

Tandem 1,3-azaprotiocyclotransfer–cycloaddition reactions between aldoximes and divinyl ketone. Remarkable rate enhancement and control of cycloaddition regiochemistry by hafnium(IV) chloride

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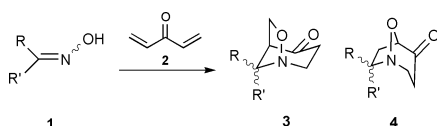
The tandem 1,3-azaprotiocyclotransfer–cycloaddition reaction between aldoximes and divinyl ketone affords the *exo*-isomers of substituted 1-aza-8-oxabicyclo[3.2.1]octan-4-ones when a substoichiometric amount of hafnium(IV) chloride is added.

As part of our continuing interest in cascade cycloaddition reactions of oximes we recently outlined our efforts to incorporate divinyl ketone **2** as a bifunctional azaprotiophile/dipolarophile component¹ in Class 2 processes.² The reaction between **2** and symmetrical ketoximes **1** ($R' = R$) proceeds smoothly to afford a regioisomeric mixture of isoxazolidinones **3** and **4**, where **4** is the major product (Scheme 1). We were able to obtain **3** ($R = R'$) as the major product by the addition of a stoichiometric amount of zinc bromide and to bias the cascade in favour of **4** ($R = R'$) by a judicious choice of solvent. Preliminary investigations of aldoxime **1** (R' or $R = H$)-**2** cascades gave **4** as the major product and **3** was rarely detected.³ The *exo*–*endo*-ratio was shown to be dependent on the geometry of the starting oxime and its propensity to isomerise under thermal conditions. The addition of zinc bromide was found to be much less effective for aldoxime cascades than for symmetrical ketoxime cascades, prompting us to seek an alternative Lewis acid. We now report a regio- and stereoselective hafnium(IV) chloride catalysed aldoxime-**2** cascade.

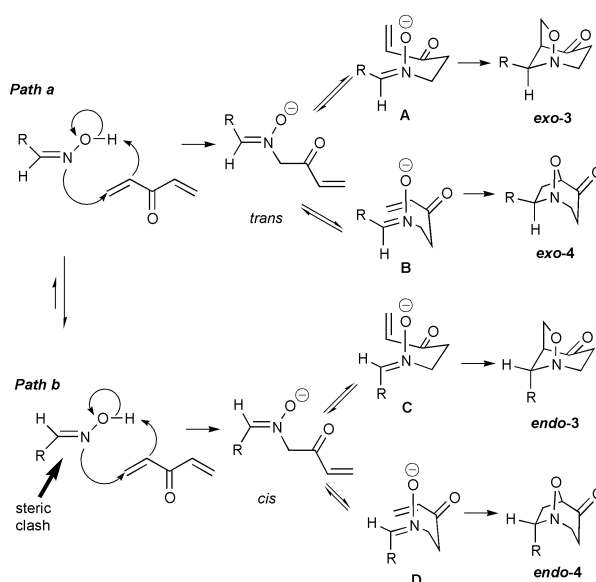
The reaction between an achiral aldoxime **1** (R or $R' = H$) and **2** can in principle occur *via* a number of pathways, including the synthetically less useful *O*-Michael addition. Polymerization of **2** is also a potential problem. Generally both *E*- and *Z*-aldoxime isomers can undergo 1,3-azaprotiocyclotransfer (herein referred to as 1,3-APT) to afford *E*- and *Z*-nitrones respectively.³ Subsequent cycloaddition of each nitron can afford four possible diastereomeric products *exo*-**3**, *exo*-**4**, *endo*-**3** and *endo*-**4** (Scheme 2). Under thermal conditions (81 °C, acetonitrile) *exo*-**4** and *endo*-**4** are the exclusive products.

Amongst the Lewis acids tested were salts of lanthanides, titanium, indium and magnesium. These have been reported to catalyze 1,3-dipolar cycloadditions.⁴ The majority of these salts directed the regioselectivity of the cascade towards *exo*-**3** but the results were capricious in terms of yield. Hafnium(IV) chloride appeared to be the least detrimental and was selected for further optimisation. The mode 2 conditions outlined in Table 1 afford reproducible results.⁵

Thus treatment of aryl and aliphatic aldoximes **1a–j** with hafnium(IV) chloride resulted in complete reversal of the



Scheme 1






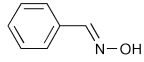
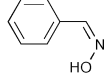
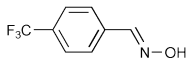
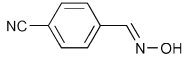
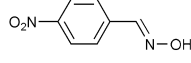
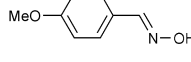
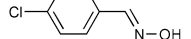
Scheme 2

selectivity of the thermally controlled cascade, giving exclusive formation of *exo*-**3a–j** (Table 1). The scope of the reaction includes aliphatic aldoximes (entries **a–c**), electron deficient aryl aldoximes (entries **f, g, h**) and electron rich aryl aldoximes (entry **i**). In many cases the addition of hafnium(IV) chloride was necessary for a reaction to occur (entries **f, g, h**).

Both *E*- and *Z*-isomers of benzaldoxime (**1d,e**) afford the same product under the hafnium(IV) chloride catalysed conditions. In the absence of hafnium(IV) chloride **1d** and **e** each afford different *exo*- and *endo*-diastereomers of **4**, due to the inability of these oxime isomers to equilibrate at 81 °C.^{2,3} Thus hafnium(IV) chloride promotes oxime isomerism. This may be by co-ordination of hafnium to the oxime *via* the hydroxy 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.^{6,7} Only a small equilibrium concentration of the *Z*-oxime is required for exclusive formation of the *Z*-nitron.⁸ Though we have evidence to suggest that hafnium(IV) chloride enhances the rate of the 1,3-APT step, its precise role is a matter of conjecture at this time.⁹

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_{nitron}–LUMO_{alkene} controlled and is predicted to result in bond formation between the oxygen and the terminal alkene carbon as in **A**, ultimately leading to **3**.¹⁰ However, Gandolfi and co-workers have shown experimentally that only strongly electron withdrawing alkenes (e.g. nitroethylene) and electron rich nitrones (e.g. triphenyl nitrones) react in this way.¹¹ Otherwise, mixtures of regio-

Table 1

Oxime 1 ^a	MODE 1: 2 (1.2 eq.), MeCN, 81 °C, 48 h			MODE 2: 2 (1.5 eq.), HfCl ₄ (0.5 eq.), THF, 66 °C, 30 min		
	Conv. ^b (%)	<i>exo</i> - 3 : 4 ^{b,c}	Yield (%) ^d	Conv. ^b (%)	<i>exo</i> - 3 : 4 ^{b,c}	Yield ^d (%)
a 	>95 ^e	1: >20	65	>95	>20:1	45
b 	25 ^e	1: >20	11	>95	>20:1	78
c 	>95 ^e	1: >20	41	>95	>20:1	37
d 	10 ^e	1: >20	—	90	>20:1	64 (71)
e 	>95	1: >20	79	90	>20:1	55 (61)
f 	<5	—	—	85	>20:1	70 (82)
g 	<5	—	—	85	>20:1	62 (73)
h 	<5	—	—	70	>20:1	63 (90)
i 	80	1:2.5	55	>95	>20:1	49
j 	>95	1:11	61	85	>20:1	57 (63)

^a The *E/Z* stereochemistry of the oxime is as illustrated. ^b Mixtures of *exo*-**4** and *endo*-**4** were formed. ^c Ratios determined by ¹H NMR, in cases where the ratio is >20:1 no traces of the minor isomer were detected. ^d Yield isolated by column chromatography, values in parentheses indicate yields based on 100% conversion of oxime. ^e Reaction carried out in a STEM block at 80 °C.

isomers are formed. Co-ordination of the hafnium to the ketone as depicted in Fig. 1 will alter the relative magnitudes of the atomic coefficients favouring **A** (leading to *exo*-**3**) over **B** (leading to *exo*-**4**).


Fig. 1

Hafnium(IV) chloride is a highly effective catalyst for aldoxime–divinyl ketone cascades. There are only a few reports¹² of the use of hafnium salts in organic synthesis. To the best of our knowledge this is the first example of a hafnium promoted 1,3-dipolar cycloaddition.

Notes and references

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- Hafnium(IV) bromide, hafnocene(IV) dichloride, hafnium(IV) ethoxide and hafnium(IV) fluoride were found to be less effective than HfCl₄.
- (*E*)-Benzaldoxime was heated in the absence of divinyl ketone under otherwise identical reaction conditions and the reaction was quenched after 30 min without being allowed to cool. The formation of (*Z*)-benzaldoxime (7%) was visible by ¹H NMR.
- Reaction between (*E*)-benzaldoxime and **2** did not proceed on treatment of the reaction mixture with a small amount of HCl gas. ¹H NMR of the reaction mixture indicated oxime isomerism had not occurred.
- The rate of 1,3-APT from (*Z*)-benzaldoxime is expected to be significantly faster than that from the corresponding (*E*)-benzaldoxime due to steric factors. For a full account see ref. 3.
- The rate enhancement is not simply due to oxime isomerism. The *Z*-isomer of **1f** reacts after 48 h in >95% conversion to afford *exo*-**4f** but after 30 min in THF at 66 °C only starting material is recovered.
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