Pergamon

Tetrahedron 54 (1998) 1221–1232

TETRAHEDRON

Diastereocontrolled Synthesis of Pyrrolidines by Nickel Promoted Tandem Cyclization-quenching of Aminobromodienes

Yolanda Cancho, Joan M. Martín, María Martínez, Amadeu Llebaria, Josep M. Moretó, and Antonio Delgado*¶

Departament de Química Orgànica Biològica, C.I.D. (C.S.I.C.), Jordi Girona 18-26, 08034 Barcelona.

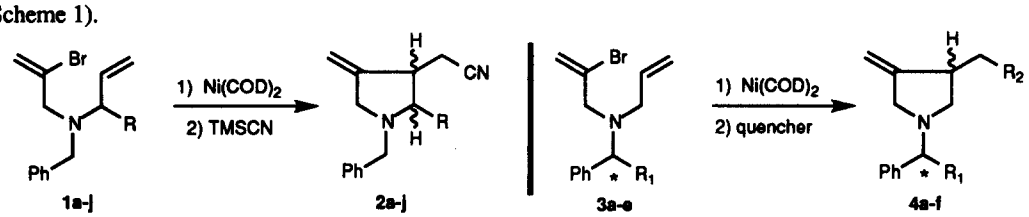
¶Universitat de Barcelona, Facultat de Farmàcia, Laboratori de Química Farmacèutica, Avgda. Joan XXIII, s/n, 08028 Barcelona,

Received 10 July 1997; accepted 11 September 1997

Abstract: The nickel promoted tandem cyclization-quenching of tethered aminobromodienes has been extended to the synthesis of 2,3,4-trisubstituted pyrrolidines. By a judicious choice of substituents on the starting aminohalodiene, the diastereoselectivity of the process can be efficiently controlled. When a chiral auxiliary on the nitrogen atom is used, enantiomerically enriched pyrrolidines can be obtained after removal of the auxiliary.

© 1998 Elsevier Science Ltd. All rights reserved.

In recent papers, we have reported on a new and mild intramolecular nickel-promoted tandem cyclization-quenching of amino-tethered vinyl bromides and alkenes leading to a diversity of heterocyclic nitrogen derivatives.[1,2] This process showed a remarkable diastereoselectivity when applied to the construction of several fused and spiro pyrrolidine derivatives. This fact, as well as the excellent overall yields found for simple 3-substituted *N*-benzyl-4-methylenepyrrolidine, and our interest in functionalized pyrrolidine derivatives as precursors of natural products, prompted us to study the effect of substitution upon the aminodiene framework on the diastereoselectivity of the process to give 2,3,4-trisubstituted pyrrolidines. On the other hand, the use of a chiral auxiliary on the nitrogen atom of the starting aminohalodiene, should hopefully lead to enantiomerically pure 3-substituted pyrrolidines after separation of the diastereomeric mixture arising from cyclization and removal of the chiral auxiliary. In this paper, we wish to report on our progress along these lines (Scheme 1).

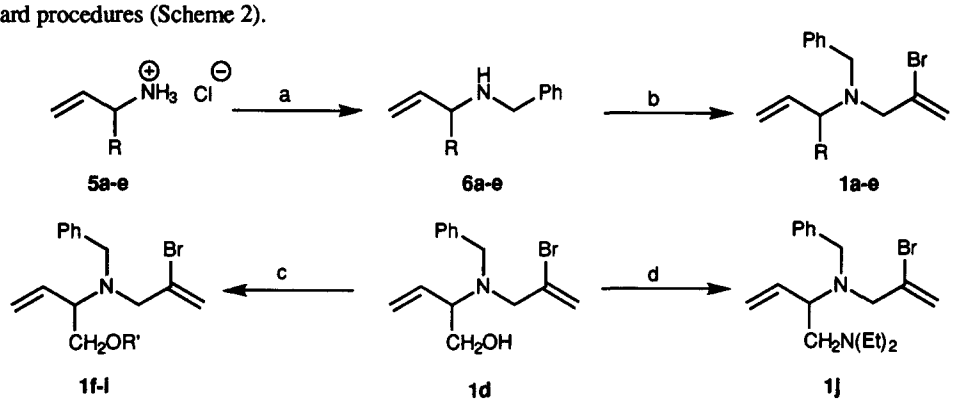


SCHEME 1

0040-4020/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(97)10220-4

Synthesis of starting materials.

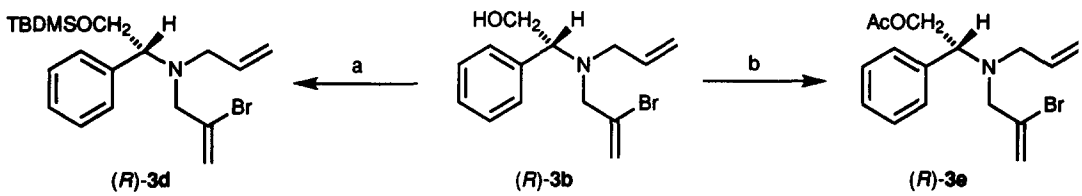
Aminohalodienes **1a-e** were obtained from allylamines **5a-e**, prepared according to Overman,[3] by benzylation and further alkylation with 2,3-dibromopropene. Compounds **1f-j** were prepared from **1d** by standard procedures (Scheme 2).



a: $PhCH_2Br$, K_2CO_3, CH_3CN; b: 2,3-dibromopropene, K_2CO_3, CH_3CN; c: TBDMSCl, imidazole, DMF (**1f** R'=TBDMS); Ac_2O, CH_2Cl_2, DMAP (**1g**: R'=$COCH_3$); PhCOCl, CH_2Cl_2, Et_3N (**1h**: R'=COPh); EtNCO, CH_2Cl_2 (**1i**: R'=CONHEt); d: 1) MsCl, Et_3N, CH_2Cl_2; 2) Et_2NH, Et_3N, CH_3CN

SCHEME 2

Aminohalodienes **3a-c** were similarly prepared from allylation of commercially available (*S*)-α-methylbenzylamine or the aminoacid derivatives[4] (*R*)-phenylglycinol and (*R*)-phenylglycine methyl ester, respectively, followed by alkylation with 2,3-dibromopropene. Compounds **3d** and **3e** were obtained from **3b**, as shown in Scheme 3.

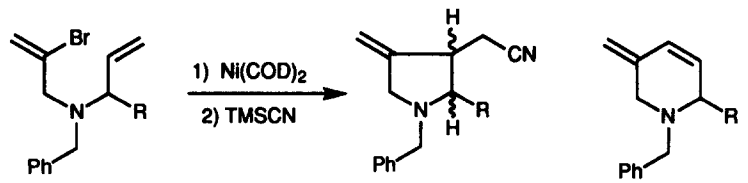


a: TBDMSCl, imidazole, DMF; b) Ac_2O, Et_3N, CH_2Cl_2

SCHEME 3

Results and Discussion.

The results of the Ni(0) promoted cyclization-quenching of aminohalodienes **1a-j** are collected in Table 1. As a general trend, cycloadducts **2a-j** were obtained in lower overall yields than those previously reported for the parent unsubstituted aminohalodiene (R_1=H), where the corresponding pyrrolidine derivative was obtained in quantitative yield.[2] Concerning diastereoselectivity, *trans*-cycloadducts were predominant in all cases with selectivities ranging from moderate to excellent depending on the nature of the substituent R.



1a-j 2a-j 9c,d,f-i

entry	substrate	R	Products (% yield) (a)		diastereosel. (b)
1	**1a**	CH_3	**2a** (92)	----	52 : 48
2	**1b**	Pr	**2b** (99)	----	70 : 30
3	**1c**	Ph	**2c** (47)	**9c** (18)	92 : 8
4	**1d**	CH_2OH	**2d** (49)	**9d** (5)	70 : 30
5	**1e**	CH_2OBn	**2e** (60)	----	80 : 20
6	**1f**	$CH_2OTBDMS$	**2f** (39)[c]	**9f** (6)	93 : 7
7	**1g**	CH_2OCOCH_3	**2g** (53)[c]	**9g** (12)	98 : 2
8	**1h**	CH_2OCOPh	**2h** (57)[c]	**9h** (18)	96 : 4
9	**1i**	$CH_2OCONHEt$	**2i** (30)	**9i** (4)	100 : 0
10	**1j**	CH_2NEt_2	**2j** (52)	----	63 : 37

(a) isolated yields; (b) *trans*:*cis* for compounds **2**, based on GC-MS of crude mixture; (c) only the *trans* isomer could be isolated.

TABLE 1

Stereochemical assignments for cycloadducts **2a-j** were based on NMR data, especially n.O.e experiments. Thus, as shown in Figure 1 for *trans*-**2g**, the stereochemical relationship is consistent with the n.O.e. enhancements observed after H_2 and H_3 irradiation. Similar n.O.e. effects were also observed for the major isomers of **2a**, **2c**, **2e**, and **2f**, where a *trans* stereochemistry was secured. On the other hand, once firmly established the relative stereochemistry by n.O.e. experiments for the above set of cycloadducts **2**, complementary ^1H NMR correlations emerged as useful tools for routine assignments. Thus, $J_{H2\text{-}H3}$,[5] was in the range of 7.2 to 9.6 Hz for the *trans*-isomers, whereas it showed a smaller value (between 5.7 and 6.3 Hz) for the *cis*-isomers. Additionally, a small difference in chemical shifts (around 0.15-0.20 ppm) was invariably found for the olefinic *exo*-methylene protons in *cis*-isomers, whereas in *trans*-isomers no significant differences were observed.[6]

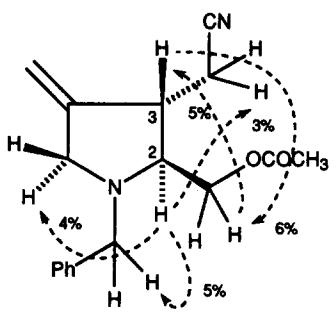


FIGURE 1

The effect of chain substitution in aminohalodienes **1** on the diastereoselectivity of the cyclization-quenching process can be properly rationalized on steric grounds. Thus, according to the well established insertion mechanism of vinylmetal intermediates upon olefins, a mutual *cis* arrangement between the

alkene and the vinylnickel moieties must be achieved.[7] As indicated in Figure 2, insertion through conformation **A**, where the olefin and the R group adopt an anticlinal disposition should be favoured over the more crowded conformation **B**, where a synclinal arrangement must be attained. This might account for the *trans* diastereoselectivity observed in the series.[8]

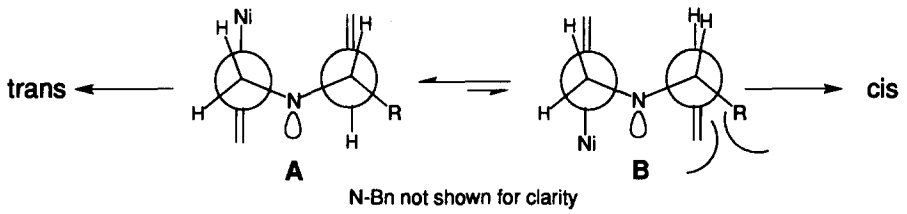


FIGURE 2

As we stated in our previous papers,[1,2] quenching with an appropriate terminating agent relies on the stabilization by coordination with the distal nitrogen atom lone pair in the intermediate alkylnickel species **2'** arising after cyclization (Figure 3). In cases where this coordination was hindered, piperidine derivatives arising presumably from a cyclopropyl carbinyl rearrangement[9,10] followed by Ni-H β-elimination predominated.[11] This mechanism might explain in our case the formation of piperidines **9** through a conformation **2'B**, in which interactions between the *N*-benzyl and the C_2 substituent are minimized at the expense of the N-Ni coordination (see Figure 3).

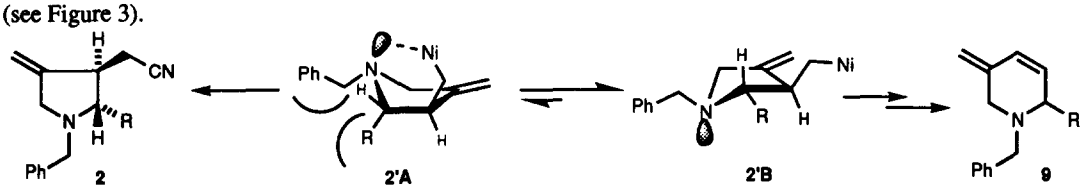
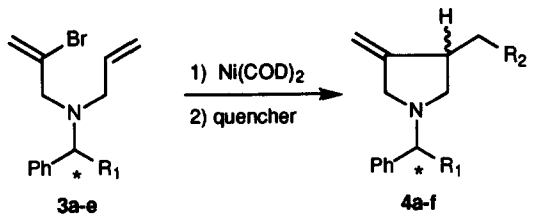


FIGURE 3

In **3a-e** series (Table 2), introduction of a α-methyl or a α-hydroxymethyl substituent on the benzyl moiety (Table 2, entries 1 and 2) showed little effect on the diastereoselectivity. However, a bulky $CH_2OTBDMS$ group (entry 4) and, even better, methoxycarbonyl (entry 3) or acetoxymethyl groups (entries 5 and 6) showed a complete diastereoselection, as evidenced from GC-MS analysis of the crude reaction mixture. In this series, the relative stereochemistry between the stereogenic centers was determined by X-ray analysis of **4g** to be α*R*,3*S* (see Scheme 4). This stereochemistry was inferred for **4e** and **4c** (see below) and was assumed to be that of **4f**, as well as that of the major diastereomer in **4b** and **4d**.

In this series, the diastereoselectivity was also dependent on the nature of the substituent at the α-benzyl position, as evidenced in Table 2. However, although the bulky $CH_2OTBDMS$ (entry 4), $COOCH_3$ (entry 3) and CH_2OAc (entries 5 and 6) groups were again the most effective ones, the origin of the diastereoselectivity remains intriguing.[12]



3a-e 4a-f

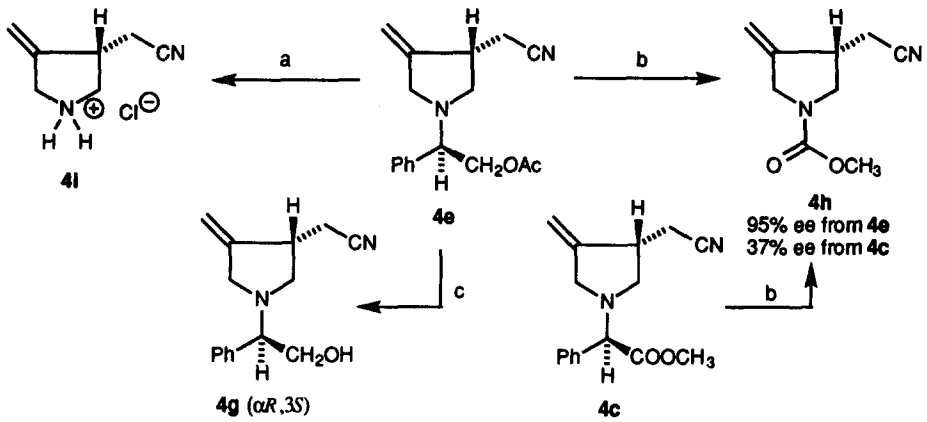
entry	substrate	R_1	quencher	R_2	Product (% yield) [a]	diast.[b]
1	(*S*)-**3a**	CH_3	TMSCN	CN	**4a** (51)	60 : 40
2	(*R*)-**3b**	CH_2OH	CO/MeOH	$COOCH_3$	**4b** (29)	63 : 37
3	(*R*)-**3c**	$COOCH_3$	TMSCN	CN	**4c** (40)	100 : 0
4	(*R*)-**3d**	$CH_2OTBDMS$	TMSCN	CN	**4d** (46)	83 : 17
5	(*R*)-**3e**	CH_2OCOCH_3	TMSCN	CN	**4e** (45)	100 : 0
6	(*R*)-**3e**	CH_2OCOCH_3	CO/MeOH	$COOCH_3$	**4f** (31)	100 : 0

(a) Isolated yield; (b) based on GC-MS of crude mixture.

TABLE 2

In order to verify the usefulness of the homochiral benzyl moiety for the synthesis of enantiomerically pure pyrrolidine derivatives, removal of the chiral auxiliary and determination of the enantiomeric excess of the resulting pyrrolidine derivative was next attempted (Scheme 4). This was achieved by treatment of single diastereomers **4c** and **4e** with neat methyl chloroformate[13] and chromatographic resolution[14] of the resulting carbamate **4h** via chiral GC (β-cyclodextrin). Whereas the carbamate arising from phenylglycinol derivative **4e** showed a 95%ee, thus proving the enantiomeric integrity of its precursor, only a 37%ee was measured for carbamate **4h** arising from methyl phenylglycinate derivative **4c**, which indicates that partial epimerization at the stereogenic center of the chiral auxiliary has taken place during the synthetic sequence. However, the same sign of rotation for both carbamates indicates that diastereoinduction proceeded in the same sense. Although at this point we cannot ascertain the origin of this epimerization, the sensitivity of α-aminoesters towards racemization is well precedented in the literature.[15] Removal of the chiral auxiliary from **4e** was also possible by treatment with 1-chloroethyl chloroformate (ACE-Cl)[16] to give, in a single operation, the more versatile pyrrolidine derivative (*S*)-**4i**. Although (*S*)-**4i** was not amenable to chiral GC chromatographic resolution, a 95% ee can be inferred based on the enantiomeric excess of its precursor.

In summary, we have extended our recently developed tandem cyclization-quenching methodology to the synthesis of several substituted pyrrolidine derivatives of general structures **2** and **4**. In both cases, the diastereoselectivity of the cyclization step can be efficiently controlled by a judicious choice of substituents on the starting aminohalodiene. Interestingly, by using a chiral auxiliary on the nitrogen atom in starting aminohalodienes **3**, enantiomerically enriched pyrrolidines, such as (*S*)-**4i**, can be obtained. Application of these findings to the synthesis of natural products of the kainoid family with potential biological interest is currently underway in our laboratory.



a: 1) ACE-Cl, cat. proton sponge, rfx; 2) MeOH, rfx; b: $ClCOOCH_3$, cat. proton sponge, rfx; c: K_2CO_3, MeOH

SCHEME 4

Acknowledgment. Financial support from CICYT and Comissionat per a Universitats i Recerca, Generalitat de Catalunya (Projects QFN 95-4718, 1995SGR 00583, 1995SGR 00439 and XT 94-4) is gratefully acknowledged. We thank Urquima S.A. for a generous gift of (*R*)-phenylglycinol. We also thank Prof. Müller (Departament de Química Inorgànica, Universitat de Barcelona) for technical support on GC chromatographic resolutions, Prof. Elies Molins (Institut de Ciència de Materials de Barcelona, CSIC) for X-ray analysis of compound **4g**, and Prof. Waldmann (Univ. Karlsruhe) for a personal communication.

EXPERIMENTAL

Elemental analyses were determined on Carlo Erba models 1107 and 1500. IR spectra were recorded on a Bomem MB-120 with Fourier transform instrument and are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions (unless otherwise indicated) on a Varian Gemini 200 and a Varian Unity 300 spectrometers, operating at 200 and 300 MHz for ^1H and 50 and 75 MHz for ^{13}C, respectively. The chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from Me_4Si, or in ppm relative to the singlet at 7.26 ppm of $CDCl_3$ for ^1H and in ppm relative to the center line of a triplet at 77.0 ppm of $CDCl_3$ for ^{13}C. Optical rotations were measured on a Perkin Elmer 141 polarimeter. The MS (EI) and MS (CI) spectra (70 eV) were obtained using a Hewlett-Packard 5989A mass spectrometer. High resolution MS (EI) spectra (70 eV) were obtained on a Auto Spec-Q instrument. GC-MS were determined on a HP 5995 mass spectrometer coupled to a gas chromatograph equipped with a fused silica capillary column SPB-5 (30 m x 0.32 mm i.d.). Chiral GC analyses were performed on a 25 m x 0.25 mm heptakis(2,3,6-tri-*o*-methyl)-β-cyclodextrin column at 110º C (isotherm). Commercial analytical-grade reagents were obtained from commercial suppliers (Aldrich Chemie, Fluka Chemie, Janssen Chimica) and were used directly without further purification. Solvents were distilled prior to use and dried by standard methods. $Ni(COD)_2$ was prepared according to a described procedure.[17] Amines **5a-e**(HCl) were prepared following a described methodology.[3] Secondary amines **6a-e** were obtained from **5a-e**(HCl) by treatment with benzyl bromide in dry CH_3CN in the presence of K_2CO_3. Aminohalodienes **1a-e**, (*S*)-**3a**, (*R*)-**3b**, and (*R*)-**3c** were prepared from the corresponding secondary amines

by treatment with 2,3-dibromopropene in CH_3CN in the presence of K_2CO_3. Carbamate **1i** was obtained from **1d** and ethyl isocyanate (CH_2Cl_2, rt). Diamine **1j** was prepared from **1d** by mesylation (MsCl, CH_2Cl_2, Et_3N) and treatment with Et_2NH. Finally, *tert*-butyl dimethylsilyl derivatives **1f** and (*R*)-**3d** were obtained from the corresponding alcohols following a standard procedure.[18]

Synthesis of cycloadducts. General method: To a solution of $Ni(COD)_2$ (1.5 mmol) in dry CH_3CN (5 mL), at room temperature under argon, a solution of the vinyl bromide (1 mmol) and Et_3N (3 mmol) in dry acetonitrile was added. The reaction mixture, which turned from yellow to red, was stirred at room temperature. When all the starting material was consumed (2.5 to 30 min, checked by tlc) the quencher (1.5-3.0 mmol of TMSCN or MeOH (5 mmol) under a stream of CO) was added and the mixture was stirred at room temperature for additional time (0.5-3 h). After filtration through Celite and careful washings with CH_2Cl_2, the mixture was partitioned between CH_2Cl_2 and saturated Na_2CO_3. Drying of the organic phases, followed by filtration and evaporation afforded the desired cycloadduct (see Tables 1 and 2).

***trans*-*N*-benzyl-3-cyanomethyl-2-methyl-4-methylenepyrrolidine (2a). ^{1}H-NMR** (300 MHz, $CDCl_3$): 1.30 (d, 3H, J= 5.1 Hz), 2.44-2.62 (cs, 4H), 2.94 (dm, 1H, J= 14.1 Hz), 3.17 (d, 1H, J= 12.9 Hz), 3.43 (d, 1H, J= 13.8 Hz), 4.08 (d, 1H, J=12.9), 4.98 (s, 1H), 5.02 (s, 1H), 7.20-7.38 (cs, 5H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 16.9 (CH_3), 19.6 (CH_2), 46.2 (CH), 57.3 (CH_2), 57.9 (CH_2), 64.1 (CH), 106.5 (CH_2), 118.2 (C), 127.0 (CH), 128.2 (CH), 128.7 (CH), 138.5 (C), 147.4 (C). **IR** (neat) : 2965, 2792, 2248, 1665, 1492, 1451. **Anal. Calcd. for $C_{15}H_{18}N_2$**: C, 79.61%, H, 8.02%, N, 12.38%. Found: C, 79.54%, H, 8.04%, N, 12.38%.

***trans*-*N*-benzyl-3-cyanomethyl-4-methylene-2-propylpyrrolidine (2b). ^{1}H-NMR** (300 MHz, C_6D_6): 0.83 (t, 3H, J= 6.9 Hz), 0.98-1.14 (cs, 1H), 1.20 -1.40 (cs, 3H), 1.72 (dd, 1H, J= 5.4, J´= 17.1 Hz), 1.81 (dd, 1H, J= 5.4, J´= 17.1 Hz), 2.12-2.30 (m, 2H), 2.69 (dm, 1H, J= 13.8 Hz), 2.85 (d, 1H, J= 12.9 Hz), 3.23 (d, 1H, J= 13.8 Hz), 3.75 (d, 1H, J= 13.2 Hz), 4.72 (s, 2H), 7.05-7.30 (sc, 5H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 14.6 (CH_3), 17.8 (CH_2), 21.1 (CH_2), 32.0 (CH_2), 43.2 (CH), 57.3 (CH_2), 57.8 (CH_2), 68.2 (CH), 107.1 (CH_2), 118.5 (C), 127.7 (CH), 128.3 (CH), 128.6 (CH), 138.(C), 147.9 (C). **IR** (neat): 2956, 2931, 2790, 2246, 1666, 1453. **Exact mass:** Calcd.: 254.178299. Found: 254.177590.

***trans*-*N*-benzyl-3-cyanomethyl-4-methylene-2-phenylpyrrolidine (2c). ^{1}H-NMR** (300 MHz, $CDCl_3$): 2.42 (dd, 1H, J= 5.7, J´=16.8 Hz), 2.60 (dd, 1H, J= 4.5, J´= 17.1 Hz), 2.70-2.82 (m, 1H), 3.04 (dm, 1H, H_5, J= 2.7, J´= 13.9 Hz), 3.06 (d, 1H, J= 12.9 Hz), 3.38 (d, 1H, J= 9.6 Hz), 3.73 (d, 1H, J= 13.8 Hz), 3.85 (d, 1H, J= 12.9 Hz), 5.02-5.07 (m, 1H), 5.08-5.12 (m, 1H), 7.20-7.56 (cs, 10H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 17.9 (CH_2), 48.3 (CH), 57.6 (CH_2), 58.0 (CH_2), 73.9 (CH), 106.3 (CH_2), 117.9 (C), 127.0 (CH), 127.8 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.9 (CH), 138.6 (C),139.9 (C), 146.9 (C). **IR** (neat) : 3029, 2794, 2248, 1667, 1494, 1453. **Exact mass**: Calcd.: 288.162649. Found: 288.161373.

***trans*-*N*-benzyl-3-cyanomethyl-2-hydroxymethyl-4-methylenepyrrolidine (2d). ^{1}H-NMR** (300 MHz, $CDCl_3$): 2.58-2.71 (cs, 3H), 2.72-2.80 (m, 1H), 3.05 (dm, 1H, J= 13.8 Hz),

3.37 (d, 1H, J= 12.9 Hz), 3.48 (d, 1H, J= 13.8 Hz), 3.60 (dd, 1H, J= 6.9, J'= 10.2 Hz), 3.87 (dd, 1H, J= 4.2, J'= 10.2 Hz), 4.07 (d, 1H, J= 12.9 Hz), 5.01-5.02 (m, 2H), 7.20-7.40 (cs, 5H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 21.4 (CH_2), 43.6 (CH), 58.8 (CH_2), 58.9 (CH_2), 64.4 (CH_2), 69.4 (CH), 107.0 (CH_2), 119.6 (C), 127.1 (CH), 128.3 (CH), 128.6 (CH), 138.7 (C), 147.5 (C). **IR** (neat): 3500, 2954, 2248, 1668, 1251. **Exact mass**: Calcd.: 242.141903. Found: 242.142798.

***trans*-*N*-benzyl-2-benzyloxymethyl-3-cyanomethyl-4-methylene-3-pyrrolidine (2e).** **^{1}H-NMR** (200 MHz, C_6D_6): 1.85 (dd, 1H, J= 5.2, J'= 16.8 Hz), 2.02 (dd, 1H, J= 5.5, J'= 17Hz), 2.25-2.41 (m, 1H), 2.50-2.60 (m, 1H), 2.71 (dm, 1H, J= 13.7 Hz), 2.95 (d, 1H, J= 13.4 Hz), 3.18 (dd, 1H, J= 6, J'= 9.6Hz), 3.26 (d, 1H, J= 13.8 Hz), 3.37 (dd, 1H, J= 4.4, J'= 9.6 Hz), 3.83 (1H, d, J= 13.4 Hz), 4.17 (s, 2H), 4.65 (s, 2H), 7.00-7.20 (cs, 10H). **^{13}C-NMR** (50MHz, $CDCl_3$): 20.9 (CH_2), 43.1 (CH), 58.5 (CH_2), 58.6 (CH_2), 67.7 (CH), 71.1 (CH_2), 73.5 (CH_2), 107.0 (CH_2), 118.4 (C), 127.0 (CH), 127.6 (CH) 127.8 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 137.8 (C), 138.4 (C), 147.2 (C). **IR** (neat): 2862, 2801, 2248, 1668, 1494, 1454. **Exact mass**: Calcd.: 332.188864. Found: 332.187746.

***trans*-*N*-benzyl-2-*tert*-butyldimethylsilyloxymethyl-3-cyanomethyl-4-methylene-3-pyrrolidine (2f).** **^{1}H-NMR** (300 MHz, C_6D_6): 0.00 (s, 6H), 0.91 (s, 9H), 2.00 (dd, 1H, J= 5.4, J'= 16.8 Hz), 2.13 (dd, 1H, J= 5.7, J'= 16.8 Hz), 2.40-2.50 (m, 1H), 2.50-2.60 (m, 1H, J= 4.2, J'= 6.6 Hz), 2.82 (dm, 1H, J= 13.8 Hz), 3.08 (d, 1H, J= 13.2 Hz), 3.34 (d, 1H, J= 13.5 Hz), 3.48 (dd, 1H, J= 6.3, J'= 10.2), 3.67 (dd, 1H, J= 4.2, J'= 10.5 Hz), 3.91 (d, 1H, J= 13.2Hz), 4.73-4.75 (m, 2H), 7.05-7.30 (cs, 5H). **^{13}C-NMR** (75 MHz, C_6D_6): -5.4 (CH_3), 18.3 (C), 21.1 (CH_2), 26.0 (CH_3), 43.7 (CH), 58.9 (CH_2), 59.0 (CH_2), 65.3 (CH_2), 69.8 (CH), 106.4 (CH_2), 118.3 (C), 127.1 (CH), 128.3 (CH), 128.5 (CH), 139.7 (C), 148.3 (C). **IR** (neat): 2954, 2930, 2858, 2360, 2248, 1712, 1471. **Exact mass**: Calcd.: 356.228384. Found: 356.229738.

***trans*-2-acetoxymethyl-N-benzyl-3-cyanomethyl-4-methylene-pyrrolidine (2g).** **^{1}H-NMR** (300 Hz, C_6D_6): 1.63 (s, 3H), 1.76-1.82 (cs, 2H), 2.21-2.31 (m, 1H), 2.36-2.45 (cs, 1H, J= 4.5 Hz), 2.67 (dm, 1H, J= 2.7, J'= 13.8 Hz), 2.90 (d, 1H, J= 12.9 Hz), 3.2 (d, 1H, J=13.8 Hz), 3.89 d, 1H, J= 13.1 Hz) 3.96 (dd, 1H, J= 3.9, J'= 11.4 Hz), 4.46 (dd, 1H, J= 4.8, J'= 11.7 Hz), 4.63-4.67 sa, 2H), 7.05-7.24 (cs, 5H). **^{13}C-NMR** (50 MHz, $CDCl_3$): 20.9 (CH_3), 20.9 (CH_2), 42.6 (CH), 58.0 (2 CH_2), 63.7 (CH_2), 67.0 (CH), 107.6 (CH_2), 118.0 (C), 127.1 (CH), 128.3, (CH) 128.5 (CH), 138.1 (C), 146.6 (C), 170.7 (C). **Anal. Calcd. for $C_{17}H_{20}N_2O_2$**: C, 71.81%, H, 7.09%, N, 9.85%, O, 11.25 %. Found: C, 71.86%, H, 7.18%, N, 9.69 %, O, 11.13 %. **IR** (neat): 2943, 2812, 2245, 1733, 1456, 1267.

***trans*-*N*-benzyl-2-benzoyloxymethyl-3-cyanomethyl-4-methylenepyrrolidine (2h).** **^{1}H-NMR** (300 MHz, C_6D_6): 1.81 (dd, 1H, J= 5.7, J'=16.8), 1.88 (dd, 1H, J= 5.4, J'= 16.8 Hz), 2.28-2.40 (m, 1H), 2.54-2.66 (m, 1H), 2.75 (dm, 1H, J= 13.8 Hz), 2.97 (d, 1H, J= 12.9 Hz), 3.24 (d, 1H, J= 13.8 Hz), 3.92 (d, 1H, J= 12.9 Hz), 4.16 (dd, 1H, J= 3.9, J'= 11.7 Hz), 4.30 (dd, 1H, J= 4.8, J'= 11.7 Hz), 4.65-4.69 (m, 2H), 7.00-7.25 (cs, 8H), 8.12-8.15 (m, 1H), 8.15-8.18 (m, 1H). **^{13}C-NMR** (75 MHz, C_6D_6): 20.7 (CH_2), 42.6 (CH), 57.7 (CH_2), 57.8 (CH_2), 64.2 (CH_2), 67.0 (CH), 107.6

(CH_2), 117.9 (C), 127.0 (CH), 128.1 (CH), 128.3 (CH), 128.4 (CH), 129.4 (CH), 129.6(CH), 133.0 (CH), 139.2 (C), 146.6 (C), 166.1 (C). **IR** (neat): 2802, 2250, 1770, 1452, 1272. **Exact mass**: Calcd.: 346.168112. Found: 346.167108.

***trans*-*N*-benzyl-3-cyanomethyl-2-(*N*-ethylcarbamoyloxymethyl)-4-methylene--pyrrolidine (2i).** **^{1}H-NMR** (300 MHz, C_6D_6): 0.80 (t, 3H, J=7.2 Hz), 1.93 (dd, 1H, J= 5.4 Hz), 2.02 (dd, 1H), 2.32-2.54 (cs, 2H), 2.72 (d, 1H, J= 13.8 Hz), 2.88-3.30 (cs, 3H, J= 12.9 Hz), 2.26 (d, 1H, J= 13.5 Hz), 3.99 (d, 1H, J= 12.9 Hz), 4.16 (bs, 2H), 4.43 (bs, 1H), 4.69 (bs, 1H), 4.73 (bs, 1H), 7.00-7.32 (cs, 5H). **^{13}C-NMR** (75 MHz, C_6D_6): 15.2 (CH_3), 20.4 (CH_2), 36.0 (CH_2), 42.7 (CH), 58.3 (CH_2), 58.4 (CH_2), 64.1 (CH_2), 68.0 (CH), 107.8 (CH_2), 118.2 (C), 127.3 (CH), 128.5 CH), 128.9 (CH), 139.3 (C), 147.8 (C), 156.1 (C). **IR** (neat): 3352, 2974, 2933, 2804, 2248, 1714, 1531. **Exact mass**: Calcd.: 313.179042. Found: 313.180357.

***trans*-*N*-benzyl-3-cyanomethyl-2-diethylaminomethyl-4-methylenepyrrolidine (2j).** Mixture of diastereomers. **^{1}H-NMR** (200 MHz, $CDCl_3$): 0.84 (t, 3H, J= 7.2 Hz), 0.93 (t, 3H, J= 7.2 Hz), 1.97-3.04 (cs, 28H), 3.22 (dd, 2H, J= 12.9 Hz), 3.43 (d, 2H, J= 13.2 Hz), 3.52 (d, 2H, J= 13.2 Hz), 4.86-4.94 (cs, 4H), 7.15-7.30 (cs, 10H). **^{13}C-NMR** (50 MHz, $CDCl_3$): 11.8 (CH_3), 14.7 (CH_3), 15.8 (CH_2), 16.1 (CH_2), 41.4 (CH), 41.8 (CH), 42.9 (CH_2), 43.2 (CH_2), 51.9 (CH_2), 52.0 (CH_2), 56.6 CH_2), 57.4 (CH), 60.1 (CH), 60.6 (CH_2), 62.3 (CH_2), 62.7 (CH_2), 109.8 (CH_2), 112.3 (CH_2), 119.4 (C), 119.8 (C), 127.1 (CH), 128.2 (CH), 128.8 (CH), 129.0 (CH), 142.6 (C), 143.2 (C). **IR** (neat): 2968, 2810, 2246, 1652, 1454. **Exact MS**: Calcd: 297.220498. Found: 297.220125.

***N*-(α-methylbenzyl)-3-cyanomethyl-4-methylenepyrrolidine (4a).** Mixture of diastereomers; (α*S*,3*R*) (major isomer): **^{1}H-NMR** (300 MHz): 1.37 (d, 3H, J=6.3 Hz), 2.31 (m, 1H), 2.46 (m, 2H), 2.84 (m, 2H), 3.02 (d, 1H, J=13.8 Hz), 3.20 (m, 2H), 4.93 (m, 1H), 4.95 (m, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 21.6 (CH_2), 22.7 (CH_3), 39.0 (CH), 57.7 (CH_2), 57.8 (CH_2), 65.1 (CH), 107.0 (CH_2), 118.6 (C), 126.8, 127.0, 128.3 (CH), 144.6 (C), 148.9 (C). **IR** (neat): 2970, 2780, 2246, 1666, 1452. **Anal. Calcd. for $C_{15}H_{18}N_2$**: C, 79.60%, H, 8.02%, N, 12.38%. Found: C, 79.86%, H, 8.25%, N, 12.69 %.

***N*-(α-hydroxymethylbenzyl)-3-methoxycarbonylmethyl-4-methylene-pyrrolidine (4b).** Mixture of diastereomers; *(αR,3S)*, (major isomer): **^{1}H-NMR** (200 MHz): 2.90 (m, 2H), 3.05 (m, 2H), 3.25 (m, 2H), 3.48 (q, 1H), 3.66 (d, 3H, J=8.2 Hz), 3.82 (m, 2H), 4.88 (m, 2H), 7.30 (m, 5H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 38.2 (CH_2), 38.7 (CH), 51.6 (C), 56.2 (CH_2), 57.1 (CH_2), 63.9 (CH_2), 69.3 (CH), 105.6 (CH), 127.9, 128.4, 128.5 (CH), 137.9 (C), 150.1 (s), 172.8 (s). **IR** (CCl_4): 3426, 2950, 1735, 1436, 1160, 1062, 886, 765, 703. **Exact mass**: Calcd.: 275.152124. Found: 275.153087.

(α*R*,3*S*)-*N*-(α-methoxycarbonylbenzyl)-3-cyanomethyl-4-methylenepyrrolidine (4c). **^{1}H-NMR** (200 MHz): 2.51 (m, 3H), 2.98 (m, 2H), 3.21 (dd, 2H), 3.67 (s, 3H), 4.01 (s, 1H), 5.02 (s, 2H), 7.37 (m, 5H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 21.4 (CH_2), 38.9 (CH), 52.1 (C), 56.9 (CH_2), 57.2 (CH_2), 72.3 (CH), 107.5 (CH_2), 118.4 (C), 128.2, 128.5, 128.7, (3xCH), 136.1 (C), 147.9 (C), 171.4 (C).

IR (CCl_4): 2952, 2246, 1745, 1453. $[\alpha]^{25}_D$ -68.7 (*c* 1, MeOH) (37% ee based on **4h**, see text). **Anal. Calcd. for $C_{16}H_{18}N_2O_2$**: C, 71.09%, H, 6.71%, N, 10.36%. Found: C, 70.99%, H, 6.73%, N, 10.27%.

***N*-[α-(*tert*-butyldimethylsilyloxymethyl)benzyl]-3-cyanomethyl-4-methylene-pyrrolidine (4d).** Mixture of diastereomers;*(αR,3S)*, (major isomer): **^{1}H-NMR** (200 MHz): -0.10 (d, 6H), -0.08 (s, 9H), 2.52 (m, 3H), 2.88 (m, 2H), 3.26 (t, 1H), 3.30 (q, 2H), 3.82 (m, 2H), 5.01 (s, 2H), 7.3 (m, 5H). **^{13}C-NMR** (75 MHz, $CDCl_3$): -5.6 (C), 18.1 (C), 21.7 (CH_2), 25.7 (C), 38.8 (CH), 58.0 (CH_2), 58.3 (CH_2), 67.4 (CH_2), 71.8 (CH), 106.9 (CH_2), 118.6 (C), 128.2, 128.0, 127.3 (3xCH), 141.0 (C), 149.0 (C). **IR** (CCl_4): 2927, 2248, 1665, 1471. **Exact mass**: Calcd.: 356.228384. Found: 356.229168.

(αR,3S)-*N*-(α-acetoxymethylbenzyl)-3-cyanomethyl-4-methylenepyrrolidine (4e). **^{1}H-NMR** (200 MHz): 1.99 (s, 3H), 2.53 (m, 3H), 2.86 (t, 2H), 3.25 (dd, 2H), 3.46 (t, 1H), 4.30 (m, 2H), 5.03 (m, 2H), 7.25 (m, 5H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 20.9 (C), 21.7 (CH_2), 38.8 (CH), 57.5 (CH_2), 57.6 (CH_2), 67.0 (CH_2), 67.9 (CH), 107.4 (CH_2), 118.5 (C), 127.9, 128.5, (3xCH), 139.3 (C), 148.3 (C), 170.6 (C). **IR** (CCl_4): 2796, 2248, 1739, 1453. $[\alpha]^{25}_D$ -63.2 (*c* 1, MeOH). **Anal. Calcd. for $C_{17}H_{20}N_2O_2$ (HCl)**: C, 63.64%, H, 6.59%, N, 8.73%, Cl, 11.05%. Found: C, 63.52%, H, 6.57%, N, 8.78%, Cl, 10.95%.

(αR,3S)-*N*-(α-acetoxymethylbenzyl)-3-methoxycarbonylmethyl-4-methylene-pyrrolidine (4f). **^{1}H-NMR** (200 MHz): 1.96 (s, 3H), 2.45 (m, 3H), 3.02 (m, 2H), 3.16 (s, 2H), 3.42 (t, 1H), 3.65 (s, 3H), 4.22 (A of an ABX, 1 H, J_{AB} =17 Hz, J_{AX}= 9 Hz), 4.38 (B of an ABX, 1 H, J_{AB} =17 Hz, J_{AX}= 9 Hz), 4.82 (m, 1H), 4.88 (m, 1H), 7.3 (m, 5H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 20.9 (C), 38.3 (CH_2), 38.8 (CH), 51.5 (C), 58.0 (CH_2), 58.4 (CH_2), 67.1 (CH_2), 68.2 (CH), 105.3 (CH_2), 127.6, 128.0, 128.3, (3xCH), 139.7 (C), 150.4 (C), 170.7 (C), 172.8 (C). **IR** (CCl_4): 2950, 2788, 1739, 1436. $[\alpha]^{25}_D$ -34.0 (*c* 1, MeOH). **Anal. Calcd. for $C_{18}H_{23}NO_4$**: C, 68.12%, H, 7.30%, N,4.41%. Found: C, 68.09%, H, 7.31%, N, 4.5%.

(αR,3S)-3-cyanomethyl-*N*-(α-hydroxymethylbenzyl)-4-methylenepyrrolidine (4g). Obtained from **4e** by treatment with K_2CO_3 (1.5 equiv.) in refluxing MeOH for 30 min. Filtration and evaporation afforded **4g** as a solid in quantitative yield. 1H-NMR (200 MHz): 2.45 (m, 3H), 2.81 (m, 2H), 3.20 (m, 2H), 3.39 (t, 1H, *J* =5.6), 3.71 (dd, 1H, *J* =6.0, *J'*=5.8), 3.79 (dd, 1H, *J* =6.0, *J'*=5.8), 4.96 (m, 2H), 7.25 (m, 5H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 21.6 (CH_2), 38.6 (CH), 56.5 (2xCH_2), 64.2 (CH_2), 69.6 (CH), 107.3 (CH_2), 118.5 (C), 127.8, 128.3, 128.4 (CH), 138.2 (C), 148.1 (CN). **IR** (CCl_4): 3380, 2245, 1666, 1450. $[\alpha]^{25}_D$ -78.2 (*c* 1.16, MeOH). **Anal. Calcd. for $C_{15}H_{18}N_2O$**: C, 74.35%, H, 7.48%, N, 11.56%. Found: C, 74.26%, H, 7.31%, N, 11.74%.

(3S)-3-cyanomethyl-*N*-methoxycarbonyl-4-methylenepyrrolidine (4h). A solution of **4e** or **4c** (0.4 mmol) and 1,8-bis(dimethylamino)naphthalene (Proton-Sponge®) (0.2 mmol) is heated with methyl chloroformate (2 mL) at reflux under argon until consumption of the starting material. The reaction mixture is then evaporated, treated with 1*N* HCl (5 mL) and evaporated again to dryness. The residue is purified through a short pad of silica gel (Hexane-EtOAc 50%) to give carbamate **4h** in 59% yield (from **4e**) or in 36% yield (from **4c**). **^{1}H-NMR** (200 MHz): 2.53 (d, 2H), 3.03 (s, 1H), 3.70 (s, 3H), 3.54 (d, 2H), 4.08

(s, 2H), 5.18 (d, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 20.3 (CH_2), 39.3 (CH), 49.7 (CH_2), 50.6 (CH_2), 52.4 (C), 108.9 (CH_2), 117.5 (C), 145.5 (C), 155.2 (C). **IR** (CCl_4): 3563, 2956, 2358, 2248, 1702. $[\alpha]^{25}_D$ -28.2 (*c* 2, MeOH) (95% ee by chiral GC, from **4e**). **Exact mass**: Calcd.: 180.089861. Found: 180.090455.

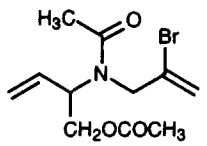
(3*S*)-3-cyanomethyl-4-methylenepyrrolidine hydrochloride (4i). Obtained as above from **4e** (0.6 mmol), 1,8-bis(dimethylamino)naphthalene (Proton-Sponge®) (0.3 mmol) and freshly distilled 1-chloroethylchloroformate (2 mL). The residue obtained after purification through a short pad of silica gel is refluxed with MeOH (2 mL) for 1h and evaporated to dryness to give **4i** in 73% yield. **^{1}H-NMR** (200 MHz): 2.77 (d, 2H), 3.25 (s, 2H), 3.65 (s, 1H), 4.01 (s, 2H), 5.27 (d, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$): 20.1 (CH_2), 37.8 (CH), 48.5 (CH_2), 49.4 (CH_2), 111,6 (CH_2), 117.4 (C), 141.3 (C). **IR** (CCl_4): 3382, 2917, 2245, 1735. $[\alpha]^{25}_D$ -56.4 (*c* 1.28, MeOH).

References and notes

1. Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133-12134.
2. Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895-5904.
3. Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901-2909.
4. For a review on the use of aminoacid and derivatives thereof in asymmetric synthesis, see: Ager, D. A.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835-875.
5. The value of the $J_{H2\text{-}H3}$ coupling constant was measured after methylene group irradiation of the CH_2CN moiety.
6. Additionally, $\Delta\delta$ (*trans-cis*) between C2 carbons in ^{13}CNMR could also be used as a diagnostic tool, since $\Delta\delta$ around 3 ppm were observed. For a related empirical use of chemical shift differences for stereochemical assignments in related compounds, see Hashimoto, K.; Konno, K.; Shirahama, H. *J. Org. Chem.* **1996**, *61*, 4685-4692.
7. Collman, J.; Hegedus, L.; Norton, G.; Finke, G. *Principles and Applications of Organotransition Metal Chemistry*.; University Science Books: Mill Valley, California, 1987.
8. In order to explain the high or complete diastereoselectivity observed for substrates bearing an ester (**1g** and **1h**) or a carbamate group (**1i**) (entries 7-9, Table 1), an additional attractive interaction between the side chain carbonyl group and the nitrogen lone pair could also be considered. Attractive interaction N→C=O has been demonstrated both in solid state and in solution; see, for example: a) Schweizer, W.B.; Procter, G.; Kaftory, M.; Dunitz; J.D. *Helv. Chim. Acta* , **1978**, *61*, 2783-2808; b) Kaftory, M.; Dunitz; J.D. *Acta Cryst.*, **1975**, *B31*, 2912-2914 and 2914-2916; c) Leonard, N.J.; Morrow, D.F.; Rogers, M.T. *J. Am. Chem. Soc.* **1957**, *79*, 5476-5479; d) Leonard, N.J. *Tetrahedron.*, **1997**, *53*, 2325-2355 and references cited therein. Additional examples where this type of interaction has also been invoked: Selectivity control in Diels-Alder reactions: e) Cordes, M.H.J.; de Gala, S.; Berson, J.A. *J. Am. Chem. Soc.* **1994**, *116*, 11161-11162; f) Cordes, M.H.J.; Berson, J.A. *J. Am. Chem. Soc.* **1996**, *118*, 6241-6251; g) Bachrach, S.M. *J. Org. Chem.* **1995**, *60*, 4395-4398. Conformational equilibrium related to bioactivity of certain analgesics: h) Bürgi, H.B.; Dunitz, J.D.; Shefter, E. *Nature new Biol.*, **1973**, *244*, 186-188. Correlation with the geometry of nucleophile approach on the attack to carbonyl or nitrile groups: i) Bürgi, H.B.; Dunitz, J.D.; Shefter, E. *J. Am. Chem. Soc.*, **1973**, *61*,

2783-2808; j) Baxter, P.W.N.; Connor, J.A.; Povey, D.C.; Wallis, J.D. *J. Chem. Soc., Chem Commun.* **1991**,1135-1137.

9. Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091-10092.
10. Trost, B. M.; Dumas, J. *Tetrahedron Lett.* **1993**, *34*, 19-22.
11. In agreement with our previous results, cyclization of **1k** under standard conditions afforded a complex mixture in which no trace of the desired cycloadduct **2** could be detected. However, this result indicates the inability of the side chain acetate carbonyl group to stabilize by coordination an alkylnickel intermediate such as **2'** (see Figure 3).



1k

12. Although in **3c** and in **3e**, a vinylnickel-carbonyl coordination could be the origin of the diastereoselection, we have been unable to find a likely explanation for our experimental results based on this hypothesis. For coordination of carbonyl groups with the metal center in organometallic nickel compounds, see: a) Sacerdoti,M.; Bertolasi, V.; Gilli, G. *Acta Crystallogr.* **1980**, *B36*, 1061; b) Schröder, W.; Pörschke, K.R.; Tsay, Y.-H.; Krüger, C. *Angew. Chem. Int. Ed. Engl.*, **1987**, *26*, 919-921; c) Carmona, E.; Gutiérrez-Puebla, E.; Monge, A.; Marín, J.M.; Paneque, M.; Poveda, M.L. *Organometallics*, **1989**,*8*, 967-975. For conformational effects due to nickel-carbonyl chelation, see: d) Shambayati, S.; Crowe, W.E.; Schreiber, S.L. *Angew. Chem. Int. Ed. Engl.*, **1990**, *29*, 256-272.
13. Wright Jr., W. B.; Brabander, H. J. *J. Org. Chem.* **1961**, *26*, 4057-4060.
14. Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; John Wiley: New York, 1994, p 359-364.
15 Waldmann, H. *Synlett* **1995**, 133-141.
16. Olofson, R. A.; Abbott, D. *J. Org. Chem.* **1984**, *49*, 2795-2799.
17. Colquhoun, H. M.; Holton, J.; Thompson, D. J.; Twigg, M. V. *New Pathways for Organic Synthesis*; Plenum: New York, 1984.
18. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191.