Enhanced stereocontrol in Diels–Alder reactions of chiral dienols†

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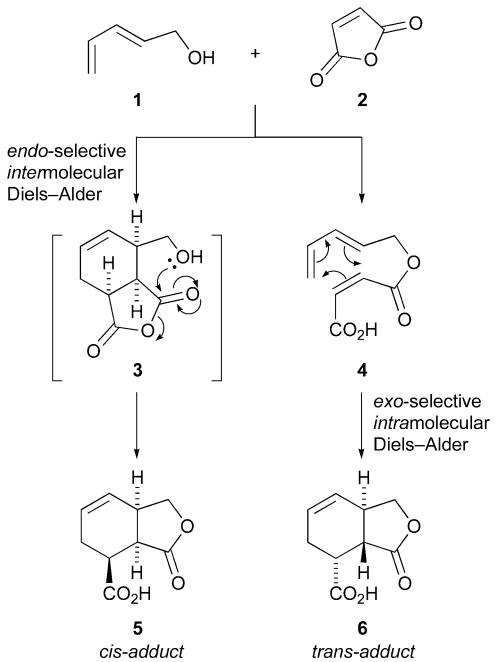
This combined experimental–computational investigation demonstrates that the presence of a removable bromine substituent on a diene leads to complete π-diastereofacial and *endo*/*exo* stereoselection in both intermolecular and intramolecular Diels–Alder reactions. The influence of the bromine upon stereoselectivity is dramatic: the cycloaddition of nonbrominated precursor **18*E***, for example, gives four diastereomeric products in a 55:13:16:16 ratio; the bromine-containing analogue gives one stereoisomer within the limits of detection. The examination of B3LYP/6-31+G(d) transition structures allows an interpretation of these experimental findings. A method for the completely stereoselective synthesis of complimentary diastereomeric products (**30*Z*** and **31*Z***) from the same simple starting materials (**28** and **2**) is reported. Discrepancies between calculation and experiment in an earlier investigation into the Diels–Alder reaction are explained.

Introduction

The Diels–Alder reaction remains as one of the most important chemical reactions.[1] Almost 80 years after the landmark report by Diels and Alder,[2] valuable new synthetic applications and important theoretical interpretations of the [4 + 2] cycloaddition continue to appear. The synthetic power and generality of the reaction are the basis for its longevity. A Diels–Alder cycloaddition involves the heat-promoted union of a diene and a dienophile and with it, the formation of a new six-membered ring, two new covalent bonds and up to four new stereocentres. The intramolecular Diels–Alder (IMDA) reaction creates two new rings.[3] The Diels–Alder reaction is by no means fully understood and fully optimised, however, since it commonly delivers more than one stereoisomeric product and, furthermore, methods to effect a switch in stereoselectivity are rare.[4] Stereocontrol is complicated by *endo*/*exo*-selectivity (*cis*/*trans*-)[5] and π-facial selectivity attributes, allowing four possible stereoisomeric cycloadducts for a concerted process with unsymmetrically substituted precursors. Herein we demonstrate methods to achieve *complete* stereocontrol in cycloaddition reactions. Moreover, we show that the same diene and dienophile precursors can be employed for the formation of different stereoisomeric products.

We recently showed that reactions between conjugated dienols **1** and maleic anhydride **2** (Scheme 1) provide either *cis*-fused **5** or *trans*-fused **6** bicyclic products as major products, depending upon how the reaction is carried out.[6] When mixtures of the two reactants are heated, an *endo*-selective intermolecular Diels–Alder reaction gives putative hydroxy anhydride intermediate **3**, which rapidly undergoes intramolecular esterification to furnish *cis*-fused lactone acids **5**. Alternatively, the pre-formed maleate half-ester derivative **4** affords *trans*-fused lactone acids **6** in high selectivity by way of an *exo*-selective[5] IMDA reaction.



Scheme 1

In a separate study, we demonstrated the stereocontrolling influence of a removable bromine substituent upon the outcome of IMDA reactions of pentadienyl acrylates (Scheme 2; Table 1, entries 1 and 2).[7,8] Thus, compared with the nonbrominated precursor **7**, the C3–bromine substituent in precursor **8** induces a dramatic improvement in both *trans*/*cis*[5] stereoselectivity and π-diastereofacial selectivity.[9] Detailed computational investigations identified destabilising torsional and steric strains operating in the transition structures (TSs) leading to cycloadducts **14**, **15** and **16**. The TS leading to the major cycloadduct **13** lacked such unfavourable interactions.

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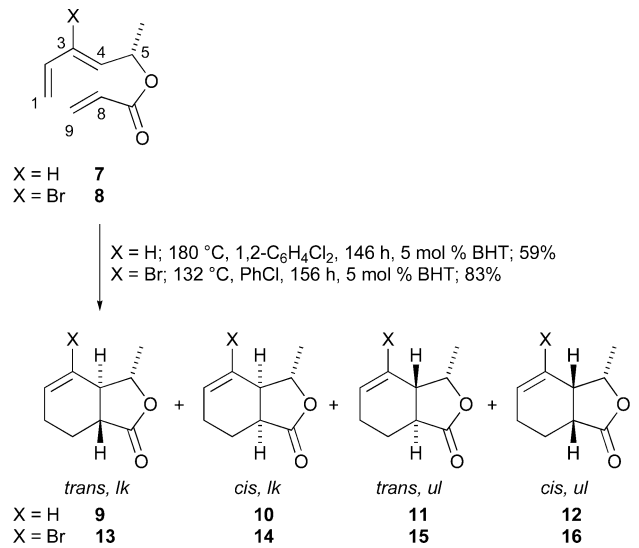
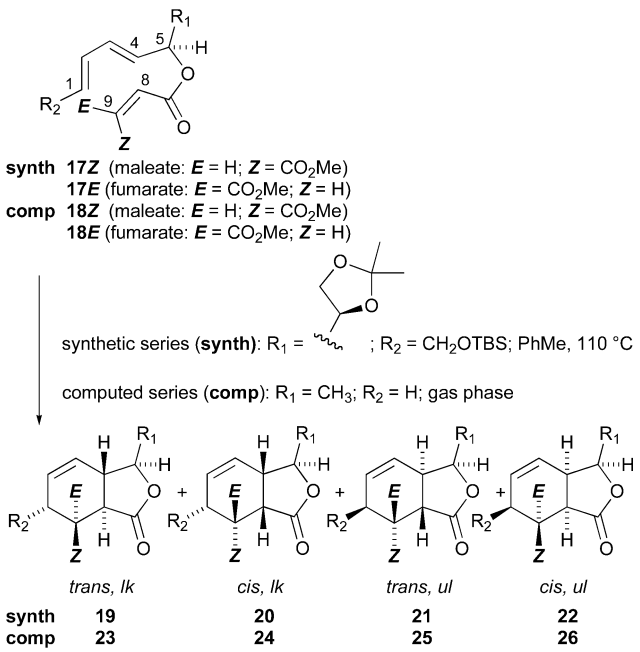
Table 1 Synthetic and computed[a] product ratios for Schemes 2 and 3

Entry	Triene	Time (h)	Yield (%)	Product ratio *trans*,*lk*:*cis*,*lk*:*trans*,*ul*:*cis*,*ul*	
1	**7**	146	59	**9**:**10**:**11**:**12**	
				Synthetic	28:30:12:30
				Computed	45:25:8:22
2	**8**	156	83	**13**:**14**:**15**:**16**	
				Synthetic	81:19:0:0
				Computed	91:8:0:1
3	**17*Z***	19	100	**19*Z***:**20*Z***:**21*Z***:**22*Z***	
				Synthetic	86:14:0:0
			18*Z*	**23*Z***:**24*Z***:**25*Z***:**26*Z***	
				Computed	85:2:12:1
4	**17*E***	39	90	**19*E***:**20*E***:**21*E***:**22*E***	
				Synthetic	72:17:0:11
			18*E*	**23*E***:**24*E***:**25*E***:**26*E***	
				Computed	62:14:10:14

[a] Populations at B3LYP/6-31+G(d) level.



Scheme 2



Scheme 3

Another investigation focused on the stereochemical outcome of IMDA reactions of C9–CO_2Me substituted trienes carrying a C5–dioxolanyl substituent and a C1–CH_2OTBS group (Scheme 3; Table 1, entries 3 and 4).[10] The C9–*Z*-CO_2Me substrate, maleate **17*Z***, gave two of the four possible cycloadducts, namely *trans*,*lk*-**19*Z*** and *cis*,*lk*-**20*Z*** (86:14, respectively) in quantitative yield. The C9–*E*-CO_2Me substrate, fumarate **17*E***, gave three of the four possible adducts, *trans*,*lk*-**19*E***, *cis*,*lk*-**20*E***, and *cis*,*ul*-**22*E*** in a ratio of 72:17:11, respectively, in 90% yield. DFT calculations carried out on truncated maleate and fumarate model systems lacking the C1 substituent, and with the C5–dioxolane group replaced by a methyl group, correctly predicted the *trans*,*lk*-adduct **23** as the major product with both *E*- and *Z*-dienophile geometries.[10] Nevertheless, significant differences exist between experiment and theory in the distribution of the minor cycloadducts. In the maleate case, *cis*,*lk*-**20*Z*** is the only minor product observed in appreciable amounts from experiments, whereas theory predicts that *trans*,*ul*-**21*Z*** should be the second most prevalent product. In the fumarate case, theory predicts a roughly even distribution of the three minor stereoisomeric cycloadducts, whereas experiments furnish only two. This unsatisfactory correlation could reflect unmodelled influences stemming from differences between the experimental and computed structures, or discrepancies in the theory (*i.e.* neglect of solvent effects).

The goals of the research described in this paper are as follows (Fig. 1): (1) to identify the origin of the disagreement between theory and experiment, summarised in Scheme 3, by conducting IMDA reactions of maleate **18*Z*** and fumarate **18*E***; (2) to enhance the stereoselectivity of maleate and fumarate IMDA reactions through incorporation of a C3–Br substituent (*i.e.* **18*Z*** *vs.* **27*Z***, **18*E*** *vs.* **27*E***, *cf.* acrylates, Scheme 2); (3) to investigate the influence of the bromine substituent upon the π-diastereofacial selectivity of intermolecular Diels–Alder reactions (*i.e.* **28** *vs.* **29**). Herein we show that both intermolecular and intramolecular cycloaddition reactions are rendered completely stereoselective by virtue of a removable bromine substituent.

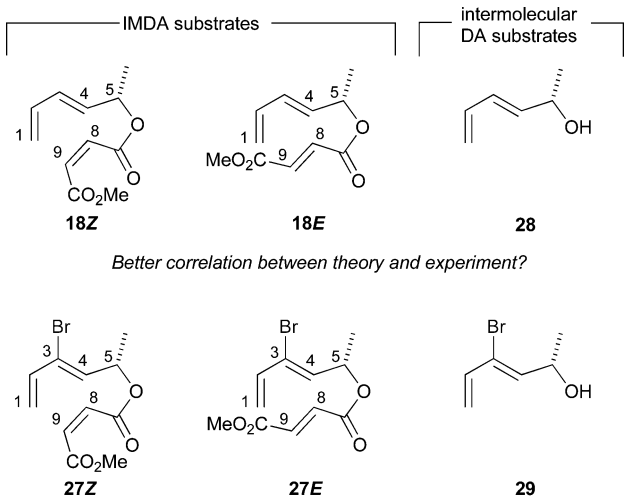
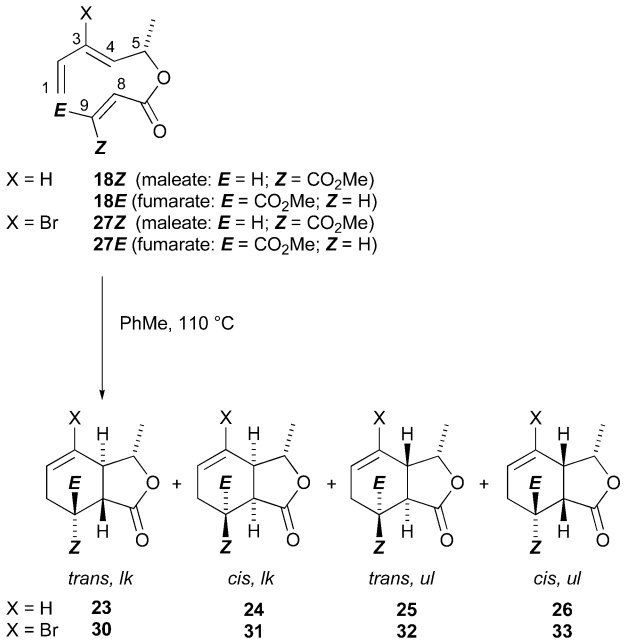


Fig. 1



Scheme 4

Results and discussion

To shed light on the discrepancy between theory and experiment, the computed "model" trienes, maleate **18*Z*** and fumarate **18*E*** were prepared.[11] Kinetically controlled[12] intramolecular Diels–Alder reactions of the two triene precursors were carried out in dilute solutions of refluxing toluene in the presence of a small amount of the antioxidant 2,6-di-*tert*-butyl-4-methyl phenol (BHT) (Scheme 4;‡ Table 2, entries 1 and 2). Four cycloadducts were formed in both cases. The cycloadducts were separated by HPLC and the relative stereochemistry of each adduct was determined by NMR experiments.[11] These IMDA reactions were faster than those of the corresponding C5-unsubstituted precursors,[13] presumably due to the reactive rotamer effect.[14]

The IMDA reaction of maleate **18*Z*** exhibits strong *trans*-selectivity (87:13, *trans*:*cis*) and *like* π-diastereofacial preference (77:23, *like*:*unlike*). Fumarate **18*E*** also underwent a *trans*-selective (71:29, *trans*:*cis*) IMDA reaction with a *like* π-diastereofacial preference (68:32, *like*:*unlike*). The isolation of the *trans*,*like*-cycloadduct as the major product from both reactions is consistent with other reports with C5-substituted pentadienyl maleates and fumarates.[10,15,16] Arseniyadis and co-workers employed the IMDA reaction of the C5–Et counterpart of fumarate **18*E*** as a key step in their synthesis of A-seco mevinic acid.[15] Compared to the C5–Me triene **18*E*** in the present study, the C5–Et triene gave slightly higher *trans*-selectivity and slightly higher *like* π-diastereofacial selectivity (*trans*,*lk*:*cis*,*lk*:*trans*,*ul*:*cis*,*ul* = 74:4:7:15 [Et][15] *vs*. 55:13:16:16 [Me]). Evidently, the smaller methyl group has a slightly weaker stereocontrolling influence upon the IMDA reaction.

The identities of the four products from the IMDA reactions of **18*Z*** and **18*E*** were correctly predicted by theory[11] with an impressive level of accuracy. Indeed, the experimental ratios of the three minor cycloadducts are in close agreement with calculated DFT Boltzmann distributions. The discrepancies found between

‡ The synthetic series depicted in Scheme 4 is enantiomeric to that shown in Scheme 3.

Table 2 Synthetic and computed[a] product ratios for Scheme 4

Entry	Triene	Time (h)	Yield (%)	Product ratio *trans*,*lk*:*cis*,*lk*:*trans*,*ul*:*cis*,*ul*	
1	**18*Z***	3	94	**23*Z*:24*Z*:25*Z*:26*Z***	
				Synthetic[b]	68:9[c]:19:4
				Computed[d]	85:2:12:1
2	**18*E***	57	71	**23*E*:24*E*:25*E*:26*E***	
				Synthetic[b]	55:13:16:16
				Computed[d]	62:14:10:14
3	**27*Z***	0.6	84	**30*Z*:31*Z*:32*Z*:33*Z***	
				Synthetic	>98:0:0:0
				Computed	99:1:0:0
4	**27*E***	10	77	**30*E*:31*E*:32*E*:33*E***	
				Synthetic	>98:0:0:0
				Computed	96:4:0:0

[a] Populations at B3LYP/6-31+G(d) level. [b] Experimental mean of GC analysis of crude reaction mixture, ^{1}H NMR analysis of the crude reaction mixture and the isolated yields after purification. The difference between the three sets of ratios was at most ±3%. [c] Previously reported by Tripathy, Franck and Onan.[9b] [d] Refer to Scheme 3; Table 1, entries 3 and 4.

theory and experiment in our earlier investigation (Scheme 2),[10] therefore, can be ascribed to unmodelled influences of the C1 and C5 substituents in trienes **17*Z*** and **17*E***. Further evidence for this conclusion comes in the form of computed product ratios from the IMDA reaction of C1–CH_2OTMS compound **34**, which can be considered a half-way point between fumarates **17*E*** and **18*E***. Theory predicts a product ratio *trans*,*lk*:*cis*,*lk*:*trans*,*ul*:*cis*,*ul* = 55:19:7:20 for **34**, with less *trans*,*ul*-adduct and more of the two *cis*-products relative to **18*E*** (Fig. 2). This result is consistent with the experimental finding with fumarate **17*E***, which carries the C1–CH_2OTBS substituent.

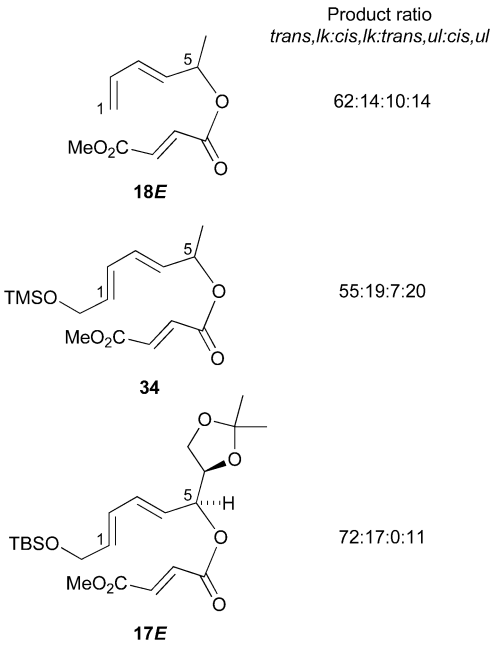


Fig. 2

The order of product abundance in the IMDA reaction of maleate **18*Z***, namely *trans*,*lk* > *trans*,*ul* > *cis*,*lk* > *cis*,*ul*, can be rationalised by consideration of interactions in the C3–C5 region of the TSs (Fig. 3). Two destabilising interactions can be identified, namely 1,3-allylic strain between C3–H and C5–CH_3 in the two *unlike* TSs, and an eclipsed C4–C5 bond in the two *cis*-TSs. These two interactions are absent in the *trans*,*lk*-TS, which leads to the major product from the reaction. They are both present in the *cis*,*ul*-TS, which leads to the least abundant product from the reaction. Of the two products formed in intermediate amount, the *trans*,*ul* cycloadduct is more abundant than the *cis*,*lk* product, which presumably indicates that the eclipsing interaction is more costly than allylic strain. It is noteworthy that the C5–*des*-methyl analogue of **18*Z*** undergoes a much less *trans*-selective reaction (58:42, *trans*:*cis*).[13] The enhanced *trans*-selectivity in the IMDA reaction of **18*Z*** can be ascribed to the destabilising interactions in TSs leading to the *cis*-isomers.

With the fumarate precursor **18*E***, both experiments and calculations show that the *trans*,*lk*-cycloadduct is the dominant product, with the remaining three isomers being formed in roughly equal amounts. The TSs leading to the four adducts from triene **18*E*** are depicted in the ESI.† The destabilising interactions are the same as those identified in the *Z*-TSs. In the case of the *E*-triene, there are negligible differences in the energies of the TSs leading

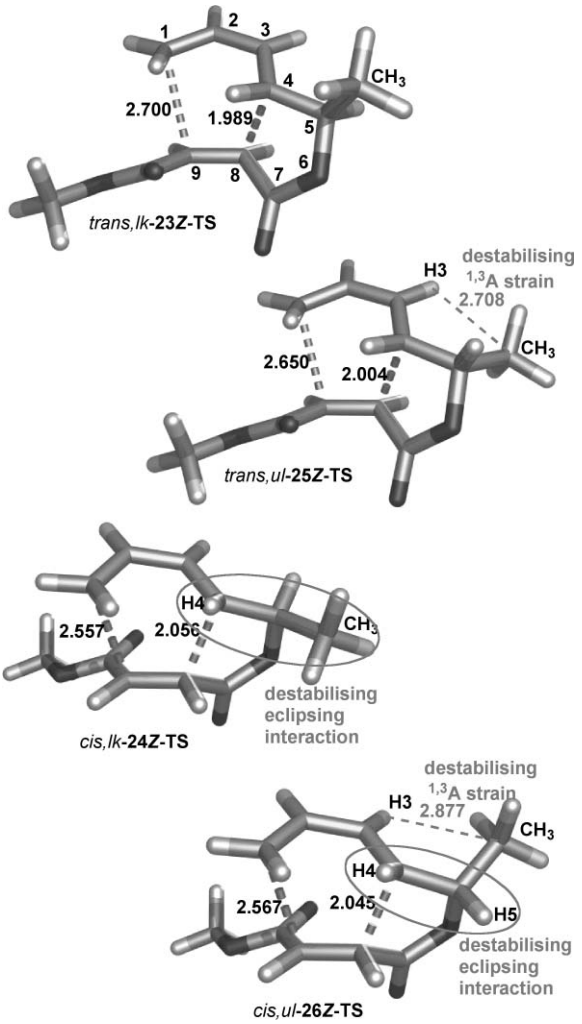


Fig. 3 IMDA TSs from **18*Z*** with destabilising interactions identified. Distances between interacting atoms, and forming bond lengths are given in Angstroms (Å). The enantiomeric *lk*-TSs are depicted for ease of comparison.

to the three minor products. Evidently, allylic strain and eclipsing interactions are finely balanced in this case.

Whilst these results confirmed the validity of the theoretical model, we were keen to develop a way to carry out these reactions in a more synthetically useful (*i.e.* a more stereoselective) manner. Borrowing from our earlier studies with pentadienyl acrylates (Scheme 2),[7] the C3–Br analogues of **18*Z*** and **18*E***, **27*Z*** and **27*E*** respectively, were analysed computationally. Very high levels of stereoselectivity in favour of the *trans*,*lk*-adduct **30** were predicted in each case. Maleate **27*Z*** and fumarate **27*E*** were prepared by esterification of dienol **29**.[11] Dienol **29**, in turn, was readily prepared by selective Stille monocoupling of the 1,1-dibromoalkane with vinyltributylstannane.[7,17] To our delight, when exposed to the standard IMDA reaction conditions, *trans*,*lk*-stereoisomer **30** was generated from these reactions with complete stereoselectivity, within the limits of detection (Table 2, entries 3 and 4). These bromine-containing cycloadducts were reductively debrominated under radical conditions (Bu_3SnH, AIBN) to give samples which were identical to those obtained from **18*Z*** and **18*E***.[11]

The most obvious effect of the bromine in these TSs (Fig. 4)[18] is to enhance the magnitude of the destabilising ^{1,3}A-strain between the C3-substituent and the C5–methyl group. The *unlike*-TSs become prohibitively high in energy relative to the *like*-TSs and are, therefore, not populated to any significant extent. The H4 $\cdots$ CH_3 eclipsing interaction still destabilises the two *cis*-TSs. Indeed, the presence of the bromine has surprisingly little effect on the overall geometries of the TSs.

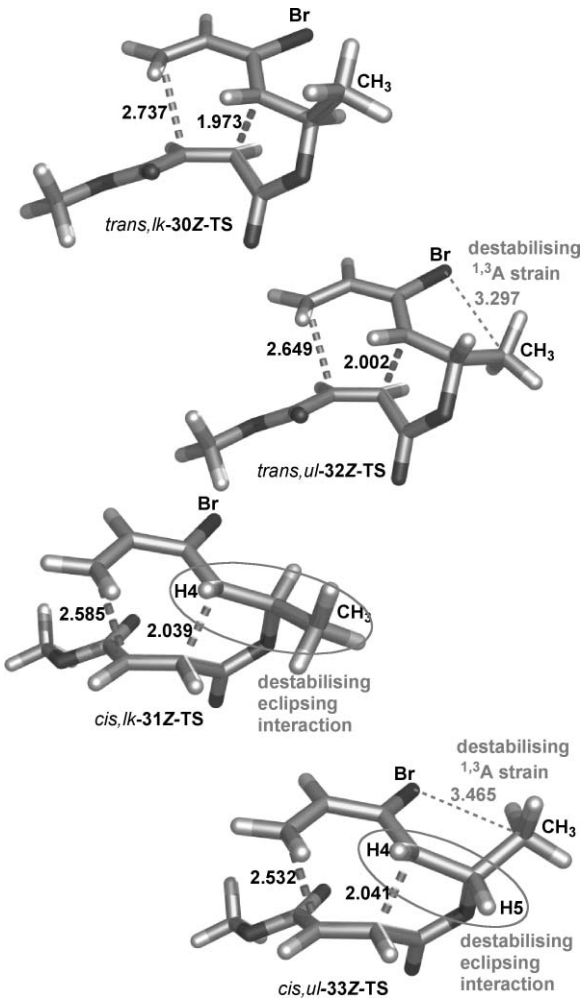
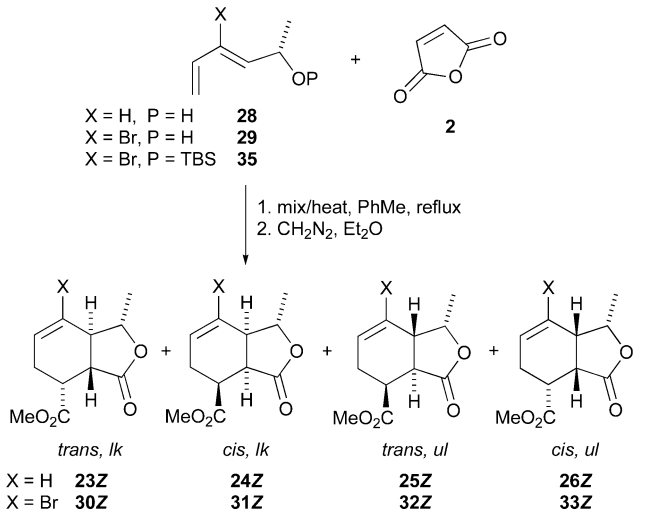


Fig. 4 IMDA TSs from **27*Z*** with destabilising interactions identified. Distances between interacting atoms, and forming bond lengths are given in Angstroms (Å). The enantiomeric *lk*-TSs are depicted for ease of comparison.

The dramatic improvement in stereoselectivity in these IMDA reactions brought about by the *cis*-C3–Br substituent led us to investigate the possibility of stereocontrol in intermolecular Diels–Alder reactions. The reaction between maleic anhydride and chiral dienol **28** (Scheme 5) as reported by Franck and co-workers[9b] gave exclusively *cis*-adducts, with modest π-diastereofacial selectivity (*cis*,*like*-**24*Z***:*cis*,*unlike*-**26*Z*** = 73:27; Table 3, entry 1). In our hands, this reaction furnishes a mixture of four stereoisomeric cycloadducts (Table 3, entry 2). The *cis*-fused isomers, resulting from the intermolecular Diels–Alder pathway, are the dominant products but the *trans*-fused bicycles, accounting for about 10% of the product mixture, result from the competing esterification–IMDA pathway (Scheme 1).[6] Nevertheless, we observe a level of π-diastereofacial selectivity between the two *cis*-isomers that is consistent with the earlier report.



Scheme 5

Chiral bromodienol **29** reacts with maleic anhydride to give two of the four possible cycloadducts, *cis*,*like*-**31*Z*** and *trans*,*like*-**30*Z***, in an 87:13 ratio. Thus, complete π-diastereofacial selectivity is witnessed in this cycloaddition. That the minor, *trans*-isomer is the result of the esterification–IMDA pathway (Scheme 1)[6] is demonstrated by the reaction of the TBS ether derivative **35**. This protected alcohol undergoes intermolecular Diels–Alder reaction to give a single isomeric product, within the limits of detection. This product furnishes material identical in all respects to *cis*,*like*-adduct **24*Z***, after silyl ether hydrolysis with concomitant lactonisation, methyl ester formation with diazomethane, and reductive debromination.[11] The very high level of *like* π-diastereofacial

Table 3 Experimental product ratios for Scheme 5

Entry	Diene	Time (h)	Yield (%)	Synthetic product ratio[a] *trans*,*lk*:*cis*,*lk*:*trans*,*ul*:*cis*,*ul*	
1[b]	**28**	72	83	**23*Z*:24*Z*:25*Z*:26*Z***	0:73:0:27
2[c]	**28**	2	71	**23*Z*:24*Z*:25*Z*:26*Z***	10:57:1:32
3	**29**	5.5	58	**30*Z*:31*Z*:32*Z*:33*Z***	13:87:0:0
4	**35**	74	58	**30*E*:31*Z*:32*Z*:33*Z***	0:>98:0:0

[a] Experimental mean of GC analysis of crude reaction mixture, ^{1}H NMR analysis of the crude reaction mixture and the isolated yields after purification. The difference between the three sets of ratios was at most ±3%. [b] As reported by Franck *et al*. Reaction carried out at room temperature for 3 days.[9b] [c] Present study.

stereoselectivity witnessed here with a *removable* bromine substituent is comparable to that seen in Prein's investigations with methyl-substituted dienes.[9c]

In summary, this work confirms the validity of the DFT model for pentadienyl maleate and fumarate IMDA reactions. The stereodirecting ability of a *cis*-bromine substituent in both intramolecular and intermolecular cycloaddition reactions of chiral dienols has been demonstrated. Thus, moderately stereoselective cycloaddition reactions are rendered *completely* stereoselective simply by the replacement of a hydrogen in the precursor by a bromine. Taken together with the ability to select either *cis* or *trans*-bicyclic lactone acids from simple dienols and maleic anhydride, operationally simple stereocontrolled approaches to enantiomerically pure bicyclic building blocks with complementary stereochemistries are now in hand.

Acknowledgements

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