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Tetrahedron Letters 46 (2005) 1627–1629

Tetrahedron Letters

The modulation of face–face π–π interactions in Lewis acid catalysis

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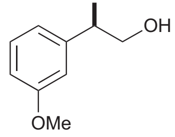
Received 15 November 2004; revised 13 January 2005; accepted 18 January 2005
Available online 1 February 2005

Abstract—The enantiomeric excess observed for the *exo*-adduct from the Lewis acid catalysed Diels–Alder reaction between cyclopentadiene and methacrolein can be increased up to 21% by simple modification of the electronics of the aromatic ring in a series of stilbene-derived diol ligands, suggesting that the proposed face–face π–π interaction between the catalyst and the dienophile can be modulated by altering the electron density on the aromatic ring.

The chemist's tool box contains a battery of catalysts able to carry out numerous synthetic transformations in high chemical yield and enantiomeric excess.[1] Mechanistic insight and structural knowledge has led to an increasing elegance in the rational design of catalysts and their fine tuning, to the degree, where yields and enantiomeric excess are consistently being reported in excess of 90%.[2]

Many reported catalysts in the literature have attributed a high degree of selectivity observed to a non-covalent face–face π–π interaction.[3] This subtle, yet highly effective interaction, has frequently been proposed with, for example, phenyl or naphthyl as the aromatic partner.[4,13] As part of our research programme into novel Lewis acids[5] we were intrigued as to whether it would be possible to modulate a proposed face–face π–π interaction by altering the electronics on an aromatic ring incorporated into the structure of a catalyst, thus adding to the points of consideration in the design of prospective catalyst architecture. Herein we report that it is possible to alter significantly the ee's observed in a Diels–Alder reaction up to 21% by simple modification of the electronics in a series of stilbene-derived diol ligands.

In choosing the catalytic system to use we adopted two initial criteria. Firstly, an easy to synthesise system that would allow rapid preparation of a variety of analogues of the aromatic ring. Secondly, a catalyst which had previously been reported to accelerate a reaction with only moderate ee, such that small changes in the energy of a preferred transition state would allow for larger fluctuations in the selectivities observed for the reaction. Based on these criteria we targeted the C_2 symmetric stilbene-derived diols **2** (Fig. 1). Jones and Guzel have shown previously that the 3-methoxystyrene derived diol **1** induces asymmetry in the Diels–Alder reaction between cyclopentadiene and methacrolein in 21% ee when complexed to a Lewis acidic metal.[6] In this report the asymmetric induction observed was rationalised by invoking a face–face π–π interaction between the double bond of the methacrolein and the aromatic ring incorporated into the structure of the catalyst. We therefore embarked upon the synthesis of the diols **8**–**12** to evaluate their reactivity in asymmetric Diels–Alder reactions and discover if it was possible to modulate the proposed face–face π–π interactions, providing a method for the fine tuning of other catalytic systems that invoke this non-covalent interaction as an explanation for selectivity.



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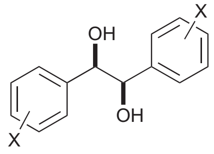

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Figure 1.

Keywords: Lewis acids; Diels–Alder reaction; π–π interactions.

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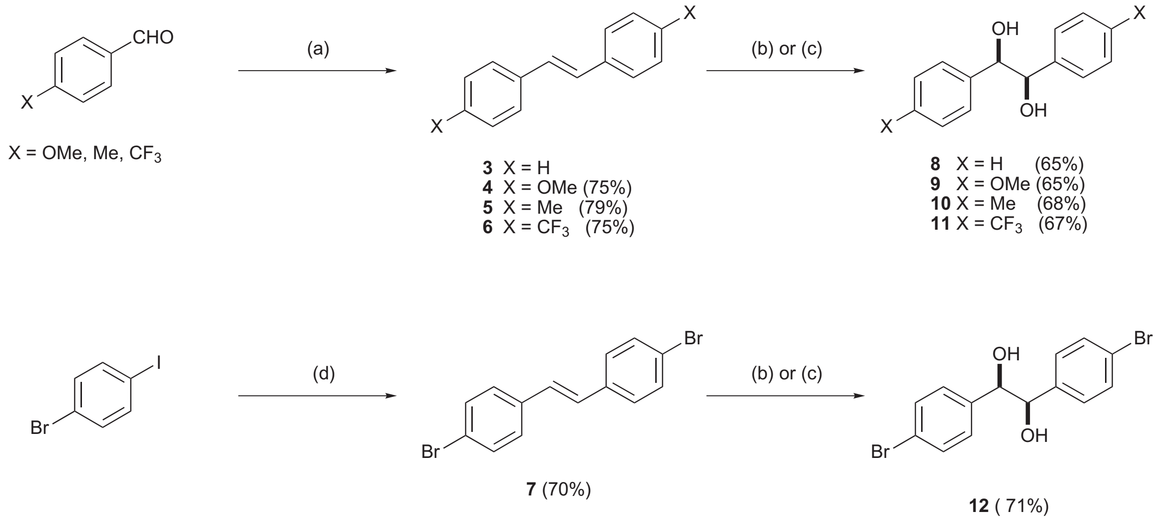
doi:10.1016/j.tetlet.2005.01.086



Scheme 1. Reagents and conditions: (a) $TiCl_4$, Zn, THF, Δ; (b) AD-mix-β, ^{t}BuOH, H_2O, $MeSO_2NH_2$, 0 °C, 48 h; (c) quinuclidine, $K_3Fe(CN)_6$, K_2CO_3, $K_2[Os(OH)_4]$, $MeSO_2NH_2$, ^{t}BuOH, H_2O, rt, 48 h; (d) $CH_2CHC_6H_4Br$, $Pd(OAc)_2$, PPh_3, NEt_3, CH_3CN, rt, 24 h.

Both routes adopted for the synthesis of our ligands **8**–**12** utilised the Sharpless asymmetric dihydroxylation as a method for introduction of asymmetry. The (*E*)-stilbenes **4**–**6** were prepared via a McMurray type reaction of the substituted aromatic aldehydes in the presence of titanium tetrachloride and zinc as reported by Dyker and Kellner,[7] and the bromo-substituted stilbene **7** was prepared via a standard Heck reaction between 4-bromoiodobenzene and 4-bromostyrene[8] (Scheme 1). The substituted stilbenes **4**–**7** along with the commercially available unsubstituted parent system **3** were then dihydroxylated under standard Sharpless conditions using $(DHQD)_2PHAL$ as the source of asymmetry followed by recrystallisation of the product to give the corresponding (*R*,*R*)-diols **8**–**12** in good yields. The enantiomeric excess of each ligand was confirmed to be >98% by preparation of the racemic diols (±)-**8**–**12** according to the method of Warren and co-workers[9] followed by ^1H NMR experiments in the presence of the chiral shift reagent $Eu(hfc)_3$; in each case the proton α to the hydroxyl group providing a handle with which to determine the ee.[10] Having prepared our family of ligands we then sort to investigate their properties in the Diels–Alder reaction, a fundamental bench-mark process for testing the effectiveness of new potential ligands in Lewis acid catalysis.

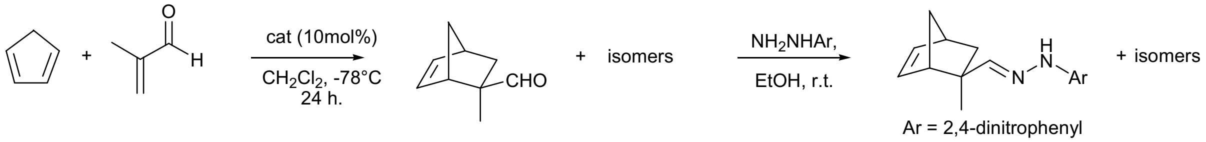
It has been well established that the method by which the active catalytic species is prepared for the Lewis acid catalysed Diels–Alder reaction can greatly influence the enantiocontrol observed. For example, it has been reported previously that no asymmetric induction was observed for the use of one of our proposed ligands **8** in the reaction between methacrolein and cyclopentadiene.[11] However, we found that consistent and repeatable results were obtained by preparation of the active catalytic species as described by Jones and Guzel.[6]

The results obtained for our catalytic studies of the reaction between cyclopentadiene and methacrolein are outlined in Table 1. In each case the (*R*,*R*) catalyst was employed within the reaction and the (*S*)-enantiomer of the *exo*-adduct was formed preferentially as determined by HPLC analysis on the 2,4-dinitrophenylhydrazine derivative.[12] Each ligand was complexed with monobromoborane or dimethylaluminium chloride as the Lewis acidic metal and we were delighted to see that in both series of Lewis acids used a clear trend was apparent indicating that it was indeed possible to modulate the proposed interaction.

With monobromoborane as the Lewis acid, when the ligand contained an electron-deficient aromatic ring **11** and **12**, a low ee of just 9% was observed for the Diels–Alder adduct (entries 1 and 2). However, as the electron density associated with the aromatic ring was increased there was a clear increase in the ee of the product, with the unsubstituted aromatic furnishing the product in 24% ee (entry 3), rising to 28% ee for the methyl substituted ligand (entry 4) and 30% for the anisole derived ligand (entry 5). A similar trend was also observed with this family of ligands when dimethylaluminium chloride was used within the reaction, with the ee of the *exo*-Diels–Alder adduct increasing by 19% from electron-deficient (11%) (entry 6) to electron-rich (30%) (entry 10). Both these series suggest that in the design of a catalytic system that invokes a face–face π–π interaction within the diastereofacial discrimination of an electron-deficient alkene then increasing the electron density on the aromatic ring leads to higher asymmetric induction being observed within the transformation, providing a more effective catalyst.

A possible transition state assembly consistent with these findings is depicted in Figure 2. It has been proposed by Corey and Loh that α-substituted dienophiles prefer to adopt an *s-cis* conformation due to steric reasons, with the metal bound *trans*- to the substituents in α,β-unsaturated aldehydes.[13] Although this is not the only possible conformation that could be adopted by the system, the effect observed suggests that the alkene is closely associated with the aromatic ring of

Table 1. Lewis acid catalysed Diels–Alder reaction between cyclopentadiene and methacrolein moderated by stilbene diols **8**–**12**



Entry	Ligand	Lewis acid	*Endo*:*Exo* ratio[a]	% Ee *exo*-adduct[b]	% Yield[c]
1	**11**	BH_2Br	25:75	9 (*S*)	68
2	**12**	BH_2Br	20:80	9 (*S*)	68
3	**8**	BH_2Br	10:90	24 (*S*)	70
4	**10**	BH_2Br	19:81	28 (*S*)	73
5	**9**	BH_2Br	7:93	30 (*S*)	79
6	**11**	$AlMe_2Cl$	29:71	11 (*S*)	69
7	**12**	$AlMe_2Cl$	11:89	14 (*S*)	64
8	**8**	$AlMe_2Cl$	10:90	26 (*S*)	73
9	**10**	$AlMe_2Cl$	19:81	27 (*S*)	70
10	**9**	$AlMe_2Cl$	15:85	30 (*S*)	81

[a] Determined by ^1H NMR on the crude reaction mixtures.

[b] Determined by HPLC on the 2,4-dinitrophenylhydrazine derivative.[12]

[c] Isolated yield of *endo*- and *exo*-isomers.

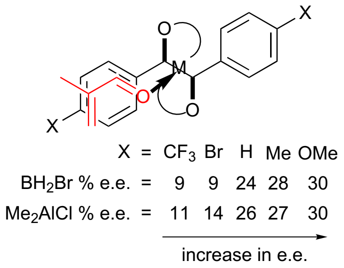


Figure 2.

the (*R*,*R*)-ligand with the diene approaching the re-face of the dienophile.

In summary, we present evidence that it is possible to modulate face–face π–π interactions between aromatic rings and electron-deficient alkenes within a Lewis acid catalysed reaction resulting in a notable influence in the ee observed. From the results presented, it appears that electron-rich aromatics increase the proposed non-covalent interaction and can increase the ee observed in the Diels–Alder reaction between cyclopentadiene and methacrolein up to 21%. We are currently investigating whether this is a general phenomenon that can be applied to a variety of known catalyst architectures where higher levels of asymmetric induction have been reported and thus provide a general point of consideration when designing potential catalyst systems. Our findings in these and related areas will be reported shortly.

Acknowledgements

The authors wish to express their gratitude to the EPSRC for a studentship GR/R41750/01 (L.D.H.) and an advanced research fellowship GR/T04113/01 (N.C.O.T.), the Royal Society and the Nuffield Foundation for equipment grants and the EPSRC HRMS service at Swansea for analyses.

References and notes

1. (a) *Asymmetric Catalysis, Rodd's Chemistry of Carbon Compounds*; Sainsbury, M., Ed.; Elsevier: Amsterdam, 2001; Vol. 5; (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 2nd ed.; Wiley-VCH: New York, 2000; (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vols. I–III; (d) Williams, J. R. *Catalysis in Asymmetric Synthesis*; Academic: Sheffield, 1999.
2. For some recent examples see: (a) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992; (b) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 5950; (c) Viton, F.; Bernardinelli, G.; Kundig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968; (d) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808; (e) Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882.
3. (a) Jones, G. B. *Tetrahedron* **2001**, *57*, 7999; (b) Jones, G. B.; Chapman, B. J. *Synlett* **1995**, 475.
4. For some examples of invoked face–face π–π interactions in catalytic asymmetric synthesis see: (a) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412; (b) Corey, E. J.; Loh, T.-P.; Roper, T. D.; Azimioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290.
5. (a) Harris, L. D.; Platts, J. A.; Tomkinson, N. C. O. *Org. Biomol. Chem.* **2003**, *1*, 457; (b) Coogan, M. P.; Haigh, R.; Hall, A.; Harris, L. D.; Hibbs, D. E.; Jenkins, R. L.; Jones, C. L.; Tomkinson, N. C. O. *Tetrahedron* **2003**, *59*, 7389.
6. Jones, G. B.; Guzel, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2023.
7. Dyker, G.; Kellner, A. *Eur. J. Org. Chem.* **1998**, *1*, 149.
8. Sengupta, S.; Sadhukhan, S. K.; Singh, R. S.; Pal, N. *Tetrahedron Lett.* **2002**, *43*, 1117.
9. Eames, J.; Mitchell, H. J.; Nelson, A.; O'Brien, P.; Warren, S.; Wyatt, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1095.
10. All compounds prepared were characterised by mp, $[\alpha]_D$, ^1H NMR, ^{13}C NMR, IR, MS and HRMS.
11. Rebiere, F.; Riant, O.; Kagan, H. B. *Tetrahedron: Asymmetry* **1990**, *1*, 199.
12. Harris, L. D.; Hall, A.; Jenkins, R. L.; Jones, C. L.; Tomkinson, N. C. O. *Tetrahedron Lett.* **2003**, *44*, 111.
13. Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966.