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Highly Efficient Diastereoselective *Exo* Diels-Alder Reactions of Homochiral 2-(N-Acylamino)-1-Thia-1,3-Dienes: A Powerful Entry into Optically Pure Thiopyrans.

Andrew S. Bell[b], Colin W.G. Fishwick[a]* and Jessica E. Reed.[a]

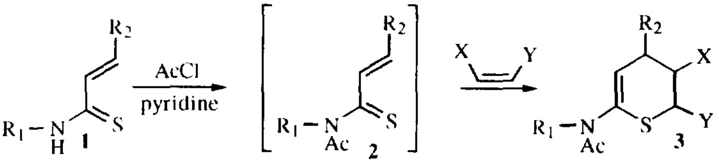
[a] School of Chemistry, University of Leeds, Leeds, LS2 9JT, UK.

[b] Discovery Chemistry, Pfizer Central Research, Sandwich, Kent, CT13 9NJ, UK.

Abstract: 4-Phenyl-2-N-(R-(-)-α-(2-naphthyl)ethylamino)-1-thia-1,3-dienes when activated by acetyl chloride, undergo extremely efficient diastereoselective *exo* Diels-Alder cycloadditions giving access to thiopyrans of high optical purity.

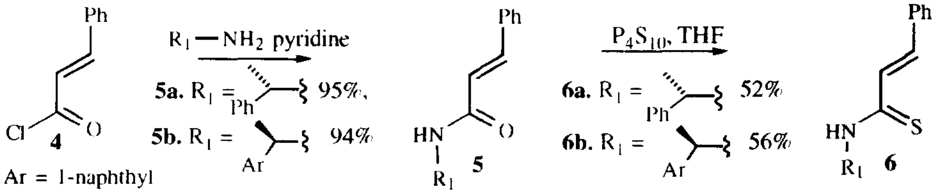
The Diels-Alder reaction is amongst the most powerful and versatile of synthetic methods and continues to attract considerable attention.[1] In particular, recent effort has been directed towards understanding the factors governing face selectivity and absolute stereochemical control. Enantioselection has been achieved using optically active dienes,[2] dienophiles,[3] and Lewis acid catalysts[4] with varying degrees of success. In contrast, despite their tremendous synthetic potential, enantioselective hetero Diels-Alder reactions,[5] have received much less attention. This is particularly true of reactions involving heterodienes. Of the few synthetic routes to optically active thiopyrans most involve homochiral dienophiles[6] and to the best of our knowledge the present work represents the first route utilising homochiral 1-thia-1,3-dienes. We hoped that homochiral dienes would induce greater control over both *endo exo* selectivity and facial selectivity giving rise to thiopyrans open to further synthetic manipulation.[7]

Previously, we described[8] the development of simple, efficient, and versatile methods for the generation and cycloadditions of reactive 2-(N-acylamino)-1-thia-1,3-dienes **2**, derived via acylation of thioamides **1**. This gave access to a range of thiopyran systems **3** with good degrees of regioselectivity and control of relative stereochemistry (**Scheme 1**). In this paper we report a highly efficient route to optically active thiopyrans obtained in excellent yields with >98% de.



Scheme 1

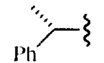
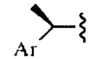
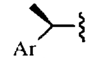
Our aim was to develop optically active versions of heterodienes **2** via incorporation of a homochiral substituent at R_1. This was attractive due to the availability of a number of optically active amines. Additionally, we envisaged that to maximise the degree of facial selectivity we required optically active amines containing bulky substituents near to the amine group and therefore near to the diene moiety. We chose to look at 4-phenyl derivatives i.e. R_2 = Ph due to their known reactivity, stability and crystalline properties. (S)-α-Methylbenzylamine and (R)-1-(1-naphthyl)ethylamine were used to prepare thiadienes, **6**, in good yields (**Scheme 2**). Cycloaddition reactions of dienes of the type **6**, after activation with acetyl chloride, with dienophiles are summarised in **Table 1**.



Scheme 2

We initially chose N-phenyl maleimide (NPM) as the dienophile trap due to its high *endo* preference e.g. for the racemic diene where R_1 = ethyl the *endo* : *exo* ratio was found to be 4 : 1 as seen in **Table 1 Entry 1.** The (S)-α-methylbenzylamine based diene, **Entry 2**, gave a mixture of 4 diastereomeric cycloadducts in 95% yield in the ratio 59:30:10:1, as established by HPLC analysis. Although the cycloaddition itself was clearly proceeding in excellent yield, the facial selectivity was disappointing. We decided to increase the size of the aryl group and were delighted to find that trapping of the acylated naphthyl based diene with N-phenyl maleimide gave an excellent yield (95%) of two diastereomeric cycloadducts in the ratio 72:28 **Entry 3**. The major component was found to be an *exo* product. This was intriguing as our previous work using a simple achiral diene (R^1 = Et) had revealed a preference for *endo* cycloadducts with N-phenyl maleimide.

Table 1 The effects of homochiral auxiliaries at R^1 on cycloaddition products.

Entry	R^1	dienophile	Temp.	Yield (%)	ratio of products
1	CH_2CH_3	NPM	r.t.	84	40 : 40 : 10 : 10 endo : exo 4 : 1
2		NPM	r.t.	95	59: 30 : 10 : 1
3		NPM	r.t.	92	72 : 28 : < 1: < 1
4		cyclopentene	-15 °C	95	98 : <1: <1 : <1

Ar = 1-naphthyl

The lowest energy conformation of the reactive diene species 7 was calculated[9] in order to predict the facial selectivity and explain the preference for *exo* addition (**Figure 1**. looking along the plane of the diene from sulphur). The bulky naphthyl group appears to be in close proximity to the 4-phenyl substituent which causes a marked twisting of the phenyl ring relative to the diene system. This π interaction leads to a conformationally locked diene in which both *endo* approaches appear to be sterically hindered accounting for the departure from the usual *endo* selectivity. The twisting appears to sterically hinder the dienophile approach from the *exo* "acyl face" of the diene favouring addition to the *exo* "naphthyl face." The more efficient π interaction of the naphthyl group of diene **7** compared with that of a phenyl group in the acyl derivative of diene **6a** may account for its improved facial selectivity.

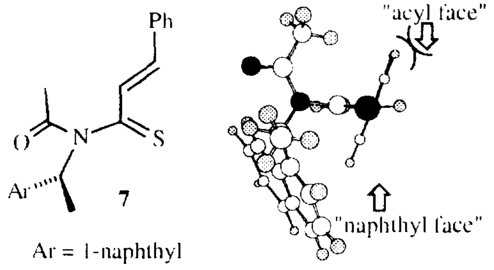


Figure 1. Energy minimised diene 7.

The absolute stereochemistry of the major cycloaddition product with N-phenyl maleimide, **8**, **Figure 2** was established using single crystal X-ray analysis and found to have the S,R,S-configuration consistent with N-phenyl maleimide addition occurring in an *exo* sense from the naphthyl face.

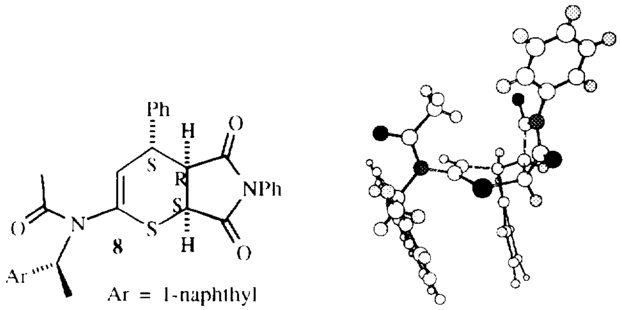
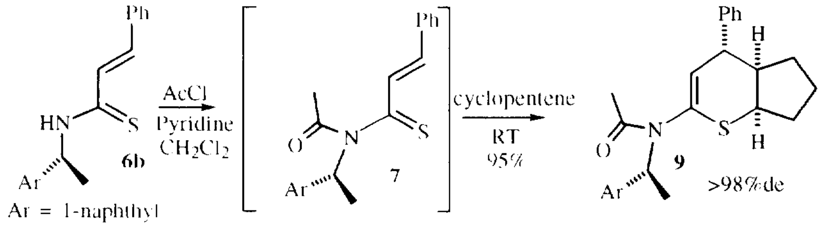


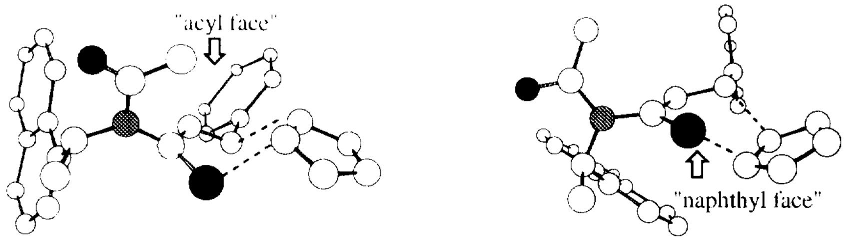
Figure 2. X-ray structure of **8**.

Given the unusual *exo* preference observed for the dienophile N-phenyl maleimide, we chose to look at trappings with cyclopentene. Previously published examples where R_1= ethyl gave exclusively *exo* products in reactions with cyclopentene.[8] When the naphthyl based diene was trapped with cyclopentene **Entry 4**, **Scheme 3**, a single crystalline adduct was obtained in 95% yield.



Scheme 3

Semi-empirical transition state calculations[9] indicate a striking preference for *exo* addition from the same face of the molecule as the naphthyl auxiliary (**Figure 3**).



"acyl face" H_f = 114.66 kcal mol^{-1} "naphthyl face" H_f = 109.16 kcal mol^{-1}

Figure 3. Transition state structures of naphthyl diene **7** with cyclopentene.

The absolute configuration of the single diastereoisomer formed from cyclopentene trapping was determined by X-ray analysis and found to be 4R, 3R, 2R resulting from *exo* addition to the naphthyl face **Figure 3.** This was in agreement with the transition state models. It may be the case that the improved selectivity seen with cyclopentene is due to the stronger *exo* preference of cyclopentene as dienophile and its more discriminate nature compared with the more reactive N-phenyl maleimide.

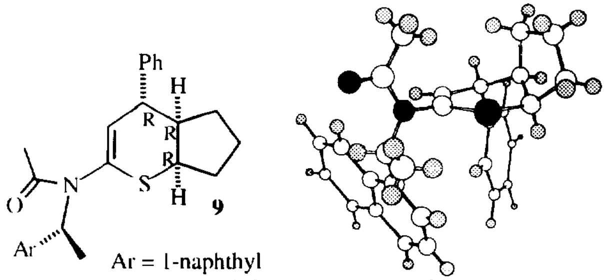


Figure 4. X-ray structure of **9**.

In conclusion we have successfully induced total *exo* selectivity and >98% diastereoselectivity in reactions involving homochiral sulphur containing heterodienes. The cycloadducts produced are open to further synthetic manipulation and this is where our current research is aimed.[6]

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9. Molecular models were constructed on a Silicon Graphics *Indigo* using MacroModel v3.0, developed by Professor W.C. Still. All models were fully optimised using AM1 Hamiltonian in MOPAC v6.0 which was optimised for parallel computation using a Silicon Graphics Challenge eight processor parallel computer. Transition structures were located *via* the SADDLE routine in MOPAC and optimised via the TS routine. Transition structures were characterised using FORCE within MOPAC.

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