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Design of a Conformationally Rigid Hydrazide Organic Catalyst

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Abstract: Conformational control was utilized to design a hydrazide organocatalyst for asymmetric Diels–Alder reactions, thus introducing a new aspect to organocatalysis. Diastereoselectivities and enantioselectivities of up to 96% were achieved by the application of the rigidified catalyst. The first crystal structure of a key iminium intermediate in an organocatalyzed process is also provided.

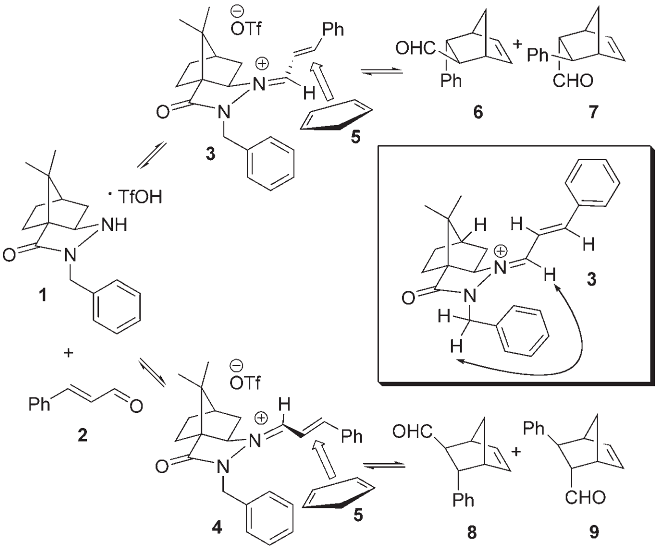
Keywords: aldehydes; conformational control; cycloaddition; hydrazides; organic catalysis

Catalysts designed to mimic the asymmetric qualities of enzymes have resulted in a rich literature.[1] Many laboratories have examined the catalytic role of simple organic molecules in a variety of organic reactions[2] that have been thoroughly illustrated by the scope of chemistry catalyzed by the amino acid proline.[3]

Proteins and peptides adopt conformations which allow them to mediate biological processes with a high degree of selectivity. Lacking the long-range interactions found in macromolecules, smaller molecules rely more heavily on local conformations to achieve selectivity in synthetic transformations. This has been successfully demonstrated through the synthesis of non-natural peptides, in which a change in conformational behavior can alter the catalytic activity.[4] Small-molecule catalysts have the potential to bridge the link between synthetic and natural catalysts through the incorporation of elements such as conformational restraints.[5] A better understanding of such interactions within a catalytic entity could facilitate the design of small organic catalysts.

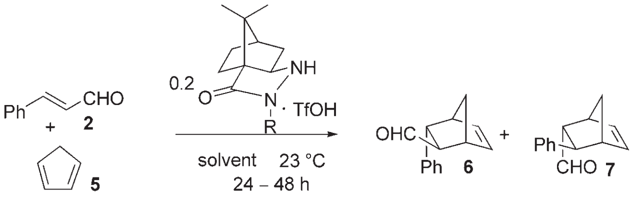
We recently described the design and synthesis of a new hydrazide-based organic catalyst that accelerates Diels–Alder reactions in water[6] and investigated the mechanism in detail.[7] Based on information gained in those studies, we now describe structural modifications that have produced the first conformationally rigid hydrazide-based catalyst. Absolute proof of the structure of a reactive iminium intermediate has been obtained by a crystal structure that provides valuable information on the key enantiodetermining step. Superior yields and selectivities have been obtained using rigidified catalyst **10** as exemplified in the enantioselective Diels–Alder[8] reactions mediated by this compound.

Condensation of catalyst **1** with aldehyde **2** results in the formation of iminium ions that can adopt one of two key geometries (**3** and **4**), as established by ^{1}H NMR.[6] The structures of these reactive iminiums can account for the enantioselectivity observed in the asymmetric Diels–Alder reaction.[9] As shown in Scheme 1, *cis*-iminium **3** leads to the major enantiomers **6** and **7** through bottom-face approach of the diene. Stereochemical bias is provided in this structure by the steric bulk of the camphor bridgehead methyl groups that impair top-face approach of the diene. *trans*-Iminium **4** leads to the minor enantiomers **8** and **9** through a process that also invokes



Scheme 1. Origin of enantioselectivity in Diels–Alder cycloadditions catalyzed by hydrazide **1**.

Table 1. Effect of substituents on the side chain of hydrazide catalysts in asymmetric Diels–Alder reactions.



Entry[a]	R	Yield [%][b]	*exo*:*endo* (**6**:**7**)	*ee* (*exo*/*endo*)[c]
1	CH_2Ph	96	1.9:1	90/88
2	CH_2(3,5-dimethylphenyl)	91	1.8:1	89/87
3	CH_2-naphthyl	82[d]	1.7:1	77/74
4	$CHPh_2$	32	1.6:1	75/58
5	$C(CH_3)_3$	10	1.1:1	6/7

[a] Reactions performed at 1 M in water using 20 mol% of catalyst and TfOH.
[b] Combined isolated yield.
[c] Enantiomeric excess determined by chiral GLC.
[d] $HClO_4$ was used in place of TfOH.

bottom-face approach of the diene. This analysis suggests that enantioselectivity is a consequence of the position of the benzyl side-chain of the catalyst that dictates the energy of transition states arising from *trans*-iminium **4**. One could therefore postulate that structural changes that favor *cis*-iminiums such as **3** would lead to a corresponding increase in the amounts of **6** and **7** resulting in higher enantioselectivities. This could be most easily accomplished through destabilization of *trans*-iminium **4** and, consequently, the transition states involved in forming **8** and **9**. The structure of **4** suggested that simply increasing the size of the benzyl group would destabilize this iminium relative to **3**.

Armed with this hypothesis, we tested several catalysts with large side chains (Table 1). The introduction of methyl groups onto the phenyl ring of the benzyl group or the use of a large planar naphthyl unit at this position did not increase selectivity relative to the benchmark benzyl side-chain when catalyzing the cycloaddition of cinnamaldehyde and cyclopentadiene (entries 1–3). Bulkier substituents such as a diphenylmethyl or *tert*-butyl group led to reduced selectivity and reactivity presumably due to increased sterics during iminium formation (entries 4 and 5).

Since simple steric modifications to the benzyl side-chain did not improve the facial selectivity of the process, a more detailed understanding of the catalyst behavior was sought. NOESY analysis of the major iminium **3**[6] showed a strong correlation between the iminium proton and the neighboring benzylic hydrogens, thus confirming the *cis*-iminium geometry (see box Scheme 1). The interaction between the iminium and aromatic protons was considerably weaker relative to that of the iminium and benzylic protons suggesting that the methylene unit of the benzyl side-chain was closer to the iminium moiety than was the phenyl ring. Given that the benzyl group could freely rotate about the C–N bond, it was apparent that alternate, undesired catalyst conformations were being accessed. The benzyl group of the catalyst could be directed away from the iminium moiety in these conformers allowing space for the undesired *trans*-iminium **4** to form resulting in lower enantioselectivities.

To investigate this effect, a dihedral driver study was conducted using PM3 semi-empirical methods.[10] The dihedral angle between the hydrazide nitrogen and benzyl side-chain (C–C–N–CO) was altered systematically in 30° increments and at each fixed dihedral angle, the energy of the conformer was minimized and the energy plotted as a function of the dihedral angle.

This analysis revealed the presence of two energy minima at dihedral angles of approximately 150° and 270° as depicted in Figure 1. The energy barrier between these conformers was on the order of ~2 kcal mol^{-1}, in principle permitting rotation about the C–N bond. The 150° conformer (**3 150°**) positioned the phenyl ring in close proximity to the iminium moiety thus inhibiting the formation of undesired *trans*-iminium **4**. This conformer would be expected to show selectivity for the major enantiomers **6** and **7** during the Diels–Alder process. In contrast, the 270° (**3 270°**) conformer could create a void in proximity to the iminium moiety. This structural gap could in principle accommodate *trans*-iminium structures similar to **4** resulting in stereochemical erosion. This study suggested that conformational restraints on the catalyst side-chain to disallow conformers similar to **3 270°** would produce an increase in enantioselectivity by raising the energy required to access transition states and iminiums related to **4**.

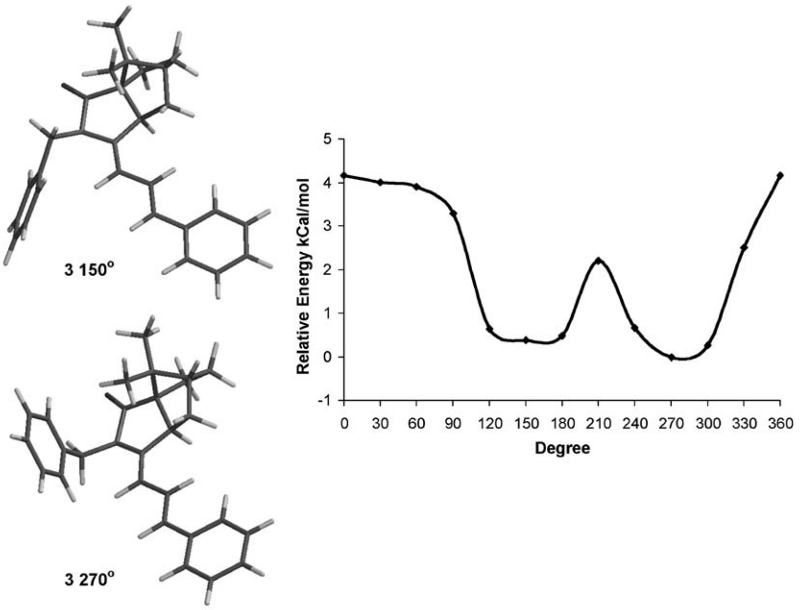
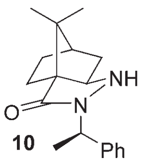


Figure 1. Plot of the energy surface of iminium **3** generated from catalyst **1** as a function of the C−C−N−CO dihedral angle.

This could be accomplished through the introduction of conformational control that would ensure exclusive access to conformers. To accomplish this restriction, the delocalized nature of the hydrazide linkage could be exploited to provide 1,3-allylic strain by the incorporation of a stereogenic centre on the benzylic side-chain to act as a conformational lock. With the introduction of a new stereogenic centre, two possible catalysts **10** and **11** could be envisaged (Figure 2).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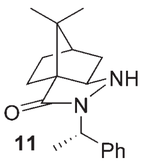
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Dihedral driver investigations were done on the iminiums that would be formed from both of these diastereomers to clarify the conformational profile of each. We were pleased to find that iminium **12** (derived from **10**) experienced one large energy minimum near the dihedral angle of 150° suggesting that a significant part of the population would exist as **12 150°** (Figure 3). At 150° the benzylic hydrogen was approximately *syn*-periplanar to the hydrazide carbonyl as anticipated by allylic-type strain, and the phenyl moiety was properly positioned to interfere with the formation of undesired *trans*-iminiums such as **4**. Thus, **10** would be expected to be a more selective catalyst than **3**.[11]

An analysis of **13** (derived from **11**) produced significantly different results as three conformers were sampled at 60°, 210° and 270° suggesting that minimal conformational selection would occur. The lowest energy conformer was found to occur at 270°, providing considerable space to accommodate a *trans*-iminium moiety and suggesting that **11** would yield lower enantioselectivities in the Diels–Alder cycloaddition relative to catalyst **1**.

Compounds **10** and **11** were synthesized and tested in the Diels–Alder cycloaddition between cinnamaldehyde and cyclopentadiene. The use of catalyst **10** maintained excellent yields while providing superior diastereoselectivities and enantioselectivities relative to catalyst **1** (Table 2, entries 1 and 2). As anticipated the mismatched catalyst **11** proved to be inferior to the original catalyst in this cycloaddition process (entry 3). The improvements in both *exo/endo* ratio and enantioselectivity gained from using conformationally rigid catalyst **10** were consistent for other substrates. Using 4-nitrocinnamaldehyde as the dienophile resulted in enantioselectivity increases when using catalyst **10**, giving an enantiomeric excess of 96% for the *exo* isomer (entries 4 and 5). The corresponding 2-substituted dienophile enjoyed similar improvements producing an *ee* of 94% for the *exo* isomer (entries 6 and 7). Catalyst **10** produced a similar improvement when used together with crotonaldehyde as the *ee* increased by 14% over the results obtained with catalyst **1** (entries 8 and 9).

We crystallized catalyst **10** whose X-ray structure gave information about the electronic properties of the hydrazide ring. One striking factor was the hybridization of the N-4 which was trigonal planar. This

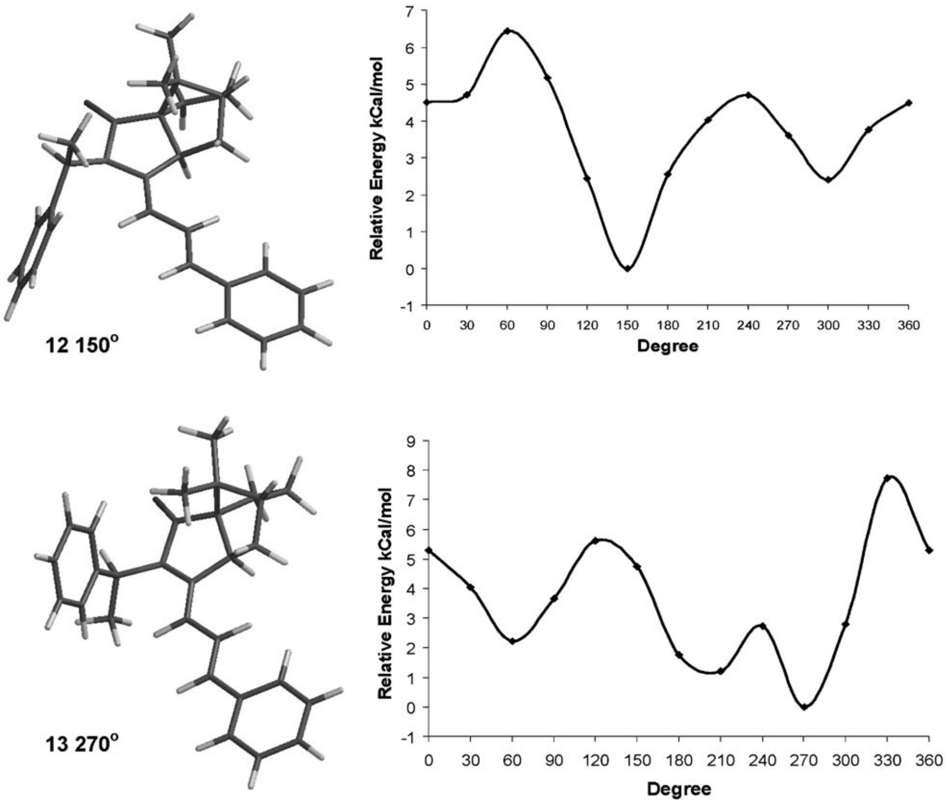


Figure 2. Plots of the energy surfaces of iminiums **12** and **13**, generated from catalysts **10** and **11** respectively, as a function of the C–C–N–CO dihedral angle.

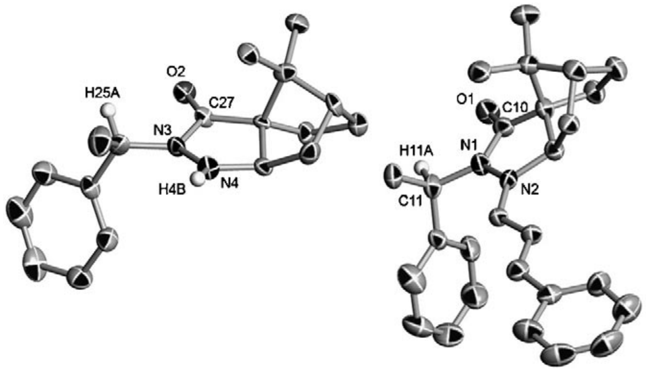


Figure 3. X-ray structures of hydrazide catalyst **10** and of intermediate iminium **12** (triflate anion omitted for clarity).

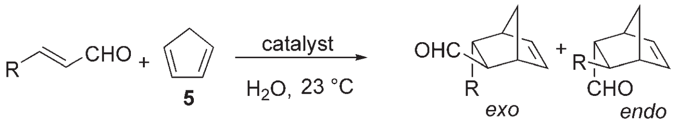
could be rationalized by resonance into the carbonyl group in addition to delocalization arising from alignment of the N–N lone pairs, consistent with an alpha-effect.[12] This was corroborated with our previous observations that hydrazide catalyst **10** was much more reactive toward iminium formation than other catalytic amine systems.[6,7]

The ability of hydrazide catalysts to rapidly and completely generate iminium ions prompted us to try to isolate the reactive species. The iminium ion **12**, derived from **10** and **2**, was prepared in 5% H_2O/CH_3NO_2 and crystallized from THF to provide material for X-ray analysis (Figure 3).[13] To our knowledge this is the first reported example of the crystallographic structure of an iminium intermediate in an organocatalyzed cycle.[14]

The hydrazide-iminium π system was completely conjugated in this structure, from the hydrazide carbonyl to the aromatic ring of the dienophile, as indicated by the complete planarity of the system. The N–CO bond was slightly elongated, relative to **10**, from 1.36 Å to 1.39 Å, and the N–N bond was slightly shortened from 1.43 Å to 1.41 Å. The small reduction in delocalization this implied could be explained by the fact that the "amide" nitrogen must donate more of its electron density, relative to **10**, to compensate for the newly generated positive charge.

Within the crystal lattice, the iminium molecule **12** showed close contacts to the triflate counterions within a distance allowable for C-H O hydrogen bonding.[15] The triflate anion is a non-coordinating ion and the likelihood of such hydrogen bonding occurring in aqueous solution with this ion was expected to be negligible. Variable temperature and concentration ^{1}H NMR experiments performed on **12** showed no significant chemical shift changes, consistent with inoperative CH hydrogen bonding in this system.[16,17]

Table 2. Effect of conformationally rigid substituents in the hydrazide-catalyzed asymmetric Diels–Alder.



Entry[a]	Catalyst	R	Yield [%][b]	*exo:endo*	*ee* [%][c] *exo/endo*
1	**1**	Ph	96	1.9:1	90/88
2	**10**	Ph	94	2.8:1	95/93
3	**11**	Ph	55	1.9:1	74/60
4	**1**	4-$NO_2C_6H_4$	93	2.2:1	92/87
5	**10**	4-$NO_2C_6H_4$	90	4:1	96/93
6	**1**	2-$NO_2C_6H_4$	90	1.2:1	87/86
7	**10**	2-$NO_2C_6H_4$	89	3.3:1	94/92
8	**1**	Me	74	1.1:1	68/72
9	**10**	Me	78	1.8:1	82/80

[a] Reactions performed at 1 M in water using 20 mol% of catalyst and TfOH.

[b] Isolated yield.

[c] Enantiomeric excess determined by chiral GLC.

Taken together, these results suggest that manipulating the conformational space available to molecules can result in superior asymmetric organic catalysts. This was exemplified by catalyst **10**, designed with careful consideration given to the reactive conformations available, that gave higher *exo/endo* ratios and enantioselectivities in the hydrazide-catalyzed Diels–Alder cycloadditions than our original catalyst **1**. We have also provided the first crystal structure of a key iminium intermediate in an organocatalyzed process. This introduces a new aspect to organocatalysis with the introduction of a rotational barrier on the facial directing side chain of our catalyst which could result in the development of novel organocatalysts.

Experimental Section

General Remarks

All solvents were used as obtained from commercial suppliers unless otherwise indicated. Standard inert atmosphere techniques were employed in handling air- and moisture-sensitive reagents. All starting materials were purchased and were used without purification unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel sheets coated with silica gel 60 F_{254}. TLC spots were visualized under ultraviolet light or developed by heating after treatment with potassium permanganate. Room temperature corresponds to 22 °C. Excess solvents were removed under vacuum at pressures obtained by water or air aspirators connected to a rotary evaporator. Trace solvents were removed on a vacuum pump. Product purification by flash chromatography was performed with silica gel 60 (230–400 mesh). Infrared (IR) spectra were obtained as neat films on a sodium chloride cell. Chemical shifts are reported downfield from tetramethylsilane (δ scale) in ppm. Mass spectroscopy (MS), using either electron impact (EI) or chemical ionization (CI), was performed on a mass spectrometer with an electron beam energy of 70 eV (for EI). Electrospray analyses were run on a triple quad mass spectrometer VG QUATTRO. High resolution mass spectroscopy (HR-MS) was performed on a mass spectrometer with an electron beam of 70 eV, or a double focusing magnetic sector mass spectrometer. GLC were performed on a gas chromatograph equipped with a split-mode capillary injection system and a flame ionization detector using CycloSil-B columns. Melting points were measured using a Melt Temp apparatus and are uncorrected.

(*S*)-(+)-10,10-Dimethyl-3-(1-phenylethyl)-3,4-diazatricyclo[5.2.1.0^{1,5}]dec-4-en-2-one

Acetic acid (0.16 mL, 3.33 mmol) was added drop wise to a solution of (*S*)-(+)-ketopinic acid[18] (7.14 g, 39.2 mmol) and (1-phenylethyl)-hydrazine (6.4 g, 47.0 mmol) in anhydrous dichloromethane (150 mL) at room temperature. The reaction mixture was stirred at that temperature until judged complete by TLC analysis (17 h), then passed through a short silica plug and the solvent was removed under vacuum. The crude hydrazonocarboxylic acid was dissolved in mesitylene (90 mL) and the resulting solution was refluxed while water was removed using a Dean–Stark apparatus. Reflux was continued until consumption of the starting material was complete as judged by TLC (36 h). The cooled reaction mixture was directly purified by flash chromatography (hexanes followed by 15% EtOAc in hexanes) to provide the desired compound as a clear oil; yield: 6.97 g (63%); IR (neat): ν = 2962, 1693, 1633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.17 (m, 5H), 5.56–5.39 (m, 1H), 2.60–2.48 (m, 1H), 2.30–2.02 (m, 4H), 1.69–1.38 (m, 5H), 1.19 (s, 1.5H major isomer), 1.15 (s, 1.5H minor isomer), 0.91 (s, 1.5H major isomer), 0.72 (s, 1.5H minor isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ (major isomer) = 174.0 (C), 173.1 (C), 141.3 (C), 128.3 (CH), 127.2 (CH), 126.8 (CH), 63.9 (CH), 51.6 (C), 49.7 (CH), 49.6 (CH), 32.0 (CH_2), 26.9 (CH_2), 24.9 (CH_2), 19.3 (CH_3), 18.8 (CH_3), 18.5

(CH_3); δ (minor isomer) = 174.0 (C), 173.2 (C), 141.8 (C), 128.2 (CH), 127.1 (CH), 126.6 (CH), 63.9 (CH), 51.7 (C), 49.9 (CH), 49.2 (CH), 31.9 (CH_2), 26.9 (CH_2), 25.1 (CH_2), 18.9 (CH_3), 18.8 (CH_3), 18.5 (CH_3); MS: *m/z* = 282.2 (M^+); HR-MS: *m/z* = 282.1718, calcd. for $C_{18}H_{22}N_2O$: 282.1732.

(*S*)-(+)-10,10-Dimethyl-3-(*R*-1-phenylethyl)-3,4-diazatricyclo[5.2.1.0^{1,5}]decan-2-one (10) and (*S*)-(+)-10,10-Dimethyl-3-(*S*-1-phenylethyl)-3,4-diazatricyclo[5.2.1.0^{1,5}]decan-2-one (11)

To a solution of (*S*)-(+)-10,10-dimethyl-3-(1-phenylethyl)-3,4-diazatricyclo[5.2.1.0^{1,5}]dec-4-en-2-one (300 mg, 1.06 mmol) in a 2:1 mixture of acetic acid and methanol (20 mL) was added sodium cyanoborohydride (636 mg, 10.1 mmol) in small portions over 1 h. The reaction mixture was stirred at room temperature until TLC indicated that the reaction was complete (21 h). Excess borohydride was quenched by the addition of 10% HCl. The products were extracted using CH_2Cl_2 and the aqueous phase was made basic using sodium hydroxide pellets then further extracted with CH_2Cl_2. The organic extracts were combined, washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum and the product was purified by flash chromatography (30% EtOAc in hexanes) to afford the desired compound **10** as a white solid; yield: 160 mg (53%); mp 79–81 °C; $[\alpha]_D$: +62.1° (*c* 1.44, $CHCl_3$); IR (neat): ν = 3249, 2958, 1662 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.35 (m, 4H), 7.26–7.22 (m, 1H), 5.50 (q, *J* = 7.0 Hz, 1H), 3.83 (br, 1H), 3.39 (dd, *J* = 8.3, 4.5 Hz, 1H), 2.19–2.11 (m, 1H), 2.07–2.01 (m, 1H), 1.90–1.81 (m, 2H), 1.58 (dd, *J* = 12.9, 8.3 Hz, 1H), 1.54 (d, *J* = 7.0 Hz, 3H), 1.28–1.23 (m, 2H), 1.22 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2 (C), 139.6 (C), 128.5 (CH), 127.6 (CH), 127.0 (CH), 64.9 (CH), 58.7 (C), 51.0 (C), 50.7 (CH), 46.8 (CH), 36.6 (CH_2), 28.7 (CH_2), 26.6 (CH_2), 20.8 (CH_3), 20.5 (CH_3), 16.3 (CH_3); MS: *m/z* = 284.2 (M^+); HR-MS: *m/z* = 284.1888, calcd. for $C_{18}H_{24}N_2O$: 284.1889.

(*S*)-(+)-10,10-Dimethyl-3-(*S*-1-phenylethyl)-3,4-diazatricyclo[5.2.1.0^{1,5}]decan-2-one (**11**) was obtained as a clear oil; yield: 102 mg (34%). $[\alpha]_D$: −73.9° (*c* 1.03, $CHCl_3$); IR (neat): ν = 3248, 2959, 1659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 2H), 7.32–7.27 (m, 2H), 7.26–7.21 (m, 1H), 5.51 (q, *J* = 7.0 Hz, 1H), 3.45 (dd, *J* = 8.3, 4.5 Hz, 1H), 3.32 (br, 1H), 2.15–2.06 (m, 1H), 1.89–1.78 (m, 3H), 1.70–1.64 (m, 1H), 1.57 (d, *J* = 7.0 Hz, 3H), 1.28–1.17 (m, 2H), 1.02 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9 (C), 139.7 (C), 128.4 (CH), 127.6 (CH), 127.5 (CH), 66.5 (CH), 58.2 (C), 50.8 (C), 50.6 (CH), 46.9 (CH), 35.4 (CH_2), 28.6 (CH_2), 26.5 (CH_2), 21.3 (CH_3), 20.1 (CH_3), 16.3 (CH_3); MS: *m/z* = 284.2 (M^+); HR-MS: *m/z* = 284.1917, calcd. for $C_{18}H_{24}N_2O$: 284.1889.

(1*R*,2*R*,3*R*,4*S*)-3-Phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1*S*,2*S*,3*S*,4*R*)-3-phenylbicyclo-[2.2.1]hept-5-ene-2-carboxaldehyde (Table 2, entry 2)

To a suspension of (*E*)-cinnamaldehyde (50 mg, 0.378 mmol) in distilled water (0.4 mL) was added (*S*)-(+)-10,10-dimethyl-3-(*R*-1-phenylethyl)-3,4-diazatricyclo[5.2.1.0^{1,5}]decan-2-one **10** (21.5 mg, 0.076 mmol) followed by CF_3SO_3H (6.7 μL, 0.07 mmol). After stirring for 1 to 2 min, cyclopentadiene (75 mg, 1.13 mmol) was slowly added and the resulting mixture was stirred at room temperature until the reaction was judged to be complete by TLC analysis. The reaction mixture was extracted twice with ether and the combined organic extracts were washed successively with water and brine then dried over Na_2SO_4. Purification by silica gel chromatography (5% EtOAc in hexanes) provided the desired material as a 2.8:1 mixture of *exo* and *endo* isomers (colorless oil, 71 mg, 94%). e*xo ee* 95%, *endo ee* 93%. Enantiomeric ratios were determined using chiral GLC analysis (Agilent/J&W CycloSil-B, 100 °C hold 3 min then 2 °C min^{-1} gradient, flow = 3.0 mL min^{-1}) *exo* isomers tr = 42.7 min, 43.8 min, *endo* isomers tr = 43.4 min, 44.3 min. ^1H NMR, ^{13}C NMR and IR data were identical to those previously reported.[6,19]

Imimium Ion from (*S*)-(+)-10,10-Dimethyl-3-(*R*-1-phenylethyl)-3,4-diazatricyclo[5.2.1.01,5]decan-2-one, (*E*)-Cinnamaldehyde and Triflic Acid for X-Ray Analysis (12)

To a solution of (*E*)-cinnamaldehyde (46.0 mg, 0.352 mmol) and (*S*)-(+)-10,10-dimethyl-3-(*R*-1-phenylethyl)-3,4-diazatricyclo[5.2.1.01,5]decan-2-one **10** (100 mg, 0.352 mmol) in 19:1 CH_3NO_2:H_2O (0.5 mL) was added CF_3SO_3H (31 μL, 0.352 mmol). After 4 h the solvent was removed under vacuum to afford a yellow oil which was dissolved in a minimum of THF. The solvent was then removed under vacuum and then the sample was redissolved in THF. This cycle was repeated several times until a pale yellow solid was obtained. This material was then dissolved in a minimum amount of THF and the mixture was allowed to stand at −20 °C to afford crystals of the iminium ion that were of suitable quality for X-ray analysis.

Supporting Information

Experimental procedures and spectral data for all new compounds.

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