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Direct Aza-Diels–Alder Reaction in Water Catalyzed by Layered α-Zirconium Hydrogen Phosphate and Sodium Dodecyl Sulfate

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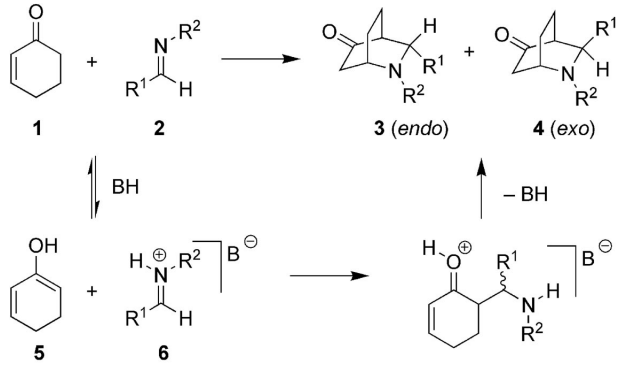
The direct aza-Diels–Alder reaction between 2-cyclohexen-1-one (**1**) and benzaldimines **2** in water is reported for the first time. The reaction occurs at 30 °C, is catalyzed by layered α-zirconium hydrogen phosphate (α-ZrP) and requires the presence of sodium dodecyl sulfate (SDS). The reaction yield is excellent, the reaction is faster and the *exo* diastereoselectivity is higher than when organic solvent is used. The one-pot, three-component version of the reaction and the recycling of both the catalyst and the aqueous mother liquor in toto (water, α-ZrP and SDS) have also been investigated.

Introduction

The aza-Diels–Alder reaction is one of the best-known processes in organic chemistry for the synthesis of six-membered, nitrogen-containing, heterocyclic compounds, which are precursors of important biological compounds such as alkaloids, peptides and aza-sugars.[1] While the reaction between preformed dienes and imines or enol ethers is well-known,[2] fewer studies have investigated the aza-Diels–Alder reaction that does not use preformed dienes (namely the direct Diels–Alder reaction), and these reactions were always carried out in organic solvents (CH_3CN, DMSO, DMF, PhMe, NPM or DCM).[3]

A typical example of a direct aza-Diels–Alder process is the reaction between 2-cyclohexen-1-one (**1**) and an aldimine **2** in the presence of a Brønsted acid (BH), which activates both reagents. The α,β-unsaturated ketone **1**, under acidic conditions, is enolized to **5**, which then undergoes a Mannich reaction with the protonated imine **6**, followed by an intramolecular aza-Michael reaction to give the *endo* and *exo* isoquinuclidines **3** and **4**, regenerating the acid catalyst; this process is formally known as a hetero Diels–Alder reaction (Scheme 1). The success of the reaction depends on the proton-donating capacity of the catalyst (acidity) and on the experimental conditions, particularly the reaction medium.

Brønsted-acid catalysis is a rapidly growing area of organocatalysis.[3c–3e,4] The application of achiral and chiral Brønsted acids in organic synthesis avoids the use of metal-based catalytic species, generally expensive, and the problem of leaching of the metal, often toxic, into the products. The class of phosphates and phosphonates of the tetravalent metals (mainly Zr^{IV}) with a layered structure is attracting the attention of researchers because of their physical-chemical properties[5] (chemical and thermal stability and high specific surface area) and high versatility;[5,6] the layered inorganic backbone of these compounds may be considered a hook onto which organic groups with different functionality may be attached, allowing for the control of both the reactivity and selectivity of the organic process. In addition, since they are insoluble in water and organic solvents, it is easy to recover them by simple filtration or centrifugation and reused.



Scheme 1. Direct Brønsted acid-catalyzed aza-Diels–Alder reaction of cyclohexenone **1** with aldimines **2**.

The α-zirconium hydrogen phosphate α-$Zr(HPO_4)_2{\cdot}H_2O$ (α-ZrP), and α-zirconium sulfophenylphosphonate methanphosphonate α-$Zr(O_3PCH_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$ (α-ZrPS-O_3H) have very different acidities; the former is a weakly

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acidic solid (pK_a = 2.0–3.0) with regularly spaced P-OH groups, while the latter is a strong acid (acid strength, H_0 = –5.6, –8.2).[5c]

Water plays an important role in the development of new synthetic processes both by improving the chemical efficiency and reducing the environmental impact.[7] Our research is always aimed at defining new, efficient, synthetic procedures by using water as a reaction medium,[7c,7d,7f,8] and in this context, we have also investigated, inter alia, the Diels–Alder reaction and its aza version by using preformed dienes.[7d,8b–8e,8i,9]

To contribute to the development of the direct Diels–Alder reaction we have focused our research on the use of water as a reaction medium, which has not previously investigated, and on the use of layered α-ZrP and α-$ZrPSO_3H$ as recyclable Brønsted-acid catalysts. In this context, we have studied the reaction of 2-cyclohexen-1-one (**1**) with benzaldimines **2** [R^1 = C_6H_4-R, R^2 = C_6H_4-*p*OMe (PMP)], an effective route to isoquinuclidines **3** and **4** (azabicyclo[2.2.2]octanes), which are the structural elements of numerous naturally occurring alkaloids with interesting biological properties.[10]

Results and Discussion

We started with the optimisation of the process in water for which N-PMP-*p*-chlorobenzaldimine (**2a**) was used along with different proton sources as Brønsted acids (**2a**/**1** = 1:10). The results are illustrated in Table 1.

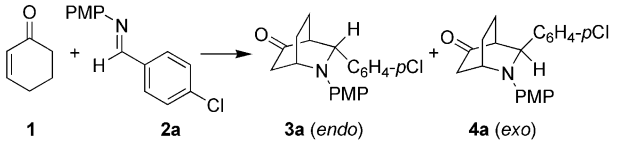
In DCM, water or in the absence of a reaction medium and in the presence of 20 mol-% of α-ZrP (with respect to the imine), we did not detect the cycloadducts **3a** and **4a** after 24 h at 30 °C (Table 1, Entries 1–3). When we increased the amount of α-ZrP to 100 mol-%, we observed adducts **3a** and **4a** in small amounts and an *endo*/*exo* ratio of 63:37 after 4 d (Table 1, Entry 4); under the same reaction conditions, we observed no products when the reaction was carried out in the absence of solvent (Table 1, Entry 5). It is well known that the combination of Brønsted acids and surfactants catalyzes the Mannich-type reaction in water.[4b,11] The addition of 0.4 equiv. of sodium dodecyl sulfate (SDS) to the reaction performed in water gave the desired adducts **3a** and **4a** after 24 h in a conversion of 93% (84% isolated yield) and with a 54:46 *endo*/*exo* ratio (Table 1, Entry 6). The reaction performed in water in the presence of only SDS yielded only 5% of the desired adducts (Table 1, Entry 7).

When the amount of cyclohexenone **1** (5 equiv.) and SDS (0.2 equiv.) was reduced by half, the reaction conversion decreased to 73% and 64%, respectively (Table 1, Entries 8 and 9). The simple use of a weak organic acid such as acetic acid did not catalyze the reaction, and we obtained only 48% product in the presence of SDS (Table 1, Entries 10 and 11). α-$ZrPSO_3H$ seemed to be more efficacious than did α-ZrP but its stronger acidity favoured the hydrolysis of the imine, as seen by the production of *p*-chlorobenzaldehyde (Table 1, Entry 12). The presence of SDS favours the Mannich reaction and provides 82% of **3a** and **4a** (Table 1, Entry 13). Amberlist®15, a highly acidic macromolecular resin with sulfonic acid functionality, greatly favours the hydrolysis of the imine (Table 1, Entries 14 and 15). A weak layered acid like α-ZrP coupled with the anionic surfactant SDS is required for the success of the direct Diels–Alder reaction in an aqueous medium. We isolated the isoquinuclidines **3a** and **4a** with excellent yield. The reaction time was six times shorter, and the *exo* adduct **4a** was 2.5 times more abundant than in the reaction carried out in toluene.[3d]

To evaluate the importance of the nature of the surfactant, we studied the reaction with α-ZrP in the presence of 0.4 equiv. of cetyl trimethyl ammonium bromide (CTAB), a cationic surfactant, or by using only dodecylbenzenesulfonic acid (DBSA),[12] which works as a Brønsted acid and a surfactant. In the first case, we observed no reaction, while in the second, we saw the competitive hydrolysis of imine (Table 1, Entries 16 and 17).

A more in-depth investigation is necessary to understand the intriguing role played by SDS. At present, we hypothesize that in an aqueous medium, SDS favours, very likely through Na^+/H^+ surface exchange,[13] proton transfer from the P-OH groups of the heterogeneous α-ZrP to the reagents, particularly the imine. Moreover, since it is known that the *endo*/*exo* diastereoselectivity of the Diels–Alder re-

Table 1. Direct aza-Diels–Alder reaction of 2-cyclohexen-1-one (**1**) with N-PMP-*p*-chlorobenzaldimine (**2a**).



1 **2a** **3a** (*endo*) **4a** (*exo*)

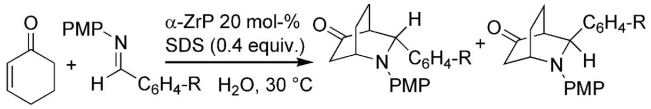
Entry[a]	Catalyst	Medium	Additive (equiv.)	Conv. [%][b]	**3a**/**4a**
1	α-ZrP	CH_2Cl_2	–	0	–
2	α-ZrP	H_2O	–	0	–
3	α-ZrP	–	–	0	–
4	α-ZrP[c]	H_2O	–	10[d]	63:37
5	α-ZrP[c]	–	–	<1[d]	–
6	α-ZrP	H_2O	SDS (0.4)	93[e]	54:46
7	–	H_2O	SDS (0.4)	5	54:46
8[f]	α-ZrP	H_2O	SDS (0.4)	73	52:48
9	α-ZrP	H_2O	SDS (0.2)	64	49:51
10	AcOH	H_2O	–	0	–
11	AcOH	H_2O	SDS (0.4)	48	51:49
12	α-$ZrPSO_3H$	H_2O	–	11[g]	54:46
13	α-$ZrPSO_3H$	H_2O	SDS (0.4)	82[g]	50:50
14	Amberlist®15	H_2O	–	0[g]	–
15	Amberlist®15	H_2O	SDS (0.4)	39[g]	48:52
16	α-ZrP	H_2O	CTAB (0.4)	0	–
17	DBSA	H_2O	–	30[g]	50:50

[a] Reaction conditions: imine **2a**, cyclohexenone (**1**, 10 equiv.), catalyst (20 mol-%) at 30 °C for 24 h, unless specified otherwise. [b] The complement to 100% is unreacted **2a** unless specified otherwise. [c] Catalyst (100 mol-%). [d] Reaction time: 4 d. [e] Yield of isolated products: 84%. [f] Cyclohexenone (**1**, 5 equiv.) [g] The complement to 100% is unreacted **2a** and *p*-chlorobenzaldehyde from the hydrolysis of **2a**.

action is affected by the use of surfactant,[9b] the interaction of the protonated imine on the Stern layer of the micellar aggregate could also explain the observed increase of *exo* adduct **4a**. The experiment with CTAB (Table 1, Entry 16) and the good solubility of **5** and **6** (R^1 = C_6H_4-*p*-Cl, R^2 = PMP) in the aqueous medium does not give much support to a solubility effect due to SDS.

In order to extend the scope of this study and to confirm the efficiency of the α-ZrP/SDS system in an aqueous medium, we also considered the aza-Diels–Alder reaction of cyclohexenone (**1**) with typical imines **2b**–**k**, performed under the previously found best conditions: α-ZrP (20 mol-%) and SDS (0.4 equiv.) in water at 30 °C. The results are illustrated in Table 2.

Table 2. Direct aza-Diels–Alder reaction in water of cyclohexenone (**1**) with N-PMP-benzaldimines **2** catalyzed by the heterogeneous Brønsted acid α-ZrP and SDS.



1 **2** **3** (*endo*) **4** (*exo*)

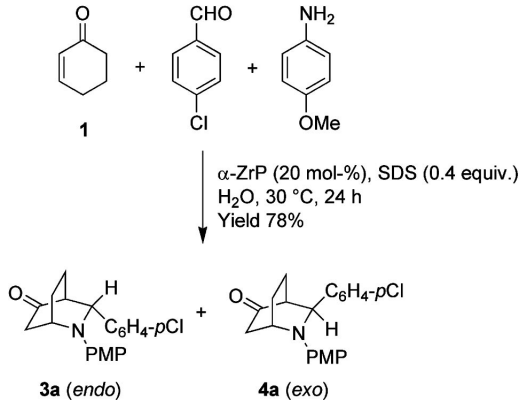
Entry[a]	Imine **2** (Ar)	*t* [h]	Conv. [%][b]	Yield [%][c]	**3/4**
1	**2a**: *p*Cl-C_6H_4	24	93	84	54:46
2	**2b**: *m*Cl-C_6H_4	24	88	79	54:46
3	**2c**: *o*Cl-C_6H_4	72	83	74	51:49
4	**2d**: C_6H_5	24	92	83	54:46
5	**2e**: *p*Br-C_6H_4	72	93	83	50:50
6	**2f**: *p*F-C_6H_4	24	95	84	56:44
7	**2g**: pO_2N-C_6H_4	72	78	70	50:50
8	**2h**: pH_3CS-C_6H_4	24	94	82	43:57
9	**2i**: pH_3CO-C_6H_4	24	88	79	42:58
10	**2j**: pH_3C-C_6H_4	24	89	80	48:52
11	**2k**: *p*NC-C_6H_4	24	90	80	55:45

[a] Reaction conditions: imine **2**, cyclohexenone **1** (10 equiv.), α-ZrP (20 mol-%), SDS (0.4 equiv.) in water 30 °C. [b] The complement to 100% is unreacted imine **2**. [c] Yield of isolated products (**3** + **4**).

The reaction yields of isolated products were excellent (70–84%), and with respect to the reactions performed in toluene,[3d] the reaction times were 3–6 times shorter, and the *exo* adducts were ≈ 2.5–3 times more abundant. The presence of hydrophobic groups such as SMe, OMe and Me increased the *exo* adduct percentage (52–58%, Table 2, Entries 8–10). This finding is in agreement with the hypothesis of an increased interaction of the aryl group of the protonated imines with micellar aggregates of SDS.

Finally, we investigated the one-pot, three–component, direct, aza-Diels–Alder reaction in water and the recovery of the catalyst. A mixture of *p*-chlorobenzaldehyde (1 equiv.), *p*-methoxyaniline (1 equiv.) and cyclohexen-2-one (**1**, 10 equiv.) in the presence of α-ZrP (20 mol-%) and SDS (0.4 equiv.) in water, at 30 °C for 24 h, gave the cycloadducts **3a** and **4a** with a 78% isolated yield and an *endo*/*exo* ratio of 56:44 (Scheme 2).

When solid Brønsted-acid catalysts are used, their activity after being recovered becomes an important issue. We recovered the α-ZrP used in the reaction of **1** with **2a**, washed it with water and reused it twice without observing any decrease in reactivity or stereoselectivity (Table 3, Entries 1–3).



Scheme 2. One-pot, three-component, direct aza-Diels–Alder reaction in water.

Table 3. Recycling of heterogeneous Brønsted acids α-ZrP in the aza-Diels–Alder reaction of 2-cyclohexen-1-one (**1**) with N-PMP-*p*-chlorbenzaldimine (**2a**).

Entry[a]	Run	Conversion [%]	**3a/4a**
1	Cycle 1	93	54:46
2[b]	Cycle 2	93	54:46
3[b]	Cycle 3	89	55:45
4	Cycle 1	93	54:46
5[c]	Cycle 2	90	54:46
6[c]	Cycle 3	91	54:46

[a] Reaction conditions: imine **2a**, cyclohexenone **1** (10 equiv.), α-ZrP (20 mol-%), SDS (0.4 equiv.) in water at 30 °C for 24 h. [b] The recovered solid α-ZrP was washed with water, and reused in a new reaction. [c] All of the reaction medium (water, α-ZrP and SDS) was recovered and reused.

For a reaction carried out in water, it is also important to recover the aqueous medium in toto so that the protocol is environmentally friendly. The aqueous mother liquor of the reaction of **1** with **2a** (water, α-ZrP and SDS), after the extraction of **3a** and **4a**, was recycled twice; we obtained the same conversion and *endo*/*exo* ratio of products as we had with unused reagents (Table 3, Entries 4–6).

Conclusions

In conclusion, we report for the first time the direct aza-Diels–Alder reaction between 2-cyclohexen-1-one (**1**) and benzaldimines **2** carried out in water as a reaction medium. The reaction is catalysed by layered α-ZrP and required the presence of a catalytic amount of SDS. Under these conditions, the reaction was faster and the *exo* diastereoselectivity was higher than that observed when the reaction was performed in toluene; the yield was excellent. The one-pot, three-component version of the reaction and the recycling of both the catalyst and the aqueous mother liquor in toto gave very satisfactory results.

Experimental Section

General: All chemicals were purchased and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 100.6 MHz, respectively, in $CDCl_3$ solution. IR spectra were recorded with a FT-IR instrument with $CHCl_3$ as the solvent. GC analyses were performed with a DB35H fused-silica capillary column (30 m, 0.53 mm diameter) with a split/split-less injector with a FID detector with hydrogen as the gas carrier. Centrifugation were performed at 12,000 rpm for 10 min. Thin Layered Chromatography analyses were performed on silica gel on aluminium plates. Column chromatography was performed with silica gel (230–400 mesh) eluting with petroleum ether/ethyl acetate, 80:20. The recrystallization of adducts **3** and **4** was performed in *n*-hexane/ethyl acetate. Melting points are uncorrected. α-Zirconium hydrogen phosphate (α-ZrP) was prepared as reported in the literature.[14] The benzaldimines **2a**–**k** are known compounds and were prepared as reported in the literature.[15] The *endo* adducts **3a**–**f** and **3j**–**k** and the *exo* adducts **4a** and **4d** are known compounds;[3a,3b,3d] the *endo* adducts **3g**–**i** and the *exo* adducts **4b**,**c**,**e**–**k** are new compounds. For all the adducts, complete characterization has been reported below.

General Procedure for Aza-Diels–Alder Reaction: Imine **2** (0.2 mmol), cyclohexenone **1** (2 mmol, 10 equiv.), catalyst α-ZrP (0.04 mmol, 20 mol-%), SDS (0.08 mmol, 0.4 equiv.) and H_2O (1 mL) were added to a 2 mL vial. The mixture was stirred at 30 °C for 24–72 h (see Table 1–Table 2). The reaction mixture was extracted with ethyl acetate (3 × 2 mL). The organic phase was separated from the aqueous medium by centrifugation, and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude *endo*/*exo* mixture of products (**3** and **4**) were purified by column chromatography, and the separated *endo*-**3** and *exo*-**4** products were recrystallized.

***rel*-(1*S*,3*R*,4*S*)-3-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2-azabicyclo-[2.2.2]octan-5-one (*endo* 3a):** [3d]Yield 31.0 mg (45%), white crystals; m.p. 170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75 (m, 1 H), 2.0 (m, 1 H), 2.14 (m, 1 H), 2.26 (m, 1 H), 2.48 (dd, J = 18.8, 2.4 Hz, 1 H), 2.71 (dd, J = 5.6, 2.7 Hz, 1 H), 2.75 (dt, J = 18.8, 3.1 Hz, 1 H), 3.73 (s, 3 H), 4.43 (m, 1 H), 4.56 (d, J = 2.3 Hz, 1 H), 6.61 (m, 2 H), 6.78 (m, 2 H), 7.27 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.25, 22.46, 46.06, 49.51, 52.09, 55.59, 65.51, 114.71 (2 C), 114.73 (2 C), 127.12 (2 C), 129.07 (2 C), 133.12, 140.74,142.08, 152.27, 211.50 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1731.3, 1510.6, 1252.6, 1040.1, 817.1 cm^{-1}.

***rel*-(1*S*,3*S*,4*S*)-3-(4-Chlorophenyl)-2-(4-methoxyphenyl)-2-azabicyclo-[2.2.2]octan-5-one (*exo* 4a):** [3b]Yield 24.6 mg (39%), pale yellow crystals; m.p. 60–62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63–1.76 (m, 2 H), 1.90 (m, 1 H), 2.24 (m, 1 H), 2.39 (dd, J = 18.8, 1.8 Hz, 1 H), 2.63 (dd, J = 5.8, 2.8 Hz, 1 H), 2.76 (dt, J = 18.8, 3.0 Hz, 1 H), 3.72 (s, 3 H), 4.43 (m, 1 H), 4.68 (d, J = 2.4 Hz, 1 H), 6.54 (m, 2 H), 6.76 (m, 2 H), 7.37 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.23, 26.29, 41.88, 48.95, 50.84, 55.63, 62.08, 114.35 (2 C), 114.87 (2 C), 127.66 (2 C), 128.98 (2 C), 133.07, 139.02,142.32, 152.21, 213.40 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1725.7, 1511.0, 1246.6, 1040.1, 817.4 cm^{-1}.

***rel*-(1*S*,3*R*,4*S*)-3-(3-Chlorophenyl)-2-(4-methoxyphenyl)-2-azabicyclo-[2.2.2]octan-5-one (*endo* 3b):** [3d]Yield 29.2 mg, (43%), yellow crystals; m.p. 125–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75 (m, 1 H), 2.04 (m, 1 H), 2.13 (m, 1 H), 2.26 (m, 1 H), 2.49 (dd, J = 18.8, 2.5 Hz, 1 H), 2.72 (dd, J = 5.7, 2.8 Hz, 1 H), 2.77 (dt, J = 18.8, 3.0 Hz, 1 H), 3.74 (s, 3 H), 4.44 (m, 1 H), 4.56 (d, J = 2.5 Hz, 1 H), 6.61 (m, 2 H), 6.79 (m, 2 H), 7.18–7.31 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.25, 22.61, 46.12, 49.51, 52.07, 55.65, 65.77, 114.77 (2 C), 114.81 (2 C), 123.92, 126.00, 127.80, 130.26, 134.91, 142.14, 144.53, 152.36, 211.46 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1730.5, 1511.0, 1251.6, 1040.2, 818.9 cm^{-1}.

***rel*-(1*S*,3*S*,4*S*)-3-(3-Chlorophenyl)-2-(4-methoxyphenyl)-2-azabicyclo-[2.2.2]octan-5-one (*exo* 4b):** Yield 24.8 mg (36%), pale brown crystals; m.p. 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70 (m, 2 H), 1.91 (m, 1 H), 2.26 (m, 1 H), 2.39 (dd, J = 18.8, 1.8 Hz, 1 H), 2.65 (dd, J = 5.8, 2.9 Hz, 1 H), 2.76 (dt, J = 18.8, 3.0 Hz, 1 H), 3.72 (s, 3 H), 4.44 (m, 1 H), 4.68 (d, J = 2.5 Hz, 1 H), 6.55 (m, 2 H), 6.76 (m, 2 H), 7.27–7.45 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.30, 26.29, 41.85, 48.92, 50.76, 55.66, 62.35, 114.42 (2 C), 114.92 (2 C), 124.45, 126.42, 127.68, 130.13, 134.93, 142.36, 142.94, 152.28, 213.33 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1725.3, 1509.0, 1246.2, 1041.0, 816.0 cm^{-1}. $C_{20}H_{20}ClNO_2$ (341.83): calcd. C 70.27, H 5.90, N 4.10; found C 70.39, H 5.82, N 4.25.

***rel*-(1*S*,3*R*,4*S*)-3-(2-Chlorophenyl)-2-(4-methoxyphenyl)-2-azabicyclo-[2.2.2]octan-5-one (*endo* 3c):** [3d]Yield 25.8 mg (38%), yellow crystals; m.p. 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80 (m, 1 H), 2.02 (m, 1 H), 2.23 (m, 2 H), 2.52 (dd, J = 18.8, 2.3 Hz, 1 H), 2.84 (ddd, J = 18.8, 3.7, 2.2 Hz, 1 H), 2.88 (dd, J = 5.2, 2.8 Hz, 1 H), 3.72 (s, 3 H), 4.47 (m, 1 H), 4.96 (d, J = 2.1 Hz, 1 H), 6.58 (m, 2 H), 6.77 (m, 2 H), 7.18 (m, 2 H), 7.38 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.22, 22.52, 45.89, 49.13, 50.22, 55.58, 62.88, 114.74 (2 C), 115.04 (2 C), 127.42, 127.50, 128.76, 130.07, 131.81, 138.67, 141.77, 152.41, 211.98 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1731.5, 1511.4, 1251.6, 1038.3, 819.3 cm^{-1}.

***rel*-(1*S*,3*S*,4*S*)-3-(2-Chlorophenyl)-2-(4-methoxyphenyl)-2-azabicyclo-[2.2.2]octan-5-one (*exo* 4c):** Yield 24.7 mg (36%), pale yellow crystals; m.p. 104–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72 (m, 2 H), 1.91 (m, 1 H), 2.33 (m, 1 H), 2.40 (dd, J = 18.7, 2.0 Hz, 1 H), 2.78 (dt, J = 18.7, 3.0 Hz, 1 H), 2.89 (dd, J = 5.5, 2.8 Hz, 1 H), 3.70 (s, 3 H), 4.47 (m, 1 H), 5.06 (d, J = 1.8 Hz, 1 H), 6.52 (m, 2 H), 6.75 (m, 2 H), 7.25 (m, 2 H), 7.43 (m, 1 H), 7.67 (m, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.74, 26.29, 42.32, 47.01, 49.52, 55.59, 59.99, 114.50 (2 C), 14.85 (2 C), 127.00, 128.62, 128.77, 130.30, 132.19, 136.83, 142.12, 152.26, 213.21 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1726.2, 1510.8, 1246.6, 1036.9, 798.3 cm^{-1}. $C_{20}H_{20}ClNO_2$ (341.83): calcd. C 70.27, H 5.90, N 4.10; found C 70.33, H 5.96, N 4.19.

***rel*-(1*S*,3*R*,4*S*)-2-(4-Methoxyphenyl)-3-phenyl-2-azabicyclo[2.2.2]-octan-5-one**[3b,d] **(*endo* 3d):** Yield 27.5 mg (45%), pale yellow crystals; m.p. 201–203 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75 (m, 1 H), 2.04 (m, 1 H), 2.15 (m, 1 H), 2.28 (m, 1 H), 2.48 (dd, J = 18.8, 2.6 Hz, 1 H), 2.76 (dd, J = 5.7, 2.9 Hz, 1 H), 2.79 (dt, J = 18.8, 3.1 Hz, 1 H), 3.73 (s, 3 H), 4.45 (m, 1 H), 4.60 (d, J = 2.6 Hz, 1 H), 6.64 (m, 2 H), 6.78 (m, 2 H), 7.22–7.35 (m, 5 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.29, 22.64, 46.07, 49.30, 52.21, 55.61, 66.18, 114.54 (2 C), 114.71 (2 C), 125.64 (2 C), 127.44, 128.86 (2 C), 142.15, 142.44, 152.04, 211.88 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1726.6, 1510.8, 1252.1, 1040.6, 818.8 cm^{-1}.

***rel*-(1*S*,3*S*,4*S*)-2-(4-Methoxyphenyl)-3-phenyl-2-azabicyclo[2.2.2]-octan-5-one**[3b] **(*exo* 4d):** Yield 23.5 mg (38%), pale yellow crystals; m.p. 111–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65 (m, 1 H), 1.75 (m, 1 H), 1.90 (m, 1 H), 2.28 (m, 1 H), 2.40 (dd, J = 18.7, 1.8 Hz, 1 H), 2.68 (dd, J = 5.8, 2.9 Hz, 1 H), 2.75 (dt, J = 18.7, 3.0 Hz, 1 H), 3.71 (s, 3 H), 4.45 (m, 1 H), 4.72 (d, J = 2.0 Hz, 1 H), 6.57 (m, 2 H), 6.75 (m, 2 H), 7.28–7.46 (m, 5 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.31, 26.29, 41.93, 48.85, 51.04, 55.65, 62.64, 114.26 (2 C), 114.84 (2 C), 126.23 (2 C) 127.35, 128.77 (2 C), 140.42, 142.65, 152.01, 213.92 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1723.1, 1510.6, 1246.0, 1041.3, 814.5 cm^{-1}.

***rel*-(1*S*,3*R*,4*S*)-3-(4-Bromophenyl)-2-(4-methoxyphenyl)-2-azabicyclo-[2.2.2]octan-5-one (*endo* 3e):** [3d]Yield 32.1 mg (42%), yellow crystals; m.p. 201–203 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75 (m, 1 H), 2.03 (m, 1 H), 2.13 (m, 1 H), 2.25 (m, 1 H), 2.47 (dd, J = 18.8, 2.4 Hz, 1 H), 2.70 (dd, J = 5.6, 2.8 Hz, 1 H), 2.74 (dt, J = 18.3, 3.1 Hz, 1 H), 3.73 (s, 3 H), 4.43 (m, 1 H), 4.54 (d, J = 2.1 Hz, 1 H), 6.60 (m, 2 H), 6.80 (m, 2 H), 7.19 (m, 2 H), 7.44 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.22, 22.44, 46.04, 49.51, 52.01, 55.58, 65.53, 114.72 (4 C), 121.26, 127.48 (2 C), 131.98 (2 C), 141.28, 142.04, 152.26, 211.49 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1731.4, 1510.5, 1251.9, 1040.1, 816.9 cm^{-1}.

***rel*-(1*S*,3*S*,4*S*)-3-(4-Bromophenyl)-2-(4-methoxyphenyl)-2-azabicyclo-[2.2.2]octan-5-one (*exo* 4e):** Yield 32.0 mg (41%), pale brown crystals; m.p. 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (m, 2 H), 1.90 (m, 1 H), 2.24 (m, 1 H), 2.39 (dd, J = 18.8, 2.8 Hz, 1 H), 2.63 (dd, J = 5.7, 2.8 Hz, 1 H), 2.76 (dt, J = 18.8, 3.0 Hz, 1 H), 3.71 (s, 3 H), 4.43 (m, 1 H), 4.66 (d, J = 2.3 Hz, 1 H), 6.54 (m, 2 H), 6.75 (m, 2 H), 7.32 (m, 2 H), 7.51 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.22, 26.26, 41.84, 48.93, 50.75, 55.61, 62.11, 114.33 (2 C), 114.85 (2 C), 121.14, 128.02 (2 C), 131.89 (2 C), 139.57, 142.27, 152.19, 213.32 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1725.8, 1513.5, 1246.8, 1040.5, 816.6 cm^{-1}. $C_{20}H_{20}BrNO_2$ (386.28): calcd. C 62.19, H 5.22, N 3.63; found C 62.36, H 5.39, N 3.72.

***rel*-(1*S*,3*R*,4*S*)-3-(4-Fluorophenyl)-2-(4-methoxyphenyl)-2-azabicyclo-[2.2.2]octan-5-one**[3d] **(*endo* 3f):** Yield 30.6 mg (47%), pale brown crystals; m.p. 154–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75 (m, 1 H), 2.03 (m, 1 H), 2.14 (m, 1 H), 2.26 (m, 1 H), 2.48 (dd, J = 18.8, 2.3 Hz, 1 H), 2.71 (dd, J = 5.5, 2.7 Hz, 1 H), 2.75 (dt, J = 18.8, 3.1 Hz, 1 H), 3.73 (s, 3 H), 4.44 (m, 1 H), 4.57 (br. s, 1 H), 6.62 (m, 2 H), 6.78 (m, 2 H), 7.00 (m, 2 H), 7.28 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.25, 22.45, 46.06, 49.53, 52.25, 55.60, 65.47, 114.71 (2 C), 114.73 (2 C) 115.76 (d, J = 21.5 Hz, 2 C), 127.28 (d, J = 8.15 Hz, 2 C), 137.84, 142.18, 152.23, 162.02 (d, J = 245.7 Hz), 211.70 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1730.9, 1513.5, 1252.4, 1238.2, 1040.3, 818.1 cm^{-1}.

***rel*-(1*S*,3*S*,4*S*)-3-(4-Fluorophenyl)-2-(4-methoxyphenyl)-2-azabicyclo-[2.2.2]octan-5-one (*exo* 4f):** Yield 24.0 mg (37%), pale yellow crystals; m.p. 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (m, 2 H), 1.90 (m, 1 H), 2.25 (m, 1 H), 2.39 (dd, J = 18.8, 1.7 Hz, 1 H), 2.63 (dd, J = 5.7, 2.9 Hz, 1 H), 2.76 (dt, J = 18.8, 2.9 Hz, 1 H), 3.72 (s, 3 H), 4.44 (m, 1 H), 4.70 (br. s, 1 H), 6.55 (m, 2 H), 6.76 (m, 2 H), 7.08 (m, 2 H), 7.40 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.20, 26.28, 41.86, 48.96, 51.02, 55.62, 61.98, 114.33 (2 C), 114.84 (2 C), 115.66 (d, J = 21.5 Hz, 2 C), 127.76 (d, J = 8.0 Hz, 2 C), 135.96, 142.41, 152.14, 162.07 (d, J = 245.5 Hz), 213.58 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1725.7, 1511.0, 1277.7, 1246.3, 1225.5, 1040.7, 816.7 cm^{-1}. $C_{20}H_{20}FNO_2$ (325.32): calcd. C 73.83, H 6.20, N 4.30; found C 73.95, H 6.29, N 4.22.

***rel*-(1*S*,3*R*,4*S*)-2-(4-Methoxyphenyl)-3-(4-nitrophenyl)-2-azabicyclo-[2.2.2]octan-5-one (*endo* 3g):** Yield 24.6 mg (35%), orange crystals; m.p. 196–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80 (m, 1 H), 2.07 (m, 1 H), 2.19 (m, 1 H), 2.27 (m, 1 H), 2.52 (dd, J = 18.8, 2.4 Hz, 1 H), 2.74 (dd, J = 5.6, 2.8 Hz, 1 H), 2.77 (dt, J = 18.8, 3.0 Hz, 1 H), 3.72 (s, 3 H), 4.46 (m, 1 H), 4.69 (d, J = 2.4 Hz, 1 H), 6.58 (m, 2 H), 6.78 (m, 2 H), 7.49 (m, 2 H), 8.18 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.27, 22.41, 46.09, 49.93, 51.87, 55.57, 65.47, 114.82 (2 C), 115.00 (2 C), 124.25 (2 C), 126.78 (2 C), 141.52, 147.36, 149.68, 152.64, 210.86 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1732.3, 1519.9, 1346.6, 1251.9, 1189.0, 1039.5, 818.5 cm^{-1}. $C_{20}H_{20}N_2O_4$ (352.32): calcd. C 68.17, H 5.72, N 7.95; found C 68.26, H 5.79, N 7.99.

***rel*-(1*S*,3*S*,4*S*)-2-(4-Methoxyphenyl)-3-(4-nitrophenyl)-2-azabicyclo-[2.2.2]octan-5-one (*exo* 4g):** Yield 24.7 mg (35%), yellow-orange crystals; m.p. 127–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58–1.75 (m, 2 H), 1.95 (m, 1 H), 2.26 (m, 1 H), 2.42 (dd, J = 18.8, 1.9 Hz, 1 H), 2.70 (dd, J = 5.8, 2.9 Hz, 1 H), 2.79 (dt, J = 18.8, 3.0 Hz, 1 H), 3.71 (s, 3 H), 4.46 (m, 1 H), 4.80 (d, J = 2.4 Hz, 1 H), 6.52 (m, 2 H), 6.76 (m, 2 H), 7.63 (m, 2 H), 8.25 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.28, 26.29, 41.90, 49.17, 50.44, 55.59, 62.21, 114.51 (2 C), 114.94 (2 C), 124.11 (2 C), 127.23 (2 C), 141.80, 147.43, 148.37, 152.52, 212.39 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1726.6, 1513.8, 1347.9, 1247.1, 1182.4, 1040.8, 817.6 cm^{-1}. $C_{20}H_{20}N_2O_4$ (352.32): calcd. C 68.17, H 5.72, N 7.95; found C 68.30, H 5.81, N 8.07.

***rel*-(1*S*,3*R*,4*S*)-2-(4-Methoxyphenyl)-3-[(4-methylthio)phenyl]-2-azabicyclo[2.2.2]octan-5-one (*endo* 3h):** Yield 25.0 mg (35%), white crystals; m.p. 155–157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74 (m, 1 H), 2.02 (m, 1 H), 2.13 (m, 1 H), 2.25 (m, 1 H), 2.45 (s, 3 H), 2.47 (dd, J = 18.8, 2.5 Hz, 1 H), 2.72 (dd, J = 5.7, 2.8 Hz, 1 H), 2.76 (dt, J = 18.8, 3.0 Hz, 1 H), 3.73 (s, 3 H), 4.43 (m, 1 H), 4.55 (d, J = 2.4 Hz, 1 H), 6.63 (m, 2 H), 6.77 (m, 2 H), 7.21 (m, 4 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.73, 22.26, 22.53, 46.06, 49.42, 52.13, 55.61, 65.76, 114.64 (2 C), 114.72 (2 C), 126.22 (2 C), 127.05 (2 C), 137.40, 139.11, 142.31, 152.14, 211.81 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1731.5, 1510.7, 1253.6, 1093.3, 894.3, 709.5, 646.6 cm^{-1}. $C_{21}H_{23}NO_2S$ (353.48): C 71.35, H 6.56, N 3.96, S 9.07; found C 71.45, H 6.68, N 4.02, S 9.13.

***rel*-(1*S*,3*S*,4*S*)-2-(4-Methoxyphenyl)-3-[(4-methylthio)phenyl]-2-azabicyclo[2.2.2]octan-5-one (*exo* 4h):** Yield 33.0 mg (47%), white crystals; m.p. 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62 (m, 1 H), 1.75 (m, 1 H), 1.89 (m, 1 H), 2.25 (m, 1 H), 2.38 (dd, J = 18.8, 1.6 Hz, 1 H), 2.50 (s, 3 H), 2.63 (dd, J = 5.7, 2.8 Hz, 1 H), 2.76 (dt, J = 18.8, 3.0 Hz, 1 H), 3.71 (s, 3 H), 4.43 (m, 1 H), 4.67 (d, J = 2.2 Hz, 1 H), 6.56 (m, 2 H), 6.75 (m, 2 H), 7.27 (m, 2 H), 7.35 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.70, 16.22, 26.24, 41.82, 48.86, 50.91, 55.57, 62.20, 114.25 (2 C), 114.77 (2 C),126.72 (2 C), 126.82 (2 C), 137.24, 137.32, 142.47, 152.01, 213.65 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1725.3, 1510.8, 1246.5, 1092.6, 909.2, 707.2, 650.6 cm^{-1}. $C_{21}H_{23}NO_2S$ (353.48): calcd. C 71.35, H 6.56, N 3.96, S 9.07; found C 71.44, H 6.62, N 4.042, S 9.19.

***rel*-(1*S*,3*R*,4*S*)-2,3-Bis(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-one (*endo* 3i):** Yield 22.3 mg (33%), pale brown crystals; m.p. 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73 (m, 1 H), 2.01 (m, 1 H), 2.12 (m, 1 H), 2.26 (m, 1 H), 2.46 (dd, J = 18.8, 2.5 Hz, 1 H), 2.72 (dd, J = 5.7, 2.9 Hz, 1 H), 2.76 (dt, J = 18.8, 3.0 Hz, 1 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 4.43 (m, 1 H), 4.55 (d, J = 2.5 Hz, 1 H), 6.64 (m, 2 H), 6.78 (m, 2 H), 6.85 (m, 2 H), 7.22 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.23, 22.44, 46.03, 49.28, 52.31, 55.13, 55.60, 65.62, 114.22 (2 C), 114.52 (2 C), 114.68 (2 C), 126.69 (2 C), 134.16, 142.50, 151.96, 158.77, 212.35 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1729.8, 1510.2, 1248.6, 1037.9, 817.9 cm^{-1}. $C_{21}H_{23}NO_3$ (337.41): C 74.75, H 6.87, N 4.15; found C 74.65, H 6.98, N 4.22.

***rel*-(1*S*,3*S*,4*S*)-2,3-Bis(4-methoxyphenyl)-2-azabicyclo[2.2.2]octan-5-one (*exo* 4i):** Yield 31.0 mg (46%), pale brown crystals; m.p. 96–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62 (m, 1 H), 1.77 (m, 1 H), 1.88 (m, 1 H), 2.26 (m, 1 H), 2.38 (dd, J = 18.7, 1.6 Hz, 1 H), 2.63 (dd, J = 5.7, 2.8 Hz, 1 H), 2.75 (dt, J = 18.7, 2.9 Hz, 1 H), 3.71 (s, 3 H), 3.82 (s, 3 H), 4.43 (m, 1 H), 4.67 (d, J = 2.4 Hz, 1 H), 6.57 (m, 2 H), 6.75 (m, 2 H), 6.92 (m, 2 H), 7.34 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.21, 26.26, 41.83, 48.83, 51.16, 55.21, 55.60, 62.06, 114.12 (2 C), 114.20 (2 C), 114.77 (2 C), 127.23 (2 C), 132.16, 142.68, 151.90, 158.83, 214.20 ppm. IR

($CHCl_3$): $\tilde{\nu}$ = 1723.1, 1512.0, 1246.7, 1036.8, 816.4 cm^{-1}. $C_{21}H_{23}NO_3$ (337.41): calcd. C 74.75, H 6.87, N 4.15; found C 74.87, H 6.95, N 4.28.

***rel*-(1*S*,3*R*,4*S*)-2-(4-Methoxyphenyl)-3-(4-methylphenyl)-2-azabicyclo-[2.2.2]octan-5-one (*endo* 3j):** [3d]Yield 24.7 mg (38%), yellow crystals; m.p. 129–131 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.74 (m, 1 H), 2.02 (m, 1 H), 2.13 (m, 1 H), 2.26 (m, 1 H), 2.32 (s, 3 H), 2.46 (dd, J = 18.8, 2.6 Hz, 1 H), 2.73 (m, J = 5.7, 2.9 Hz, 1 H), 2.77 (dt, J = 18.8, 3.0 Hz, 1 H), 3.73 (s, 3 H), 4.44 (m, 1 H), 4.56 (d, J = 2.5 Hz, 1 H), 6.64 (m, 2 H), 6.78 (m, 2 H), 7.12 (m, 2 H), 7.20 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.01, 22.28, 22.55, 46.05, 49.24, 52.30, 55.61, 66.00, 114.47 (2 C), 114.70 (2 C), 125.51 (2 C), 129.57 (2 C), 136.97, 139.18, 142.55, 151.96, 212.13 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1727.8, 1510.5, 1252.1, 1040.4, 816.1 cm^{-1}.

***rel*-(1*S*,3*S*,4*S*)-2-(4-Methoxyphenyl)-3-(4-methylphenyl)-2-azabicyclo-[2.2.2]octan-5-one (*exo* 4j):** Yield 26.7 mg (42%), pale yellow crystals; m.p. 55–57 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.64 (m, 1 H), 1.76 (m, 1 H), 1.89 (m, 1 H),2.27 (m, 1 H), 2.37 (s, 3 H), 2.39 (dd, J = 18.7, 1.8 Hz, 1 H), 2.65 (dd, J = 5.8, 2.9 Hz, 1 H), 2.76 (dt, J = 18.7, 3.0 Hz, 1 H), 3.71 (s, 3 H), 4.44 (m, 1 H), 4.68 (br. s, 1 H), 6.57 (m, 2 H), 6.75 (m, 2 H), 7.20 (m, 2 H), 7.32 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.29, 21.05, 26.27, 41.88, 48.81, 51.09, 55.63, 62.41, 114.20 (2 C), 114.80 (2 C), 126.12 (2 C), 129.45 (2 C), 136.94, 137.32, 142.72, 151.91, 214.10 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1723.6, 1511.8, 1245.7, 1040.6, 816.5 cm^{-1}. $C_{21}H_{23}NO_2$ (321.41): calcd. C 78.47, H 7.21, N 4.36; found C 78.35, H 7.38, N 4.24.

***rel*-(1*S*,3*R*,4*S*)-4-[2-(4-Methoxyphenyl)-5-oxo-2-azabicyclo[2.2.2]-oct-3-yl]benzonitrile (*endo* 3k):** [3d]Yield 29.2 mg (44%), pale yellow crystals; m.p. 165–167 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.79 (m, 1 H), 2.06 (m, 1 H), 2.17 (m, 1 H), 2.27 (m, 1 H), 2.50 (dd, J = 18.8, 2.3 Hz, 1 H), 2.72 (dd, J = 5.6, 2.8 Hz, 1 H), 2.75 (dt, J = 18.8, 3.0 Hz, 1 H), 3.73 (s, 3 H), 4.45 (m, 1 H), 4.64 (d, J = 2.1 Hz, 1 H), 6.58 (m, 2 H), 6.78 (m, 2 H), 7.43 (m, 2 H), 7.61 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.26, 22.42, 46.07, 49.83, 51.84, 55.57, 65.63, 111.43, 114.80 (2 C), 114.93 (2 C), 118.61, 126.66 (2 C), 132.79 (2 C), 141.60,147.69, 152.57, 210.91 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2231.8, 1733.6, 1511.0, 1252.0, 1040.1, 817.7 cm^{-1}.

***rel*-(1*S*,3*S*,4*S*)-4-[2-(4-Methoxyphenyl)-5-oxo-2-azabicyclo[2.2.2]oct-3-yl]benzonitrile (*exo* 4k):** Yield 24.0 (36%), pale yellow crystals; m.p. 71–73 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.80 (m, 1 H), 2.07 (m, 1 H), 2.19 (m, 1 H), 2.26 (m, 1 H), 2.52 (dd, J = 18.9, 2.5 Hz, 1 H), 2.74 (dd, J = 5.6, 2.8 Hz, 1 H), 2.77 (dt, J = 18.9, 3.0 Hz, 1 H), 3.72 (s, 3 H), 4.46 (m, 1 H), 4.69 (d, J = 2.4 Hz, 1 H), 6.58 (m, 2 H), 6.77 (m, 2 H), 7.49 (m, 2 H), 8.18 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.25, 26.26, 41.88, 49.08, 50.43, 55.57, 62.30, 111.35, 114.45 (2 C), 114.91 (2 C), 118.63, 127.13 (2 C), 132.66 (2 C), 141.87, 146.32, 152.44, 212.62 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2231.3, 1712.3, 1510.7, 1246.8, 1224.1, 1040.7, 816.2 cm^{-1}. $C_{21}H_{20}N_2O_2$ (332.40): calcd. C 75.88, H 6.06, N 8.43; found C 75.86, H 5.98, N 8.52.

Supporting Information (see also the footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra.

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[1] a) R. J. Sundberg, S. Q. Smith in *The Alkaloids* (Ed.: G. A. Cardel), Academic Press, **2002**, Vol. 59, p. 261; b) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435; c) D. L. Boger, S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, San Diego, CA, **1987**.

[2] a) K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588; b) S. Kobayashi, H. Ishitani, *Chem. Rew.* **1999**, *99*, 1069–1094; c) N. S. Josephsohn, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 4018–4019; d) O. G. Mancheno, M. Arrayas, J. C. Carretero, *J. Am. Chem. Soc.* **2004**, *126*, 456–457; e) Y. Yamaschita, K. Mikzuki, S. Kobayashi, *Tetrahedron Lett.* **2005**, *46*, 1803–1806; f) T. Akiyama, J. Itoh, K. Fuchibe, *Angew. Chem. Int. Ed.* **2006**, *45*, 4796–4798.

[3] a) G. Babu, P. T. Perumal, *Tetrahedron* **1998**, *54*, 1627–1638; b) G. Shanthi, P. T. Perumal, *Synth. Commun.* **2005**, *35*, 1319–1327; c) H. Sundén, I. Ibrahem, L. Eriksson, A. Cordova, *Angew. Chem. Int. Ed.* **2005**, *44*, 4877–4880; d) H. Liu, L. F. Cun, A. Q. Mi, Y. Z. Jiang, L. Z. Gong, *Org. Lett.* **2006**, *8*, 6023–6026; e) M. Rueping, C. Azap, *Angew. Chem. Int. Ed.* **2006**, *45*, 7832–7835.

[4] a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999–1010; b) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758.

[5] a) G. Alberti, M. Casciola, U. Costantino, R. Vivani, *Adv. Mater.* **1996**, *8*, 291–303; b) R. Vivani, F. Costantino, G. Alberti, M. Nocchetti, *Microporous Mesoporous Mater.* **2008**, *107*, 58–70; c) M. Curini, O. Rosati, U. Costantino, *Curr. Org. Chem.* **2004**, *8*, 591–606.

[6] a) U. Costantino, F. Fringuelli, M. Nocchetti, O. Piermatti, *Appl. Catal. A: General* **2007**, *326*, 100–105; b) U. Costantino, M. Nocchetti, F. Marmottini, R. Vivani, *Eur. J. Inorg. Chem.* **1998**, 1447–1452; c) A. Hu, H. L. Ngo, W. Lin, *J. Mol. Catal. A* **2004**, *215*, 177–186.

[7] a) C. J. Li,; T. H. Chan, *Organic reaction in Aqueous Media*; Whiley, N. Y. **1997**; b) P. T. Anastas, *Green Chemistry: Theory and Practice*; Oxford University Press, Oxford **1998**; c) *Organic Synthesis in Water* (Ed.: P. A. Grieco), Blackie Academic and Professional, London **1998**; d) F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro, *Eur. J. Org. Chem.* **2001**, 439–455; e) S. Kobayashhi, K. Manabe, *Chem. Eur. J.* **2002**, *8*, 4095–4102; f) F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro, *Curr. Org. Chem.* **2003**, *7*, 1661–1689; g) C. J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165; h) *Organic Reactions in Water* (Ed.: U. M. Lindstrom), Blackwell Publishing **2007**.

[8] a) D. Amantini, F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro, *Green Chem.* **2001**, *3*, 229–232; b) F. Fringuelli, M. Matteucci, O. Piermatti, F. Pizzo, M. C. Burla, *J. Org. Chem.* **2001**, *66*, 4661–4666; c) O. A. Attanasi, L. De Crescentini, P. Filippone, F. Fringuelli, F. Mantellini, M. Matteucci, O. Piermatti, F. Pizzo, *Helv. Chim. Acta* **2001**, *84*, 513–525; d) D. Amantini, F. Fringuelli, F. Pizzo, *J. Org. Chem.* **2002**, *67*, 7238–7243; e) D. Amantini, F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2003**, *68*, 9263–9268; f) F. Fringuelli, O. Piermatti, F. Pizzo, *Synthesis* **2003**, *10*, 2331–2334; g) F. Fringuelli, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2004**, *69*, 2315–2321; h) F. Fringuelli, F. Pizzo, S. Tortoioli, L. Vaccaro, *Org. Lett.* **2005**, *7*, 4411–4414; i) R. Girotti, A. Marrocchi, L. Minuti, O. Piermatti, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **2006**, *71*, 70–74; j) S. Bonollo, F. Fringuelli, F. Pizzo, L. Vaccaro, *Green Chem.* **2006**, *8*, 960–964; k) S. Bonollo, F. Fringuelli, F. Pizzo, L. Vaccaro, *Synlett* **2007**, *17*, 2683–2686; l) F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro in *Organic Reaction in Water* (Ed.: U. M. Lindstrom), Blackwell Publishing, **2007**, chapter 5, p. 146–184.

[9] a) F. Fringuelli, A. Taticchi, *Dienes in the Diels–Alder Reaction*, Wiley, New York, **1990**; b) F. Fringuelli, A. Taticchi, *The Diels–Alder Reaction. Selected Practical Methods*, Wiley, Chichester, **2002**.

[10] a) G. R. Krow, C. A. Johnson, J. P. Guare, D. Kubrak, K. J. Henz, D. A. Shaw, S. W. Szczepanski, J. T. Carey, *J. Org. Chem.* **1982**, *47*, 5239–5243; b) A. B. Holmes, J. Thompson, A. J. G. Baxter, J. Dixon, *J. Chem. Soc., Chem. Commun.* **1985**, 37–39; c) G. R. Krow, S. W. Szczepanski, J. Y. Kim, N. Liu, A. Sheikh, Y. Xiao, J. Yuan, *J. Org. Chem.* **1999**, *64*, 1254–1258.
[11] a) T. Akiyame, J. Takaya, H. Kagoshima, *Adv. Synth. Catal.* **2002**, *344*, 338–347; b) T. Akiyame, J. Takaya, H. Kagoshima, *Synlett* **1999**, 1426–1428.
[12] a) K. Manabe, Y. Mori, S. Kobayashi, *Synlett* **1999**, 1401–1402; b) K. Manabe, S. Kobayashi, *Org. Lett.* **1999**, *1*, 1965–1967; c) K. Manabe, Y. Mori, S. Kobayashi, *Tetrahedron* **2001**, *57*, 2537–2544.
[13] G. Alberti, M. G. Bernasconi, M. Casciola, U. Costantino, *J. Inorg. Nucl. Chem.* **1980**, *42*, 1631–1636.
[14] G. Alberti, S. Allulli, U. Costantino, M. A. Massucci, *J. Inorg. Nucl. Chem.* **1975**, *37*, 1779–1786.
[15] A. Alexakis, A. Tomassini, S. Leconte, *Tetrahedron* **2004**, *60*, 9479–9484.

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