X=Y–ZH systems as potential 1,3-dipoles. Part 57: Cascade 1,3-azaprotio cyclotransfer–cycloaddition reactions between aldoximes and divinyl ketone: remarkable rate enhancement and control of cycloaddition regiochemistry by Lewis acids

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Abstract—The tandem 1,3-azaprotio cyclotransfer–cycloaddition reaction between aldoximes and divinyl ketone affords the *exo*-isomers of substituted 1-aza-7-oxabicyclo[3.2.1]octan-4-ones when a substoichiometric amount of hafnium(IV) chloride, zirconium(IV) chloride or aluminium(III) chloride is added. © 2002 Elsevier Science Ltd. All rights reserved.

In the preceding two papers in this series concerned with divinyl ketone as a dual function azaprotiophile/dipolarophile we discussed its uncatalysed reactions with ketoximes[1] and aldoximes.[2] In the reactions with aldoximes the importance of solvent effects, the oxime *E/Z*-geometry and rate of thermal *E/Z*-isomerisation were identified as key factors. In this paper we report that remarkable rate enhancements and control of cycloaddition regiochemistry are engendered by substoichiometric amounts of HfCl₄, ZrCl₄ and AlCl₃.

Our zinc(II) bromide catalysed methodology, which was shown to be effective in the reactions of symmetrical ketoximes with divinyl ketone, proved to be less rewarding for aldoximes.[1] Zinc(II) bromide catalysed reaction between cyclohexanone oxime **1a** and **2** affords **3a** with a selectivity of >20:1[1] (Scheme 1), whereas the analogous process involving **1b** affords a 1:1 mixture of **3b** and **4b**. Thus we sought to identify a suitable Lewis acid for these aldoxime processes. Our initial screening efforts focused on the reaction between **1b** and **2**. Utilising the SK233 Automated Workstation, we screened several Lewis acids, including lanthanide triflates and salts of titanium, magnesium and indium.[3] Though we found several Lewis acids capable of directing the process towards **3**, most were capricious in terms of yield (Table 1). Yb(OTf)₃ and In(OTf)₃ afforded **3b** in low yields (Table 1, entries 3 and 4) whereas InCl₃ afforded a 2:1 ratio of **3** and **4**. HfCl₄ was

considered the most promising candidate for further optimisation.

Screening of several additional commercially available salts (HfBr₄, HfCp₂Cl₂, Hf(OEt)₄ and HfF₄) revealed that only the chloride and bromide promote the reaction, with the former being higher yielding; in all other cases the crude reaction mixture contained substantial amounts of unreacted oxime. Similarly, variation of solvent identified anhydrous THF as the most suitable. We were able to decrease the loading of HfCl₄ from 2.0 to 0.5 mol equiv. with respect to oxime but any further reduction resulted in loss of selectivity and lower conversion. The process could be carried out at room temperature, maintaining the same degree of regio- and diastereoselectivity but reaction times were drastically increased (>48 h). Thus our optimum
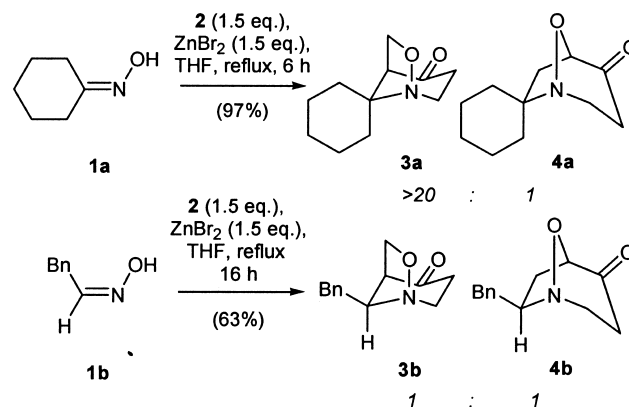
Scheme 1.

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Table 1. Effect of Lewis acids on the reaction between **1b** and **2**

Entry	Lewis acid	Time (h)	Ratio 3/4[a]	Yield (%)[b]
1	–[c]	48	1:>20[d]	60
2	HfCl$_4$	1	20:1	45
3	Yb(OTf)$_3$	2	>20:1	19
4	In(OTf)$_3$	1	>20:1	9
5	InCl$_3$	22	2:1	36

Reaction conditions: oxime (1.0 mol equiv.), divinyl ketone (1.5 mol equiv.), Lewis acid (2.0 mol equiv.), THF, reflux.
[a] Measured by the ^{1}H NMR spectra of the crude products.
[b] Yield isolated after column chromatography.
[c] Reaction conditions: oxime (1.0 mol equiv.), divinyl ketone (1.2 mol equiv.), Lewis acid (2 mol equiv.) acetonitrile, reflux, 48 h.
[d] 3:1 mixture of *exo*-**4** and *endo*-**4** obtained.

conditions for this process (Scheme 2) were used to investigate the scope of the reaction for a range of aldoximes (Table 2).

Oximes **1a–k** afford the corresponding isomers **3a–k** as single isomers; **4** was not detected in any case. The reactions of *Z*-**1e** and *E*-**1e** afford the same product (*exo*-**3e**) under the hafnium(IV) chloride catalysed conditions. Under thermal conditions *Z*-**1e** leads to the formation of *exo*-**4e** whereas *E*-**1e** affords *endo*-**4e**.[2] Interestingly, zinc(II) bromide (1.5 mol equiv.) catalysed the reaction of *Z*-**1e** and **2** under the reaction conditions described in Scheme 2, affording a mixture of *exo*-**3** and *exo*-**4** after 30 min, whereas the analogous ZnBr$_2$ catalysed reaction of *E*-**1e** afforded only unreacted oxime after 30 min.[4]

The ^{1}H NMR of **3** and **4** are distinguished by diagnostic ABX systems in their respective spectra. In **3** (Fig. 1) H6′ and H6 are the most deshielded protons and appear as a double doublet at δ 4.1 ppm (dihedral angle H5–H6$\approx$90°), while H5 occurs as a doublet at δ 2.9 ppm. In **4** H5 is the most deshielded proton and appears as a doublet at δ 4.4 ppm (dihedral angle H5–H6$\approx$90°).[1] The stereochemistry of *exo*-**3d–k** was assigned by n.O.e. studies: irradiation of H8 results in enhancement at H2 (Fig. 1). The stereochemistry of *exo*-**3b** was confirmed by X-ray crystallography (Fig. 2) while that of *exo*-**3c** was assigned by comparison of J_{H5-H8} (0 Hz) with that obtained for *exo*-**3b** (J_{H5-H8}=0 Hz).

The mechanism of the reaction is a matter of conjecture. We believe that the rate determining step is either oxime isomerisation or 1,3-APT.[2] Oxime isomerisation may be promoted by co-ordination of hafnium to the oxime hydroxyl moiety and the subsequent lowering of its pK_a or the release of a catalytic amount of HCl from hafnium(IV) chloride and traces of water, promoting formation of a nitroso intermediate (Scheme 3). Heating *E*-**1e** in the absence of **2** and the presence of HfCl$_4$ under otherwise identical reaction conditions and quenching the reaction
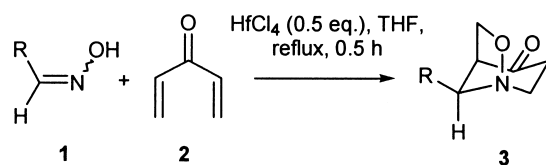
**Table 2**. HfCl$_4$ catalysed synthesis of type-**3** isomers

| Oxime	Structure	Conversion (%)[a]	Yield (%)[b]
1a		>95	38
1b		>95	45
1c		>95	37
1d		>95	78
Z-**1e**		90	55
E-**1e**		90	64
1f		85	70
1g		85	62
1h		70	63
1i		>95	49
1j		85	57
1k		>95	63

Reaction conditions: **1** (1 mol equiv.), **2** (1.5 mol equiv.), HfCl$_4$ (0.5 mol equiv.), THF, reflux, 30 min.
[a] Measured from the ^{1}H NMR spectra of the crude products. In all cases no other regio- or diastereomers were detected.
[b] Yield isolated after column chromatography.

after 30 min without cooling showed the formation of *Z*-**1e** (7%) by ^{1}H NMR. The reaction between *E*-**1e** and **2** did not proceed on treatment of the reaction mixture with a small amount of HCl gas, indicating that a Brønsted acid catalysed
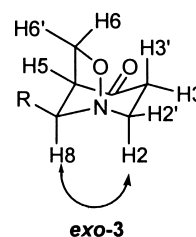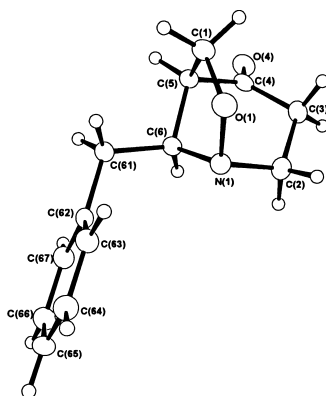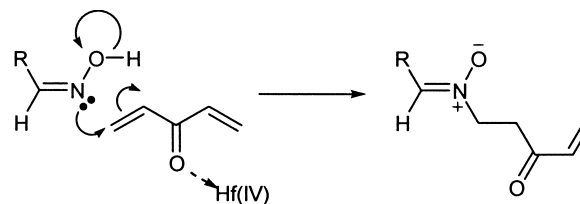

Scheme 2.

Figure 1.

Figure 2. X-Ray crystal structure of *exo*-**3b**.
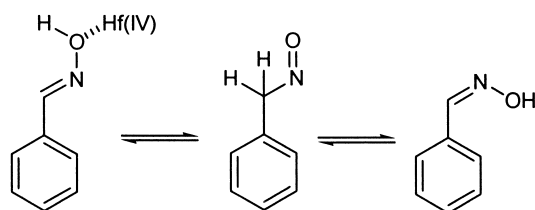
Scheme 3.

pathway does not account for the result in Table 2 (^{1}H NMR of the reaction mixture indicated that oxime isomerisation had not occurred).

If the rate of *E/Z* oxime isomerisation is increased sufficiently, *Z*-oxime 1,3-APT will become the rate determining step.[2] Reaction of *Z*-**1f** under thermal conditions (THF, reflux) does not proceed within 30 min, indicating that hafnium(IV) chloride promotes the 1,3-APT step. The observed rate enhancement may be due to lowering the LUMO energy of divinyl ketone **2** by coordination of Hf(IV) to the carbonyl moiety. It has recently been reported that a mixtures of ZnI_2 and $BF_3 \cdot OEt_2$ catalyse 1,3-APT (Scheme 4).[5]

The regiochemistry, which is dictated by the relative magnitudes of the interacting orbital coefficients, is completely reversed by the addition of hafnium(IV) chloride. This particular cycloaddition is expected to be $HOMO_{nitrone}-LUMO_{alkene}$ controlled and this type of interaction is predicted to result in bond formation between the oxygen and the terminal alkene carbon as in **A**,
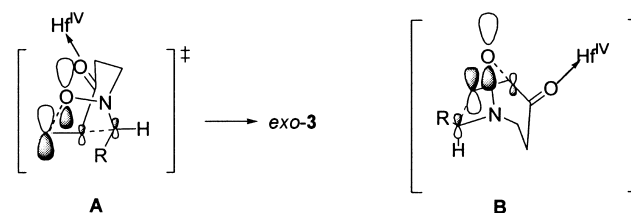

Scheme 4.

Figure 3.

ultimately leading to *exo*-**3** (Fig. 3).[6] However, Gandolfi and co-workers have experimentally shown that only strongly electron withdrawing alkenes (e.g. nitroethylene) and electron rich nitrones (e.g. triphenyl nitrones) react in this way.[7] Otherwise, mixtures of regioisomers are formed. Co-ordination of the hafnium to the ketone as depicted in Fig. 3 will alter the relative magnitudes of the orbital coefficients favouring **A** (leading to **3**) over **B** (leading to **4**).

Further screening revealed that aluminium and zirconium salts were also active in the process (Table 3) affording *exo*-**3** isomers in comparable yields. In all cases single isomers were obtained. We were able to reduce the loading of $AlCl_3$ to 25 mol%, but any further reduction resulted in loss of selectivity and conversion.

In summary, we have identified three Lewis acids that are effective in the cascade 1,3-azaprotio cyclotransfer-1,3-dipolar cycloaddition cascades between aldoximes and divinyl ketone. Studies aimed at developing asymmetric versions of this protocol are in progress.

1. Experimental

Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Mass spectral data were obtained on an Autospec instrument at 70 eV. Nuclear magnetic resonance spectra were recorded on Brucker AM

Table 3. Comparison of $HfCl_4$, $ZrCl_4$ and $HfCl_4$ as catalysts

Oxime	$HfCl_4$		$ZrCl_4$		$AlCl_3$	
	Conversion[a] (%)	Yield[b] (%)	Conversion[a] (%)	Yield[b] (%)	Conversion[a] (%)	Yield[b] (%)
1d	>95	78	>95	65	>95	65
E-**1e**	90	64	90	60	90	60
1f	85	70	85	64	80	58
1i	>95	49	>95	43	>95	51

Reaction conditions: **1** (1 mol equiv.), **2** (1.5 mol equiv.), $HfCl_4$ (0.5 mol equiv.), THF, reflux, 30 min; **1** (1 mol equiv.), **2** (1.5 mol equiv.), $ZrCl_4$ (0.5 mol equiv.), THF, reflux, 30 min; **1** (1 mol equiv.), **2** (1.5 mol equiv.), $AlCl_3$ (0.25 mol equiv.), THF, reflux, 30 min.
[a] Measured from the ^{1}H NMR spectra of the crude products. In all cases no other regio- or diastereomers were detected.
[b] Yield isolated after column chromatography.

250, Brucker DPX 300 and Brucker DRX 500 machines. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane (TMS) as internal standard. All spectra were recorded in deuteriochloroform. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet, bs=broad singlet, C_q=quaternary carbon. Microanalyses were obtained using a Carbo Erba MOD11016 instrument. Infra-red data were recorded on films, prepared by evaporation of a dichloromethane solution on a Spectra-Tech Inc. Trough Plate Ark on a Nicolet Magna-IR 560 spectrometer. HPLC analysis was performed on Gilson instruments. X-Ray analysis was performed on a Stoe STADI 4-circle machine or a Nonius Kappa CCD area-detector diffractometer. The term 'petroleum ether' refers to the fraction of petroleum ether with boiling point between 40–60°C. Column chromatography was performed using flash silica gel (Merck 9385). Aldoximes and **2** were prepared as previously described.[2]

1.1. General procedure for $HfCl_4/ZrCl_4$ catalysed tandem 1,3-APT cycloaddition

A solution of oxime (1 mmol) in dry THF (20 mL) was added to a solution of $HfCl_4$ (0.161 g, 0.5 mmol) or $ZrCl_4$ (0.117 g, 0.5 mol) in dry THF (20 mL) under a nitrogen atmosphere. Divinyl ketone (135 μL, 1.5 mmol) was added and the reaction mixture was immersed in a pre-heated oil bath at 82°C and magnetically stirred under a nitrogen atmosphere. After 30 min the reaction was allowed to cool to room temperature, poured into aqueous saturated $NaHCO_3$ (40 mL) and stirred for 5 min. If necessary the mixture was filtered through Celite, the phases were separated and the aqueous layer extracted with dichloromethane (2×40 mL). The combined extracts were washed with water (40 mL), dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (diethyl ether–pentane). Yields for the $HfCl_4/ZrCl_4$ catalysed processes are reported in Table 3.

1.2. General procedure for $AlCl_3$ catalysed tandem 1,3-APT cycloaddition

A 1.0 M solution of $AlCl_3$ in nitrobenzene (250 μL, 0.25 mmol) was added to a solution of oxime (1.0 mmol) and DVK (135 μL, 1.5 mmol) in dry THF (40 mL) and the reaction mixture was immersed in a pre-heated oil bath at 82°C. After 30 min the reaction was allowed to cool to room temperature, poured onto aqueous saturated $NaHCO_3$ solution (40 mL) and stirred for 5 min. If necessary the mixture was filtered through Celite, the phases were separate and the aqueous layer extracted with dichloromethane (2×40 mL). The combined extracts were washed with water (40 mL), dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. The residue was then purified by flash chromatography (diethyl ether–pentane). Yields are as reported in Table 3.

1.2.1. 8-*exo*-Benzyl-7-oxa-1-azabicyclo[3.2.1]octan-4-one (*exo*-3b). (Z)-Phenylacetaldoxime (0.270 g, 2 mmol) and divinyl ketone (270 μL, 3 mmol) were reacted according to the general procedure ($HfCl_4$ catalyst) for 30 min. Subsequent work up afforded a sticky orange solid. Flash chromatography, eluting with diethyl ether, afforded the product (0.194 g, 45%) that crystallised from ethanol as colourless needles, mp 97–99°C. Found: C, 71.6; H, 7.15; N, 6.2; $C_{13}H_{15}NO_2$ requires C, 71.9; H, 6.95; N, 6.45%; δ_H (500 MHz) 7.20–7.38 (m, 5H, ArH), 4.16 (dd, 1H, J=8.3 and 1.6 Hz, H6), 4.12 (dd, 1H, J=8.3 and 5.1 Hz, H6′), 3.68 (dd, 1H, J=14.3 and 9.5 Hz, H2′), 3.50 (t, 1H, J=7.3 Hz, H8), 3.06 (distorted dd, 1H, J=5.1 Hz, H5), 3.02 (dd, 1H, J=14.0 and 7.3 Hz, PhCHH), 3.02 (ddd, 1H, J=14.3, 9.6 and 6.9 Hz, H2), 2.65 (dddd, 1H, J=16.5, 9.6, 9.5 and 0.8 Hz, H3′), 2.59 (dd, 1H, J=14.0 and 7.3 Hz, PhCHH) and 2.27 (dd, 1H, J=16.5 and 6.9 Hz, H3); m/z (EI; %) 217 (M^+, 100), 126 (50), 117 (27), 91 (79), 84 (78) and 76 (39); ν (cm^{-1}, film) 1714 (C=O).

1.2.2. 8-*exo*-Ethyl-7-oxa-1-azabicyclo[3.2.1]octan-4-one (*exo*-3c). Propionaldoxime (0.073 g, 1 mmol) and divinyl ketone (135 μL, 1.5 mmol) were reacted according to the general procedure ($HfCl_4$ catalyst) for 30 min. Subsequent work up afforded a brown oil. Flash chromatography, eluting with diethyl ether, afforded the product (0.058 g, 37%) as a colourless oil. HRMS Found: 155.0940, $C_8H_{13}NO_2$ requires 155.0946; δ_H (500 MHz) 4.11 (d, 1H, J=8.0 Hz, H6), 3.98 (dd, 1H, J=8.0 and 5.3 Hz, H6′), 3.68 (dd, 1H, J=14.3 and 9.5 Hz, H2′), 3.14 (dd, 1H, J=7.8 and 6.4 Hz, H8), 3.05 (ddd, 1H, J=14.3, 10.8 and 6.4 Hz, H2), 3.04 (m, 1H, H5), 2.66 (dddd, 1H, J=16.4, 10.8, 9.5 and 0.8 Hz, H3′), 2.28 (dd, 1H, J=16.4 and 6.4 Hz, H3), 1.63 (m, 1H, CHHCH₃), 1.38 (m, 1H, CHHCH₃) and 1.02 (t, 3H, CH₃); m/z (EI; %) 155 (M^+, 72), 126 (25), 84 (69) and 70 (69); ν (cm^{-1}, film) 1717 (C=O).
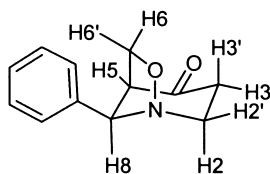
1.2.3. 8-*exo*-*tert*-Butyl-7-oxa-1-azabicyclo[3.2.1]octan-4-one (*exo*-3d). Pivalaldoxime (0.101 g, 1 mmol) and divinyl ketone (135 μL, 1.5 mmol) were reacted according to the general procedure ($HfCl_4$ catalyst) for 30 min. Work up followed by flash chromatography eluting with 3:1 v/v diethyl ether–pentane afforded the product (0.143 g, 78%) which crystallised from dichloromethane–pentane as colourless prisms, mp 80–82°C. Found: C, 65.7; H, 9.4; N, 7.5; $C_{10}H_{17}NO_2$ requires: C, 65.55; H, 9.35; N, 7.65%; δ_H (500 MHz) 4.06 (m, 2H, H6′ and H6), 3.64 (dd, 1H, J=14.2 and 9.8 Hz, H2′), 3.29 (m, 1H, H5), 3.05 (ddd, 1H, J=14.2, 9.9 and 7.0 Hz, H2), 2.76 (s, 1H, H8), 2.66 (ddd, 1H, J=16.8, 9.9 and 9.8 Hz, H3′), 2.30 (dd, 1H, J=16.8 and 7.0 Hz, H3) and 1.02 (s, 9H, 3×CH₃); m/z (EI; %) 184 (M+1, 100), 156 (36) and 86 (26); ν (cm^{-1}) 1712 (C=O).
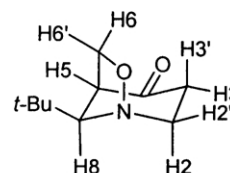
Signal Irradiated	Enhancement (%)				
	H2′	H5	H2	H8	3 x CH₃
H2	18.0			4.5	
3 x CH₃	0.7	1.0		1.1	

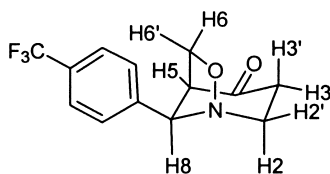### 1.2.4. 8-*exo*-Phenyl-7-oxa-1-azabicyclo[3.2.1]octan-4-one (*exo*-3e). (E)-Benzaldoxime (0.121 g, 1 mmol) and divinyl ketone (135 μL, 1.5 mmol) were reacted according

to the general procedure. Work up followed by flash column chromatography eluting with 3:1 v/v diethyl ether−pentane afforded the product (0.132 g, 64%) as a pale yellow oil. Found: C, 70.65; H, 6.5; N, 7.05; $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9; δ_H (400 MHz) 7.45−7.25 (m, 5H, 5×PhH), 4.48 (s, 1H, H8), 4.10 (d, 1H, J=7.9 Hz, H6), 3.80 (dd, 1H, J=14.3 and 9.5 Hz, H2'), 3.70 (dd, 1H, J=7.9 and 5.0 Hz, H6'), 3.31 (d, 1H, J=5.0 Hz, H5), 3.19 (ddd, 1H, J=14.3, 10.8 and 6.4 Hz, H2), 2.73 (dt, 1H, J=16.4 and 10.2 Hz, H3') and 2.37 (dd, 1H, J=16.4 and 6.4 Hz, H3); m/z (%) 204 (M+1, 9), 203 (M$^+$, 67), 186 (32), 132 (36), 117 (44), 104 (38), 91 (35), 83 (37), 77 (34) and 55 (100); ν (cm^{-1}, dichloromethane solution) 1715 (C=O).

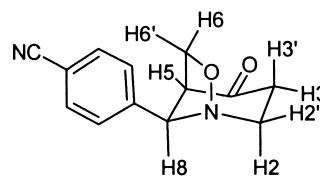| Signal Irradiated	Enhancement (%)			
	H8	H5	H2	Ph
H8			5.0	7.0
H5	5.0			6.0
H2	**11.0**			

1.2.5. 8-*exo*-(4-Trifluorophenyl)-7-oxa-1-azabicyclo-[3.2.1]octan-4-one (*exo*-3f). (*E*)-4-Trifluoromethylbenzaldoxime (0.189 g, 1 mmol) and divinyl ketone (135 μL, 1.5 mmol) were reacted according to the general procedure (HfCl$_4$ catalyst) for 30 min. Work up afforded a colourless solid, comprising *exo*-**3f** and unreacted oxime (15%). Flash chromatography, eluting with diethyl ether, afforded the product (0.191 g, 70%) which crystallised from dichloromethane−pentane as colourless needles, mp 135°C. Found: C, 57.55; H, 4.5; N, 5.1; $C_{13}H_{12}NO_2F_3$ requires C, 57.55; H, 4.45; N, 5.15%; δ_H (500 MHz) 7.62 (m, 4H, 4×ArH), 4.54 (s, 1H, H8), 4.15 (d, 1H, J=8.1 Hz, H6), 3.85 (dd, 1H, J=14.4 and 9.5 Hz, H2'), 3.67 (dd, 1H, J=8.1 and 5.0 Hz, H6'), 3.49 (d, 1H, J=5.0 Hz, H5), 3.23 (ddd, 1H, J=14.4, 10.8 and 6.4 Hz, H2), 2.78 (distorted ddd, 1H, J=16.5, 10.8 and 9.5 Hz, H3') and 2.42 (dd, 1H, J=16.5 and 6.4 Hz, H3); m/z (FAB; %) 272 (M+1, 33) and 55 (100); ν (cm^{-1}, film) 1717 (C=O).

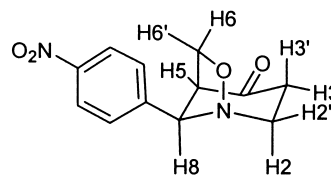| Signal Irradiated	Enhancement (%)		
	H8	H5	H2
H8		1.7	**4.3**
H2	**7.6**		

1.2.6. 4-(4-Oxo-7-oxa-1-azabicyclo[3.2.1]oct-8-yl)benzo-nitrile (*exo*-3g). 4-[(*E*)-(Hydroxyimino)methyl]benzonitrile (0.146 g, 1 mmol) and divinyl ketone (135 μL, 1.5 mmol) were reacted according to the general procedure

(HfCl$_4$ catalyst) for 30 min. Work up afforded a yellow-orange crystalline solid, comprising of *exo*-**3g** and unreacted oxime (15%). Flash chromatography, eluting with diethyl ether, afforded the product (0.141 g, 62%) which crystallised from dichloromethane−pentane as colourless prisms, mp 148−150°C. Found: C, 68.2; H, 5.25; N, 12.5; $C_{13}H_{12}N_2O_2$ requires: C, 68.4; H, 5.3; N, 12.3%; δ_H (500 MHz; CDCl$_3$) 7.67 (m, 2H, 2×ArH), 7.60 (m, 2H, 2×ArH), 4.52 (s, 1H, H8), 4.15 (d, 1H, J=8.1 Hz, H6), 3.84 (dd, 1H, J=14.5 and 9.6 Hz, H2'), 3.63 (dd, 1H, J=8.1 and 5.0 Hz, H6'), 3.33 (d, 1H, J=5.0 Hz, H5), 3.22 (ddd, 1H, J=14.5, 10.8 and 6.4 Hz, H2), 2.77 (dt, 1H, J=16.5 and 10.3 Hz, H3') and 2.42 (dd, 1H, J=16.5 and 6.4 Hz, H3); m/z (EI; %) 228 (M$^+$, 20), 142 (36), 129 (32), 116 (44), 115 (31), 83 (39), 55 (100), 49 (43) and 42 (36); ν (cm^{-1}, film) 2228 (CN) and 1714 (C=O).
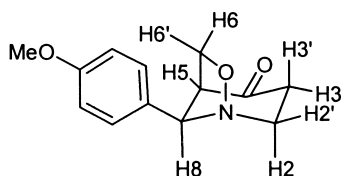

Signal Irradiated	Enhancement (%)		
	H8	H5	H2
H8		1.9	**4.3**
H5	2.6		
H2	**9.5**		

1.2.7. 8-*exo*-(4-Nitrophenyl)-7-oxa-1-azabicyclo-[3.2.1]octan-4-one (*exo*-3h). (*E*)-4-Nitrobenzaldoxime (0.166 g, 1 mmol) and divinyl ketone (135 μL, 1.5 mmol) were reacted according to the general procedure (HfCl$_4$ catalyst) for 30 min. Work-up afforded a yellow crystalline solid comprising of *exo*-**3h** and unreacted oxime (30%) only. Flash chromatography, eluting with diethyl ether, afforded the product (0.156 g, 63%) which crystallised from dichloromethane−pentane as colourless needles, mp 150−152°C. Found: C, 57.85; H, 4.9; N, 11.45; $C_{12}H_{12}N_2O_4$ requires: C, 58.05; H, 4.85; N, 11.3%; δ_H (500 MHz; CDCl$_3$) 8.24 (d, 2H, J=8.9 Hz, 2×ArH), 7.67 (d, 2H, J=8.4 Hz, 2×ArH), 4.55 (s, 1H, H8), 4.15 (d, 1H, J=8.1 Hz, H6), 3.85 (dd, 1H, J=14.4 and 9.5 Hz, H2'), 3.63 (dd, 1H, J=8.1 and 5.0 Hz, H6'), 3.36 (dd, 1H, J=5.0 Hz, H5), 3.21 (ddd, 1H, J=14.4, 9.4 and 6.4 Hz, H2), 2.78 (dt, 1H, J=16.2 and 10.3 Hz, H3') and 2.43 (dd, 1H, J=16.2 and 6.4 Hz, H3); m/z (EI; %) 248 (M$^+$, 15), 231 (19), 177 (16), 116 (41), 89 (18) and 55 (100); ν (cm^{-1}, film) 1716 (C=O), 1518 (NO) and 1348 (NO).
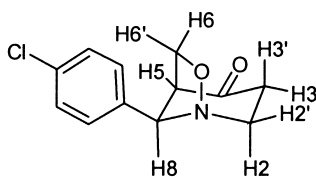

Signal Irradiated	Enhancement (%)		
	H8	H5	H2
H8		2.6	**5.4**
H2	**10.9**		

1.2.8. 8-*exo*-(4-Methoxyphenyl)-7-oxa-1-azabicyclo-[3.2.1]octan-4-one (*exo*-3i).

(*E*)-4-Methoxybenzaldoxime (0.151 g, 1 mmol) and divinyl ketone (135 μL, 1 mmol) were reacted according to the general procedure (HfCl$_4$ catalyst) (1 mmol scale) for 30 min. Work up followed by flash chromatography eluting with 3:1 v/v diethyl ether–pentane afforded the product (0.114 g, 49%) which crystallised from dichloromethane–pentane as colourless plates, mp 107–109°C. Found: C, 66.7; H, 6.35; N, 5.75; C$_{13}$H$_{15}$NO$_3$ requires: C, 66.9; H, 6.5; N, 6.0%; δ_H (300 MHz) 7.37 (d, 2H, *J*=8.8 Hz, 2×ArH), 6.90 (d, 2H, *J*=8.8 Hz, 2×ArH), 4.46 (s, 1H, H8), 4.12 (d, 1H, *J*=7.9 Hz, H6), 3.86–3.80 (m, 4H, H2 and MeO), 3.74 (ddd, 1H, *J*=7.9, 4.8 and 0.6 Hz, H6′), 3.30 (d, 1H, *J*=4.8 Hz, H5), 3.20 (ddd, 1H, *J*=14.3, 10.8 and 6.4 Hz, H2), 2.75 (m, 1H, H3′) and 2.38 (dd, 1H, *J*=16.4 and 6.4 Hz, H3); *m/z* (EI; %) 233 (M$^+$, 100), 162 (49), 151 (58), 135 (33), 134 (53) and 55 (62); ν (cm^{-1}, film) 1715 (C=O).
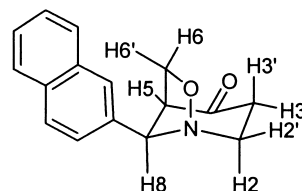

Signal Irradiated	Enhancement (%)		
	H8	H5	H2
H8		2.5	**5.1**
H2	**9.7**		

1.2.9. 8-*exo*-(4-Chlorophenyl)-7-oxa-1-azabicyclo-[3.2.1]octan-4-one (*exo*-3j).

(*E*)-4-Chlorobenzaldoxime (0.155 g, 1 mmol) and divinyl ketone (135 μL, 1.5 mmol) were reacted according to the general procedure (HfCl$_4$ catalyst). Work-up afforded a yellow solid comprising of *exo*-3i and unreacted oxime (15%). Flash chromatography, eluting with 4:1 v/v diethyl ether–pentane, afforded the product (0.135 g, 57%) which crystallised from dichloromethane–pentane as colourless rods, mp 144–146°C. Found: C, 60.35; H, 5.15; N, 5.95; C$_{12}$H$_{12}$NO$_2$Cl requires: C, 60.65; H, 5.15; N, 5.9%; δ_H (500 MHz) 7.40 (d, 2H, *J*=8.5 Hz, 2×ArH), 7.34 (d, 2H, *J*=8.5 Hz, 2×ArH), 4.45 (s, 1H, H8), 4.12 (d, 1H, *J*=8.0 Hz, H6), 3.82 (dd, 1H, *J*=14.4 and 9.6 Hz, H2′), 3.68 (dd, 1H *J*=8.0 and 5.0 Hz, H6′), 3.29 (d, 1H, *J*=5.0 Hz, H5), 3.20 (ddd, 1H, *J*=14.4, 10.8 and 6.4 Hz, H2), 2.74 (dt, 1H, *J*=16.5 and 10.3 Hz, H3′) and 2.39 (dd, 1H, *J*=16.5 and 6.4 Hz, H3); *m/z* (EI; %) 239 ^{37}(M$^+$, 11), 237 ^{35}(M$^+$, 33), 166 (22), 151 (20), 138 (21), 115 (27), 89 (23), 83 (21), 75 (22) and 55 (100); ν (cm^{-1}, film) 1705 (C=O).

Signal Irradiated	Enhancement (%)		
	H8	H5	H2
H8		2.6	**4.9**
H2	**10.1**		

1.2.10. 8-*exo*-(2-Napthyl)-7-oxa-1-azabicyclo[3.2.1]-octan-4-one (*exo*-3k).

(*E*)-2-Napthaldoxime (0.171 g, 1 mmol) and divinyl ketone (135 μL, 1.5 mmol) were reacted according to the general procedure (HfCl$_4$ catalyst) for 30 min. Work up followed by flash chromatography eluting with diethyl ether afforded the product (0.160 g, 63%) which crystallised from dichloromethane–pentane as colourless plates, mp 123–125°C. Found: C, 75.65; H, 5.85; N, 5.25; C$_{16}$H$_{15}$NO$_2$ requires: C, 75.85; H, 5.95; N, 5.55%; δ_H (500 MHz) 7.99 (s, 1H, ArH), 7.84 (m, 3H, 3×ArH), 7.63 (m, 3H, 3×ArH), 4.65 (s, 1H, H8), 4.15 (d, 1H, *J*=7.9 Hz, H6), 3.88 (dd, 1H, *J*=14.4 and 9.5 Hz, H2′), 3.75 (dd, 1H, *J*=7.9 and 4.8 Hz, H6′), 3.43 (d, 1H, *J*=4.8 Hz, H5), 3.27 (ddd, 1H, *J*=14.4, 10.8 and 6.4 Hz, H2), 2.79 (dt, 1H, *J*=16.4 and 10.2 Hz, H3′) and 2.43 (dd, 1H, *J*=16.4 and 6.4 Hz, H3); *m/z* (EI; %) 253 (M$^+$, 30), 128 (40), 110 (34), 98 (100) and 55 (52); ν (cm^{-1}, film) 1716 (C=O).

Signal Irradiated	Enhancement (%)		
	H8	H5	H2
H8		2.5	**4.6**
H2	**10.0**		

1.3. Single-crystal X-ray analyses

Crystallographic data for compound **3b** were measured on a Nonius KappaCCD area-detector diffractometer using a mixture of area detector ω- and ϕ-scans and Mo Kα radiation (λ=0.71073 Å). All three structures were solved by direct methods using SHELXS-86[8] and were refined by full-matrix least-squares (based on F^2) using SHELXL-97.[9] All non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model. The residuals wR_2 and R_1, given below, are defined as $wR_2 = (\sum[w(F_o^2 - F_c^2)^2]/\sum[wF_o^2)^2])^{1/2}$ and $R_1 = \sum\|F_o| - |F_c\|/\sum|F_o|$.

Crystal data for **3b**. C$_{13}$H$_{15}$NO$_2$, *M*=217.26, monoclinic, space group *P*2$_1$/*a*, *a*=6.7256(1), *b*=17.5126(3), *c*=9.4990(2) Å, β=97.898(1)°, *U*=1108.21(3) Å^3, *Z*=4, *D*$_c$=1.30 g cm^{-3}, μ=0.088 mm^{-1}, *F*(000)=464, *T*=150 K.

Data collection. 2.00<θ<27.5°; 2174 unique data were collected [R_{int}=0.076]; 1905 reflections with F_o>4.0σ(F_o).

Structure refinement. Number of parameters=145, goodness of fit, *s*=1.032; wR_2=0.0941, R_1=0.0361.

Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC183748. Copies of the data can be obtained, free of charge, on application to CCDC, 12

Union Road, Cambridge, CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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