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SYNTHESIS OF α-AMINO ACIDS USING TRANSITION METAL CATALYSIS - ALKYLATION OF SCHIFF BASES DERIVED FROM α-AMINO ACID ESTERS (REGIO, STEREO-SELECTIVITY)

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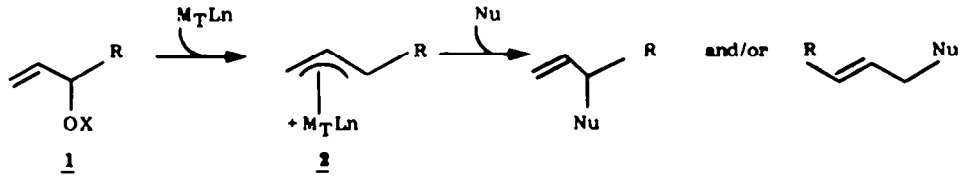
Abstract : A general approach to the synthesis of γ,δ-unsaturated α-amino acid esters is described. Schiff bases derived from glycine and alanine esters were alkylated in the presence of palladium or molybdenum catalysts under neutral or basic conditions using allylic carbonates, esters or halides, (20 - 95 % yield). These less stabilized nucleophiles reacted with the η^3 allyl species on the side opposite to the palladium and they can be classified as soft nucleophiles. The regioselectivity was studied with various unsymmetrical electrophiles. After hydrolysis, several functionalized α-amino acids of biological interest (enzymes inhibitors) were obtained. Asymmetric palladium allylic alkylation of the benzophenone imine glycine methyl ester using $Pd(OAc)_2$ + (+)DIOP was achieved with up to 68 % ee ; the enantioselective Pd-promoted alkylation of this new and useful prochiral nucleophile for the synthesis of α-amino acids is one of the highest ee known.

INTRODUCTION.

Transition metal catalysis is becoming an important synthetic methodology for chemo, regio and stereoselective carbon-carbon bond formation. For allylic alkylations, palladium is widely used as a catalyst in organic synthesis.[1-3] Catalysts such as molybdenum[4], tungsten[5], nickel[6] and rhodium[7] complexes have been recently introduced to achieve selective transformation and to modify the reactivity of the allylic complexes such as **2**, generated *in situ* by oxidative addition of an allylic substrate **1** (ethers, alcohols, esters, carbonates, etc.). (scheme I).



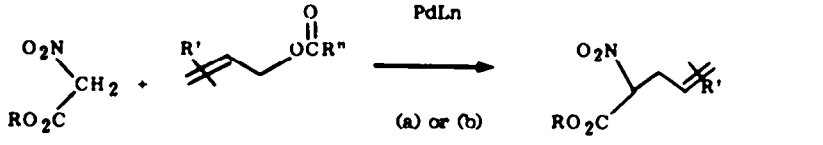
M_T = Pd, Ni, Mo, W ...

Scheme I

The usefulness of this methodology in synthesis has been demonstrated by the utilization of carbanions and heteronucleophiles. Of particular interest, with palladium catalysis that area has been extensively studied and applied to soft active methylene compounds such as malonates, acetoacetates etc. and harder organometallic nucleophiles.

Our research was recently focused on potential routes to α-amino acids that rely upon palladium-alkylation under very mild conditions of carbonucleophile precursors, such as α-nitro acetic esters[8] (scheme II), and Schiff bases derived from glycine methyl ester[9] which, after acidic hydrolysis, gave the corresponding α-amino acids. Since the earlier reports of Stork et al.[10] and Yamada[11] on the classical

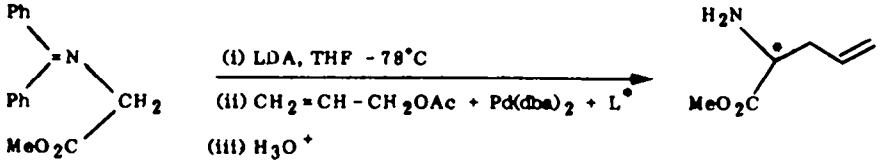
alkylation of amino acid esters derived from Schiff bases, elegant and efficient routes to α-amino acids have been widely reported using strong bases[12] and phase transfer conditions.[13] Schiff bases of α-amino acid esters are interesting carbonucleophiles and are capable of expanding the scope of transition metal allylic alkylation. We have found[9] that when allylic carbonates[14] are used as alkylating derivatives the alkylation of Schiff bases of glycine ester can be performed under mild and neutral conditions. We have also reported[15] that the anion of the benzophenone imine of glycine methyl ester can be used as a new and interesting prochiral nucleophile in enantioselective palladium-promoted alkylation (scheme III).



(a) R" = CH_3 NaH or KF/Alumina.

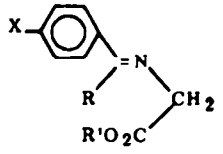
(b) R" = OEt without base.

Scheme (II)



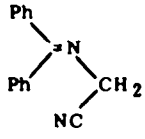
Scheme (III)

Here we report chemo, stereo- and regiochemical results obtained for the catalytic alkylation of Schiff bases **4**, **5**, **6**, **7**, **8** and **9** derived from glycine ester, aminoacetonitrile and alanine esters with various η^3 allyl intermediates of type **11**, generated catalytically *in situ* from the allylic substrates **10** (e.g. allylic esters, carbonates and halides) Scheme IV. This catalyzed carbon-carbon bond formation leads to γ, δ-unsaturated, functionalized, α-amino acids which constitute an important class of biologically active compounds as they may act as enzyme inactivators.[16]



4 : X = H ; R = Ph ; R' = Me

5 : X = Cl ; R = H ; R' = Et



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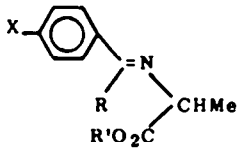
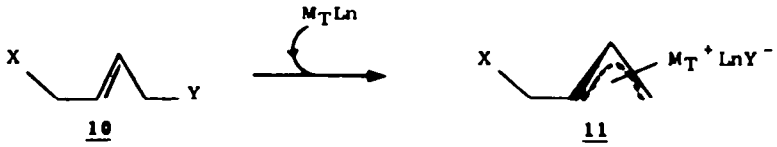


7 : X = H ; R = Ph ; R' = Me

8 : X = H ; R = Ph ; R' = Et

9 : X = Cl ; R = H ; R' = Et



10 **11**

Scheme IV

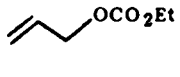
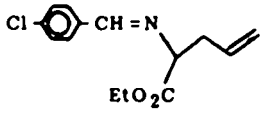
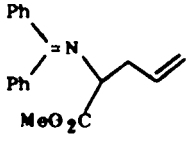
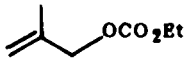
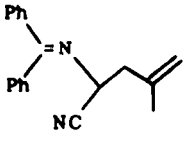
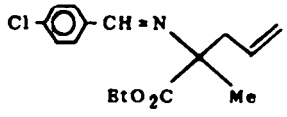
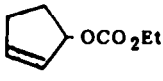
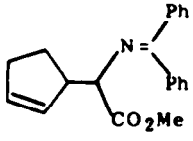
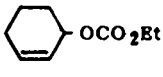
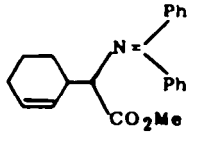
RESULTS.

1 - Alkylation of Schiff bases under neutral conditions.

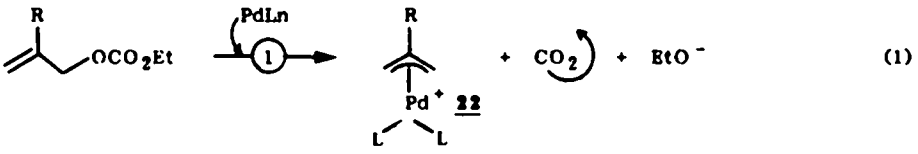
The Schiff bases used 4, 5, 6, 7 and 8 are crystalline and readily synthesized according to the O'Donnell procedure.[17] The alanine derivative 9 is obtained from the corresponding alanine ethyl ester hydrochloride and p-chlorobenzaldehyde, in the presence of triethyl amine. In order to compare the reactivity of these different Schiff bases, the alkylation was first carried out with allyl and 2-methyl allyl carbonate 12 and 15.

As shown in table I (entry 1), the reaction of p-chlorobenzaldehyde imine 5 proceeded smoothly in 1 h at room temperature. The benzophenone imine derivatives 4, 6 appeared to be less reactive, since the reaction required 2 h at 20°C in the presence of the $Pd(dppe)_2$ a catalyst, giving 14 and 16 respectively (entries 2,3).

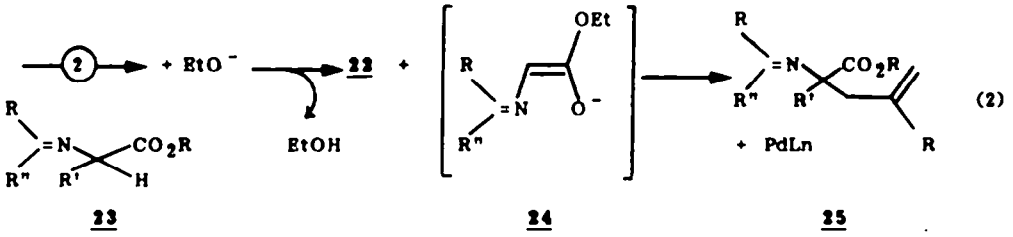
TABLE I - Palladium alkylation of Schiff bases under neutral conditions.

Entry	Schiff base	Allylic substrate	Time (h)	T° (C)	Catalyst (%)	Products		Yield (%)
1	5	 12	1	20	$Pd(dppe)_2$(5)		13	74
2	4	12	2	20	$Pd(dppe)_2$(5)		14	80
3	6	 15	2	20	$Pd(dppe)_2$(5)		16	65
4	8	12	25	25	$Pd(dppe)_2$(5)	no reaction		-
5	9	12	5	25	$Pd(dba)_2$(5) + (dppe)X10		17	95
6	4	 18	1.5	25	$Pd(dppe)_2$(3)		19	80
7	4	 20	2	25	$Pd(dppe)_2$(5)		21	70

The benzophenone imine of alanine ethyl ester 8 was unreactive under the same conditions (entry 4). In contrast, the aldimine 9 could be readily alkylated to give an almost quantitative yield of the α,α-dialkylated product 17 (entry 5). This difference in reactivity between 7 and 9 can be explained by the following mechanism :



(1)



(2)

23 **24** **25**

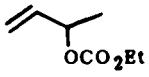
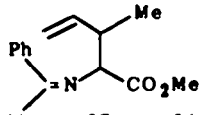
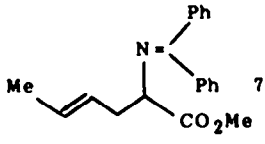
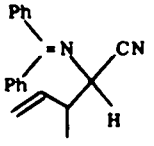
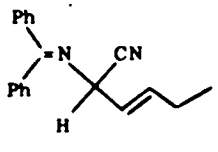
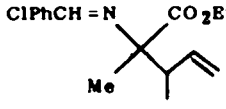
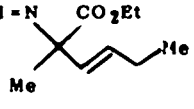
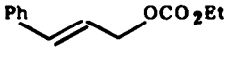
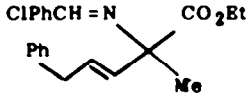
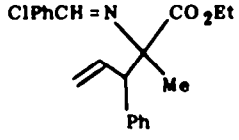
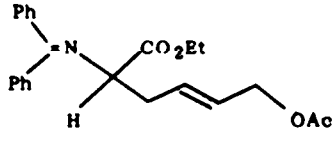
The classical oxidative addition of palladium(O) catalyst affords the electrophilic η^3 species **22** with simultaneous formation of carbon dioxide and ethoxide anion eq.(1). The ethoxide anion deprotonates the Schiff base **23**, followed by nucleophilic addition of the enolate **24** on the cationic η^3 allyl palladium affording the alkylated Schiff bases **25** with regeneration of the catalyst eq. (2). Ketimine (R = R" = Ph) reactivity of alanine ester is blocked at step (2) because the benzophenone imine alanine ethyl ester Schiff base is not acidic enough and the ethoxide anion cannot pick up the proton.[18] In contrast to the aldimine moiety (R = p-ClC$_6$CH$_4$, R" = H) there is a substantial increase in the acidity of the α-proton of the Schiff base[18] and thus the deprotonation reaction can occur.

The two cyclic allylic carbonates **18** and **20** have shown similar reactivity with glycine methyl ester Schiff bases. The alkylation of the cyclopentenyl carbonate **18** proceeded rapidly (2 h, 25°C) and gave **19** (entry 6) in 80 % yield. Under the same conditions, the cyclohexenyl carbonate **20** rendered a 70 % yield of the corresponding alkylated product **21** (entry 7).

The alkylation of the Schiff bases was also studied with unsymmetrically substituted carbonates such as **26**, **33** and **36** as shown in table II. The reaction with glycine and alanine ester Schiff bases **4**, **6**, **9** was carried out in THF using various ligands. In the case of the Schiff bases **4** and **9**, the dppe ligand favored the linear products **28** and **34** over the branched products **27** and **35** (entries 1, 5). Surprisingly, alanine Schiff base **9** showed some tendency to be alkylated with **26** at the more sterically hindered allylic terminus by using dppe as a ligand and gave **31** and **32** in a 6/4 ratio (entry 3). The branched product **31** was obtained as single product (entry 4) using a larger (more crowding) ligand such as PPh_3.[19]

Since our first observation of the chemo, regio and selective alkylation of 1,4-hydroxyacetates[20], bifunctional 1,4-allylic derivatives have been widely used in directing nucleophile attack (e.g. chloroacetates,[21] vinyl epoxides,[22] acetate phosphonates).[23] More recently, we have shown that 1,4-acetoxy carbonates reacted chemoselectively with nitroacetic esters.[8] Thus, the reaction of Schiff base of glycine methyl ester (20°C, 2 h) with (Z)-4-acetoxy-2 butenyl ethyl carbonate is highly chemo, regio and stereoselective. The Schiff base **4** underwent exclusive attack at the 4-position of the acetoxy group and afforded the highly functionalized α-alkylated, γ,δ-unsaturated ester **37** with E stereochemistry entry (6). This material has been recently used as an intermediate in natural product synthesis.[24]

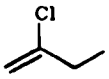
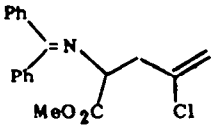
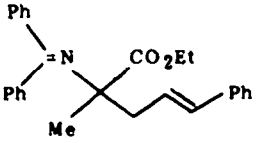
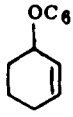
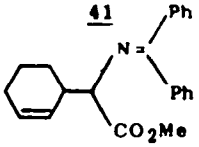
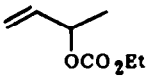
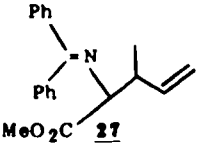
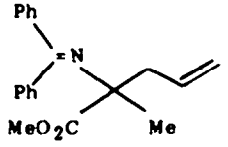
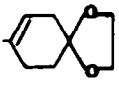
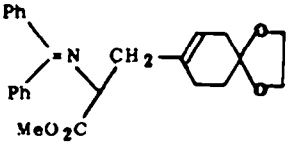
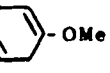
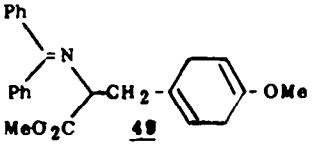
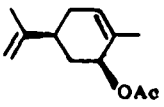
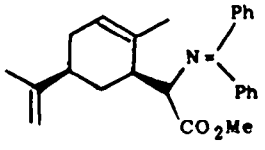
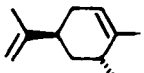
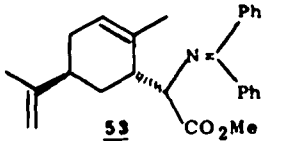
TABLE II - Palladium alkylation at 20°C of Schiff bases under neutral conditions with unsymmetrical allylic substrates.

Entry	Schiff base	Allylic substrate	Time (h)	Catalyst (%) Ligand (%)	Products	Yield (%)
1	4	 **26**	7	Pd(dppe)$_2$(2.5)	 **27** 34 : 66  **28**	75
2	6	**26**	72	Pd(dba)$_2$(2.5) PCy_2Ph (5)	 **29** 80 : 20  **30**	75
3	9	**26**	24	Pd(dppe)$_2$(5)	 **31** 60 : 40  **32**	65
4	9	**26**	60	Pd(dba)$_2$(5) $P(Ph)_3$(20)	100 : 0	70
5	9	 **33**	48	Pd(dppe)$_2$(5)	 **34** 75 : 25  **35**	93
6	4	 **36**	12	Pd(dppe)$_2$(5)	 **37**	70

2 - Allylation of Schiff bases under basic conditions.

The utilization of the anions of these less stabilized carbanions in transition metal catalyzed alkylation with allyl esters or halides is also particularly efficient, some examples are shown in table III. The reactions proceeded in THF, at low temperature (entries 1 - 3). The lithium enolate of benzophenone imine alanine methyl ester reacted with cinnamyl acetate **40** and afforded (entry 2 table III) the linear product **41** as a single product (compare with entry 5 table II). The 2,6-dichlorobenzoate **42** reacted at low temperature (-40°C) and gave the derivative **21** in good yield (80 %) entry 3.

TABLE III - Palladium and molybdenum catalyzed alkylation of Schiff bases under basic conditions

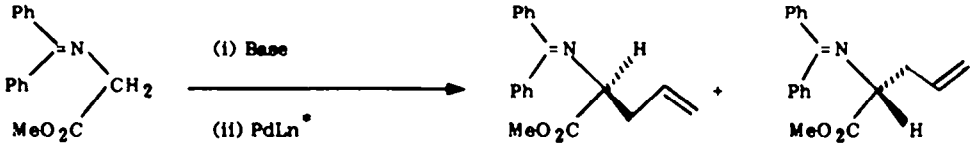
Entry	Schiff Base*	Allylic substrate	Catalyst (%) Ligand (%)	Temp. (°C)	Time (h)	Product	Yield (%)
1	**4**(a)	 **38**	$Pd(dba)_2$(5) $P(Ph)_3$(10)	-60	6	 **39**	75
2	**7**(a)	 **40**	$Pd(dba)_2$(4) dppe(8)	-40 +25	24	 **41**	92
3	**4**(a)	 **42**	$Pd(dba)_2$(3) dppe(6)	-40	2	 **21**	80
4	**4**(b)	 **43**	$Mo(CO)_6$(15)	60	1.5	 **27**	50
5	**7**(c)	 **44**	 $(CO)_2Mo(CH_3CN)_2$ (5)	12	25	 **45**	28
6	**4**(a)	 **46**	 PdCl/2(5) dppe (10)	6	45	 **47**	20
7	**4**(a)	 **48**	$Pd(dba)_2$(5) dppe(10)	48	25	 **49**	85
8	**4**(a)	 **50**	$Pd(dba)_2$(3) dppe (6)	25	6	 **51**	20
9	**4**(a)	 **52**	$Pd(dba)_2$(3) dppe (6)	25	6	 **53**	39

*In the form of the corresponding enolate performed by treatment with : (a) LDA ; (b) N,O-Bis (trimethylsilyl) acetamide (BSA) ; (c) NaH

Interestingly these nucleophiles, in their sodio enolate form or in the presence of BSA, reacted in the presence of molybdenum catalysts in moderate yields. Thus it is possible to achieve clean alkylation of glycine ester in the presence of $Mo(CO)_6$ at the more substituted carbon giving the alkylated Schiff bases **27** in 50 % yield (entry 4). Molybdenum-catalyzed alkylation of the alanine Schiff base proceeded in lower yield 28 % (entry 5). The alkylation of **4** with functionalized cycloalkenyl acetate **46**, **48** highlighted the synthetic usefulness of this methodology and gave in fair to good yields (20 and 85 %) the derivatives **47** and **49**. The highly functionalized 2'-cycloalkenyl derivative **49** is a valuable intermediate for the synthesis of an irreversible inhibitor (anticapsine) of glucosamine-6-phosphate synthetase.[25] The stereochemistry of the reaction was examined with the cis carveol acetate **50** and trans carveol benzoate **52**. The treatment of these two derivatives with the lithium enolate derived from benzophenone imine glycine methyl ester in the presence of Pd(o) catalyst gave the cis **51** and trans **53** alkylated products in moderate yield (20 and 39 %), respectively. Since it is known that oxidative addition occurs with inversion of configuration[2], the retention of configuration at the allylic center indicates that the Schiff bases anions reacted on the η^3 allyl species at the side opposite to the palladium. These less stabilized carbonucleophiles can be classified as soft nucleophiles in the palladium-catalyzed allylation.

3 - Enantioselective alkylation.

In recent years enantioselective C-C bond forming methods using transition metal catalysis have been widely developed.[26] A particular interest of the system described above is its potential to be used in the synthesis of highly substituted chiral α-amino acids.[27] In our preliminary study the diphenyl imine glycine methyl ester **4** has been shown to be an interesting prochiral nucleophile[15] in Pd - catalyzed alkylation[28] and, in this regard several ligands have been tested. Carefully examining the different factors[29] in this reaction (scheme V) we found that the ratio of palladium to chiral phosphine is crucial. At least 3 to 4 phosphorus per palladium were necessary to maximize enantioselective C-C bond forming. Enantioselectivity was effected by the nature of the catalyst, as well as the base, in generating the corresponding anion as shown in table IV.



4 **14**

Scheme V

TABLE IV - Enantioselective alkylation of benzophenone imine of glycine methyl ester **4** with allylic acetate

Entry	Base	Catalyst (%) Ligand (%)	Temp. (°C)	Time (h)	Product	Yield (%)	ee (%)
1	LDA	$Pd(dba)_2$ (3) (-)DIOP (6)	-35	6	(S)	62	38.5
2	LDA	"	-55	0.25	(S)	50	55
3	t.BuOK	$Pd(dba)_2$ (3) (+)DIOP (6)	-60	4	(R)	22	7
4	LHMDS	$Pd(OAc)_2$ (3) (+)DIOP (6)	-60	3	(R)	68	68

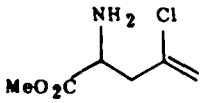
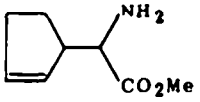
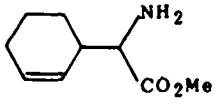
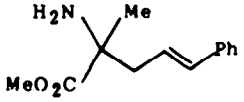
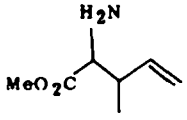
The carbanion generated by the action of LDA at -35°C afforded the α-alkylated product in 38.5 ee. Lowering the reaction temperature increased the enantioselectivity up to 55 % (entries 1-2). The nature of

the base also exhibited a dramatic influence. enantiomeric excess (7 %) was observed using t-BuOK (entry 3). Interestingly, the use of $Pd(OAc)_2$ (+)DIOP as the catalyst at -60°C increased the enantiomeric excess up to 68 %. This catalyst is the most efficient one (compare entries 2 and 4).

4 - Hydrolysis of alkylated Schiff Bases. Synthesis of α-alkylated and α,α-dialkylated aminoesters.

The alkylated Schiff bases can be readily hydrolyzed into the corresponding α-mono and α,α'-dialkylated amino acid esters in good yields (table V). Thus, we have prepared 2-chloroallyl glycine **54**, enzyme inactivators of γ-cystathionase,[16a] and the methyl analogue **58** of methyl ester of trans-2 amino-5 phenyl-4 pentenoic acid, which is an inhibitor of S adenosyl transferase.[30] The 2(2'cycloalkenyl) glycinates synthesized here are also of biological interest, since 2-(2'cyclopentenyl) glycine **56** has been isolated from a natural source,[31] the cyclohexenyl analogs ester **57** have also been recently synthesized.[32] The unusual amino acid γ, δ-dihydroisoleucine synthesized here **59** has also been isolated as the lactone hydrochloride on hydrolysis of α- and β- amanitin.[33]

TABLE V - Hydrolysis of α-mono and α,α'-dialkylated Schiff bases

Schiff base	Methode	Time (h)	Aminoester		Yield (%)
39	(A)	1		**54**	80
19	(A)	2		**56**	60
21	(A)	1.5		**57**	50
41	(B)	2		**58**	70
27	(B)	2		**59**	80

method (A) 10 % HCl ; method (B) 15 % of citric acid then treatment with solid K_2CO_3.

CONCLUSION

The transition metal catalyzed alkylation of Schiff bases of α-amino acid esters provides an especially attractive approach for the synthesis of α-mono and α,α'-disubstituted α-amino acids of biological interest. We have expanded the scope of palladium neutral alkylation using allylic carbonates to the less stabilized carbonucleophiles such as Schiff bases of α-amino esters which are important synthons in organic synthesis. It is noteworthy that in these reactions a large variety of allylic halides and allylic esters can be used under basic conditions at low temperature in THF. This methodology offers some other advantages over the classical alkylation particularly in controlling regio and enantioselectivity by the use of a metal template. Much more work remains to be done to improve enantioselectivity ; however the enantioselective catalytic Pd-allylic alkylation of the benzophenone imine of the glycine methyl ester is one of the highest enantiomeric excess known using a prochiral nucleophile.

EXPERIMENTAL SECTION

General methods

All reactions were carried out under argon. THF and DME are distilled over sodium benzophenone ketyl, CH_2Cl_2 is distilled from CaH_2. Reagents and solutions were introduced via syringes into flame dried glassware. Flash chromatography was carried out on SiO_2 (Merck or S.D.S. Kieselgel 230-400 Mesh). TLC was performed on Merk SiO_2 plates. Melting points were determined on a Kofler hot stage and are uncorrected. I.R. Spectra were recorded on a Perkin-Elmer 297 spectrophotometer. Proton magnetic Resonance spectra (^{1}H-NMR) were recorded at 80 and 200 MHz on Brüker W.P. 80 and A.M. 200 spectrometers, respectively. Chemical shifts are reported in ppm down field from tetramethylsilane (TMS) with notation specifying the number of protons, the multiplicity of the signal ; s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet) and the coupling constants. Optical rotations were measured using a Perkin-Elmer 241 automatic polarimeter. Microanalyses were performed by the laboratory of Université Pierre et Marie Curie. 2-cyclohexene-1-ol ; 1,2-dichloro-2-propene ; 1-acetoxy-2-propene are commercially available from Aldrich Chemical Co. Di cyclohexyl phenyl phosphine (PCy_2Ph) ; molybdenum hexacarbonyle ; (+)DIOP ; palladium acetate are commercially available from Strem Chemicals. The carbonates **12**, **15**, **26**, **33**, were prepared from the corresponding allylic alcohols using a published procedure.[14b] The ketimines Schiff bases **4**, **6**, **7**, **8** were prepared according a described procedure[17] and the aldimines **5**, **9** from the glycine or alanine ethyl ester hydrochloride and p-chlorobenzaldehyde as previously described.[10] The different catalysts used were prepared using essentially described procedures : bis(dibenzylideneacetone) palladium(0) : $(Pd(dba)_2)$[34] ; $Pd(dppe)_2$; $Pd(PPh_3)_4$[35] ; η^3 allyl molybdenum dicarbonyle-bis-acetonitrile bromide[36] and μ di(chloro η^3 allyl) palladium.[37]

Preparation of starting materials.

2-Cyclopentyl ethyl carbonate **18**. To a solution of 2-cyclopentene-1-ol (1.68 g, 20 mmol) and ethyl chloroformate (2.1 ml, 22 mmol) in dry methylene chloride (20 ml) was dropwise added pyridine (1.8 ml, 22 mmol) stirred for 1 h at 0°C, allowed to warm up to room temperature for 2 h and then quenched with 10 % aqueous HCl (10 ml). The aqueous layer was decanted and extracted with methylene chloride (15 ml). The combined organic layer with saturated aqueous NaCl were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated to give 2.65 g (85 %) carbonate **18** as a colorless oil.

I.R. (film) : 1735, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 80 MHz) 6.2-5.4 (m,3H) ; 4.2 (q,2H) ; 2.6-1.6 (m,4H) ; 1.3 (t,3H).

2-Cyclohexenyl ethyl carbonate **20**. (prepared from 2-cyclohexen-1-ol according to the procedure described above).

I.R. (film) : 3040, 2940, 1735, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 80 MHz) : 6.2-5.7 (m,2H) ; 5.3-5.1 (m,1H) ; 4.2 (q,2H) ; 2.3-1.5 (m,6H) ; 1.3 (t,3H). Calc. for $C_9H_{14}O_3$ C : 63.53 % ; H : 8.23 % ; Found : C : 62.85 ; H : 8.24.

(Z) Ethyl (4-acetoxy-2-butenyl) carbonate **36**. 1-acetoxy-4-hydroxy-2-butene (7.14 g, 70 mmol). (From (Z) 2-butene-1,4-diol, NaH (1 eq.), acetic anhydride (1 eq.), 45 % yield).

Ethyl chloroformate (6.2 ml, 1.1 eq.) and pyridine (7.36 ml, 1.1 eq.) are stirred at 0°C in dry CH_2Cl_2 (50 ml) for 1 h at 20°C for another hour. The mixture was poured into cold water (20 ml), the aqueous layer extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layer were washed with 5 % aqueous HCl (20 ml) and saturated aqueous NaCl (20 ml) dried ($MgSO_4$) and distilled (100°C 1 torr), obtained 12.74 g as a colorless liquid (100 % yield).

I.R. (film) : 1735 cm^{-1} ; ^{1}H-NMR ($CDCl_3$, 80 MHz) : 1.35 (t,3H) ; 2.1 (s,3H) ; 4.2 (q,2H) ; 4.7 (m,4H), 5.75 (m,2H).

Benzoate **42**.

To a solution of 2-cyclohexen-1-ol (1.96 g, 20 mmol) and 2,4-dichlorobenzoyl chloride (2.52 g, 22 mmol) in dry methylene chloride (20 ml) was added dropwise pyridine (1.8 ml, 22 mmol). The mixture was stirred for 1 h at 0°C, allowed to warm up to room temperature for 3 h and then quenched with water (15 ml). The aqueous layer was decanted and extracted with methylene chloride (20 ml). The combined organic layers were washed with 5 % aqueous HCl, then with water (pH 7), and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was chromatographed (hexane/ethyl acetate : 9 /1) R_f = 0.5 to yield 5.50 g (83 %) of benzoate **42** as colorless oil.

I.R. : 1735, 1570 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 80 MHz) : 1.6-2.7 (m,4H) ; 5.8-6.1 (m,2H ; 6.2-6.4 (m,1H) ; 7.1-7.8 (m, 3H). Calc. for $C_{13}H_{12}O_2Cl_2$: C : 57.56 ; H : 4.42 ; Cl : 26.20. Found : C : 55.88 ; H : 3.91 ; Cl : 26.35.

(1,4-Dioxaspiro 4.5.7-decane-8-yl)methylacetate **46**.

To a stirred solution of (1,4-dioxaspiro 4.5.7-decene-8-yl-methanol (3.43 g, 20 mmol). (From $LiAlH_4$ reduction of methyl(1,4-dioxaspiro 4.5.7-decene)-8-carboxylate[38]) acetic anhydride (2.1 ml, 1.1 eq.) in dry CH_2Cl_2 (20 ml) was added at 0°C pyridine (1.77 ml, 1;1 eq.). The mixture was then allowed to warm up overnight and worked up as above for carbonate **36** (80 % yield after chromatography, ethyl acetate/hexane : 1/1, R_f = 0.4, oil).

I.R. (film) : 1735 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 80 MHz) : 1.62-2.42 (m,6H) ; 2.1 (s,3H) ; 4 (s,4H) ; 4.55 (s,2H) ; 5.75 (m,1H).

Acetate **50**.

To a solution of (-)cis-carveol (4 g, 26.3 mmol) and DMAP (0.4 g, 2.6 mmol) in dry CH_2Cl_2 (60 ml) was added Ac_2O (6 ml, 40 mmol) dropwise with stirring for 30 min. at 0°C. The mixture was allowed to warm up to room temperature for 4 h and CH_2Cl_2 (100 ml) was added. The mixture was washed with 10 % aqueous HCl (2 x 50 ml), then washed with saturated NaCl solution (30 ml). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was chromatographed (hexane/ethyl acetate : 7/3) to afford 5 g (98 % yield) of **50** as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 250 MHz) : 5.55 (m, 1H) ; 5.4 (m, 1H) ; 4.5 (s,2H) ; 2.38-2.22 (m,1H) ; 2.2-2.1 (m,2H) ; 2.05 (s,3H) ; 1.72 (s,3H); 1.62 (s,3H) ; 1.5-1.4 (m,2H).

Benzoate 52.

To a solution of (-)cis-carveol (2 g, 13.1 mmol) triphenylphosphine (5.17 g, 19.7 mmol) and benzoïc acid (2.4 g, 19.7 mmol) in dry THF (15 ml) was added diethyl azodicarboxylate (3.43 g, 19.7 mmol) dropwise with stirring at 0°C and the reaction mixture was left overnight at 0°C. The THF was then removed in vacuo and the residue was dissolved in a mixture of cyclohexane/ethyl acetate : (9/1) and filtered through a short pad of celite. The solvent was removed under reduced pressure and the residue was chromatographed (hexane/ethylacetate : 9/1) to yield 3 g (89 % yield) of benzoate trans-carveol 52. ^{1}H-NMR ($CDCl_3$, 250 MHz) : 8-7.4 (m,5H) ; 5.8 (m,1H) ; 5.5 (m,1H) ; 4.7 (s,2H) ; 2.4-1.7 (m,5H) ; 1.7 (s,6H).

General procedure for palladium-catalyzed alkylation of Schiff bases under neutral conditions.

To a mixture of the Schiff base (1 mmol) and the allylic carbonate (1 mmol) in dry THF (1 ml) is added as solution of palladium catalyst (0.05 mmol) in THF (0.5 ml). At the end of the reaction (1-5 h) (cf Table I) monitored by TLC analysis, the solution is concentrated in vacuo, the residue triturated with ether (10 ml) and the resulting suspension filtered through a short pad of celite 545. The clear solution is then concentrated and the residue submitted to flash chromatography (Eluent : ethyl acetate-hexane mixtures).

Ethyl 2(4-chloro benzylidene)amino -4-pentenoate 13.

74 % yield, oil, I.R. (film) : 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 80 MHz) : 1.3 (t, 3H ; 2.7 (d,2H) ; 4-4.4 (q, 2H and t,1H) ; 5.3-4.8 (m,2H) ; 6.1-5.6 (m,1H) ; 6.8 (d,2H) ; 7.6 (d,2H) ; 8.1 (s,1H).

Methyl 2(Diphenyl methylene)amino -4-pentenoate 14.

80 % yield, oil, (hexane/ethyl acetate : 4/1, R_f : 0.4). I.R. (film) : 1736, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 80 MHz) : 2.65 (m,2H) ; 3.75 (s,3H) ; 4.2 (t,1H) ; 4.9-5.3 (m,2H) ; 5.5-6.0 (m,1H ; 7.2-7.8 (m,10H). Calc. for $C_{19}H_{19}NO_2$: C : 77.8 ; H : 6.6 ; N : 4.8 ; Found : C : 76.5 ; H : 6.75 ; N : 4.46.

2(Diphenyl methylene)amino -4-methyl-4 pentenonitrile 16.

65 % yield, oil, I.R. (film) : 2250, 1660, 1620 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 80 MHz) : 1.6 (s,3H) ; 2.7 (m,2H) ; 4.45 (t,1H) ; 5.0 (m,2H) ; 7.85-8 (m,10H).

Ethyl 2(4-chlorobenzylidene)amino -2-methyl-4-pentenoate 17.

95 % yield, oil, I.R. (film) : 1735, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 80 MHz) : 1.1 (t,3H) ; 1.42 (s,3H) ; 1.5 (s,3H) ; 2.65 (d,2H) ; 3.72 (q,2H) ; 4.8 (s,2H) ; 7.45 (d,2H) ; 8.37 (s,1H).

Methyl N-(diphenyl methylene)-2(2'-cyclopentyl)glycinate 19.

80 % yield, oil, I.R. (film) : 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 80 MHz) : 2.3-1.9 (m,4H) ;3.0 (m,1H) ;3.75 (s,3H) ;4.25 (d,1H) ; 5.7-6.1 (m,2H) ; 7.1-7.8 (m,10H).

Methyl 2(Diphenyl methylene) amino -3-methylene-4-pentenoate 27 and methyl 2-(diphenyl methylene)amino -4-hexenoate 28.

34 : 66 mixture of isomers 75 % yield, oil, I.R. (film) : 1745, 1665 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 80 MHz) 27 : 1.0 and 1.1 (d,3H, J=7 Hz) ; 3.05 (m,1H) ; 3.73 (s,3H) ; 4.05 (d,1H, J=7 Hz) ; 5-5.2 (m,2H) ; 5.5-6.01 (m,1H) ; 7.1-8 (10H,m). 28 : 1.65 (d,3H, J=6.4 Hz) ; 2.15 (m,2H) ; 3.75 (s,3H) ; 4.2 (dd,1H, J=6.4 Hz, J=8 Hz) ; 5.5 (m,2H) ; 7.1-8 (m,10H).Calc.for $C_{20}H_{21}NO_2$ C : 78.2 ; H : 6.8 ; N : 4.5 ; Found : C : 77.72 ; H : 6.66 ; N : 3.91.

2(Diphenyl methylene)amino -3-methyl-4-pentenonitrile 29 and 2- (diphenyl methylene)amino -4-hexenonitrile 30.

80-20 mixture of isomers 75 % yield, oil, I.R. (film) : 2260 (weak), 1625, 1600 cm^{-1}

^{1}H-NMR ($CDCl_3$, 80 MHz) 29 : 1.1 and 1.2 (d,3H, J=7 Hz) ; 2.75 (m,1H) ; 4.2 (m,1H) ; 5.05-6.1 (m,3H) ; 7.15-8 (m,10H) ; 30 : 1.70 (d,2H) ; 2.6 (m,2H) ; 4.2 (m,1H) ; 5.05-6 (m,2H) ; 7.1-8 (m,10H). Calc. for $C_{18}H_{18}N_2$: C : 82.4, H : 6.9, N : 10.2 ; Found : C : 82.95 ; H : 6.72 ; N : 9.76.

Ethyl 2(4-chlorobenzylidene)amino-2,3-dimethyl-4-pentenoate 31 and Ethyl 2(4-chlorobenzylidene)amino-2-methyl-4-hexenoate 32

60 : 40 mixture of isomers 65 % yield, I.R. (film) : 1730, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 80 MHz) : 31 : 1.3 (t,3H) ; 1.42-1.75 (m,6H) ; 3.35-3.9 (m,1H) ; 4.25 (q,2H) ; 4.7-5 (m,2H) ; 5.4-6 (m,1H) ; 7.43 (d,2H) ; 7.8 (d,2H) ; 8.35 (s,1H). 32 1.15 (t,3H) ; 1.5-1.7 (m,3H) ; 2.6 (d,2H) ; 4.23 (q,2H) ; 5.5 (m,2H) ; 7.2-7.9 (m,4H) ; 8.27 (s,1H).

Ethyl 2 (4-chlorobenzylidene)amino-2-methyl-3-phenyl-4-pentenoate 35 and Ethyl 2 (4-chlorobenzylidene)amino-2-methyl-5-phenyl-4-pentenoate 34.

75 : 25 mixture of isomers, 93 % yield, oil, I.R. (film) : 1730, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 80 MHz) : 34 : 1.6 (s,3H) ; 2.87 (d,2H) ; 3.8 (s,3H) ; 6.02-6.8 (m,2H) ; 7.15-7.35 (m,9H) ; 8.3 (s,1H). 35 : 1.87 (s,3H) ; 4.35 (m,2H) ; 5.02-5.38 (m,1H) ; 6.02-6.8 (m,1H) ; 7.15-7.88 (m,9H) ; 8.3 (s,1H).

(4 E)-Methyl-6-acetoxy-2-(diphenyl methylene)amino -4-hexenoate 37.

70 % yield, oil, I.R. (film) : 1730, 1610 cm^{-1}

^{1}H-NMR ($CDCl_3$, 80 MHz) : 2.0 (s,3H) ; 2.6 (m,2H) ; 3.75 (s,3H) ; 4.2 (t,1H, J=7 Hz) ; 4.53 (m,2H) ; 5.75 (m,2H, $J_{AA'}$=17 Hz) ; 7,1-8 (m,10H). Calc. for $C_{22}H_{23}NO_4$: C : 72.2 ; H : 6.3 ; N : 3.8. Found : C : 71.46 ; H : 6.20 ; N :3.90

General procedure for molybdenum and palladium catalyzed alkylation of Schiff bases with sodium hydride or lithium diisopropylamide as bases.

a) In a typical procedure, Schiff base 8 (281 mg, 1 mmol) in dry THF (1ml) was added to a suspension of NaH (40 mg, 1 mmol, 50 % in mineral oil) in dry THF (1 ml) and the mixture was stirred for 1 h under argon. A solution of (η^3 C_3H_7)$(CH_3CN)_2$ $MoBr(CO)_2$ (18 mg, 5 mol %), dppe (40 mg, 10 mol %) and allyl acetate 44 (110 mg, 1.1 mmol) in dry THF (1 ml) was stirred for 20 min. at room temperature under argon and then was added to the above mixture. The reaction mixture was stirred at room temperature for 12 h.

Saturated NH_4Cl solution (2 ml) was added and the organic layer was extracted with ether (2 x 10 ml) and then washed with saturated NaCl solution (2 x 3 ml). Evaporation of the solution under reduced pressure yielded to a yellow oil which was chromatographed (hexane/ethyl acetate : 9/1, R_f : 0.3) to give 80 mg (25 % yield) of 45 as a yellow oil.

Ethyl 2(Diphenylmethylene)amino 2-methyl 4-pentenoate 45.

I.R. (film) : 1735, 1645 cm^{-1}. ^1H-NMR ($CDCl_3$, 80 MHz) : 1.10 (t,3H) ; 1.42 (s,3H) ; 2.75 (d,2H) ; 3.72 (q,2H) ;5.05-5.35 (m,2H) ; 5.72-6.30 (m,1H) ; 7.20-7.85 (m,10H).

b) Molybdenum-catalysed alkylation of Schiff base 4 using bis(trimethylsilyl) acetamide (BSA) as a base : synthesis of 27. Schiff base 4 (253 mg, 1 mmol) carbonate 26 (160 mg, 1 mmol), BSA (0,246 ml, 1 mmol) and $Mo(CO)_6$ (45 mg, 15 mol %) in dry DME (3 ml) are refluxed for 1.5 hours. After usual "work up" and "flash chromatography" (ether/hexane : 4.5/5.5 ; R_f : 0.6) 140 mg (50 % of pure 27 (oil) was obtained.

I.R. (film) : 1745, 1655 cm^{-1} ; ^1H-NMR ($CDCl_3$, 80 MHz) : 1 and 1.1 (d,3H,J=7 Hz) ; 3 (m,1H) ; 3.75 (s,3H) ; 4.05 (d,1H,J=6Hz) ; 4.95-5.2 (m,2H) ; 5.5-6.2 (m,1H) ; 7.1-8 (m,10H).

c) In a typical run, 0.40 ml of 2.5 M n-BuLi (1.0 mmol) was added dropwise to a solution of dry N,N-diisopropylamine (0.14 ml, 1.0 mmol) in dry THF (1 ml) at 0°C. After being stirred at 0°C for 30 min., the solution was cooled to -60°C and the Schiff base 4 (253 mg, 1 mmol), dissolved in dry THF (1 ml), was added dropwise. About 30 min. was allowed for enolate formation, a solution of bis(dibenzylideneacetone) palladium (0) (17 mg, 3 mol %), dppe (24 mg, 6 mol %) and 2,3-dichloropropene (122 mg, 1.1 mmol) in anhydrous THF (1 ml) was added to the above mixture. After stirring for 2 h at -60°C, the reaction mixture was quenched with saturated NH_4Cl solution (2 ml) and ether (20 ml) was added. The organic layer was decanted, washed with saturated NaCl solution (2 x 3 ml) and then dried over anhydrous $MgSO_4$. Concentration under reduced pressure gave a crude product, which was purified by flash chromatography (hexane/ethyl acetate : 9/1, R_f : 0.3) to yield 262 mg (80 % yield) of 39 as a white solid (mp 68-70°C).

Methyl 2(Diphenyl methylene)amino 4-chloro 4-pentenoate 39.

I.R. (film) : 3060, 2960, 1730, 1620, 1440, 1280, 1000 cm^{-1}. ^1H-NMR ($CDCl_3$, 80 MHz) : 3.0 (d,2H) ; 3.75 (s,3H) ; 4.50 (t,1H) ; 5.25 (d,2H) ; 7.25-8.0 (m,10H). Calc. for $C_{19}H_{18}O_2NCl$: C : 69.62 ; H : 5.49. Found : C : 69.59 ; H : 5.41.

Ethyl 2(Diphenyl methylene)amino 2-methyl 5-phenyl 4-pentenoate 41. (Hexane/ethyl acetate : 9.5/0.5, R_f : 0.5) yellow oil, 88 % yield.

I.R. (film) : 3100, 2900, 1950, 1870, 1730, 1630, 1605 cm^{-1}. ^1H-NMR ($CDCl_3$, 60 MHz) : 1.05 (t,3H) ; 1.45 (s,3H) ; 2.85 (d,2H) ; 3.70 (q,2H) ; 6.30-6.65 (m,2H) ; 7-7.85 (m, 15H).

Methyl N-(Diphenyl methylene)-2-2-cyclohexanyl glycinate 21. (mixture of diastereoisomers) hexane/ethyl : acetate 9/1, R_f : 0.6) colourless oil 75 % yield.

I.R. (film) : 1730 cm^{-1}. ^1H-NMR ($CDCl_3$, 80 MHz) : 1.2-2.2 (m,6H) ; 2.8-3.2 (m,1H) ; 3.75 (s,3H) ;3.9 (d,1H, one isomer) ; 4.1 (d,1H, other isomer) ; 5.3-5.7 (m,2H) ; 7.2-7.8 (m,10H). Calc. for $C_{22}H_{23}O_2N$: C : 79.28 ; H : 6.91. Found : C : 78.86 ; H : 6.75.

Methyl 2(Diphenyl methylene)amino-3(1,4-dioxaspiro 4.5.7-decan-6-yl) propenoate 47. (Hexane/ethyl : acetate 9.5/0.5, R_f : 0.25) 20 % yield.

^1H-NMR ($CDCl_3$, 80 MHz) : 1.5-2.1 (m,6H) ; 2.7 (d,2H) ; 3.75 (s,3H) ; 3.95 (b,4H) ; 4.2 (t,1H) ; 5.4 (m,2H) ; 7.3-7.9 (m,10H).

Methyl 2(4-chlorobenzylidene) amino 3(4-methoxy 1,4-cyclohexadienyl) propionate 49. Yellow oil, 85 % yield, (Crude).

^1H-NMR (acetone d_6, 80 MHz) : 2.55 (m,6H) ; 3.30 (m,1H) ; 3.32 (s,3H) ;3.62 (s,3H) ; 4.42 (m,1H) ; 5.32 (m,1H) ; 7.42 (d,2H, J=6 Hz) ; 7.80 (d,2H, J=6 Hz) ; 8.35 (s,1 H).

cis Methyl N-(Diphenyl methylene)-2-carveyl glycinate 51. Rdt 20 % (ethylacetate/hexane : 1/9 R_f, : 0.3). ^1H-NMR ($CDCl_3$, 250 MHz) : 1.2-1.4 (m,H_5 and H'5) ; 1.6-1.95 (m,H_4) ; 1.65-1.70 (2d,3H,J=0 Hz) ; 1.75 (s,3H) ; 1.9-2.4 (m,H_3 and H'3) ; 2.85 (m, H_6,$J_{H6-H5ax}$=9.7 Hz) ; 3.75-3.8 (2s,3H) ; 4.32-4.35 (2d,1H,J=2.9 Hz) ; 4.7 (m,2H) ; 5.55 (m,1H) ; 7-7.8 (m,10H).

trans Methyl N-(Diphenyl methylene)-2-carveyl glycinate 53. Rdt 39 % (ethyl acetate/hexane : 1/9, R_f : 0.4). ^1H-NMR ($CDCl_3$, 250 MHz) : 1.2-1.4 (m,2H_5 and H'5) ; 1.6-1.9 (m,H_4) ; 1.6-1.70 (2s,3H) ; 1.75 (s,3H) ;1.9-2.20 (m,H_3 and H'3) ; 2.85 (m,H_6,$J_{H6-H5ax}$=4.9 Hz) ; 3.75-3.8 (2s,3H) ; 4.3 (m,1H) ; 4.55-4.7 (m,2H) ; 5.55 (m,1H) ; 7-7.8 (m,10H).

General procedure for enantioselective alkylation of Schiff bases 4 with palladium catalyst.

In a typical run, 0.36 ml of 2.5 M n-BuLi (0.9 mmol) was added dropwise to a solution of hexamethyldisilazane (0.19 ml, 0.9 mmol) in dry THF (1 ml) at 0°C. After being stirred at 0°C for 30 min., the solution was cooled to -60°C and the Schiff base 4 (253 mg, 1 mmol), dissolved in dry THF (1 ml), was added dropwise. An orange solution resulted. About 30 min. was allowed for enolate formation, a solution of $Pd(OAc)_2$ (7 mg, 3 mol %), (+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4 bis(diphenyl phosphino)butane (+)DIOP (29.9 mg, 6 mol %) and allylacetate 44 (110 mg, 1.1 mol), prepared at room temperature under argon, in anhydrous THF (1 ml), was added to the above mixture under argon. After stirring for 3 h at -60°C, the reaction mixture was quenched with saturated NH_4Cl solution (2 ml) and allowed to warm to ambient temperature. Ether (20 ml) was added, the layers were separated, and the aqueous phase was extracted with ether (2 x 5 ml). The organic layers were combined, washed with saturated NaCl solution (2 x 3 ml), dried over anhydrous $MgSO_4$. Concentration under reduced pressure gave a crude product which was purified by flash chromatography (hexane/ethyl acetate 4/1, R_f : 0.5) to yield 200 mg (68 % yield) of 14 as a colorless oil. The rotation of allylated product was $(\alpha)_D^{25°}$ = +78.3° (c = 0.89 in chloroform). Allylic allylation produced the R isomer with 68 % optical yield. The optical yields obtained were determined by HPLC with (R) 3,5-dinitrophenylbenzoylglycine as chiral stationary phase[40] and as eluant : hexane/THF : 98.5/1.5 (errors within ± 2 % for multidata calculation by integrator D 2000).

General procedure for hydrolysis of alkylated Schiff bases.

Method A : Methyl 2-amino-4-chloro-4-pentenoate 54.

To a solution of Schiff base 39 (328 mg, 1 mmol) in ether (10 ml) was added 10 % aqueous HCl (5 ml, 6 mmol) dropwise with stirring for 1 h at room temperature. The aqueous layer was decanted and extracted with ether (2 x 10 ml) and the combined organic layers were discarded. The aqueous layer was neutralized with solid potassium carbonate and ether (15 ml) was added and then stirred for 30 mn. The aqueous layer was decanted and extracted with ether (2 x 10 ml) the combined organic layers were dried over anhydrous $MgSO_4$ and evaporated in vacuo to afford 120 mg (80 % yield of 54 as an oil).

I.R. (film) : 3400, 2980, 1730, 1630, 1440, 1150 cm^{-1}. ^1H-NMR ($CDCl_3$, 80 MHz) : 1.70 (b,2H) ; 2.75 (m,2H) ; 3.80 (s,3H) ;3.85 (m,1H) ; 5.35 (d,2H).

(E) Methyl 2-amino-6-acetoxy-4-hexenoate 55.

I.R. (film) : 3500, 1730, 1620 cm^{-1}. ^1H-NMR ($CDCl_3$, 60 MHz) : 2.0 (s,3H) ; 2.5 (m,2H) ; 3.5 (t,1H) ;3.75 (s,3H) ; 4.5 (m,2H) ; 5.6 (m,2H).

Methyl 2(2'-cyclohexenyl) glycinate 57. (mixture of diastereoisomers) oil, 56 % yield.

I.R. (film) : 3340, 3020, 2920, 1740, 1590 cm^{-1}. ^1H-NMR ($CDCl_3$, 200 MHz) ; 1.5-2 (m, 8H) ; 2.5-2.6 (m,1H) ; 3.3 (d,1H, one isomer) ; 3.5 (d,1H, other isomer) ; 3.7 (s,3H) ; 5.4-5.5 (m,1H) ; 5.8-5.9 (m,1H). Calc. for $C_9H_{15}O_2N$: C : 63.91 ; H : 8.87 ; N : 8.28. Found : C : 63.91 ; H : 8.88 ; N : 8.15.

Methyl 2(2'-cyclopentenyl) glycinate 56. oil, 57 % yield.

I.R. (film) : 3350, 3050, 1730, 1580 cm^{-1}. ^1H-NMR ($CDCl_3$, 80 MHz) : 1.5-2.5 (m,6H) ; 2.5 (m,1H) ; 3.75 (s,3H) ; 4.15-4.25 (m,1H) ; 5.6 (m,1H) ; 5.8 (m,1H). Calc. for $C_8H_{13}O_2N$: C : 61.94 ; H : 8.39 ; N : 9.03. Found : C : 61.05 ; H : 8.35 ; N : 8.87.

Method B : Ethyl 2-amino-2-methyl-5-phenyl-4-pentenoate 58.

To a solution of Schiff base 41 (397 mg, 1 mmol) in ether (10 ml) was added 15 % citric acid (4 ml) dropwise with stirring for 2 h at room temperature. The aqueous layer was decanted and extracted with ether (2 x 10 ml) and the combined organic layers were removed. The aqueous layer was neutralized with solid potassium carbonate and ether (15 ml) was added and then stirred for 30 min. The organic layer was decanted and extracted with ether (2 x 15 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated in vacuo to afford 162 mg (70 % yield) of 58 as a oil.

I.R. (film) : 3320, 2980, 1750, 1600 cm^{-1}. ^1H-NMR ($CDCl_3$, 80 MHz) : 1.30 (t,3H) ; 1.40 (s,3H) ; 1.90 (b,2H) ; 2.27-2.90 (m,2H) ;4.20 (q,2H) ; 5.95-6.70 (m,2H) ; 7.35 (b,5H).

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