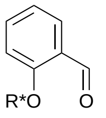
Effects of lanthanide complexes on the facial reactivity of 2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)benzaldehyde in hetero-Diels–Alder reactions and a model to account for such effects

Richard P. C. Cousins,[a] Woan Chee Ding,[b] Robin G. Pritchard[b] and Richard J. Stoodley*[b]

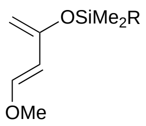
[a] *Medicinal Science, Glaxo Wellcome Medicines Research Centre, Stevenage, Hertfordshire, UK SG1 2NY*
[b] *Department of Chemistry, UMIST, PO Box 88, Manchester, UK M60 1QD*

Changes in the facial reactivity of 2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)benzaldehyde towards (*E*)-1-methoxy-3-(*tert*-butyldimethylsiloxy)buta-1,3-diene in the presence of lanthanide(fod)$_3$ complexes can be correlated with the ionic radius of the lanthanide metal.

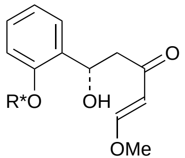
Recently, we reported notable 1,5-asymmetric inductions in the reaction of the salicylaldehyde derivative **1** with Danishefsky's diene **2** in the presence of Lewis acids.[1] The use of $BF_3{\cdot}OEt_2$ and $SnCl_4$ (100 mol% of each) in THF led to *ca*. 27 : 3 : 63 : 7 mixtures of compounds **4**–**7**, which were transformed by the action of TFA into 90 : 10 mixtures of the dihydropyranones **6** and **7**. With $ZnCl_2$ (100 mol%) in THF and Eu(fod)$_3$ (5 mol%) in toluene, the cycloadducts **8** and **10** were produced in ratios of 86 : 14 and 25 : 75; the cycloadducts **8** and **10** were converted into the dihydropyranones **6** and **7** in the presence of TFA. Clearly, $BF_3{\cdot}OEt_2$ and $ZnCl_2$ in THF promoted attack mainly at the *si*-face of the aldehyde moiety of compound **1** whereas Eu(fod)$_3$ in toluene induced preferential *re*-face addition.



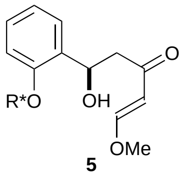
1



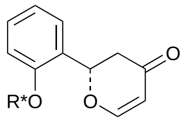
2 R = Me
3 R = Bu^t



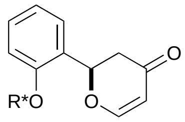
4



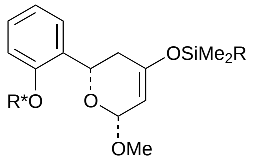
5



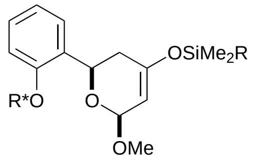
6



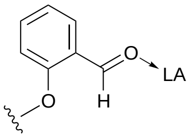
7



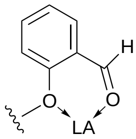
8 R = Me
9 R = Bu^t



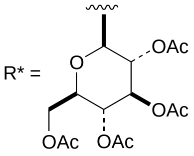
10 R = Me
11 R = Bu^t



12



13



Here we describe efforts that have led to improvements in the practicality and stereoselectivity of the hetero-Diels–Alder reaction; we also propose a model to account for the variation in the facial reactivity of the salicylaldehyde derivative **1**.

Seeking initially to increase the stabilities of the cycloadducts† (compounds **8** and **10** were very prone to undergo desilylative eliminations to give the pyranones **6** and **7**), we investigated the reaction of the aldehyde **1** with the diene **3**[2]‡ under the afore-cited cycloaddition conditions. The use of $ZnCl_2$ in THF and Eu(fod)$_3$ in toluene afforded the cycloadducts **9** and **11** in ratios of 67 : 33 and 18 : 82. From the latter reaction, it was possible to isolate the cycloadduct **11**,§ mp 175–176 °C, $[\alpha]_D$ +53 (*c* 0.3, CH_2Cl_2), in 75% yield after crystallisation. In accord with its structure, the cycloadduct **11** was transformed into the dihydropyranone **7** (82% yield after crystallisation).

Expecting that a 'matched' chiral europium(III) complex would improve the diastereoselectivity, the use of (+)-Eu(hfc)$_3$, (−)-Eu(hfc)$_3$, (+)-Eu(tfc)$_3$ and (−)-Eu(tfc)$_3$ (5 mol% of each) as promoters was studied in toluene. Surprisingly, there was little difference in the effects of the enantiomeric catalysts and the selectivities were poor. Thus, the cycloadducts **9** and **11** were produced in ratios of 59 : 41 and 61 : 39 with (+)-Eu(hfc)$_3$ and (−)-Eu(hfc)$_3$, and in ratios of 45 : 55 and 47 : 53 with (+)-Eu(tfc)$_3$, and (−)-Eu(tfc)$_3$.

The importance of the metal in lanthanide(fod)$_3$ complexes in determining the facial reactivity of the aldehyde **1** towards the diene **3** is illustrated by the results shown in Table 1. In the first

Table 1 Outcome of the reaction of aldehyde **1** and diene **3** in the presence of lanthanide(fod)$_3$ complexes[a]

Catalyst	Lanthanide ionic radius/Å[b]	Ratio **9** : **11**[c]
La(fod)$_3$	1.06	< 5 : 95
Ce(fod)$_3$[d]	1.03	< 5 : 95
Pr(fod)$_3$	1.01	< 5 : 95
Nd(fod)$_3$	0.99	< 5 : 95
Eu(fod)$_3$[e]	0.95	18 : 82
Gd(fod)$_3$	0.94	26 : 74
Dy(fod)$_3$	0.91	55 : 45
Ho(fod)$_3$	0.89	61 : 39
Er(fod)$_3$	0.88	69 : 31
Yb(fod)$_3$	0.86	66 : 34

[a] Typically, the reactions were conducted using aldehyde **1** (0.1 mmol), diene **3** (0.2 mmol) and the complex (*ca*. 4 mol%) in dry toluene (2 cm^3). [b] Ref. 3. [c] The ratio was determined by 300 MHz ^{1}H NMR spectroscopic analysis of the crude product and/or the derived pyranones **6**/**7**. [d] The reaction involving Ce(fod)$_3$ was significantly slower than the others (requiring *ca*. 48 h for completion compared with *ca*. 5 h). [e] The use of different concentrations of Eu(fod)$_3$ (*ca*. 10 and *ca*. 0.5 mol%) did not affect the ratio of cycloadducts produced.

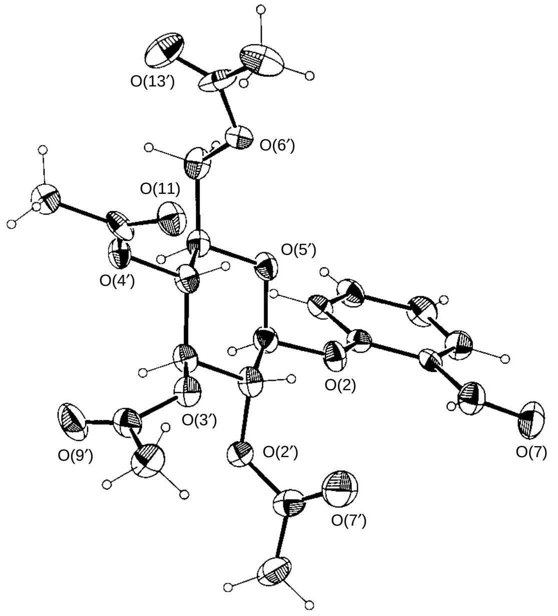


Fig. 1 Molecular structure of compound **1**

four examples, essentially complete (>95 : 5) *re*-face selectivity of the aldehyde **1** was observed. In the remaining examples, there was (in the main) a gradual increase in *si*-face selectivity as the ionic radius of the lanthanide metal decreased. Significantly, from a synthetic standpoint, it was possible to isolate the cycloadduct **11** in 90% yield after crystallisation from the reaction of the salicylaldehyde **1** (11 mmol) and the diene **3** in the presence of Pr(fod)$_3$.

In the hope that its solid-state structure would reveal 'preorganisation' that might shed light on the stereoinductions, compound **1** was subjected to an X-ray crystallographic analysis. The molecular structure,¶ shown in Fig. 1 with its atomic labelling, indicates that the *re*-face of the aldehyde moiety is shielded by the 2′-*O*-acetyl group of the sugar.‖

Evidence that the solid-state conformation of compound **1** was maintained in solution (C_6D_6) was adduced from an NOED spectroscopic study. Thus, irradiation of the anomeric hydrogen atom (1′-H) caused an 8% enhancement of the aryl 3-hydrogen atom (3-H); similarly, irradiation of 3-H enhanced 1′-H by 6%.

From the afore-cited findings, we propose that compound **1** can be activated by Lewis acids in two ways. The formation of a monodentate complex of type **12**, in which the Lewis acid is coordinated to the aldehyde carbonyl O-atom *syn* to the aldehyde H-atom, is postulated to be the basis of the *si*-face reactivity; this pattern is predominant in aldol reactions induced by $BF_3{\cdot}OEt_2$ and $SnCl_4$ and in hetero-Diels–Alder reactions promoted by $ZnCl_2$ and the 'late' lanthanides. The generation of a chelated complex, *e.g.* of type **13** in which the Lewis acid is coordinated to the aldehyde carbonyl O-atom and the glycosidic O-atom, provides a possible explanation for the *re*-face selectivity; this behaviour is a feature of cycloaddition reactions initiated by the 'early' lanthanides. Presumably, because of the 'lanthanide contraction' (in which the radii of lanthanide cations decrease with increasing atomic number),[3] the 'late' lanthanides favour heptacoordination (and, therefore, the formation of monodentate complexes) whereas the 'early' lanthanides prefer octacoordination (and, as a consequence, are able to form chelated complexes).[4]

The results reported herein are of both mechanistic and synthetic note. Although the catalytic activity of lanthanide complexes in hetero-Diels–Alder reactions has been extensively investigated since Danishefsky's foundation studies,[5] the finding that the nature of the cation can have a significant impact upon the facial reactivity of a chiral aldehyde is novel.** The possibility that this effect is linked to the ionic radius of the lanthanide cation and its ability to form a monodentate *versus* a bidentate complex warrants further study. From a synthetic context, the technology permits the efficient assembly of compounds **7** and **11** in multi-gram quantities; earlier, only the dihydropyranone **6** was accessible in high yield.[1]

We thank the CVCP for an ORS award (to W. C. D.) and a referee for drawing our attention to ref. 8.

Footnotes and References

* E-mail: richard.stoodley@umist.ac.uk

† Our interest in such cycloadducts stems from the expectation that their dihydropyran rings can be elaborated into glycopyranose-like structures; such products, which may be regarded as 'scaffolded' disaccharides, represent a novel and potentially interesting class of compounds.

‡ The diene **3** was prepared by a modification of the literature route (see ref. 2) in which (*E*)-4-methoxybut-3-en-2-one was treated with *tert*-butyldimethylsilyl triflate and triethylamine (see ref. 6).

§ New compounds displayed analytical and spectral properties that supported their assigned structures.

¶ *Crystal data* for **1**: $C_{21}H_{24}O_{11}$, M = 452.4, monoclinic, space group $P2_1$ (no. 4), a = 12.625(6), b = 6.929(5), c = 13.262(4) Å, β = 97.89(3)°, U = 1149(11) Å^3, Z = 2, D_c = 1.307 g cm^{-3}, $F(000)$ = 476, μ(Mo-Kα) = 1.00 cm^{-1}, crystal size 0.40 × 0.15 × 0.15 mm. A total of 1947 reflections were measured, 1658 unique (R_{int} = 0.084) after an empirical absorption correction (max., min. transmission = 1.00, 0.84), on a Rigaku AFC6S diffractometer using ω–2θ scans (λ = 0.71069 Å) at 20 °C. The structure was solved by direct methods and refined by full-matrix least-squares based on F^2, with all non-hydrogen atoms anisotropic and hydrogen atoms constrained in calculated positions. The final cycle converged to R = 0.054 and wR^2 = 0.138 based on 679 observed reflections [$I > 2\sigma(I)$] and 293 variables (R = 0.190, wR^2 = 0.210 for all data). CCDC 182/579.

‖ A related shielding effect was noted in the X-ray structure of 5-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1,4-naphthoquinone and invoked to account for the high facial reactivity of the dienophile in Diels–Alder reactions (see ref. 7).

** The enantioselectivities of Diels–Alder reactions catalysed by complexes of lanthanide(OTf)$_3$ and (*R*)-binaphthol can be influenced by added achiral ligands and by the lanthanide metal (see ref. 8).

1 R. P. C. Cousins, A. D. M. Curtis, W. C. Ding and R. J. Stoodley, *Tetrahedron Lett.*, 1995, **36**, 8689.
2 R. E. Ireland, P. A. Aristoff and C. F. Hoyng, *J. Org. Chem.*, 1979, **44**, 4318.
3 F. A. Cotton, G. Wilkinson and P. L. Gaus, *Basic Inorganic Chemistry*, 3rd edn., Wiley, New York, 1995, p. 267 and 616.
4 S. Cotton, *Lanthanides and Actinides*, MacMillan, London, 1991, p. 58.
5 G. A. Molander, *Chem. Rev.*, 1992, **92**, 29.
6 H. Emde, D. Domsch, H. Feger, U. Frick, A. Götz, H. H. Hergott, K. Hofmann, W. Kober, K. Krägeloh, T. Oesterle, W. Steppan, W. West and G. Simchen, *Synthesis*, 1982, 1.
7 B. Beagley, A. D. M. Curtis, R. G. Pritchard and R. J. Stoodley, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1981.
8 S. Kobayashi and H. Ishitani, *J. Am. Chem. Soc.*, 1994, **116**, 4083.

Received in Liverpool, UK, 24th June 1997; 7/04463A