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SYNTHESIS AND RETRO AZA DIELS-ALDER REACTION OF SOME NEW ISOQUINUCLIDINE DERIVATIVES

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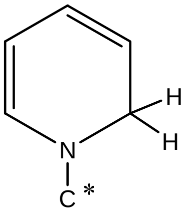
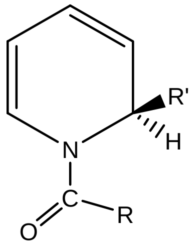
Abstract - *N*-Benzyl- and *N*-(α-methoxycarbonylethyl)-2,4,6-triphenyl-1,2-dihydropyridines were submitted to Diels-Alder reactions with maleic anhydride or *N*-phenylmaleimide yielding, diastereoselectively, the corresponding *endo-anti* adducts. These novel isoquinuclidines showed to be resistant to *N*-alkylation or *N*-protonation, undergoing an unexpected fragmentation *via* a retro aza Diels-Alder process.

INTRODUCTION

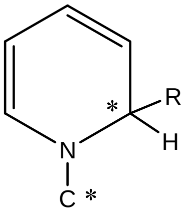
As an ongoing project aiming the preparation of new chiral phase-transfer catalysts, presenting a rigid cyclic structure, we decided to investigate the Diels-Alder (DA) reactions of chiral *N*-substituted-1,2-dihydropyridines with suitable dienophiles, a well established route for constructing the isoquinuclidine skeleton. In the literature, modest to good π-facial diastereoselectivities were observed for DA reactions of 1,2-dihydropyridines **I** and **II** bearing a stereogenic center either at the exocyclic substituent attached to the nitrogen atom[1] or at C-2 of the 1,2-dihydropyridine ring.[2] However, to our knowledge, there is no literature report on this kind of reaction involving 1,2-dihydropyridines of type **III**, with two stereocenters, one at C-2 and the other at the nitrogen substituent.



I



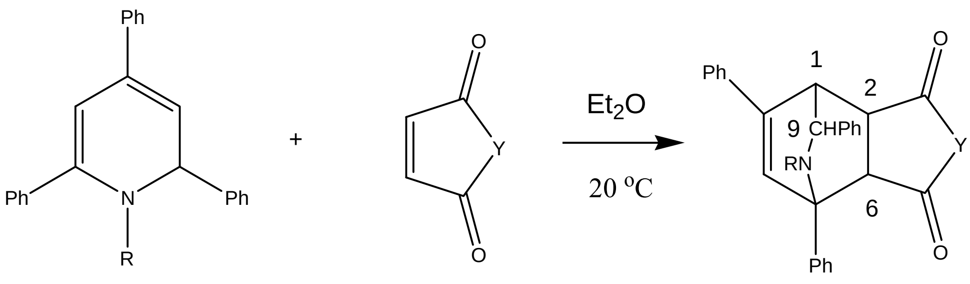
II



III

RESULTS AND DISCUSSION

In an attempt to prepare new dienes of type **II** and **III**, *N*-benzyl-2,4,6-trimethylpyridinium and *N*-(±)-(α-methoxycarbonylethyl)-2,4,6-trimethylpyridinium tetrafluoroborates[3] were submitted to reduction with NaBH$_4$, but complex mixtures of products were obtained in both cases. However, using the same reducing agent, *N*-benzyl-2,4,6-triphenyl-1,2-dihydropyridine **1a** was successfully prepared.[4] In order to test the reactivity of this kind of azadiene, we performed the DA reaction of **1a** with maleic anhydride and *N*-phenylmaleimide (Scheme 1). Although some decrease of reactivity would be expected, due to the presence of the electron withdrawing phenyl groups, the DA reactions proceeded smoothly for each dienophile, yielding, in each case, only one adduct (**2a** (85%) or **3a** (90%)). This result prompted us to perform the reduction of *N*-(±)-(α-methoxycarbonylethyl)-2,4,6-triphenylpyridinium tetrafluoroborate with NaBH$_4$. The non-isolable epimeric equimolar mixture of the resulting 1,2-dihydropyridines **1b** was submitted to reaction with maleic anhydride or *N*-phenylmaleimide, yielding the new racemic diastereoisomeric DA adducts **2b** (20%) and **2b'** or **3b** (35%) and **3b'** (20%), respectively (Scheme 1).



1
R=Bn (**a**)
or
(+/-)-
MeCHCO$_2$Me (**b**)

2 (Y=O)
or
3 (Y=NPh)

Scheme 1

These newly prepared isoquinuclidines were fully characterized by ^{1}H NMR (Table 1).

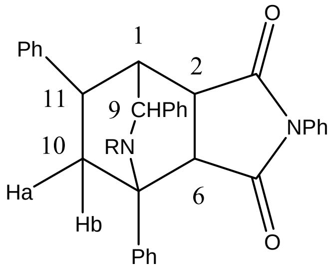
Table 1. Selected ^{1}H NMR data for adducts **2** and **3**

compound	Y	H-1	H-2	H-6	H-9
2a	O	3.84-3.78	3.71	4.50	4.00
		m	dd; J=8.3/3.0 Hz	d; J=8.3 Hz	d; J=2.1 Hz
2b	O	3.76-3.58	3.90-3.82	4.47	4.40
		m	m	d; J=7.2 Hz	d; J=3.2 Hz
2b'*	O	3.90-3.82	4.09	4.52	4.90
		m	dd;J=8.4/3.0 Hz	d; J=8.4 Hz	d; J=2.4 Hz
3a	NPh	3.93-3.91	3.63	4.47	4.10
		m	dd; J=8.0/2.7 Hz	d; J=8.0 Hz	d; J=2.4 Hz
3b	NPh	3.97-3.94	3.59	4.38	4.51
		m	dd; J=7.8/2.7 Hz	d; J=8.1 Hz	d; J=2.4 Hz
3b'	NPh	4.25-4.18	4.13	4.53	5.21
		m	dd; J=8.1/3.0 Hz	d; J=7.8 Hz	d; J=2.4 Hz

* data collected from a mixture of **2b** and **2b'**

In order to access the stereochemical features of such adducts, we turned our attention to the coupling constant between H-1 and H-2. Although for analogous adducts the observed value of *ca*. 3 Hz has been considered[5] as indicative of an *endo* configuration, the inspection of molecular models for compounds **2** and **3** indicates that very similar $J_{1,2}$ values would be expected for the *endo* and *exo* isomers. Moreover, for compounds **2** and **3**, besides assigning an *endo* or *exo* configuration, it would be necessary to determine the relative position of H-9, that could point either towards the olefinic bond (*syn*-orientation) or opposite to it (*anti*-orientation). In this sense, it should be mentioned that, for similar compounds, Krow et al.[2] found that the reduction of the olefinic bond of a *syn*-adduct, using Pd/C and hydrogen, gave rise to a product for which the resonance signal of *syn* H-9 was shifted downfield relatively to the same signal in the original adduct. Coherently, no such effect was observed upon hydrogenation of the *anti*-oriented adduct. In our case, hydrogenation of the olefinic double bond of isoquinuclidines **3b** and **3b'** showed to be completely stereoselective, yielding the new saturated compounds **4b** (50%) and **4b'** (50%), for which some selected ^{1}H NMR data are presented in Table 2.

Table 2. Selected ^{1}H NMR data for compounds **4b** and **4b'** (R=MeCHCO$_2$Me)



H	**4b**	**4b'**
1	3.40-3.24; m	3.50-3.42; m
2	3.15; dd; J=10/2.1 Hz	3.91; dd; J=9.7/2.8 Hz
6	3.70; dd; J=10/2.7 Hz	4.29; J=9.7/3.0 Hz
9	4.48; d; J=2.7 Hz	5.07; d; J=3.1 Hz
10a	2.40; dd; J=14/6.6 Hz	2.49; dd; J=14/6.2 Hz
10b	2.79; ddd; J=14/12/3.0 Hz	2.97; ddd; J=14/11/3.0 Hz
11	3.40-3.24; m	3.36-3.28; m

For compounds **3b** and **4b** or **3b'** and **4b'**, close values for the H-9 chemical shifts were observed. This fact suggests that H-9, in compounds **3b** and **3b'**, is not affected by the double bond anisotropy and, therefore, must be *anti*-oriented. Additionally, as an evidence for the *endo* configuration of **3b** and **3b'**, it should be pointed out that the hydrogenated analogs (**4b** and **4b'**) present a long range coupling (*ca.* 3 Hz) between H-6 and one of the methylene protons at C-10. Such coupling can only be attributed to a W conformation of the four sigma bonds, linking *exo*-H-6 and H-10b (Figure 1). Furthermore, for compounds **4b** and **4b'**, the magnitude of the coupling constants between H-10b and H-11 (*ca.* 12 Hz) indicates that they are eclipsed, as a result of an *exo* hydrogen addition to the double bond of adducts **3b** and **3b'**.

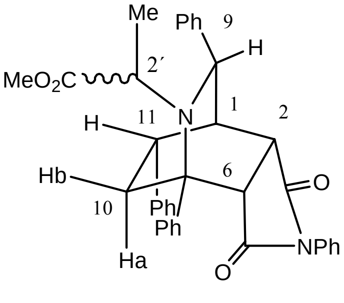


Figure 1

The above arguments seemed to support an *endo-anti* stereochemistry for adducts **2** and **3**. In fact, this configuration was further confirmed by single crystal X-ray analysis of adducts **2a** and **3b** (Figure 2).

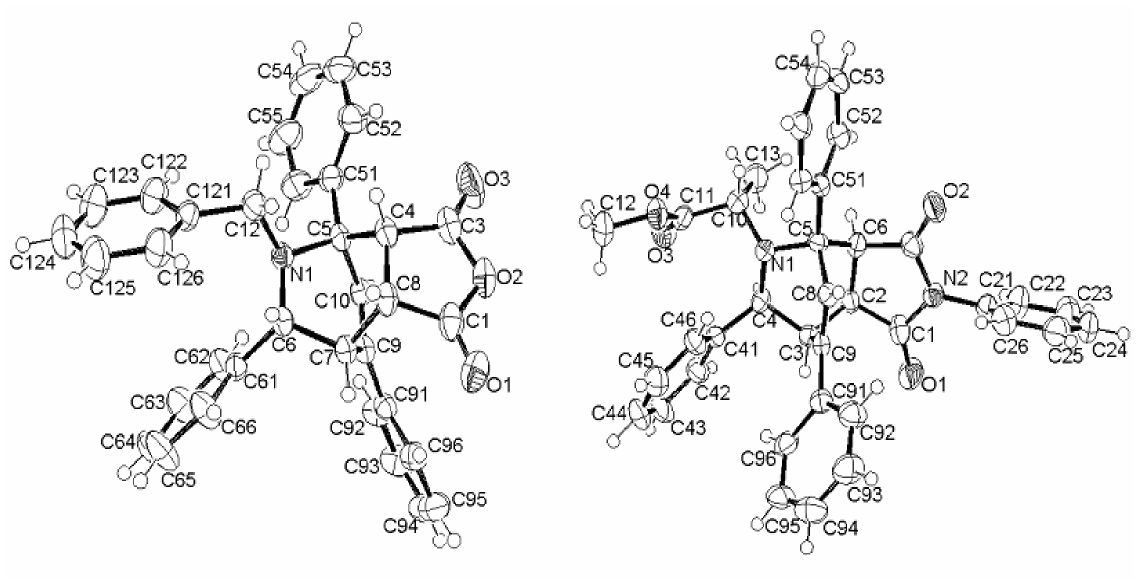
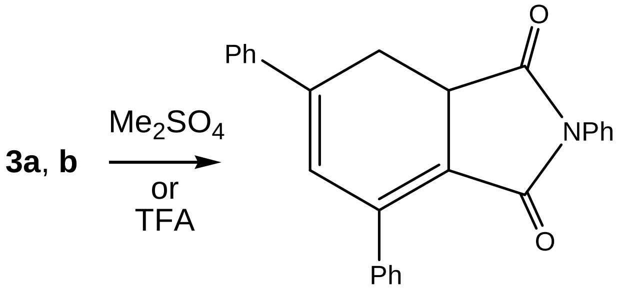


Figure 2. ORTEP structures of the DA adducts **2a** and **3b**

As for the origin of the high *endo*-*anti*-diastereoselectivity of the DA reactions of 2,4,6-triphenyl-1,4-dihydropyridines **1**, we believe that it could be attributed to: (i) the low reactivity of dienes **1**, due to conjugation between the dihydropyridine ring double bonds and the two 4,6-phenyl π-density,[6] and (ii) the steric hindrance to the *syn* approach of the dienophile, due to the presence of the phenyl group at C-2 of the diene.

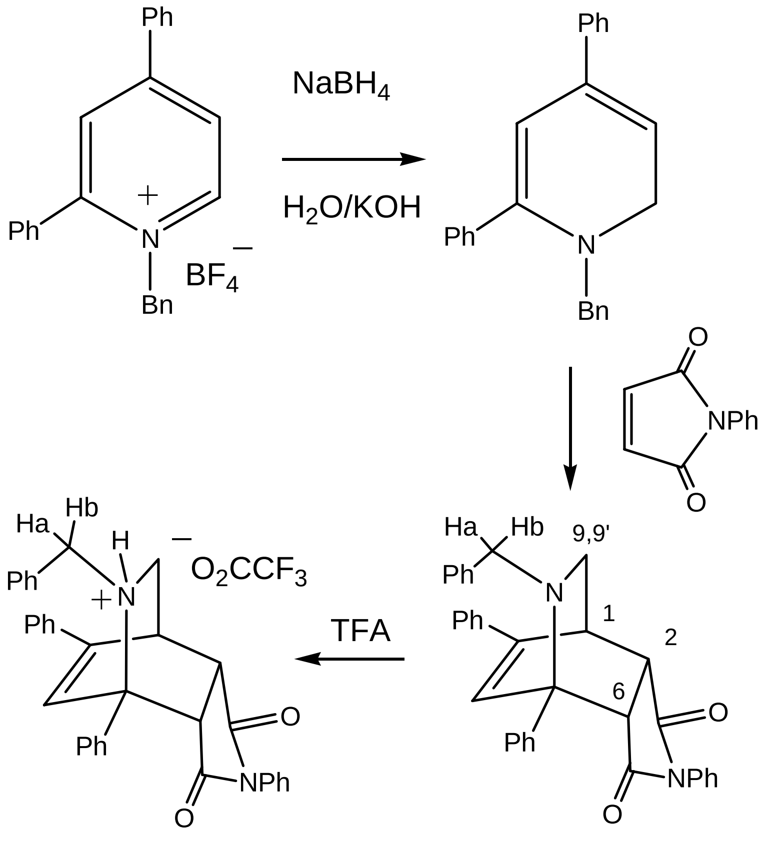
As a next step for the construction of the molecular framework of the model catalyst, we attempted the alkylation of the isoquinuclidine nitrogen. Adducts **3a** and **3b** failed to react with MeI, at room temperature, with complete recovery of the starting material. Surprisingly, the reaction of the same adducts with Me_2SO_4, under reflux in MeCN, afforded a mixture containing benzaldehyde. The lack of NMR proton signals attributable to the isoquinuclidine nitrogen substituent suggested the occurence of a retro aza Diels-Alder reaction[7] (Scheme 2). In fact, diene **5**[8] could be isolated (55%) from the crude reaction mixture. It should be noted that uppon treatment of a $CHCl_3$ solution of adducts **3a** or **3b** with TFA, at room temperature, the retro aza Diels-Alder reaction was still observed.



5 (55%)

Scheme 2

As previously reported, hindered *N*-substituted 2-azanorbornenes are prone to heterocycloreversion.[7b] In order to try to cicumvent such drawback, the less hindered DA adduct **6** was prepared (43%), and submitted to reaction with TFA (Scheme 3), affording the corresponding stable isoquinuclidinium salt **7**. For the obtained product, the observed deshielding of the 9, 9', 1, 2, 6, and benzylic protons, and the change in multiplicity of the Hb signal (d in **6**; dd in **7**; see Figure 3) were consistent with the protonation of the isoquinuclidine nitrogen.



7 **6** (43%)

Scheme 3

Inspired by this promising result, we attempted the methylation of **6** with Me_2SO_4/MeCN. However, heterocycloreversion was again observed, probably driven by the high stability of the highly conjugated diene **5**.

CONCLUSION

The easy cycloreversion of this kind of adducts precluded the preparation of isoquinuclidinium salts, as originally planned. However, such reaction could find application in the synthetic functionalization of primary amines[9] and aminoacids,[10] having the amino group temporarily locked into a pyridinium salt ring. Efforts in this sense are in progress in our laboratory.

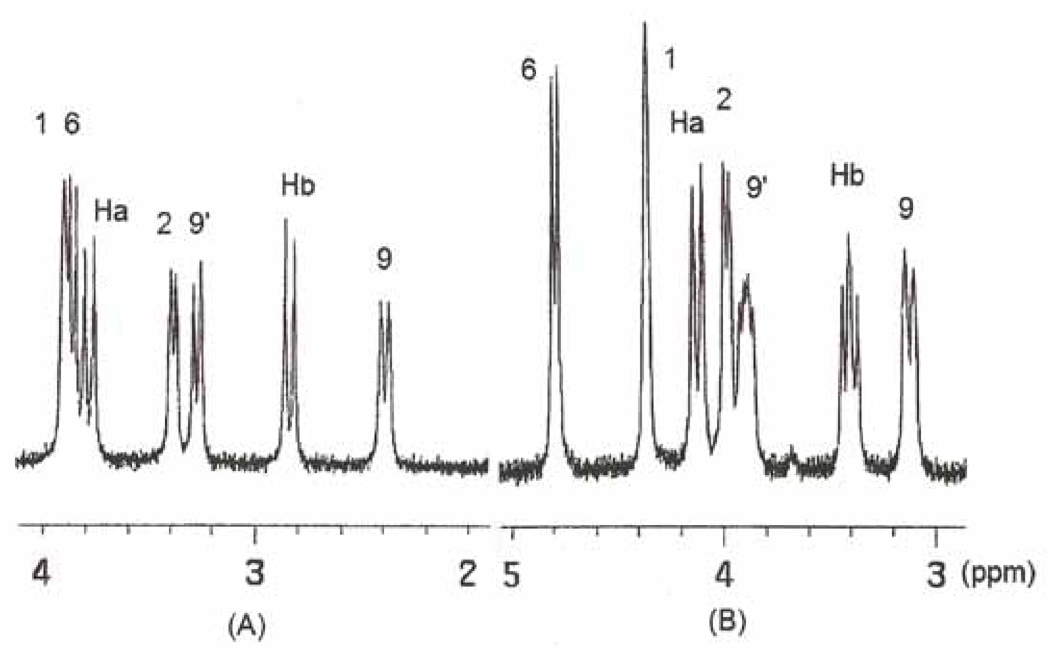


Figure 3. ^{1}H NMR spectra of adducts **6** (**A**) and **7** (**B**)

EXPERIMENTAL

Commercial reagents were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded, respectively, at 200 MHz (Bruker AC 200) or 300 MHz (Varian Inova) and at 50 or 75 MHz. All spectra are reported in δ (ppm) relative to TMS. *N*-Benzyl-2,4,6-triphenyl-1,2-dihydropyridine was prepared according to the literature procedure.[4]

***N*-(±)-(α-Methoxycarbonylethyl)-2,4,6-triphenyl-pyridinium tetrafluoroborate.** To a stirred solution of 4.2 g (30 mmol) of L-alanine methyl ester hydrochloride in 100 mL of CH_2Cl_2, Et_3N (6.1 g; 60 mmol) was added, followed by 2,4,6-triphenylpyrilium tetrafluoroborate (12 g; 30 mmol; *via goose-neck*). Each portion of this salt was added after complete dissolution of the previous one. After stirring for 2 h at rt, acetic acid (3.6 g; 60 mmol) was added. Stirring was maintained for 2 h, the solvent removed under reduced pressure and the resulting oily residue was treated with Et_2O and washed with water. Crystallization from EtOH yielded a colorless solid (50 % yield); mp 219-220 °C; ^{1}H NMR ($CDCl_3$): δ 7.93 (s, 2H, Ar), 7.84 - 7.52 (m, 15H, Ar), 5.56 (q, 1H, J = 7.2 Hz), 3.68 (s, 3H), 1.50 (d, 3H, J = 7.2 Hz); Anal. Calcd for $C_{27}H_{24}NO_2BF_4$: C, 67.38; H, 5.03; N, 2.91. Found: C, 67.30; H, 4.96; N, 3.15

***N*-(±)-(α-Methoxycarbonylethyl)-2,4,6-triphenyl-1,2-dihydropyridines.** To a stirred solution of *N*-(±)-(α-methoxycarbonylethyl)-2,4,6-triphenylpyridinium tetrafluoroborate (4.8 g; 10 mmol) in MeCN/MeOH (1 : 1), $NaBH_4$ (0.38 g; 10 mmol) was added, in small portions *via goose-neck*, at 0 °C, and under N_2 atmosphere. The resulting mixture was further stirred for 1 h. After removing the solvent under reduced pressure, and adding Et_2O, the mixture was eluted through a pad of SiO_2. Concentration of the organic extract yielded a yellow oil as an equimolar mixture of the expected diastereoisomeric dihydropyridines, that was submitted, without separation, to the subsequent DA reaction; ^{1}H NMR ($CDCl_3$): δ 7.76 - 7.73 (m, 2H, Ar), 7.63 - 7.51 (m, 10H, Ar), 7.39 - 7.18 (m, 18H, Ar), 6.08 (d, 1H, J = 1.5 Hz), 5.98 (d, 1H, J = 1.5 Hz), 5.87 (dd, 1H, J = 6.6 and 1.2 Hz), 5.74 (dd, 1H, J = 6.6 and 1.2 Hz), 5.28 (d, 1H, J = 6.6 Hz), 5.15 (d, 1H, J = 6.6 Hz), 4.19 (q, 1H, J = 6.6 Hz), 3.93 (q, 1H, J = 7.2 Hz), 3.63 (s, 3H), 3.46 (s, 3H), 1,48 (d, 3H, J = 7.2 Hz), 1.30 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 173.6, 173.1, 146.0, 145.1, 143.9, 137.8 (2C), 136.1, 129.1, 129.0, 128.8 (2C), 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.4, 127.3, 127.2, 127.0 (2C), 126.7, 126.5, 126.0 (2C), 124.8, 124.2, 108.9, 108.2, 58.9, 56.4, 56.3, 55.0, 52.0, 51.9, 16.4, 16.2

***N*-Benzyl-2,4-diphenyl-1,2-dihydropyridine.** 0.85 g (2.1 mmol) of *N*-benzyl-2,4-diphenyl-1,2-pyridinium tetrafluoroborate was dissolved in MeCN/MeOH (1 : 1), and the resulting solution, maintained under nitrogen atmosphere, was cooled to 0 °C. To this mixture was added an aqueous solution of KOH (0.12 g; 2.0 mmol) and $NaBH_4$ (0.079 g; 2.0 mmol). After stirring for 2 min., the reaction mixture was poured into Et_2O. The ethereal phase was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The crude resulting solid (0.36 g), impurified with some tetrahydropyridine, was submitted to the DA reaction; ^{1}H NMR ($CDCl_3$): δ 7.64 - 7.22 (m, 15H, Ar), 5.80 (d, 1H, J = 1.5 Hz), 5.30 (m, 1H), 4.07 (s, 2H), 4.06 (d, 2H); ^{13}C NMR ($CDCl_3$): δ 149.5, 139.8, 139.3, 137.7, 137.3, 129.0, 128.8, 128.6, 128.5, 128.4, 128.3 (2C), 128.0, 127.5, 127.0, 125.7, 108.5, 104.8, 54.2, 48.8

DA reactions-Typical Procedure

A mixture of *N*-benzyl-2,4,6-triphenyl-1,2-dihydropyridine (**1a**; 0.16 g; 0.40 mmol) and maleic anhydride (0.040 g; 0.40 mmol), in Et_2O (2 mL), was stirred overnight. The suspended solid was filtered and crystallized (MeCN) yielding **2a**, as white crystals (85% yield); mp 205 - 207 °C; ^{1}H NMR ($CDCl_3$): δ 7.97 (dd, 2H, Ar, J = 8.7 and 1.5 Hz), 7.56 - 6. 34 (m, 19H, Ar and olefinic), 4.50 (d, 1H, J = 8.3 Hz), 4.00 (d, 1H, J = 2.1 Hz), 3.84 - 3.78 (m, 1H), 3.78 (d, 1H, J = 12 Hz), 3.71 (dd, 1H, J = 8.3 and 3.0 Hz), 3.15 (d, 1H, J = 12 Hz); ^{13}C NMR ($CDCl_3$): δ 171.3, 170.2, 142.8, 141.9, 140.3, 137.6, 136.6, 133.2, 129.8, 129.2, 128.4, 128.3, 127.6, 127.0, 126.7, 125.3, 66.1, 65.6, 56.4, 44.4, 44.3, 43.0. Anal. Calcd for $C_{34}H_{27}NO_3$: C, 82.09; H, 5.47; N, 2.82. Found: C, 81.71; H, 5.55; N, 2.85

Adduct **3a** was prepared analogously by using *N*-phenylmaleimide (90 % yield); mp 200 - 201 °C; ^{1}H NMR ($CDCl_3$): δ 8.06 (d, 2H, Ar, J = 8.1 Hz), 7.53 - 6.83 (m, 24H, Ar), 4.47 (d, 1H, J = 8.0 Hz), 4.10 (d, 1H, J = 2.4 Hz), 3.93 - 3.91(m, 1H), 3.88 (d, 1H, J = 12 Hz), 3.63 (dd, 1H, J = 8.0 and 2.7 Hz), 3.27 (d, 1H, J = 12 Hz); ^{13}C NMR ($CDCl_3$): δ 176.4, 175.8, 143.4, 141.3, 141.2, 138.2, 136.9, 132.7, 131.7, 130.1, 129.2, 128.9, 128.5, 128.3, 128.0, 127.5, 127.4, 127.0, 126.7, 126.4, 126.3, 125.2, 66.8, 65.9, 56.6, 45.0, 43.8, 42.3; Anal. Calcd for $C_{40}H_{32}N_2O_2$: C, 83.89; H, 5.59; N, 4.90. Found: C, 83.80; H, 5.83; N, 4.72

Adduct **2b** was prepared in a similar manner, by using *N*-(±)-(α-methoxycarbonylethyl)-2,4,6-triphenyl-1,2-dihydropyridines and maleic anhydride. It was isolated in 20 % yield by treating the diastereoisomers mixture with MeOH; mp 216 - 220 °C; ^{1}H NMR (C_6D_6): δ 7.80 - 7.00 (m, 15H, Ar), 6.90 (d, 1H, J = 2.1 Hz), 4.90 (d, 1H, J = 2.4 Hz), 4.09 (dd, 1H, J = 8.4 and 3.0 Hz), 3.90 - 3.82 (m, 1H), 3.69 (s, 3H), 3.25 (q, 1H, J = 7.5 Hz), 0.90 (d, 3H, J = 7.5 Hz)

Adducts **3b** and **3b’** were prepared by reaction of *N*-(±)-(α-methoxycarbonylethyl)-2,4,6-triphenyl-1,2-dihydropyridines (3.9 g; 10 mmol) with *N*-phenylmaleimide (1.7 g; 10 mmol), in Et_2O (20 mL). The solid mixture of adducts **3b** and **3b’** was dissolved in hot MeOH. Slow concentration of the methanolic solution resulted in the separation of **3b** (35%) and **3b’** (20%). Each isolated adduct was crystallized from MeCN, yielding white crystals.

3b: mp 200 - 203 °C; ^{1}H NMR ($CDCl_3$): δ 7.98 (m, 2H, Ar), 7.48 - 6.81 (m, 19H, Ar), 4.51 (d, 1H, J = 2.4 Hz), 4.38 (d, 1H, J = 8.1 Hz), 3.97 - 3.94 (m, 1H), 3.59 (dd, 1H, J = 7.8 and 2.7 Hz), 3.40 (q, 1H, J = 6.6 Hz), 2.87 (s, 3H), 1.22 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$): δ 176.4, 174.9, 173.0, 142.7, 140.3, 139.5, 136.9, 133.3, 131.5, 128.9, 128.5, 128.4, 128.3, 128.1, 127.8, 127.2, 127.0, 126.3, 125.2, 65.3, 58.8, 53.3, 51.0, 46.0, 45.1, 44.1, 12.6

3b’: mp 204 - 207 °C; ^{1}H NMR (C_6D_6): δ 8.08 (s, 2H, Ar), 7.95 - 6.79 (m, 19H, Ar), 5.21 (d, 1H, J = 2.4 Hz), 4.53 (d, 1H, J = 7.8 Hz), 4.25 - 4.18 (m, 1H), 4.13 (dd, 1H, J = 8.1 and 3.0 Hz), 3.57 (q, 1H, J = 7.5 Hz), 3.34 (s, 3H), 0.90 (d, 3H, J = 7.5 Hz); ^{13}C NMR (C_6D_6): δ 177.1, 176.5, 175.6, 145.6, 140.7, 140.1, 137.0, 132.9, 131.7, 129.7, 128.8, 128.3, 128.2, 128.0, 127.9, 126.8, 126.4, 125.1, 65.3, 58.9, 55.0, 51.5, 45.8, 44.9, 43.9, 20.0; Anal. Calcd for $C_{37}H_{32}N_2O_4$: C, 78.15; H, 5.67; N, 4.93. Found: C, 78.14; H, 5.61; N, 4.96

Adduct **6** was prepared in 43 % yield, according to the typical procedure; mp 126 - 129 °C; ^{1}H NMR ($CDCl_3$): δ 7.60 (dd, 2H, Ar, J = 8.4 and 5.0 Hz), 7.59 - 7.21 (m, 17H, Ar), 6.89 (dd, 2H, Ar, J = 7.5 and 6.0 Hz), 3.90 (bs, 1H), 3.86 (d, 1H, J = 8.4 Hz), 3.78 (d, 1H, J = 13 Hz), 3.39 (dd, 1H, J = 8.4 and 3.3 Hz), 3.27 (dd, 1H, J = 10 and 2.1 Hz), 2.84 (d, 1H, J = 13 Hz), 2.39 (dd, 1H, J = 10 and 2.7 Hz); ^{13}C NMR ($CDCl_3$): δ 176.6, 174.3, 142.8, 139.4, 139.3, 137.0, 131.7, 128.9 (2C), 128.5, 128.4, 128.2, 128.1, 127.8, 126.8, 126.4, 125.8, 124.8, 64.1, 57.7, 54.6, 52.8, 43.6, 47.0; Anal. Calcd for $C_{34}H_{28}N_2O_2 \cdot H_2O$: C, 79.35; H, 5.88; N, 5.44. Found: C, 79.56; H, 5.85; N, 5.21

Hydrogenation of adducts 3b and 3b’. Adduct **3b** or **3b’** (0.10 g; 0.18 mmol), in MeOH (250 mL), was submitted to hydrogenation using 0.077 g of 5 % Pd/C and hydrogen in a Parr apparatus. After shaking for 20 h, the catalyst was removed by filtration over Celite,® and the methanolic solution was concentrated. The resulting oily crude product was treated with MeOH yielding a white solid.

Adduct **4b** was obtained in 50 % yield after crystallization from MeCN; mp 218 - 222 °C; ^{1}H NMR

($CDCl_3/C_6D_6$): δ 8.10 - 6.37 (m, 20H, Ar), 4.48 (d, 1H, J = 2.7 Hz), 3.70 (dd, 1H, J = 10 and 2.7 Hz), 3.36 (q, 1H, J = 6.9 Hz), 3.40 - 3.24 (m, 2H), 3.15 (dd, 1H, J = 10 and 2.1 Hz), 2.89 (s, 3H), 2.79 (ddd, 1H, J = 14, 12 and 3.0 Hz), 2.40 (dd, 1H, J = 14 and 6.6 Hz), 0.92 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3/C_6D_6$): δ 175.4, 175.2, 172.5, 142.9, 140.5, 140.1, 131.8, 130.5, 129.2, 129.1, 128.3, 128.0, 127.9, 127.3, 127.6, 127.4, 127.3, 127.0, 126.8, 126.4, 125.8, 125.7, 63.1, 62.2, 54.9, 50.5, 45.6, 45.3, 40.1, 37.1, 31.4, 13.0

Adduct **4b'** was obtained in 50 % yield after crystallization from MeCN; mp 213 - 225 °C; ^{1}H NMR ($CDCl_3$): δ 7.95 - 6.40 (m, 20H, Ar), 5.07 (d, 1H, J = 3.1 Hz), 4.29 (dd, 1H, J = 9.7 and 3.0 Hz), 3.91 (dd, 1H, J = 9.7 and 2.8 Hz), 3.65 (s, 3H), 3.50 - 3.42 (m, 1H), 3.36 - 3.28 (m, 1H), 3.32 (bq, 1H, J = 7.5 Hz), 2.97 (ddd, 1H, J = 14, 11 and 3.0 Hz), 2.49 (dd, 1H, J = 14 and 6.2 Hz), 0.88 (d, 3H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$): δ 176.8, 176.5, 176.4, 145.4, 140.8, 140.6, 131.6, 129.4, 128.8, 128.6, 128.4 (2C), 128.2, 128.1, 127.9, 127.8 (2C), 127.1, 126.8, 126.5, 126.0 (2C), 63.2, 62.4, 56.3, 51.4, 44.9, 44.7, 40.5, 37.3, 31.5, 19.2

Retro aza DA reaction. A solution of adduct **3a** (0.11 g; 2.0 mmol), in 2 mL of $CHCl_3$, was treated, at rt, with 22 μL of CF_3CO_2H (0.033 g; 3.0 mmol). The reaction was monitored by TLC (hexane : EtOAc; 9:1) until complete consumption of the adduct. A yellow oil was obtained after removal of the solvent, and purified by column chromatography (hexane : EtOAc; 9:1) yielding **5**, as a yellow solid (0.043 g; 1.1 mmol; 55%); mp 171.5 - 173 °C; ^{1}H NMR ($CDCl_3$): δ 7.80 - 7.50 (m, 15H, Ar), 6.80 (d, 1H, J = 2.9 Hz), 4.00 (dd, 1H, J = 17 and 8.6 Hz), 3.40 (dd, 1H, J = 17 and 8.6 Hz), 2.90 (td, 1H, J = 17, 17 and 2.9 Hz); ^{13}C NMR ($CDCl_3$): δ 174.7, 165.8, 145.1, 144.8, 138.8, 136.0, 132.2, 129.6, 129.2, 128.9, 128.3, 127.9, 126.6, 126.5, 125.9, 117.1, 40.8, 27.0; Anal. Calcd for $C_{26}H_{19}NO_2$: C, 82.76; H, 5.04; N, 3.71. Found: C, 82.15; H, 5.14; N, 3.64.

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3. *N*-Benzyl-2,4,6-trimethylpyridinium tetrafluoroborate was prepared by reacting 2,4,6-trimethylpyrilium tetrafluoroborate with benzylamine, in EtOH, at rt, for 6 h. By pouring the reaction mixture into Et_2O, a colorless solid (47% yield) was collected by filtration, and crystallyzed from EtOH; mp 124 - 125 °C; ^{1}H NMR ($CDCl_3$): δ 7.62 (s, 2H, Ar), 7.37 - 7.35 (m, 3H, Ar), 6.89 - 6.86 (m,

2H, Ar), 5.76 (s, 2H), 2.71 (s, 6H), 2.58 (s, 3H); ^{13}C NMR (CDCl$_3$): δ 159.0, 154.9, 131.5, 129.6, 128.8, 128.6, 125.0, 55.0, 21.4, 20.8; Anal. Calcd for $C_{15}H_{18}NBF_4$: C, 60.20; H, 6.02; N, 4.68. Found: C, 60.21; H, 6.03; N, 4.83; *N*-(±)-(α-methoxycarbonylethyl)-2,4,6-trimethylpyridinium tetrafluoroborate was prepared as follows: a mixture of 2 equiv. of alanine and 1 equiv. of 2,4,6-trimethylpyrilium tetrafluoroborate in water was heated under reflux for 5 h. After removal of water, the residue was extracted with hot EtOH. Concentration of the ethanolic solution afforded a white solid identified as the double salt $[(C_8H_{11}NCHMeCO_2).(C_8H_{11}NCHMeCO_2H)^+]BF_4^-$ (30 % yield) after crystallyzation from EtOH/Et$_2$O; mp 155 - 157 °C (decomp.); ^{1}H NMR (D$_2$O): δ 7.74 (s, 4H, Ar), 5.62 (q, 2H, J = 7.0 Hz), 2.64 (bs, 12H), 2.36 (s, 6H), 2.78 (d, 6H, J = 7.0 Hz); ^{13}C NMR (D$_2$O): δ 173.2, 158.9, 155.5, 129.8, 128.6, 62.8, 21.7, 21.0, 20.8, 15.8; Anal. Calcd for $C_{22}H_{31}N_2O_4BF_4$; C, 55.67; H, 6.59; N, 5.91. Found: C, 55.44; H, 6.48; N, 6.12; this salt was treated with excess of Me$_2$SO$_4$ and an equimolar amount of K$_2$CO$_3$, in MeOH. After heating under reflux for 4 h, the reaction mixture was poured into Et$_2$O, and the precipitate was recrystallized from EtOH/Et$_2$O yielding an hygroscopic white solid (100% yield); ^{1}H NMR (D$_2$O): δ 7.44 (s, 2H, Ar), 5.60 (q, 1H, J = 7.0 Hz), 3.70 (s, 3H), 2.63 (bs, 6H), 2.36 (s, 3H), 1.80 (d, 3H, J = 7.0 Hz); ^{13}C NMR (D$_2$O): δ 173.4, 159.7, 154.8, 129.5, 128.5, 62.7, 54.2, 20.8, 20.6, 15.7.

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