Sulfinyl *versus* allylic stereocontrol in Diels–Alder cycloadditions of hydroxy 2-sulfinyl butadienes

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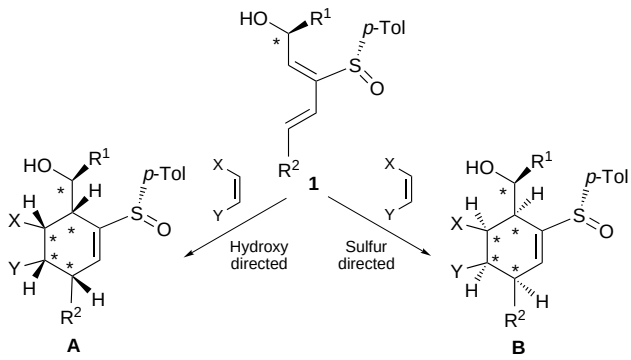
Enantiopure hydroxy 2-sulfinyl butadienes undergo a highly face selective Diels–Alder cycloaddition with *N*-phenylmaleimide and phenyltriazolinedione controlled by the chiral sulfur atom; the related enantiopure sulfonyl dienes display complimentary π-facial selectivity.

The asymmetric Diels–Alder reaction is a fundamental process in contemporary organic synthesis since up to four enantio- and diastereo-merically pure stereogenic centres are created in a single step.[1] Within this field, the use of enantiopure dienes is comparatively less developed and the clarification of issues concerning stereocontrol for these protocols is a current challenge.[2] In most studies involving enantiopure dienes, the chiral auxiliary is only utilized to induce asymmetry in the Diels–Alder process, and further asymmetric transformations are not readily envisaged. In contrast, simple 2-sulfinyl dienes are especially appealing substrates since, after a highly selective Diels–Alder cycloaddition,[3,4] a vinyl sulfoxide, which may undergo subsequent chirality transfer operations,[5] is generated. Here we report the first examples of highly diastereoselective sulfur directed Diels–Alder cycloadditions of enantiopure hydroxy 2-sulfinyl dienes which display a non-reinforcing relationship of stereocontrolling elements.[6]

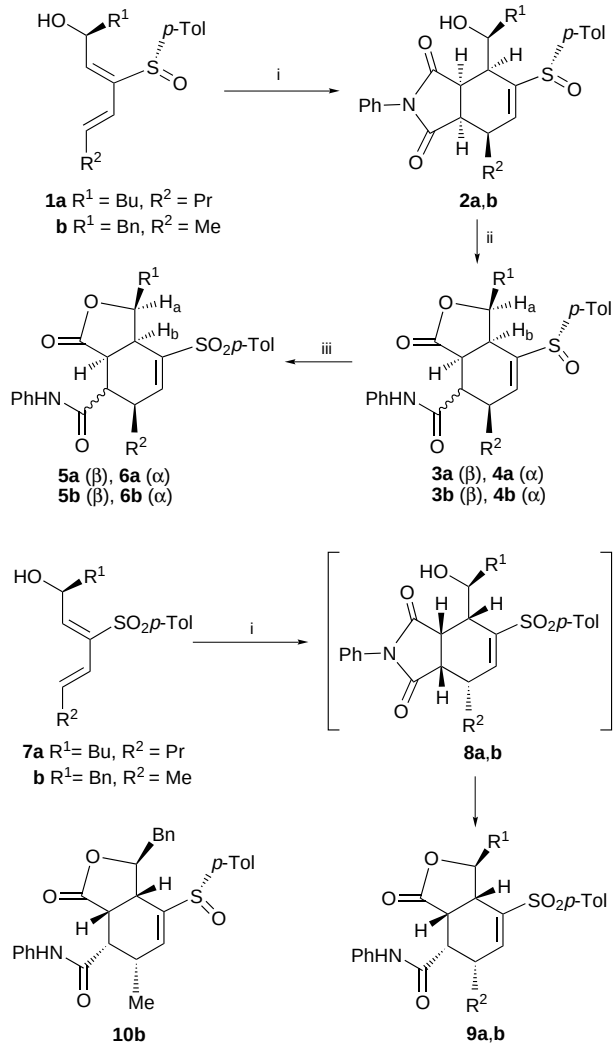
We have recently described a short and completely stereocontrolled route to enantiopure dienes **1** (Scheme 1).[7] At the onset of this research we envisioned that dienes **1** would provide a unique opportunity to assess the relative π-facial stereodirecting abilities of two powerful elements of stereocontrol in a Diels–Alder process,[4,8,9] and lead to enantiopure cycloadducts **A** or **B**. It should be noted that for dienes **1**, the allylic hydroxy-bearing stereocentre and the sulfinyl auxiliary are expected to direct the approach of the dienophile with maximum efficiency due to mutual 1,3-allylic strain,[10] and to *opposite* faces of the diene moiety.[11]

To gain insight into the stereochemical outcome of a basic intermolecular Diels–Alder process, we selected *N*-phenylmaleimide (NPM) and diene **1a**[7] for our initial studies, and the results obtained are shown in Scheme 2. In this fashion, cycloadduct **2a** was produced as a single isomer (300 MHz ^{1}H NMR analysis of the crude reaction mixture) and isolated in good yield after recrystallization. Treatment of a solution of **2a** with silica gel resulted in spontaneous lactonization and partial epimerization to produce a separable 25 : 75 mixture of amides **3a** (β-amide) and **4a** (α-amide) which displayed significant NOE enhancements between H_a and H_b (11.5 and 10.4% respectively).‡

To extend the scope of our methodology, and seeking additional support for the stereochemical assignments, we prepared enantiopure hydroxy sulfonyl diene **7a** from sulfoxide **1a** by a simple oxidation with magnesium monoperoxyphthalate (MMPP).[12] Diene **7a** underwent smooth cycloaddition



Scheme 1



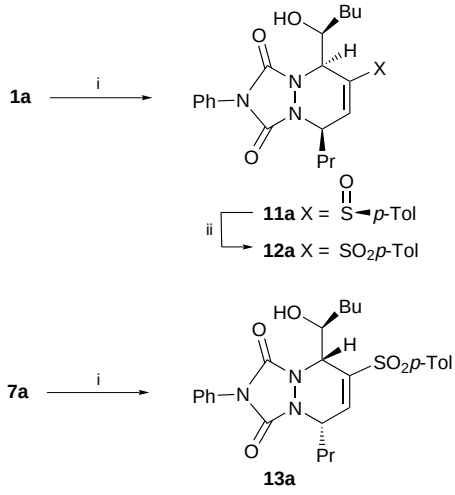
Scheme 2 *Reagents and conditions*: i, NPM (1–1.5 equiv.), toluene, room temp., 2–5 d, 70% for **2a**, 69% for **2b**, 86% for **9a** and 82% for **9b**; ii, SiO_2, CH_2Cl_2, room temp., 4 d, 91% for **3a**/**4a** and 95% for **4b**; iii, MCPBA, (1.5 equiv.), CH_2Cl_2, −78 °C to room temp., 2–5 h, 80% for **5a**, 83% for **6a** and 75% for **6b**

with NPM affording the very unstable cycloadduct **8a**§ as a single isomer which lactonized spontaneously in the reaction medium to give **9a**. This result shows that the allylic hydroxy group is a powerful element of stereocontrol in these cases.[9] The diastereomeric relationship found between amides **9a** and **5a**/**6a** (prepared by oxidation of pure samples of **3a** and **4a**), along with the NOE enhancements observed for **3a** and **4a**, conclusively establish that the π-facial selectivity of the cycloaddition between **1a** and NPM is exclusively controlled by the chiral sulfur atom.

Encouraged by these results we sought to test the generality of this sulfoxide directed cycloaddition by studying the reaction of diene **1b**,[7] with a bulkier R^1 substituent, and NPM which afforded a 95 : 5 mixture of cycloadduct **2b** and sulfinyl amide **10b**,¶ respectively, as judged by ^{1}H NMR analysis of the crude reaction mixture. Treatment of **2b**, isolated by recrystallization, with SiO_2 resulted in smooth cyclization and epimerization affording amide **4b** along with trace amounts of **3b**. Oxidation of **4b** afforded sulfone **6b** while the cycloaddition between sulfonyl diene **7b** and NPM produced diastereomeric sulfonyl amide **9b**. We believe that lactones **3a** and **3b** undergo a facile epimerization at the amide-bearing carbon due to the location of the R^1 substituent in the sterically demanding concave region of the molecule, while for lactones **9**, R^1 is placed in the convex face. The enhanced degree of epimerization found for R^1 = Bn *versus* Bu is likely to be related to the different steric requirements of these substituents.

Scheme 3 gathers our results for the cycloaddition between sulfinyl diene **1a**, sulfonyl diene **7a** and phenyltriazolinedione (PTAD). These cycloadditions took place with complete facial selectivity and in high yield to produce adducts **11a** and **13a** respectively. Standard oxidation of **11a** afforded **12a** whose spectral features clearly indicated a diastereomeric relationship to **13a**. These observations establish a sulfur-directed π-facial selectivity for hydroxy sulfoxide **1a**, and an allylic-directed π-facial selectivity for hydroxy sulfone **7a**.

In summary, readily available enantiopure acyclic hydroxy 2-sulfinyl butadienes,[7] which display a nonreinforcing relationship of stereocontrolling elements,[6] undergo a highly face-selective Diels–Alder cycloaddition with *N*-phenylmaleimide and phenyltriazolinedione to generate densely functionalized cycloadducts. To the best of our knowledge, the complete reversal of facial selectivity found for sulfoxides **1**, relative to related sulfonyl dienes **7**, is unprecedented and demonstrates that the sulfinyl functionality is not just synthetically useful but also an extremely powerful element of stereocontrol for intermolecular Diels–Alder cycloadditions, Further studies on the scope and limitations of this methodology, including its intramolecular variant as well as applications toward natural products syntheses, will be reported in due course.



Scheme 3 *Reagents and conditions*: i, PTAD (1.5–2.0 equiv.), CH_2Cl_2, −78 °C to room temp., 1 h, 87% for **11a** and 79% for **13a**; ii, MCPBA (1.5 equiv.), CH_2Cl_2, −78 °C to room temp., 4 h, 88%

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Notes and References

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‡ Pure amide **3a** also yielded a 25 : 75 mixture of **3a** and **3b** upon treatment with SiO_2.

§ Careful examination of the crude reaction mixture by 300 MHz ^{1}H NMR spectroscopy at intermediate reaction times showed mixtures of diene **7a**, cycloadduct **8a** and lactone **9a**.

¶ Pure **10b**, isolated by chromatography of the mother liquors of **2b**, afforded sulfonyl amide **9b** upon oxidation with MCPBA.

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