A new chiral ligand for the Fe–Lewis acid catalysed asymmetric Diels–Alder reaction

Marion E. Bruin and E. Peter Kündig*

Département de Chimie Organique, Université de Genève 30 Quai Ernest Ansermet, CH-1211 Genève 4, Switzerland. E-mail: peter.kundig@chiorg.unige.ch

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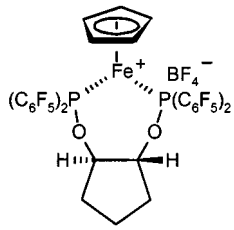
The readily accessible enantiopure hydrobenzoin forms the backbone of the new bidentate ligand BIPHOP-F that is shown here to provide the chiral environment for a highly enantioselective Fe–Lewis acid catalysed Diels–Alder reaction between α,β-enals and dienes.

The high versatility of the Diels–Alder reaction in the synthesis of six-membered ring compounds and the potential for the control of up to four stereogenic centres make this transformation one of the key reactions in organic synthesis. Lewis acid catalysis has further enhanced its scope. Recent focus in this area has been on the use of chiral Lewis acids as catalysts and both main group and transition metal Lewis acids have yielded impressive results.[1,2]

Our earlier report in this area centred on the chiral Cp iron(II) Lewis acid **1** containing the electron poor C_2-symmetric



(*R*,*R*)-**1**

bidentate phosphorus ligand CYCLOP-F derived from *trans*-cyclopentane-1,2-diol **2**.[2a,3a] While both enantiomers of **2** are available by diastereoselective synthesis[3b] or enzymatic resolution,[4] the synthesis of **2** in larger quantities is time consuming and costly.

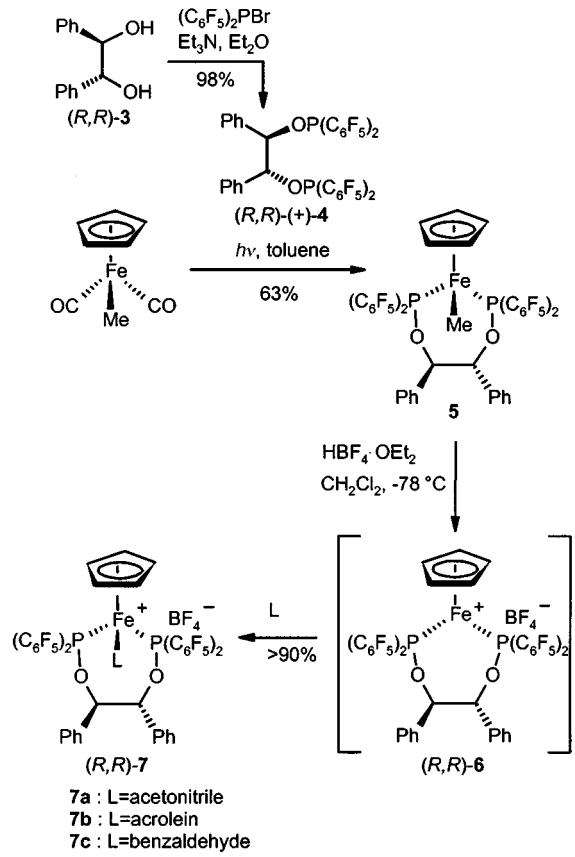
We here report on the new ligand BIPHOP-F (**4**) and on its use in the Fe–Lewis acid catalysed Diels–Alder reaction. Models suggested that hydrobenzoin **3** would be a good candidate for replacement of the cyclopentanediol backbone. As diol **3** is readily synthesised *via* Sharpless dihydroxylation,[5] we were surprised to find that its previous use in the synthesis of bidentate phosphorous ligands is limited to a single report.[6]

Ligand **4**† was prepared in near quantitative yield by reaction of (*R*,*R*)- or (*S*,*S*)-hydrobenzoin [(*R*,*R*)-**3** or (*S*,*S*)-**3**] with *bis*(pentafluorophenyl)phosphorus bromide[7] in the presence of triethylamine. The Lewis acid catalyst **6** was obtained by photolytic ligand exchange in [$CpFe(CO)_2Me$] followed by protolytic demethylation of complex **5**[2a] (Scheme 1). The unsaturated Fe complex **6** was trapped *in situ* with either acetonitrile, acrolein, or benzaldehyde to give, after precipitation with hexane, complexes **7a**–**c**, respectively.

Complex **7a** is stable and is readily characterised. The acetonitrile ligand is strongly bound and the complex does not exhibit catalytic activity towards the Diels–Alder reaction between enals and dienes. Complexes **7b** and **7c** are stable at ambient temperature in the solid state and can be weighed out in air without degradation. In CH_2Cl_2 solution, the aldehyde ligands in **7b** and **7c** are labile and in the absence of excess free aldehyde, the complexes slowly decompose at temperatures above −20 °C. Both **7a** and **7b** can be used as precatalysts in Diels–Alder reactions between α,β-enals and dienes (Table 1). 2,6-Di-*tert*-butylpyridine was added to scavenge residual acid impurities that adversely affected enantioselectivities. We subsequently found that 2,6-dimethylpyridine was equally efficient.

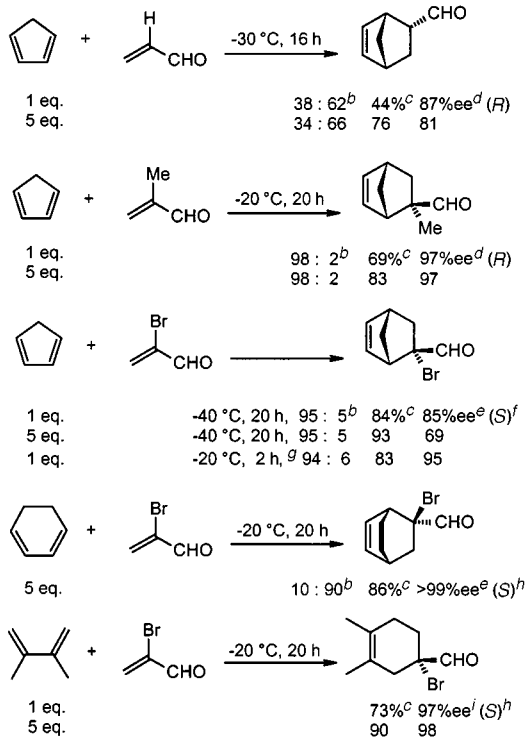
The results in Table 1 show that *exo/endo* ratios, yields, and enantiomeric excess obtained matched, and in some cases slightly exceeded, those realised with catalyst **1**. Increasing the quantity of diene led to a faster reaction and to higher yields but in some cases, *e.g.* the reactions between cyclopentadiene and acrolein or α-bromoacrolein, resulted in a drop of enantioselectivity. This presumably is due to the competitive uncatalysed background reaction. The sense of asymmetric induction observed is the same for both Lewis acids **1** and **6**. Indeed, the chiral catalyst sites are very similar. Fig. 1‡ shows the chiral pocket of the catalysts **6** and **1**[2a] and the postulated position of methacrolein in the transition state assembly.§ The diene approaches the alkene C_α-*si*-face of the *s*-trans conformer of the coordinated enal. The *re*-face is shielded by a pentafluorophenyl ring of the ligand and the ligand backbone.

In summary, the new C_2-symmetric bidentate phosphorus ligand BIPHOP-F **4** derived from (*R*,*R*)- or (*S*,*S*)-hydrobenzoin **3** described here proved to be an effective ligand in the Fe^{II}



Scheme 1

Table 1 Diels–Alder reactions with complex **7b**[a]



[a] The Diels–Alder reactions were carried out in freshly distilled CH_2Cl_2 (1 M solution) with 5 mol% precatalyst **7b** and 5 mol% of 2,6-di-*tert*-butylpyridine or 2,6-dimethylpyridine. Analogous results were obtained with **7c**. [b] *exo/endo* Ratio. [c] Isolated yield after flash-chromatography. [d] The ee was determined by GC analysis of the diasteromeric acetals obtained by reaction with (2*R*,4*R*)-pentanediol.[8] The absolute configuration was assigned by comparing the sign of $[\alpha]_D^{20}$ with literature values.[8,9] [e] The enantiomeric excess was determined from the ^{1}H NMR spectrum in the presence of the chiral shift reagent Eu(hfc)$_3$. [f] The absolute configuration was assigned by comparison with literature data.[10] [g] Slow addition of the diene (1 h). [h] The absolute configuration assigned is based on the presumption of attack of the enal C_α-*si*-face (same as in the first three examples in the Table). [i] The enantiomeric excess was determined by GC analysis on a chiral column (MN FS-Lipodex E).

catalysed asymmetric Diels–Alder reaction of α,β-enals with dienes and its ease of synthesis merits attention for other applications in asymmetric catalysis.

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Notes and references

† (*S*,*S*)-**4**: mp (toluene): 124 °C. $[\alpha]_D^{20}$ −82 (CH_2Cl_2, *c* = 2.31).^{1}H NMR (C_6D_6, 400 MHz): δ 6.89–6.82 (m, 4H, *o*-H_{arom}), 6.81–6.68 (m, 6H, *m*,*p*-H_{arom}), 5.23–5.17 (m, 2H, CHOP). ^{31}P NMR (C_6D_6, 162 MHz): δ 87.2 (p, *J* 40 Hz). IR (CH_2Cl_2): 1640m, 1517s, 1480s, 1380m, 1290m, 1202w, 1143w, 1091s, 980s, 919w, 882w, 800w, 638w, 585w. Elemental analysis: Calc. for $C_{38}H_{20}F_{20}O_2P_2$: C, 48.43; H, 1.28. Found: C, 48.37, H, 1.60%.

‡ The site of **1** was taken from the X-ray structure of $[(\eta^5\text{-}C_5H_5)Fe(MeCN)(CYCLOP\text{-}F)][PF_6]$.[2a] The site of **6** was modelled from the X-ray structure of the complex $[(\eta^5\text{-}C_5H_4CF_3)Fe(Me)(BIPHOP\text{-}F)]$ (**8**). The synthesis of **8** and the X-ray structure determination will be reported in a forthcoming full paper.

§ Based on accommodation of methacrolein in the chiral pocket with geometry optimization by molecular mechanics (MM+) and EHMO. Details will be reported in a forthcoming full paper.

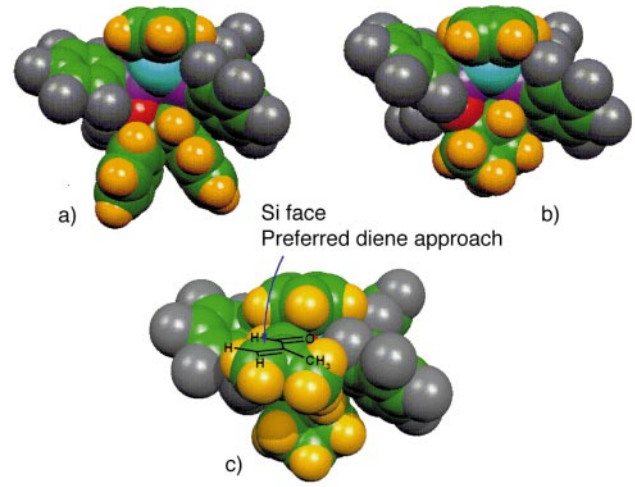

Fig. 1 (a) Coordination site of catalyst (*R*,*R*)-**6**, (b) coordination site of catalyst (*R*,*R*)-**1** and (*c*) catalyst (*R*,*R*)-**1** + methacrolein. The diene approach to the methacrolein C_α-*si*-face is indicated by the arrow.‡

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