HETEROCYCLES, Vol. 78, No. 12, 2009, pp. 2963 - 2978. © The Japan Institute of Heterocyclic Chemistry
Received, 15th July, 2009, Accepted, 11th September, Published online, 15th September, 2009
DOI: 10.3987/COM-09-11797

STEREOSELECTIVE SYNTHESIS OF ISOQUINUCLIDINONES BY DIRECT IMINO-DIELS-ALDER TYPE REACTION CATALYZED BY L-PROLINE

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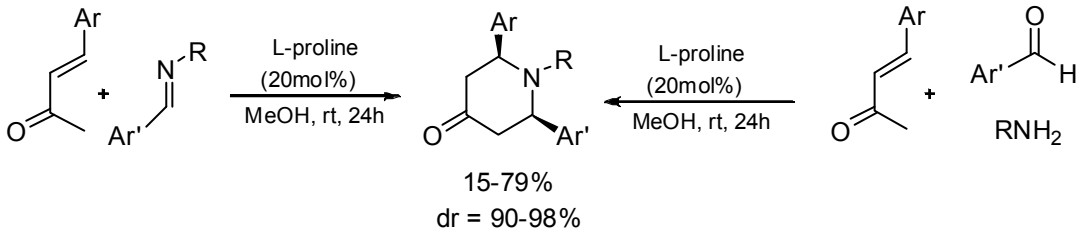
Abstract – A general synthesis of isoquinuclidinones (2-azabicyclo[2.2.2]octan-5-ones), has been developed by one-pot three component imino-Diels-Alder type reaction catalyzed by L-proline. Simple and commercially available α,β-unsaturated cyclic ketones, aromatic aldehydes and either aliphatic or aromatic primary amines were used. The reaction proceeds with excellent *exo*-diastereoselectivity (>99%) and moderated enantioselectivity (30-64%).

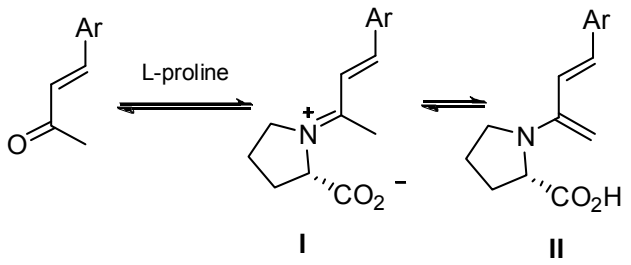
INTRODUCTION

Over the past few years organocatalysis has become very popular for a wide range of enantioselective transformations.[1] In particular, L-proline and other chiral amines[2] have been reported to catalyze asymmetric aldol,[3] Michael,[4] Mannich,[5] Diels-Alder,[6] hetero-Diels-Alder[7] and related addition reactions. As part of our ongoing interests in the stereoselective synthesis of piperidin-4-ones, we have previously developed methodologies employing the imino-Diels-Alder reaction of 2-amino-1,3-butadienes with aldimines.[8]



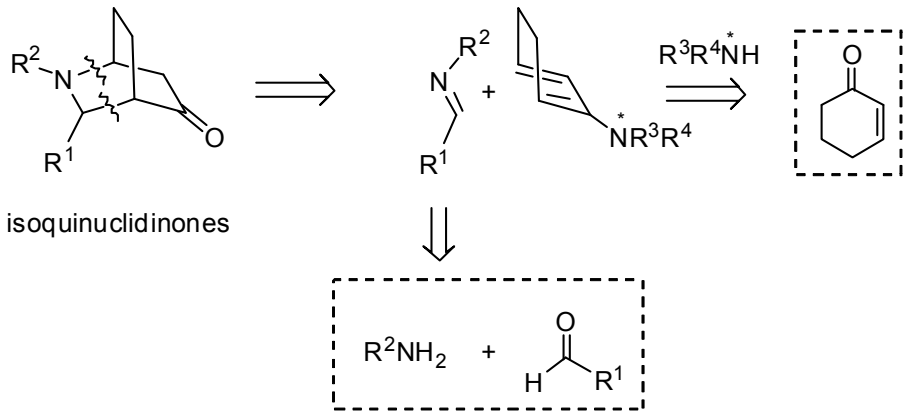
Scheme 1. Synthesis of 2,6-diarylpiperidin-4-ones by an imino-Diels-Alder cycloaddition of enones with imines

Recently, we reported an efficient route to *meso*- and *cis*-2,6-diarylpiperidin-4-ones by imino-Diels-Alder reaction of an acyclic enone with an aldimine in the presence of L-proline as a catalyst (Scheme 1).[9a] Alternatively, this procedure can be carried out more conveniently by generating the aldimine *in situ* from an aryl aldehyde and a primary amine.[9b] In both cases, the proline-promoted cycloaddition occurs through in situ generation of a 2-amino-1,3-butadiene **II**, produced by tautomerization of iminium ion **I** (Scheme 2).



Scheme 2. Proline-catalyzed *in situ* formation of 2-amino-1,3-butadienes

Using cyclic enones as substrates for these cycloadditions, we envisoned extending this methodology to the synthesis of more complex heterocyclic ring systems such as isoquinuclidinones (2-azabicyclo [2.2.2]octan-5-ones), which are common structures of alkaloids having important biological properties.[10] Retrosynthetically, isoquinuclidinones can be obtained by an imino-Diels-Alder cycloaddition between an imine and a 2-amino-1,3-diene derived from cyclohexenone, as shown in Scheme 3.



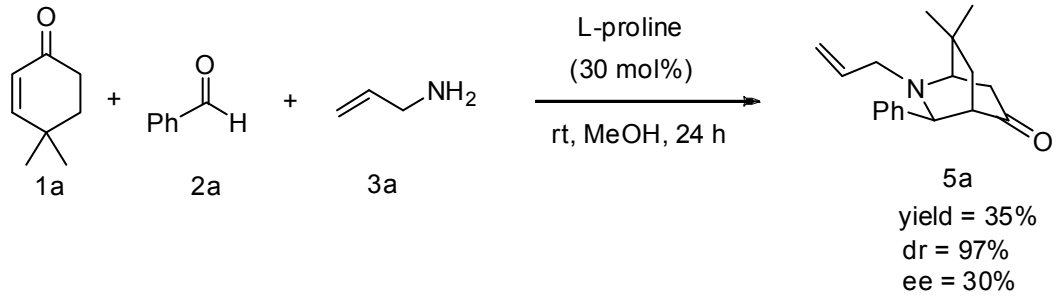
Scheme 3. Retrosynthesis of isoquinuclidinones via three component imino-Diels-Alder reaction

Furthermore, the use of L-proline as a chiral catalyst (R^3R^4*NH) to generate the 2-amino-1,3-diene *in situ* provides an opportunity to control enantiofacial selectivity in the Diels-Alder cycloaddition. Isoquinuclidinones have previously been prepared by an imino-Diels-Alder reaction between a cyclohexenone and an imine in the presence of Lewis[11] or a Brönsted acid.[12] Córdova et al.[13] reported the

first enantioselective proline-catalyzed imino-Diels-Alder reaction between cyclohexenones, formaldehyde and 4-methoxyaniline in a single pot. Although high enantioselectivity was observed, the reaction was restricted to the use of formaldimines and ethyl *N*-(*p*-methoxyphenyl)-α-imino-glyoxalate as the imines. In this report, we demonstrate the application of this methodology to the enantioselective synthesis of isoquinuclidinones, by a proline-catalysed three-component imino-Diels-Alder coupling of cyclohexenone, an aldehyde, and a primary amine.

RESULTS AND DISCUSSION

We initially investigated as a model system the proline-catalyzed reaction between the commercially available 4,4-dimethylcyclohexenone **1a** (2 mmol), benzaldehyde **2a** (1 mmol), and allylamine **3a** (1.1 mmol) in methanol (2 mL). After vigorously stirring the mixture for 24 hours, the reaction was quenched by extraction and the crude product was purified by columm chromatography on silica gel to furnish the desired isoquinuclidine **5a** as a mayor diastereoisomer (97% diastereoselectivity), in 35% yield and 30% enantiomeric excess (Scheme 4). This product was shown to have the *exo* relative stereochemistry by NMR.



Scheme 4. Synthesis of *N*-allyl-3-phenyl-2-azabiciclo[2.2.2]octan-2-one, **5a**

The *exo* product was confirmed by NOESY experiments that showed a strong nuclear Overhauser enhancement (NOE) between the aromatic protons at the ortho position and the ones of the methyl group in the bridge, suggesting that the phenyl group has to be on the same side of the bridge (Figure 1).

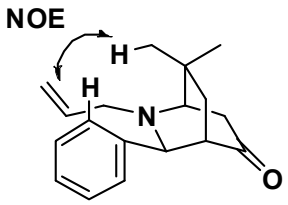


Figure 1. Observed NOE in compound **5a**

Encouraged by this experiment, we investigated different reaction conditions to optimize this process (Table 1). First, we studied the effect of the solvent. Neither anhydrous solvents nor use of inert atmosphere conditions were found to be necessary or beneficial. We conducted the reaction with different organic solvents and reaction times, and found that the highest enantioselectivity as well as efficiency was obtained in MeOH for seven days (Table 1, entry 2). When DMSO and CH_2Cl_2 were used, only 10% of compound **5a** was observed. When the reaction was performed in THF, CH_3CN, DMF, toluene or dioxane, none of the desired bicyclic product was obtained; only starting material was recovered from these reaction mixtures.

The concentration of the substrate also affects the yield of the reaction.[14] Thus, increasing the number of equivalents of α,β-unsaturated ketone **1a** from two to four and with a longer reaction time, increased the product yield to 77% and the enantioselectivity slightly, to 37% ee (Table 1, entry 2). Lower or higher molar ratios gave no beneficial results.

Table 1. Optimization of reaction conditions for the proline-catalyzed imino-Diels-Alder reaction of cyclohexenone **1a** with aldehyde **2a** and amine **3a**

Entry	Additive	Molar ratio[a]	T (ºC)	Time (d)	Yield (%)[b]	dr (%)[c]	ee (%)[d]
1	-	2:1:1.1	25	1	35	97	30
2	-	4:1:1.1	25	7	77	>99	37
3	-	4:1:1.1	5	7	16	50	20
4	-	4:1:1.1	15	7	61	75	24
5	-	4:1:1.1	35	5	94	>99	30
6	-	4:1:1.1	60	2	77	>99	16
7	NaCl	4:1:1.1	25	7	70	98	15
8	LiCl	4:1:1.1	25	7	90	>99	20
9	$CaCl_2$	4:1:1.1	25	7	76	>99	13
10	NH_4Cl	4:1:1.1	25	7	80	>99	10

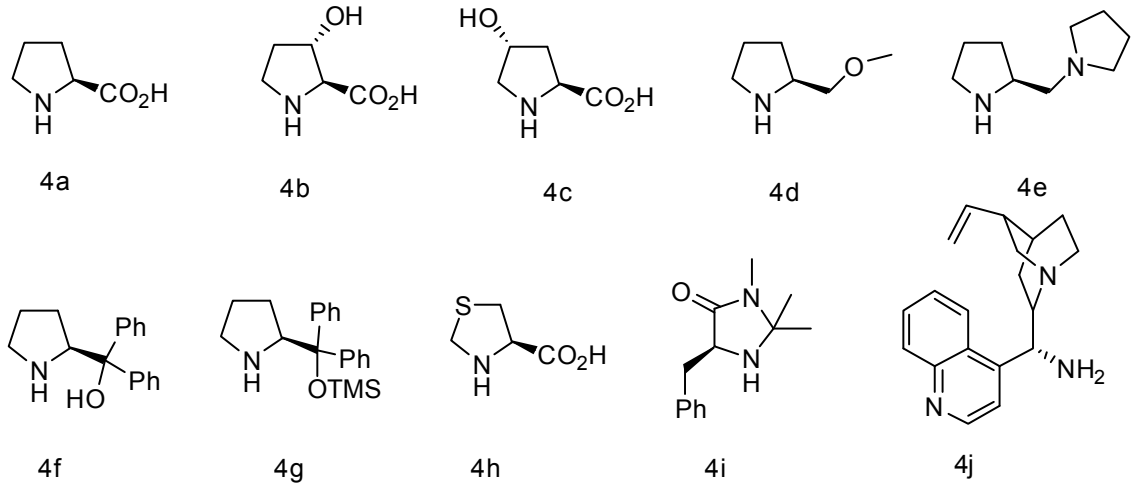
a) Molar ratio of ketone 1a to aldehyde 2a and amine 3a in MeOH. b) Isolated yield after column chromatographic purification on silica gel. c) Determined by ^{1}H NMR (*exo* vs *endo*). d) The enantiomeric excess of the major product was determined by chiral-phase HPLC analyses.

Another important factor was the effect of reaction temperature (Table 1, entries 3-6) on the reaction yield and enantioselectivity. When the reaction was carried out in methanol at lower temperatures (Table 1, entries 3-4), lower yields, diastereo- and enantioselectivities were obtained; and at higher temperatures (Table 1, entries 5-6) the yields increased but lower enantioselectivities were observed. We conclude that the best result was when the reaction was carry out at room temperature. Thus, the performance of the reaction at 25 ºC could give the desired product **5a** in 77% yield with high diastereoselectivity (>99%) and 37% ee (Table 1, entry 2).

The addition of achiral alkali cations as additives has been reported in the literature to increase the enantioselectivity of catalyzed asymmetric transformations.[15] Thus, we decided to investigate the effect of this positive additive effect on our reaction. Unfortunately, we found that in our case the addition of salts (Table 1, entries 7-10) increased the yield of the reaction but sacrified the enantioselectivity.

In addition to proline we also investigated other organocatalysts to mediate the model reaction (Table 2).

Table 2. Catalysts screened for the direct three-component imino-Diels-Alder of cyclohexenone **1a**



Entry[a)]	Catalyst	Additive	Yield (%)[b)]	dr (%)[c)]	ee (%)[d)]
1	4a		77	>99	37
2	4a	DMAP	21	91	40
3	4b		39	>99	23
4	4c		62	>99	19
5	4d		32	>99	12
6	4e		20	50	0
7	4e	*p*-TSA	40	84	23
8	4f		11	50	0
9	4f	*p*-TSA	36	84	0
10	4g	*p*-TSA	15	90	0
11	4h		27	>99	20
12	4i		20	>99	0
13	4i	PhCOOH	18	>99	0
14	4i	*p*-TSA	11	>99	0
15	4j		12	84	0

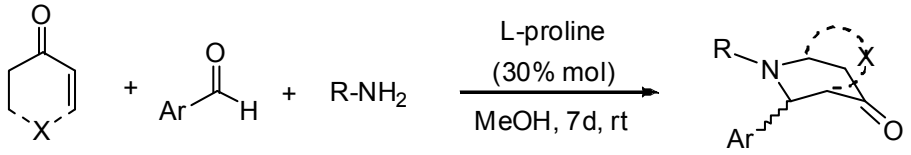
a) The reaction of enone **1a** (4 mmol), aldehyde **2a** (1 mmol), amine **3a** (1.1 mmol) and catalyst **4a-j** (30 mol%) was performed in MeOH for 7 days. b) Isolated yield after column chromatographic purification on silica gel. c) Determined by ^{1}H NMR (*exo* vs *endo*). d) The enantiomeric excess of the major product was determined by chiral-phase HPLC analyses.

The catalyst screen revealed that L-proline **4a** (Table 2, entries 1, 2), proline derivatives **4b-4e** (Table 2, entries 3-7) and **4h** (Table 2, entry 11) all catalyzed the asymmetric formation of the corresponding

bicyclic compound **5a**. However, L-proline afforded the highest stereoselectivity under the reaction conditions. When prolinol **4f-4g** (Table 2, entries 8-10), imidazole **4i** (Table 2, entries 12-14) and cinchone **4j** (Table 2, entry 15) derivatives were used no enantioselectivity was found even when an acid co-catalyst (*p*-toluensulfonic acid or benzoic acid) was added.

Based on these results and the practical aspects of employing proline catalysis we decided to investigate the scope of the three-component aza-Diels-Alder reaction for the synthesis of isoquinuclidines **5**, for an expanded set of different α,β-unsaturated cyclic ketones, aromatic aldehydes and aromatic or aliphatic amines (Table 3).

Table 3. Proline-catalyzed three component imino-Diels-Alder reaction[16]



1 a-c **5a-n**

Entry[a)]	Compound	X	Ar	R	Yield (%)[c)]	dr (%)[e)]	ee (%)[f)]
1	**5a**	Me_2C	Ph	allyl	77	>99	37
2[b)]	**5b**	Me_2C	*p*-$MeOC_6H_4$	allyl	40[g)]	90	44[g)]
3	**5c**	Me_2C	*p*$Me_2NC_6H_4$	allyl	65	>99	12
4	**5d**	Me_2C	*p*- NC-C_6H_4	allyl	29	>99	36
5	**5e**	Me_2C	*p*- Br-C_6H_4	allyl	45	>99	28
6	**5f**	Me_2C	*p*- Cl-C_6H_4	allyl	30	90	33
7[b)]	**5g**	Me_2C	*o*- Br-C_6H_4	allyl	41	60	51
8	**5h**	Me_2C	*o*- I-C_6H_4	allyl	30[d)]	50	60
9	**5i**	Me_2C	3-Py	allyl	54[d)]	50	30
10[b)]	**5j**	Me_2C	Ph	PMP	30	83	20
11[b)]	**5k**	Me_2C	Ph	Ph	30	>99	0
12[b)]	**5l**	(CH_2)	Ph	PMP	40	>99	64
13	**5m**	(CH_2)	Ph	allyl	21[d)]	60	27
14	**5n**	$(CH_2)_2$	Ph	allyl	84[d)]	50	32

a) Multicomponent reaction: enone **1a** (4 mmol), aldehyde **2a** (1 mmol), amine **3a** (1.1 mmol) and L-proline (30 mol%) in MeOH (4 mL) for 7 days. b) Reaction with preformed aldimines: enone **1a** (4 mmol), imine(1 mmol), L-proline (30 mol%) in MeOH (4 mL) for 7 days. c) Isolated yield *(exo* product) after chromatographic purification. d) Yield of reaction mixture of diastereoisomers. e) Determined by ^{1}H NMR of the crude reaction mixture (*exo vs endo*). f) The enantiomeric excess of the major product *exo* was determined by chiral-phase HPLC analysis (ODH or IA columns). g) In multicomponent fashion compound **5b** is obtained in 43% yield and 25% ee.

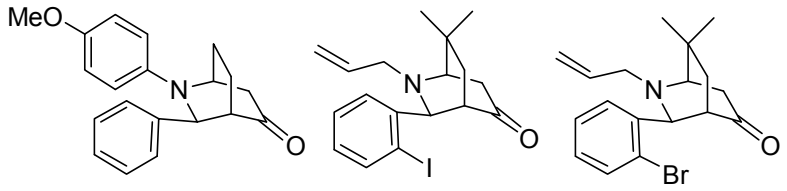
We chose as α,β-unsaturated cyclic ketone 4,4-dimethylcyclohexenone **1a** (entries 1-11), cyclohexenone **1b** (entries 12-13) and cycloheptenone **1c** (entry 14). The best yield was obtained with cycloheptenone **1c**

(entry 14) and 4,4-dimethylcyclohexenone **1a** (entry 1); the ee is moderate in both cases but the diastereoselectivity is higher with **1a**. It is noteworthy that the two methyl groups at the C-4 position in the cyclohexenone seem to enhance the yield and ee of the reaction (entry 1 vs 13).

The structure of the aryl moiety does not affect the enantiomeric excess, regardless of the presence of electron-rich aryl substituents (MeO, Me_2N, entries 2-3) or electron poor groups (CN, entry 4). When the aryl substituent is a halogen, we observed higher ee values having the halogen in the C-2 position (entries 7-8) versus C-4 (entries 3-6). The use of heterocyclic aldehydes did not improve the ee values (entry 9).

The influence of the *N*-substituent of the imine on the enantioselectivity is not clear. Thus, when we employed the PMP group as the *N*-substituent of the imine, the enantioselectivity of the cycloaddition range from 20% (entry 10) with 4,4-dimethylcyclohexenone to 64% with cyclohexenone (entry 12). As aliphatic amines, we used allylamine which have the additional and attractive advantage that the allyl group can be easily removed after the cycloaddition.[9]

In general we can conclude that the enantioselectivity for this imino Diels-Alder reaction between α,β-unsaturated cyclic ketones, aromatic aldehydes and *N*-allyl or *N*-*p*-methoxyphenylamines depends on each combination. The best results were obtained during the formation of (*exo*)-2-(4-methoxyphenyl)-3-phenyl-2-azabicyclo[2.2.2]octan-5-one **5l**, and the *N*-allyl-isoquinuclidine-2-aryl-substituted products **5h** and **5g** (Figure 2).

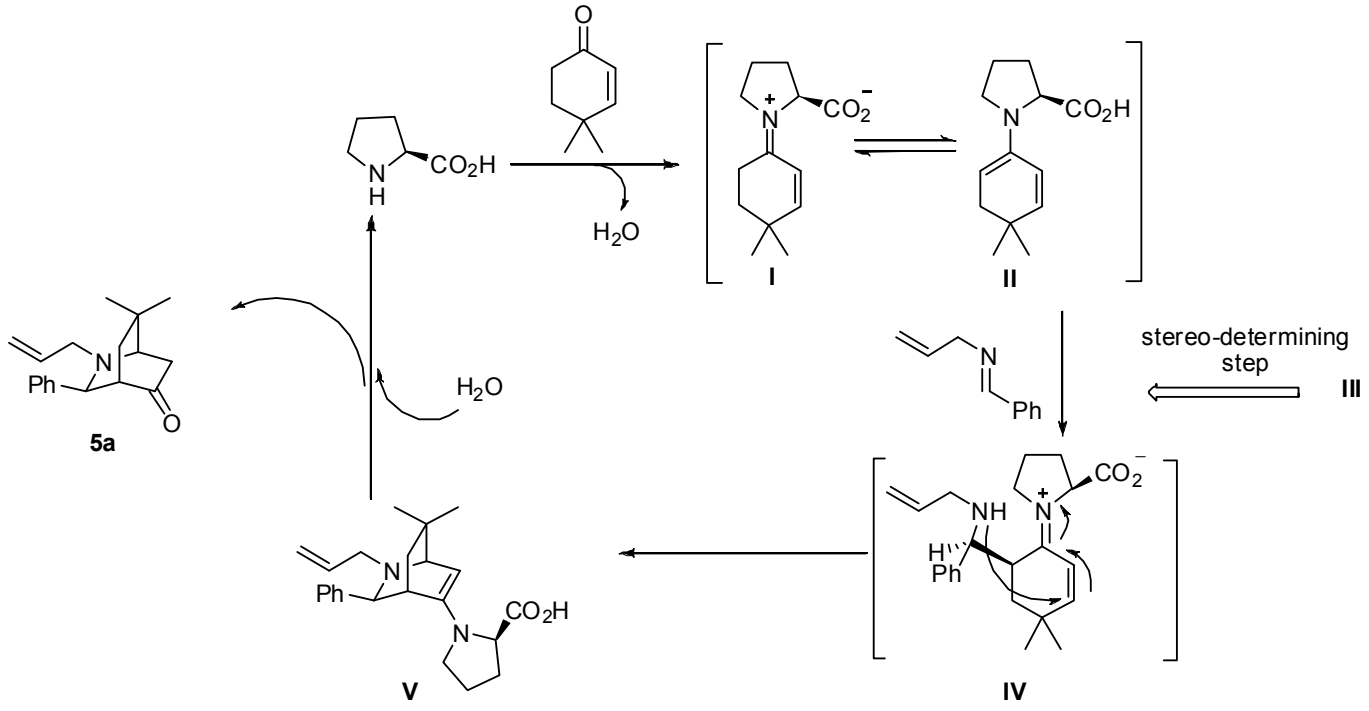


5l 40% (64%ee) **5h** 30% (60%ee) **5g** 41% (51%ee)

Figure 2. Isoquinuclidines obtained by the three component aza-Diels-Alder reaction

MECHANISTIC ANALYSIS

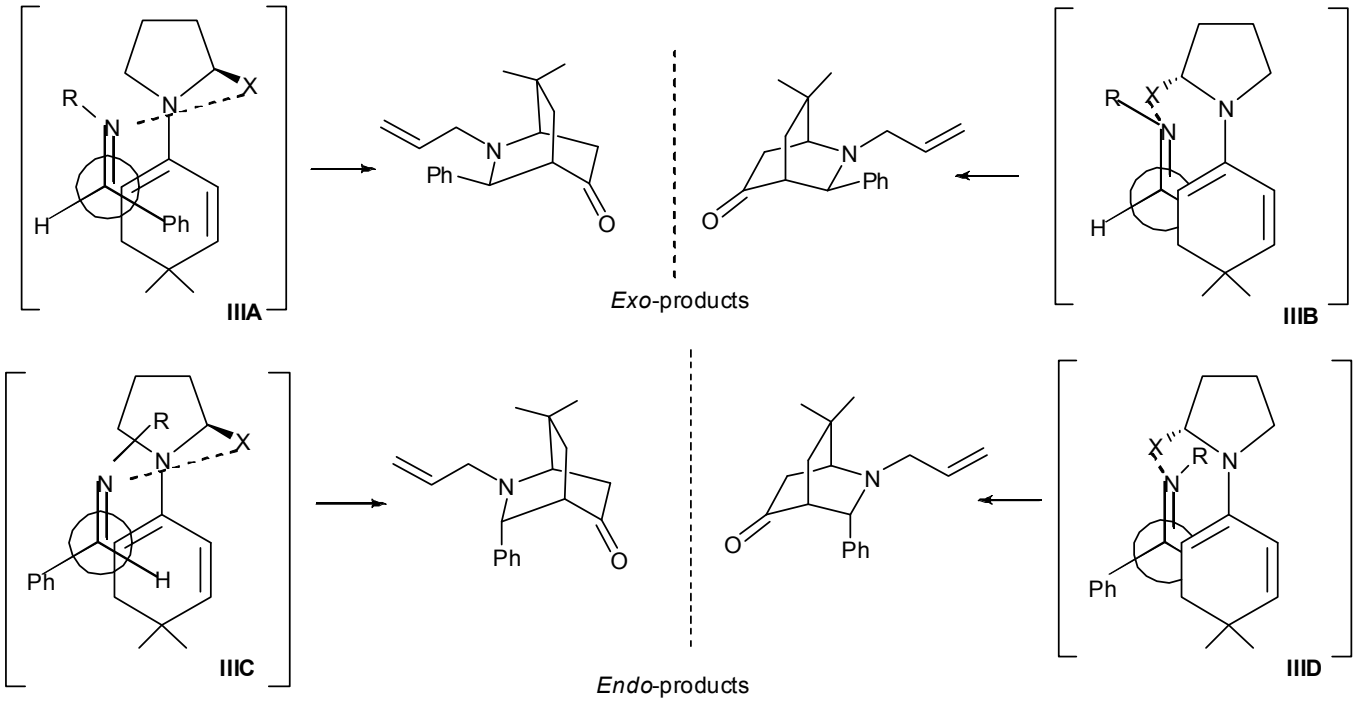
Based on previous experience with reactions involving chiral amine-derived dienes,[17] the following mechanism is proposed to account for the stereochemical outcome of the cycloaddition reaction (Scheme 5). Thus, L-proline initially condenses with the enone to create an iminium zwitterion **I**, which rapidly tautomerizes to the putative chiral 2-aminodiene **II** (a "Barbas dienamine").[18] Next, the imine adds to the chiral diene **II** stereoselectively (*via* transition state **III**, a key step which controls the diastereo- and the enantioselectivity of the process) to form the activated iminium species **IV**. This zwitterion intermediate **IV** then collapses via a 6-*endo-trig* cyclization to furnish the Diels-Alder adduct **V**, which is hydrolyzed by adventitious water to produce isoquinuclidinone **5** with release of the catalyst.



Scheme 5. Proposed pathway for the proline-catalyzed aza-Diels-Alder reaction leading to isoquinuclidinones **5a-n**

As indicated in Scheme 5, the key step governing enantioselectivity of the cycloaddition occurs when the chiral dienamine intermediate **II** adds to the imine. There are four possible transition states **IIIA-IIID** to consider to explain the diastereo- and enantioselectivity of this step (Scheme 6). In transition states **IIIA** and **IIIB** the aryl group of the approaching imine may л-stack with the diene, with the R group (R = allyl) of the approaching imine lying *exo* to the diene system. Conversely, for transition states **IIIC** and **IIID**, the R substituent may form a favourable л-interaction with the diene, in which case the *endo* product would be obtained. Since the observed product of the reaction is the *exo* isomer, there appears to be a strong bias for transition states **IIIA** and **IIIB** during the critical first bond-forming step of the cycloaddition.

The enantioselectivity can be accounted for by considering the degree of coordination between the proline ring substituent X (of the diene component) and the available electron pair of the imine nitrogen. If a strong hydrogen bond can form between these two entities (as for transition states **IIIA** and **IIIC**), the reaction would occur from the *si*-face of the chiral diene[13,19] to afford just one of the enantiomeric products. However, if there is only weak coordination, the imine could also add via the *re*-face of the diene (via transition states **IIIB** and **IIID**) yielding the other enantiomeric adduct. In our case, stereofacial control favors formation of one stereoisomeric adduct but not with complete enantioselectivity. Based on reports of similar examples in the literature, it is likely that the *exo*-product coming from transition state **IIIA** is the one that predominates in the enantiomeric mixture.



Scheme 6. Plausible transition states **IIIA-IIID**

CONCLUSION

In summary, we have described a general synthesis of isoquinuclidinones by a three-component imino-Diels-Alder reaction catalyzed by L-proline, using several α,β-unsaturated cyclic ketones, aromatic aldehydes, and aromatic amines or allyl amine as reactants. The cycloaddition reaction is catalyzed by proline and proceeds with excellent *exo* diastereoselectivity (>99%) and moderate enantioselectivity (30-64%). It is the first time, to the best of our knowledge, that an aliphatic amine (allylamine) has been used in this kind of transformation. Further exploration of this methodology and its application to problems in synthesis are ongoing in our laboratory.

EXPERIMENTAL

General: All comercially available reagents were purchased from Aldrich or Fluka, amines and aldehydes were distilled previously to their use. Thin Layered Chromatography analyses were performed on Merk silica gel plates 60 and visualized by UV light (λ= 254 nm) or K_2MnO_4 solution. Flash column chromatography was performed with Merk silica gel (60, 230-400 *mesh*) eluting with hexane/ethyl acetate mixtures. ^1H and ^{13}C NMR spectra were recorded at 300 or 400 MHz and 75 or 100 MHz, respectively in $CDCl_3$ solution. Tetramethylsilane was used as internal standard for ^1H and the residual solvent signals as standard for ^{13}C. Chemical shifts are given in ppm. The data is being reported as s = singlet, br s = broad singlet, d = doublet, dd = double doublet, t = triplet, q = quatriplet, qn = quintuplet

and m = multiplet or unresolved, chemical shifts in ppm and coupling constant(s) in Hz. HPLC was carried out using a Waters LC Module I plus with V- UV photodiode array detector. Enantiomeric excess were determined by HPLC using Daicel Chiracel OD-H and Daicel Chiralpak IA columns. Mass spectra were obtained by EI (70 eV) with Finnigan-Mat 95 and VG Autospec M spectrometers or by ESI or APCI with Agilent Technologies G 1946B. The adduct (exo)-2-(4-methoxyphenyl)-3-phenyl-2-azabicyclo-[2.2.2]octan-5-one (**5l**) is known compound.[11] For all the new adducts, complete characterization has been reported below.

General procedure for the preparation of isoquinuclidines 5a-n: To a mixture of aldehyde **2** (1 mmol, 1 eq.) and amine **3** (1.1 mmol, 1.1 eq.) (in case of preformed aldimine, 1 mmol was used) in MeOH (4 mL) was added L-proline (30 mol%) and α,β-unsaturated ketone **1** (4 mmol, 4 eq.). The reaction mixture was allowed to stir at room temperature for 7 days. Then, the solvent (MeOH) was evaporated under reduced pressure. CH_2Cl_2 (10 mL) was added to the reaction crude and the organic layer was washed with brine (3 x 10 mL). The organic layer was dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexane/EtOAc) to afford the desired pure isoquinuclidine **5a-n**. Partial decomposition of these products have been observed after prolonged storage.

(*exo*)-2-Allyl-7,7-dimethyl-3-phenyl-2-azabicyclo[2.2.2]octan-5-one (5a): Yield 207 mg (77%), yellow oil. R_f 0.46 (hexane/EtOAc 5:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H), 1.30 (dd, *J* = 13.7, 4 Hz, 1H), 1.33 (s, 3H), 1.65 (dd, *J* = 13.5, 1.86 Hz, 1H), 2.32 (m, 1H), 2.40 (dd, *J* = 18.6, 2.8 Hz, 1H), 2.70 (dd, *J* = 18.6, 2.4 Hz, 1H) , 2.80 (m, 1H), 3.04 (dd, *J* = 14, 8.6 Hz, 1H), 3.17 (m, 1H), 3.87 (s, 1H), 5.15 (m, 2H) , 5.89 (m, 1H), 7.27 (m, 1H), 7.36 (dd, *J* = 9.6 Hz, 2H), 7.49 (d, *J* = 6 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 27.73 (CH_3), 28.19 (CH_3), 33.88 (CH_2), 34.42 (CH_2), 34.63 (C), 53.49 (CH), 55.62 (CH_2), 59.59 (CH), 62.92 (CH), 117.40 (CH_2), 127.07 (CH), 127.44 (2 x CH), 128.34 (2 x CH), 136.15 (CH), 140.35 (C), 216.08 (C) ppm. HPLC (37% ee) (Daicel Chiralpak IA, hexane/ EtOH 90:10, flow rate 0.8 mL/min, λ= 205.7): major isomer: t_R = 5.30 min.; minor isomer: t_R = 5.82 min. HRMS calcd for $C_{18}H_{23}NO$: 269.17742, found 269.177260.

(*exo*)-2-Allyl-3-(4-methoxyphenyl)-7,7-dimethyl-2-azabicyclo[2.2.2]octan-5-one (5b): Yield 129 mg (43%), yellow oil. R_f 0.52 (hexane/EtOAc 5:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.91 (s, 3H), 1.28 (dd, *J* = 13.5, 4.2 Hz, 1H), 1.32 (s, 3H), 1.64 (dd, *J* = 13.5, 1.8 Hz, 1H), 2.27 (m, 1H), 2.40 (dd, *J* = 18.6, 2.7 Hz, 1H), 2.71 (dd, *J* = 18.6, 2.4 Hz, 1H), 2.79 (t, *J* = 2.4 Hz, 1H), 3.04 (dd, *J* = 8.7, 13.8 Hz, 1H), 3.15 (m, 1H), 3.81 (s, 3H), 3.82 (s, 1H), 5.15 (m, 2H), 5.90 (m, 1H), 6.91 (d, *J* = 9 Hz, 2H), 7.41 (d, *J*= 9 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 27.11 (CH_3), 27.58 (CH_3), 33.22 (CH_2), 33.77 (CH_2), 34.01 (C), 53.05 (CH), 55.58 (CH_3), 54.95 (CH_2), 59.04 (CH), 61.79 (CH), 113.15 (2 x CH), 116.67 (CH_2), 127.80 (2 x

CH), 131.58 (C), 135.61 (CH), 158.46 (C), 215.64 (C) ppm. HPLC (25% ee) (Chiralpak IA, hexane/ EtOH 90:10, flow rate 0.8 mL/min, λ= 199.4): major isomer: t_R = 7.16 min.; minor isomer: t_R = 8.74 min. HRMS calcd for $C_{19}H_{25}NO_2$: 299.1885, found 299.1889.

(*exo*)-2-Allyl-3-(4-(dimethylamino)phenyl)-7,7-dimethyl-2-azabicyclo[2.2.2]octan-5-one (5c) : Yield 207 mg (65%), orange oil. R_f 0.42 (hexane/EtOAc 3:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H), 1.30 (m, 1H), 1.34 (s, 3H), 1.74 (dd, *J* = 13.5, 1.8 Hz, 1H), 2.29 (m, 1H), 2.40 (dd, *J* = 18.6, 2.7 Hz, 1H), 2.71 (dd, *J* = 18.9, 2.4 Hz, 1H), 2.75 (t, *J* = 2.7 Hz, 1H), 2.96 (s, 6H), 3.03 (dd, *J* = 13.8, 8.7 Hz, 1H), 3.20 (m, 1H), 3.80 (s, 1H), 5.15 (m, 2H), 5.89 (m, 1H), 6.76 (d, *J* = 9 Hz, 2H), 7.35 (d, *J* = 9 Hz, 2H) ppm. ^{13}C-NMR (75 MHz,$CDCl_3$) δ = 27.82 (CH_3), 28.28 (CH_3), 34.03 (CH_2), 34.45 (CH_2), 34.72 (C), 40.67 (2 x CH_3), 53.90 (CH), 55.60 (CH_2), 59.67 (CH), 62.50 (CH), 112.50 (2 x CH), 117.28 (CH_2), 127.91 (C), 128.25 (2 x CH), 136.57 (CH), 149.90 (C), 216.86 (C) ppm. HPLC (12% ee) (Daicel Chiralpak IA, hexane/ 2-propanol 99:1, flow rate 0.5 mL/min, λ= 257.9): major isomer: t_R = 9.88 min.; minor isomer: t_R = 10.88 min. HRMS calcd for $C_{20}H_{28}N_2O$: 312.2202, found 312.2206.

(*exo*)-4-(2-Allyl-7,7-dimethyl-5-oxo-2-azabicyclo[2.2.2]octan-3-yl)benzonitrile (5d): Yield 85 mg (29%), brown oil. R_f 0.42 (hexane/EtOAc 5:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H), 1.32 (m, 4H), 1.50 (d, *J* = 15 Hz*;* 1H), 2.31 (m, 1H), 2.46 (m, 1H), 2.70 (d, *J* = 18.6 Hz, 1H), 2.82 (m, 1H), 3.10 (d, *J* = 6 Hz, 2H), 3.90 (s, 1H), 5.17 (m, 2H), 5.86 (m, 1H), 7.61 (d, *J* = 6 Hz, 2H), 7.67 (d, *J* = 9 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 27.69 (CH_3), 28.28 (CH_3), 33.90 (C), 34.59 (CH_2), 34.70 (CH_2), 53.01 (CH), 55.95 (CH_2), 59.86 (CH), 63.03 (CH), 111.10 (C), 118.11 (CH_2), 118.82 (C), 128.27 (2 x CH), 132.34 (2 x CH), 135.45 (C), 146.42 (C), 214.79 (C) ppm. HPLC (36% ee) (Daicel Chiralpak IA, hexane/ EtOH 90:10, flow rate 0.8 mL/min, λ= 222.1): major isomer: t_R = 10.42 min.; minor isomer: t_R = 25.24 min. MS (APCI) calcd for $C_{19}H_{22}N_2O$: 294.17, found 295.1

(*exo*)-2-Allyl-3-(4-bromophenyl)-7,7-dimethyl-2-azabicyclo[2.2.2]octan-5-one (5e): Yield 155 mg (45%), orange oil. R_f 0.5 (hexane/EtOAc 3:1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.91 (s, 3H), 1.28 (m, 1H), 1.32 (s, 3H), 1.61 (dd, *J* = 13.8, 2.1 Hz, 1H), 2.26 (m, 1H), 2.40 (dd, *J* = 18.6, 2.7 Hz, 1H), 2.65 (dd, *J* = 18.6, 2.4 Hz, 1H), 2.78 (m, 1H), 3.05 (dd, *J* = 14.1, 8.4 Hz, 1H), 3.12 (m, 1H), 3.81 (s, 1H), 5.16 (m, 2H), 5.86 (m, 1H), 7.36 (d, *J* = 8 Hz, 2H), 7.48 (d, *J* = 8 Hz, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 27.81 (CH_3), 28.27 (CH_3), 33.87 (CH_2), 34.52 (CH_2), 34.70 (C), 53.34 (CH), 55.77 (CH_2), 59.78 (CH), 62.62 (CH), 117.75 (CH_2), 120.94 (C), 129.23 (2 x CH), 131.57 (2 x CH), 135.87 (CH), 139.57 (C), 215.55 (C) ppm. HPLC (28% ee) (Daicel Chiralpak IA, hexane/ EtOH 90:10, flow rate 0.8 mL/min, λ= 222.4): major isomer: t_R = 7.88 min.; minor isomer: t_R = 17.04 min. HRMS calcd for $C_{18}H_{22}BrNO$: 349.0864, found 349.0857.

(*exo*)-2-Allyl-3-(4-chlorophenyl)-7,7-dimethyl-2-azabicyclo[2.2.2]octan-5-one (5f): Yield 91 mg (30%), yellow oil. R_f 0.37 (hexane/EtOAc 5:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 3H), 1.27 (m, 1H), 1.31 (s, 3H), 1.52 (dd, *J* = 13.5, 1.8 Hz, 1H), 2.27 (m, 1H), 2.43 (m, 1H), 2.68 (dd, *J* = 18.7, 2.4 Hz, 1H), 2.79 (t, *J* = 3 Hz; 1H), 3.11 (m, 2H), 3.84 (s, 1H), 5.15 (m, 2H), 5.88 (m, 1H), 7.33 (d, *J* = 9 Hz, 2H), 7.42 (d, *J* = 9 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 27.83 (CH_3), 28.30 (CH_3), 33.89 (CH_2), 34.54 (CH_2), 34.73 (C), 53.43 (CH), 55.80 (CH_2), 59.83 (CH), 62.61 (CH), 117.74 (CH_2), 128.65 (2 x CH), 128.86 (2 x CH), 132.88 (C) , 135.92 (CH), 139.05 (C), 215.56 (C) ppm. HPLC (33% ee) (Daicel Chiralpak IA, hexane/ EtOH 90:10, flow rate 0.5 mL/min, λ= 219.5): major isomer: t_R = 11.33 min.; minor isomer: t_R = 17.99 min. HRMS calcd for $C_{18}H_{22}ClNO$: 303.1390, found 303.1399.

(*exo*)-2-Allyl-3-(2-bromophenyl)-7,7-dimethyl-2-azabicyclo[2.2.2]octan-5-one (5g): Yield 142 mg (41%), dark orange oil. R_f 0.58 (hexane/EtOAc 3:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 3H), 1.31 (m, 1H), 1.34 (s, 3H), 1.60 (dd, *J* = 13.6, 1.2 Hz, 1H), 2.40 (dd, *J* = 12.4, 2.8 Hz, 1H), 2.53 (m, 1H), 2.77 (dd, *J* = 18.2, 2.4 Hz, 1H), 2.83 (s, 1H), 3.06 (d, *J* = 7 Hz, 2H), 4.10 (s, 1H), 5.19 (m, 2H), 5.87 (m, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 27.65 (CH_3), 28.31 (CH_3), 34.04 (CH_2), 34.40 (C), 34.54 (CH_2), 49.81 (CH), 55.67 (CH_2), 59.82 (CH), 62.72 (CH), 117.73 (CH_2), 124.07 (C), 127.19 (CH), 128.78 (CH), 129.71 (CH), 133.36 (CH), 135.93 (CH), 138.25 (C), 215.33 (C) ppm. HPLC (51% ee) (Daicel Chiralpak IA, hexane/ EtOH 90:10, flow rate 0.2 mL/min, λ= 223.1): major isomer: t_R = 27.19 min.; minor isomer: t_R = 24.63 min. HRMS calcd for $C_{18}H_{22}BrNO$: 347.0885, found 347.0899.

(*exo*)-2-Allyl-3-(2-iodophenyl)-7,7-dimethyl-2-azabicyclo[2.2.2]octan-5-one (5h): Yield 30 mg (15%), brown oil. R_f 0.36 (hexane/EtOAc 5:1). ^{1}H-NMR (400 MHz , $CDCl_3$): δ = 0.93 (s, 3H), 1.35 (s, 3H), 1.59 (m, 2H), 2.40 (dd, *J* = 14, 1.9 Hz, 1H), 2.48 (s, 1H), 2.75 (dd, *J* = 14, 1.4 Hz, 1H), 2.83 (s, 1H), 3.05 (d, *J* =4 Hz, 2H), 3.94 (s, 1H), 5.13 (d, *J*= 8 Hz, 1H), 5.17 (d, *J* = 17 Hz, 1H), 5.85 (m, 1H), 7.00 (t, *J* = 5 Hz, 1H), 7.41 (t, *J* = 5.5 Hz, 1H), 7.87 (m, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 30.87 (CH_3), 31.86 (CH_3), 36.58 (C), 38.01 (CH_2), 45.46 (CH_2) , 51.92 (CH), 56.73 (CH_2), 59.32 (CH), 69.03 (CH), 99.85 (C), 117.02 (CH_2), 128.29 (CH), 128.35 (CH), 129.30 (CH), 136.45 (CH), 139.72 (CH), 142.94 (C), 213.25 (C) ppm. HPLC (60% ee) (Daicel Chiralpak IA, hexane/ EtOH 90:10, flow rate 0.8 mL/min, λ= 204.8): major isomer: t_R = 7.43 min.; minor isomer: t_R = 6.45 min. MS (ESI) calcd for $C_{18}H_{22}INO$: 395.07, found 396.0.

(*exo*)-2-Allyl-7,7-dimethyl-3-(pyridin-3-yl)-2-azabicyclo[2.2.2]octan-5-one (5i): Yield 73 mg (27%), yellow oil. R_f 0.44 (hexane/EtOAc/Et_3N 5:4:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.91 (s, 3H), 1.29 (s, 3H), 1.33 (m, 1H), 1.49 (d, *J* = 15 Hz, 1H), 2.40 (d, *J* = 21 Hz, 1H), 2.65 (m, 2H), 2.80 (m, 1H), 3.15 (m,

2H), 3.91 (s, 1H), 5.15 (m, 2H), 5.89 (m, 1H), 7.15 (m, 1H), 7.71 (m, 1H), 7.81 (d, *J* = 9 Hz, 1H), 8.54 (m, 1H) ppm.^{13}C-NMR (75 MHz, $CDCl_3$) δ = 27.79 (CH_3), 28.46 (CH_3), 34.46 (C), 34.66 (2 x CH_2), 51.06 (CH), 56.03 (CH_2), 60.03 (CH), 64.79 (CH), 117.67 (CH_2), 121.52 (CH), 121.96 (CH), 135.84 (CH), 136.35 (CH), 149.70 (CH), 160.43 (C), 214.73 (C) ppm. HPLC (30% ee) (Daicel Chiralpak IA, hexane/2-propanol 90:10, flow rate 0.5 mL/min, λ= 202.8): major isomer: t_R = 20.20 min.; minor isomer: t_R = 25.57 min. MS (APCI) calcd for $C_{17}H_{22}N_2O$: 270.17, found 271.1.

(*exo*)-2-(4-Methoxyphenyl)-7,7-dimethyl-3-phenyl-2-azabicyclo[2.2.2]octan-5-one (5j): Yield 100 mg (30%), yellow oil. R_f 0.31 (hexane/EtOAc 5:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 3H), 1.11 (s, 3H), 1.80 (dd, *J* = 14, 2.4 Hz, 1H), 1.98 (dd, *J* = 13.6, 3.2 Hz, 1H), 2.69 (m, 2H), 2.85 (d, *J* = 15 Hz, 1H), 3.69 (s, 3H), 4.13 (s, 1H), 4.77 (s, 1H), 6.58 (d, *J* = 9 Hz, 2H), 6.70 (d, *J* = 9 Hz, 2H), 7.24 (m, 5H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 29.50 (CH_3), 30.82 (CH_3), 36.69 (C), 38.98 (CH_2), 43.11 (CH_2), 54.86 (CH), 55.58 (CH_3), 59.85 (CH), 62.14 (CH), 114.03 (2 x CH), 114.69 (2 x CH), 125.97 (2 x CH), 127.50 (CH), 128.88 (2 x CH), 141.42 (C), 142.31 (C), 151.24 (C), 211.97 (C) ppm. HPLC (20% ee) (Daicel Chiralpak IA, hexane/EtOH 90:10, flow rate 0.8 mL/min, λ= 232.6): major isomer: t_R = 12.85 min.; minor isomer: t_R = 15.82 min. HRMS calcd for $C_{22}H_{25}NO_2$: 335.1885, found 335.1896.

(*exo*)-7,7-Dimethyl-2,3-diphenyl-2-azabicyclo[2.2.2]octan-5-one (5k): Yield 91 mg (30%), orange oil. R_f 0.55 (hexane/EtOAc 3:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.09 (s, 3H), 1.48 (s, 3H), 1.53 (m, 1H), 1.76 (dd, *J* = 12 Hz, 1H), 2.61 (m, 3H), 3.98 (m, 1H), 4.83 (s, 1H), 6.78 (d, *J* = 9 Hz, 3H), 7.16 (m, 2H), 7.28 (m, 1H), 7.37 (m, 4H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 28.45 (CH_3), 28.77 (CH_3), 34.04 (CH_2), 34.76 (C), 39.45 (CH_2), 53.59 (CH), 59.58 (CH), 63.20 (CH), 115.63 (2 x CH), 118.72 (CH), 127.18 (2 x CH), 127.2 (CH), 128.58 (2 x CH), 129.06 (2 x CH), 138.96 (C), 148.43 (C), 214.50 (C) ppm. HPLC (0% ee) (Daicel Chiralpak IA, hexane/2-propanol 99:1, flow rate 0.3 mL/min, λ= 255.8): major isomer: t_R = 31.13 min.; minor isomer: t_R = 35.01 min. HRMS calcd for $C_{21}H_{23}NO$: 305.1780, found 305.1780.

(*exo*)-2-(4-Methoxyphenyl)-3-phenyl-2-azabicyclo[2.2.2]octan-5-one (5l)[11]: Yield 123 mg (40%), yellow oil. R_f 0.57 (hexane/EtOAc 1:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.64 (m, 1H), 1.75 (m, 1H), 1.91 (m, 1H), 2.28 (m, 1H), 2.42 (dd, *J* = 14, 1.1 Hz, 1H), 2.68 (m, 1H), 2.80 (m, 1H), 3.72 (s, 3H), 4.46 (s, 1H), 4.72 (s, 1H), 6.57 (d, *J* = 6 Hz, 2H), 6.76 (d, *J* = 6 Hz, 2H), 7.31 (d, *J* = 5 Hz, 1H), 7.41 (m, *J* = 8.2, 4H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 16.35 (CH_2), 26.28 (CH_2), 41.90 (CH_2), 48.86 (CH), 51.02 (CH), 55.62 (CH_3), 62.62 (CH), 114.26 (2 x CH), 114.83 (2 x CH), 126.22 (2 x CH), 127.33 (CH), 128.75 (2 x CH), 140.42 (C), 142.64 (C), 152.00 (C), 213.83 (C) ppm. HPLC (64% ee) (Daicel Chiralpak IA, hexane/EtOH 90:10, flow rate 0.8 mL/min, λ= 203.4): major isomer: t_R = 18.40 min.; minor isomer: t_R = 19.43 min. HRMS calcd for $C_{20}H_{21}NO_2$: 307.1572, found 307.1572.

(*exo*)-2-Allyl-3-phenyl-2-azabicyclo[2.2.2]octan-5-one (5m): Yield 30 mg (12%), yellow oil. R_f 0.50 (hexane/EtOAc 5:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.61 (m, 2H), 1.82 (m, 1H), 2.13 (m, 2H), 2.34 (s, 1H), 2.85 (d, *J* = 18 Hz, 1H), 3.10 (m, 2H), 3.35 (m, 1H), 3.94 (s, 1H), 5.08 (d, *J* = 9 Hz, 1H), 5.21 (d, *J* = 15 Hz, 1H), 5.80 (m, 1H), 7.29 (m, 2H), 7.37 (t, *J* = 6 Hz, 1H), 7.51 (d, *J* = 6 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$) δ =16.38 (CH_2), 27.74 (CH_2), 38.47 (CH_2), 50.30 (CH), 51.65 (CH), 56.80 (CH_2), 63.82 (CH), 116.93 (CH_2), 127.18 (CH), 127.29 (2 x CH), 128.35 (2 x CH), 136.19 (CH), 141.19 (C), 215.58 (C) ppm. HPLC (27% ee) (Daicel Chiracel ODH, hexane/2-propanol 99:1, flow rate 0.8 mL/min, λ= 207.6): major isomer: t_R = 8.81 min.; minor isomer: t_R = 9.26 min. HRMS calcd for $C_{16}H_{19}NO$: 241.14612, found: 241.145920.

(*exo*)-6-Allyl-7-phenyl-6-azabicyclo[3.2.2]nonan-8-one (5n): Yield 125 mg (49%), yellow oil. R_f 0.41 (hexane/EtOAc 10:1). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.44 (m, 1H), 1.57 (m, 1H), 1.71 (m, 2H), 1.84 (m, 1H), 1.97 (m, 1H), 2.25 (d, *J* = 18.4 Hz, 1H), 2.64 (d, *J* = 8 Hz, 1H), 2.82 (dd, *J* = 18.4, 4.8 Hz, 1H), 3.08 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.16 (dd, *J* = 14.4, 2 Hz, 1H), 3.43 (m, 1H), 4.01 (s, 1H), 5.19 (m, 2H), 5.91 (m, 1H), 7.27 (m, 1H), 7.36 (t, *J* = 6 Hz, 2H), 7.48 (d, *J* = 6 Hz, 2H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$,) δ = 20.22 (CH_2), 23.56 (CH_2), 36.49 (CH_2), 38.83 (CH_2), 51.20 (CH), 55.04 (CH), 57.18 (CH_2), 64.37 (CH), 117.18 (CH_2), 127.11 (CH), 127.67 (2 x CH), 128.39 (2 x CH), 136.21 (CH), 141.31 (C), 214.52 (C) ppm. HPLC (32% ee) (Daicel Chiralpak IA, hexane/EtOH 90:10, flow rate 0.6 mL/min, λ= 211.0): major isomer: t_R = 7.60 min.; minor isomer: t_R = 9.47 min. HRMS calcd for $C_{17}H_{21}NO$: 255.1623, found: 255.1632.

ACKNOWLEDGEMENTS

We thank the Ministero de Educación y Ciencia (MEC-07-CTQ2007-61048) for financial support for this work. A FICYT doctoral fellowship to N. Q. is gratefully acknowledged.

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