2-one [(6*R*)-6s]
Colorless oil; TLC: R_f 0.76 (hexane/EtOAc = 7/3); $[\alpha]_D^{30}$ +66.6 (*c* = 2; CH_2Cl_2).

IR (film): ν = 1660, 1742 cm^{-1}.

^1H NMR ($CDCl)_3$: δ = 0.76 (d, 3 H, *J* = 6.9 Hz), 0.83 (t, 3 H, *J* = 7.3 Hz), 1.11 (d, 3 H, *J* = 6.9 Hz), 1.30 (sext, 2 H, *J* = 7.3 Hz), 1.64 (s, 3 H), 1.92 (q, 2 H, *J*=7.0 Hz), 2.06 (dsept, 1 H, *J* = 6.9, 2.4 Hz), 2.51 (dd, 1 H, *J* = 13.3, 7.0 Hz), 2.73 (dd, 1 H, *J* = 13.3, 7.6 Hz), 5.24 (m, 1 H), 5.42 (d, 1 H, *J* = 2.4 Hz), 5.46 (m, 1 H), 7.43 (m, 3 H), 7.57 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 13.5, 15.1, 19.0, 22.4, 27.3, 31.8, 34.7, 45.7, 61.5, 84.4, 123.5, 126.6, 128.7, 130.3, 136.0, 136.6, 162.1, 171.1.

MS: *m/z* (%) = 313 (M^+, 3), 231 (53), 230 (100), 145 (80), 105 (53), 55 (68), 43 (93).

HRMS for $C_{20}H_{27}NO_2$ calcd 313.2042, found 313.2042.

Hydrolysis of Oxazinones (6*R*)-6a and 12; Synthesis of AMAAs (*S*)-7a and 13; General Procedure
The corresponding oxazinone (0.5 mmol) was dissolved in THF (2 mL) and 2M HCl (3 mL) and the mixture was stirred at r.t. for 3 h. The solvents were evaporated and the residue was dissolved in a mixture of THF (2 mL) and aq 1M $LiOH{\cdot}H_2O$ (1.5 mL). The solution was stirred overnight at r.t., the solvent evaporated (15 Torr), and the crude was purified using a Dowex-50 column (H_2O and 10% NH_4OH) yielding the free amino acids.

(*S*)-α-Allylalanine [(*S*)-7a]
White solid; yield: 57%; (*S*)-**7a**·HCl: $[\alpha]_D^{25}$ -13.4 (*c* = 1.3; D_2O), lit.[8d] $[\alpha]_D$ -14.4 (*c* = 1.3; D_2O).

^1H NMR (D_2O): δ = 1.44 (s, 3 H), 2.41 (dd, 1 H, *J* = 14.7, 8.9 Hz), 2.62 (dd, 1 H, *J* = 14.7, 7.0 Hz), 5.22 (m, 2 H), 5.71 (m, 1 H).

(*S*)-2-Methyl-4-methyleneproline (13)

White solid; yield: 79%; mp 240–250 °C (dec.); $[\alpha]_D^{25}$ -29.5 (*c* = 1; H_2O).

IR (KBr): ν = 1609, 3070, 3426 cm^{-1}.

^1H NMR (D_2O): δ = 1.57 (s, 3 H), 2.65 (d, 1 H, *J* = 16.5 Hz), 2.97 (d, 1 H, *J* = 16.5 Hz), 3.97 (s, 2 H), 5.14 (s, 1 H), 5.18 (s, 1H).

^{13}C NMR (H_2O, acetone): δ = 21.1, 41.4, 48.4, 70.7, 110.6, 139.8, 176.7.

Anal. Calcd for $C_8H_{11}NO_2$: C 59.54, H 7.86, N 9.93. Found: C 59.09, H 7.57, N, 9.29.

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References

(1) For reviews see:
(a) Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon: Oxford, 1989.
(b) Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238.
(c) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1540.
(d) North, M. *Contemp. Org. Synth.* **1996**, 323.
(e) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708.
(f) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225.
(2) For some examples see:
(a) Polese, A.; Formaggio, F.; Crisma, M.; Valle, G.; Toniolo, C.; Bonora, G. M.; Broxterman, Q. B.; Kamphuis, J. *Chem. Eur. J.* **1996**, *2*, 1104.
(b) Higginbotton, M.; Kneen, C.; Ratcliffe, G. S. *J. Med. Chem.* **1992**, *35*, 1572.
(c) Altmann, K.-H.; Altmann, E.; Mutter, M. *Helv. Chim. Acta* **1992**, *75*, 1198.
(d) Obrecht, D.; Bohdal, U.; Daly, J.; Lehmann, C.; Schönholzer, P.; Müller, K. *Tetrahedron* **1995**, *51*, 10883.
(e) Obrecht, D.; Altolfer, M.; Lehmann, C.; Schönholzer, P.; Müller, K. *J. Org. Chem.* **1996**, *61*, 4080.
(f) Bisang, C.; Weber, C.; Inglis, J.; Schiffer, C. A.; van Gunsteren, W. F.; Jelesarov, I.; Bosshard, H. R.; Robinson, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7904.

(g) Hernández, J.-F.; Kornreich, W.; Rivier, C.; Miranda, A.; Yamamoto, G.; Andrews, J.; Taché, Y.; Vale, W.; Rivier, J. *J. Med. Chem.* **1993**, *36*, 2860.
(3) For some examples see:
(a) Horwell, D. C.; Ratcliffe, G. S.; Roberts, E. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 169.
(b) Khosla, A.; Stachowiak, K.; Sunby, R. R.; Bumpus, F. G.; Pirion, F.; Lintner, K.; Fermandjian, S. *Proc. Nat. Acad. Sci. U.S.A.* **1981**, *78*, 757.
(c) Boesten, W. H. J.; Dassen, B. H. N.; Kleijans, J. C. S.; van Agen, B.; van der Wal, S.; de Vries, N. K.; Shoemaker, H. E.; Meijer, E. M. *J. Agric. Food Chem.* **1991**, *39*, 154.
(4) For some examples see:
Yano, S.; Nakanishi, Y.; Ikuina, Y.; Ando, K.; Yoshida, M.; Saitoh, Y.; Matsuda, Y.; Bando, C. *J. Antibiot.* **1997**, *50*, 992.
Yamashita, T.; Iijima, M.; Nakamura, H.; Isshiki, K.; Naganawa, H.; Hattori, S.; Hamada, M.; Ishizuka, M.; Takeuchi, T. *J. Antibiot.* **1991**, *44*, 557.
Horn, W. S.; Smith, J. L.; Bills, G. F.; Raghoobar, S. L.; Helms, G. L.; Kurtz, M. B.; Marrinan, J. A.; Frommer, B. R.; Thornton, R. A.; Mandala, S. M. *J. Antibiot.* **1992**, *45*, 1692.
Becker, D.; Kiess, M.; Brückner, H. *Liebigs Ann/Recueil* **1997**, 767.
(5) (a) Kiick, D. M.; Cook, P. F. *Biochemistry* **1983**, *22*, 375.
(b) Stinson, J. C. *Chem. Eng. News* **1992**, *70*(39), 46.
(6) (a) O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591.
(b) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507.
(c) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. V.; Parmár, V. S.; Kumar, R.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851.
(7) Recently O'Donnell's glycine-benzophenone Schiff base ($Ph_2C{=}NCH_2CO_2t$-Bu) has been monoalkylated under PTC conditions using cinchonium or cinchonidinium salts as catalysts at -60 or -78 ºC with up to 99.5% ee (Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414) or at r.t. with up to 94% ee (Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595).
(8) (a) Schöllkopf, U.; Westphalen, K.-O.; Schröder, J.; Horn, K. *Liebigs Ann. Chem.* **1988**, 781.
(b) Studer, A.; Seebach, D. *Liebigs Ann.* **1995**, 217.
(c) Zydowsky, T. M.; de Lara, E.; Spanton, S. G. *J. Org. Chem.* **1990**, *55*, 5437.
(d) Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276.
(e) Belokon, Y. N.; Chernoglazova, N. I.; Kochetkov, C. A.; Garbalinskaya, N. S.; Belikov, V. M. *J. Chem. Soc., Chem. Commun.* **1985**, 171.
(9) Berkowitz, D. B.; Smith, M. K. *J. Org. Chem.* **1995**, *60*, 1233.
Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; Lapeña, Y. *Tetrahedron* **1997**, *53*, 5891.
Ayoub, M.; Chassaing, G.; Loffet, A.; Lavielle, S. *Tetrahedron Lett.* **1995**, *36*, 4069.
Ferey, V.; Toupet, L.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 430.
(10) For preliminary communications see:
(a) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 995.
(b) Chinchilla, R.; Galindo, N.; Nájera, C. *Tetrahedron: Asymmetry* **1998**, *9*, 2769.
(c) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nájera, C. *Tetrahedron: Asymmetry* **1998**, *9*, 2223.
(11) We have shown that chiral 1,2,3,6-tetrahydro-2-pyrazinones from alanine can also be diastereoselectively alkylated under PTC conditions: Abellán, T.; Nájera, C.; Sansano, J. M. *Tetrahedron: Asymmetry* **1998**, *9*, 2211.
(12) Caplar, V.; Lisini, A.; Kajfez, Kolbah, D.; Sunjic, V. *J. Org. Chem.* **1978**, *43*, 1355.
(13) Cowper, R. M.; Davidson, L. H. *Organic Syntheses*; Wiley: New York, 1943; Collect Vol. II, p 480.
(14) For X-ray diffraction data see ref. 10a.
(15) The AM1 semiempirical method, as implemented in Hyperchem 5 from Hypercube Inc., was used for these calculations.
(16) Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz, H. *Chem. Ber.* **1994**, *127*, 2435, and references cited therein.
(17) O'Donnell, M. J.; Lugar, C, W.; Pottorf, R. S.; Zhou, C.; Scott, W. L.; Cwi, C. L. *Tetrahedron Lett.* **1997**, *38*, 7163.
O'Donnell, M. J.; Zhou, C.; Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070.
(18) Seebach, D.; Beck, A. K.; Studer, A. In *Modern Synthetic Methods 1995*; VCH Publishers: Basel, 1995; Vol. 7, p 1.
(19) D-isovaline and α-aminoisobutyric acid (Aib) are the α,α-disubstituted α-amino acids which are found primarily in nature: see ref. 1b.
(20) For synthesis of cyclic AMAAs by dialkylation of chiral cyclic alanine templates see:
(a) Schöllkopf, U.; Hinrichs, R.; Lonsky, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 143.
(b) Bajgrowicz, J.; El Achquar, A.; Roumestant, M.-L.; Pigière, C.; Viallefont, P. *Heterocycles* **1986**, *24*, 2165.
(c) Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs. Ann. Chem.* **1989**, 1215.
(21) For synthesis of cyclic AAs by dialkylation of glycine templates see:
Mazón, A.; Nájera, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1855.
Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656.
(22) Prepared from 3-chloro-2-chloromethylprop-1-ene by reaction with NaI in acetone.
(23) Manfre, F.; Kern, J.-M.; Biellmann, J.-F. *J. Org. Chem.* **1992**, *57*, 2060.
(24) Non-chiral imino esters of glycine and alanine have been previously allylated under neutral Pd(0)-catalysis: Genêt, J. P.; Juge, S.; Achi, S.; Mallart, S.; Ruiz Montes, J.; Levif, G. *Tetrahedron* **1988**, *44*, 5263.
Chiral Oppolzer's benzophenone glycine equivalent has been diastereoselectively allylated under neutral Pd(0)-catalysis: Voigt, K.; Stolle, A.; Salaün, J.; de Meijere, A. *Synlett* **1995**, 226.
(25) For selected references, see:
Denniel, V.; Bauchat, P.; Danion, D.; Danion-Bougot, R. *Tetrahedron Lett.* **1996**, *37*, 5111.
Ojima, I.; Tzamarioudaki, M.; Eguchi, M. *J. Org. Chem.* **1995**, *60*, 7078.
(26) Kurokawa, N.; Ohfune, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6041.
Ohfune, Y.; Hori, K.; Sakaitani, M. *Tetrahedron Lett.* **1986**, *27*, 6079.
Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1985**, *26*, 5307.
(27) Kawatsura, M.; Uozumi, Y.; Hayashi, T. *Chem. Commun.* **1998**, 217.
(28) Kihara, M.; Ikeuchi, M.; Jinno, K.; Kashimoto, M.; Kobayashi, Y.; Nagao, Y. *Tetrahedron* **1993**, *49*, 1017.
(29) Cativiela, C.; Diaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 261.
(30) *Dictionary of Organic Compounds*; Chapman & Hall: New York, 1982.
(31) Acher, F.; Azerad, R. *Tetrahedron: Asymmetry* **1994**, *5*, 731.

(32) Achiwa, K.; Terashima, S.; Mizuno, H.; Takamura, N.; Kitagawa, T.; Ichikawa, K.; Yamada, S. *Chem. Pharm. Bull.* **1970**, *18*, 61.

(33) Kruizinga, W. H.; Bolster, J.; Kellog, R. M.; Kamphuis, J.; Boesten, W. H. J.; Meijer, E. M.; Schoemaker, H. E. *J. Org. Chem.* **1988**, *53*, 1826.