# Asymmetric Hetero-Diels-Alder Reactions with Heterocumulenes

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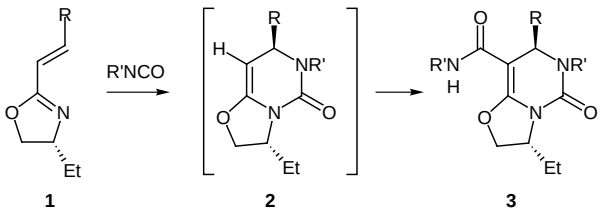
**Abstract:** Chiral 2-alkenyloxazolines and 2-alkenylthiazolines react with isocyanates and ketenes to give formal hetero-Diels-Alder adducts with complete diastereocontrol. In each case an electron-rich double bond in the adduct is prone to a second addition of the heterocumulene. In the case of the oxazoline adducts the second addition is faster than the first, while with thiazolines the second addition is slower so that a different heterocumulene can be incorporated.

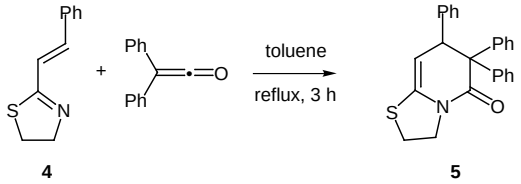
**Key words:** Diels-Alder reactions, heterocycles, isocyanates, ketenes, piperidines

We have recently reported the reactions of alkenyloxazolines **1** with isocyanates as a stereocontrolled entry into the oxazolo[3,2-*c*]pyrimidine ring system (Scheme 1).[1] Although stepwise,[2] this reaction can formally be considered to be an aza-Diels-Alder reaction.[3] In all cases thus far reported, the initial adduct **2** undergoes a second, faster, reaction with the isocyanate to give products **3**. We consider this to be a limitation of our methodology, and sought ways to alleviate the problem. Also, asymmetric hetero-Diels-Alder reactions involving carbon-carbon dienophiles would be more versatile. We now report an extension of our earlier work which addresses both of these concerns.



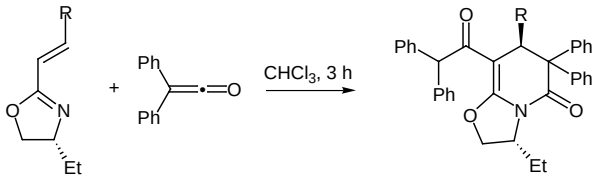

**Scheme 1**

We reasoned that ketenes would be appropriate carbon-carbon dienophiles since they are isoelectronic with isocyanates. Also, since we might expect a stepwise reaction, our mechanistic model leads us to expect high, if not complete, diastereoselectivity. In 1979 Sakamoto reported the reaction of an alkenylthiazoline with diphenylketene to give a product in which only a single equivalent of the ketene was incorporated (Scheme 2).[4] We felt that this approach would open up significant possibilities, and have therefore investigated the reactions of both alkenyloxazolines and alkenylthiazolines with diphenylketene. The reactions of thiazolines with selected isocyanates have also been investigated.




**Scheme 2**

Diphenylketene, prepared according to the procedure of Taylor,[5] was allowed to react with oxazolines **6** and **7**. In line with earlier results, this led to the formation of a single stereoisomer of the double-addition products **8**[6] and **9**.[7] These reactions were conducted in the minimum volume of chloroform to enable stirring of a homogeneous solution. Reactions in the absence of solvent (which are optimal with isocyanates) or in toluene (as reported by Sakamoto with thiazoline **4**) were much less satisfactory. We have assigned the stereochemistry of **8** and **9** based on our mechanistic model for the analogous reactions with isocyanates, computational data and a single crystal X-ray diffraction of compound **18** (*vide infra*). This therefore represents a formal asymmetric aza-Diels-Alder reaction involving a carbon-carbon dienophile.



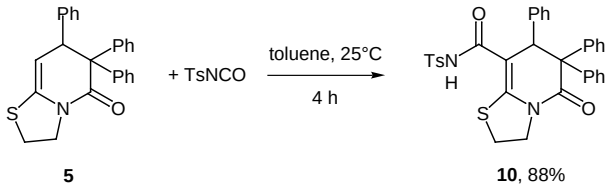

**6**, R = Me
**7**, R = Ph

**8**, R = Me, 62%
**9**, R = Ph, 26%

**Scheme 3**

We conclude from this that it is the thiazoline component rather than the ketene which leads to the formation of only 1:1 adducts in the work of Sakamoto. Compound **4** was prepared by condensation of 2-methylthiazoline with benzaldehyde,[8] and allowed to react with diphenylketene to give **5** as previously shown by Sakamoto (Scheme 2).

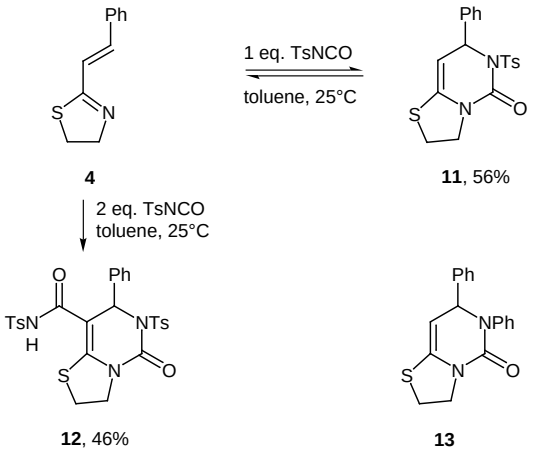
Clearly in this case the alkenylthiazoline reacts faster with the heterocumulene than does the product **5**. However, upon stirring **5** in toluene with tosyl isocyanate compound **10** was formed in satisfactory yield. We can therefore introduce two different heterocumulenes, so that this chemistry has a significant advantage over our previously reported work.




**5** **10**, 88%

**Scheme 4**

Under similar conditions both single and double adducts with tosyl isocyanate **11** and **12** have been isolated. Compound **11** proved to be unstable and prone to a retro-Diels-Alder reaction; however the addition of the second tosyl group stabilised this compound. With the less reactive phenyl isocyanate only a single addition product **13** was obtained from **4** under a wide variety of conditions, optimal being heating an equimolar mixture of starting materials neat (150°C, 15 h, 55 %).

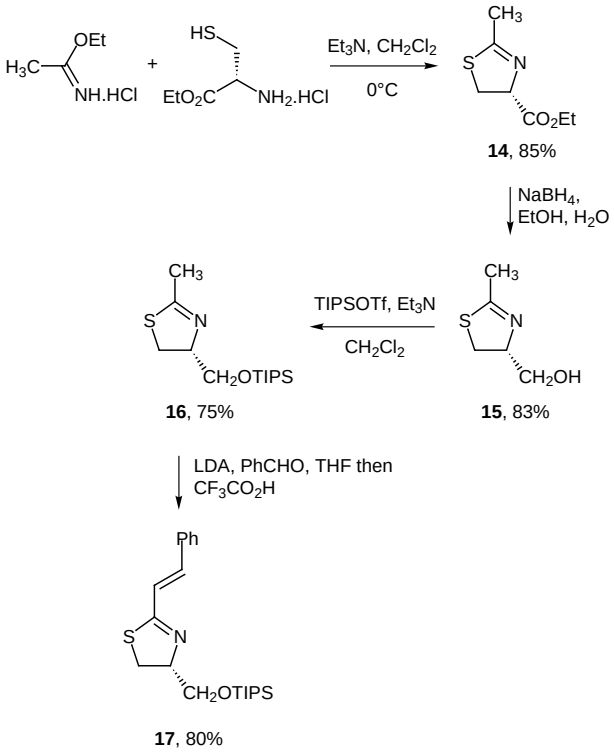



**4** **11**, 56%

**12**, 46% **13**

**Scheme 5**

With these results in hand, we needed to verify that the reactions with thiazolines also proceed with good diastereocontrol. A suitable thiazoline was prepared from cysteine as shown in Scheme 6. Cysteine ethyl ester hydrochloride was allowed to react with ethyl acetimidate hydrochloride to give ethyl 2-methylthiazoline-4-carboxylate **14**.[9] While this reaction is known to proceed with partial racemisation,[10] conditions leading to single enantiomers, while marginally less convenient, are known.[11] Sodium borohydride reduction was followed by protection as the triisopropylsilyl ether. Since this chemistry should be amenable to solid support, we elected to use a particularly bulky protecting group to verify that it did not hinder the reaction; also we felt that a less hindered protecting group might not withstand the conditions for the subsequent condensation with benzaldehyde (toluene, iodine, reflux).[8] In the event the chemistry proceeded smoothly, although the yield of the final step to give **17** was relatively low (55%). However, carrying out this transformation in a stepwise manner using LDA to deprotonate the 2-methylthiazoline followed by trifluoroacetic acid to effect elimination[12] gave more satisfactory results (80% over two steps). The enantiomeric excess of **17** was shown by chiral GC-MS to be 39.7%.



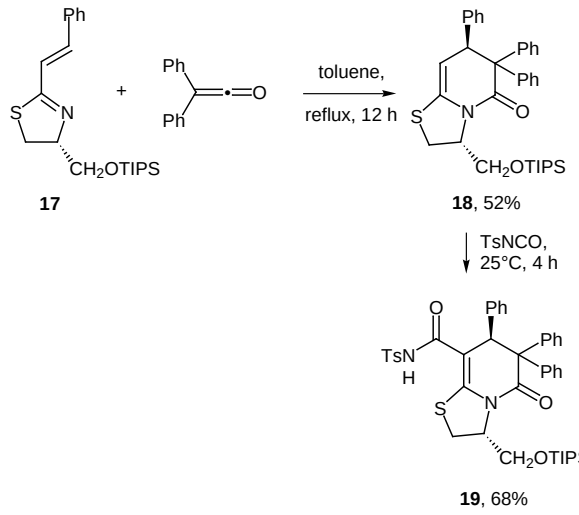

**14**, 85%

**16**, 75% **15**, 83%

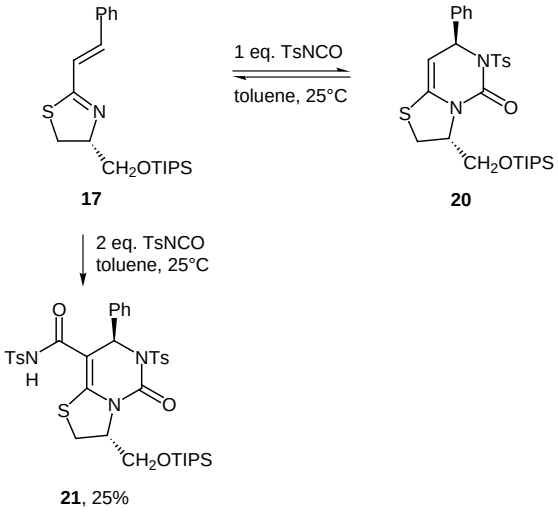
**17**, 80%

**Scheme 6**

We were then delighted to find that the reactions of **17** with diphenylketene and tosyl isocyanate proceed with total stereocontrol. Reaction with diphenylketene proceeded smoothly to give compound **18**[13] as a single diastereoisomer within the detection limits of 400 MHz $^1$H NMR. Subsequent reaction with tosyl isocyanate gave **19**. Recrystallisation of compound **18** from pentane gave crystals suitable for X-ray diffraction, although not surprisingly the triisopropylsilyl group showed disorder. While the crystal selected for analysis was found to be racemic, we were able to demonstrate by chiral HPLC on the crude reaction mixture that no racemisation occurred during the formation of **18**. As expected from our previous work,[1] the phenyl group at the new stereogenic centre is on the opposite side of the bicyclic ring system to the substituent on the thiazoline (Figure 1).[14]




**Scheme 7**




**Scheme 8**

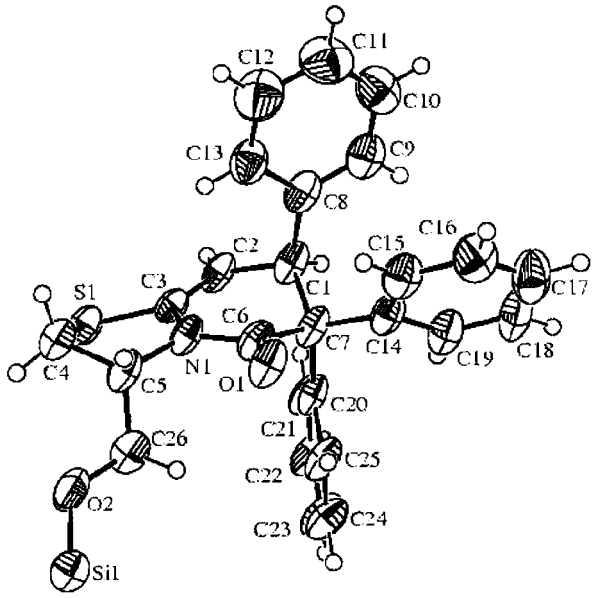



**Figure 1** Solid state structure of compound **18**. Isopropyl carbons omitted for clarity

Reaction of **17** with tosyl isocyanate also gave a single stereoisomer of the single adduct **20**, but this compound, like the analogous compound **11**, proved to be unstable and prone to a retro-Diels-Alder reaction. Once again though, the double-addition product **21**[15] proved to be much more stable, the low yield being due more to difficulties encountered in purification.

In summary, the reactions of unsaturated oxazolines with diphenylketene follow a similar course to our previously-reported reactions of oxazolines with isocyanates.[1] However, the reactions of unsaturated thiazolines with isocyanates and with diphenylketene allow the introduction of two different heterocumulenes in a controlled manner, and therefore open up many opportunities for the modification of the products. These reactions are currently under investigation and will be reported in due course.

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## References and Notes

(1) Elliott, M. C.; Kruiswijk, E. *Chem. Commun.*, 1997, 2311; Elliott, M. C.; Hibbs, D. E.; Hughes, D. S.; Hursthouse, M. B.; Kruiswijk, E.; Malik, K. M. A. *J. Chem. Cryst.*, **1998**, *28*, 663.
(2) Elliott, M. C.; Kruiswijk, E.; Willock, D. J. *Tetrahedron Lett.*, **1998**, *39*, 8911.
(3) Tietze, L.; Kettschau, G. *Top. Curr. Chem.*, **1997**, 189, 1.
(4) Sakamoto, M; Miyazawa, K.; Kuwabara K.; Tomimatsu, Y. *Heterocycles*, **1979**, *12*, 231.
(5) Taylor, E. C.; McKillop, A.; Hawks, G. H. *Org. Synth. Coll. Vol. VI*, **1988**, 549.
(6) Selected spectroscopic data for 8: $\delta_H$ (400 MHz; $CDCl_3$) 7.56 (2 H, dd, *J* 8.2, 1.0, aromatic CH), 7.34 (2 H, apparent t, *J* 7.7, aromatic CH), 7.26 – 6.88 (14 H, m, aromatic CH), 6.66 (2 H, dd, *J* 7.2, 1.4, aromatic CH), 5.97 (1 H, s, $Ph_2CH$), 4.62 (1 H, apparent dq, *J* 1.1, 6.5, C*H*-N), 3.93 (1 H, dd, *J* 8.6, 1.1, one of $CH_2O$), 3.77 (1 H, dd, *J* 8.6, 6.5, one of $CH_2O$), 3.67 (1 H, q, *J* 6.8, C*H*Me), 1.75 – 1.64 (2 H, m, $CH_2CH_3$), 0.97 (3 H, t, *J* 7.4, $CH_3$) and 0.95 (3 H, d, *J* 6.8, $CH_3$).
(7) Selected spectroscopic data for **9**: $\delta_H$ (400 MHz; $CDCl_3$) 7.67 (2 H, d, *J* 7.4, aromatic CH), 7.33 (2 H, apparent t, *J* 7.6, aromatic CH), 7.22 – 6.85 (19 H, m, aromatic CH), 6.65 (2 H, d, *J* 7.1, aromatic CH), 6.06 (1 H, s, $Ph_2CH$), 4.78 (1 H, s, PhC*H*), 4.54 (1 H, apparent dq, *J* 1.2, 6.5, C*H*-N), 3.69 (1 H, dd, *J* 8.7, 1.4, one of $CH_2O$), 3.61 (1 H, dd, *J* 8.7, 6.3, one of $CH_2O$), 1.67 – 1.59 (2 H, d, $CH_2CH_3$) and 0.94 (3 H, t, *J* 7.4, $CH_3$).
(8) Wehrmeister, H. L. *J. Org. Chem.*, **1962**, *27*, 4418.
(9) Barton, M. A.; Kenner, G. W.; Sheppard, R. C. *J. Chem. Soc. C*, **1966**, 1061.

(10) Meyers, A. I.; Whitten, C. E. *Heterocycles* **1976**, *4*, 1687; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Heterocycles* **1993**, *36*, 473.
(11) C. D. J. Boden, G. Pattenden and T. Ye, *Synlett* **1995**, *417*; F. Almqvist, D. Guillaume, S. J. Hultgren and G. R. Marshall, *Tetrahedron Lett.*, **1998**, *39*, 2293.
(12) Meyers, A.I.; Durandetta, J. L.; Munavu, R. *J. Org. Chem.* **1975**, *40*, 2025; Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250.
(13) Selected spectroscopic data for **18**: $\delta_H$ (400 MHz; $CDCl_3$) 7.57 - 7.53 (2 H, m, aromatic CH), 7.35 - 7.32 (3 H, m, aromatic CH), 7.09 (1 H, d, *J* 7.4, aromatic CH, 7.03 (2 H, apparent t, *J* 7.2, aromatic CH), 6.97 (1 H, d, *J* 7.3, aromatic CH), 6.90 (2 H, apparent t, *J* 7.6, aromatic CH), 6.70 (2 H, d, *J* 7.2, aromatic CH), 6.56 (2 H, d, *J* 7.8, aromatic CH), 5.43 (1 H, d, *J* 6.0, alkene CH), 4.92 - 4.87 (1 H, m, C*H*-N), 4.09 (1 H, d, *J* 6.0, C*H*Ph), 3.47 (1 H, dd, *J* 9.6, 3.9, one of C$H_2$S), 3.40 (1 H, dd, *J* 11.3, 6.4, one of C$H_2$O), 3.28 (1 H, d, *J* 11.3, one of C$H_2$O), 2.91 (1 H, apparent t, *J* 9.6, one of C$H_2$S) and 1.0 - 0.9 (21 H, m, *i*Pr$_3$Si).
(14) Selected crystallographic data for **18**: $C_{35}H_{43}NO_2SSi$ ($M_r$ 569.85), monoclinic, $P2_1/a$, $a$ = 13.311(2), $b$ = 16.811(3), $c$ = 14.525(2) Å. β = 102.73(3)°, Z = 4, V = 3170.4(9) Å$^3$, $D_c$ = 1.194 gcm$^{-3}$, Mo-$K_\alpha$ radiation, λ = 0.71073 Å, 2.24 ≤ 2θ ≤ 26.31°. 6633 reflections were collected of which 6354 were unique. 3239 reflections having $I > 2.0\sigma(I)$ were used for refinement (429 parameters), converging to $R$ = 0.0820 and $R_w$ = 0.2135. The isopropyl groups of the protecting group were heavily disordered. Full data have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (+44) 1223 336033. Email: deposit@ccdc.cam.ac.uk).
(15) Selected spectroscopic data for **21**: $\delta_H$ (400 MHz; $CDCl_3$) 7.72 (2 H, d, *J* 8.2, aromatic CH), 7.36 - 7.33 (6 H, m, aromatic CH + NH), 7.28 (2 H, d, *J* 8.3, aromatic CH), 7.19 (2 H, d, *J* 8.0, aromatic CH), 7.02 (2 H, d, *J* 8.2, aromatic CH), 6.12 (1 H, s, C*H*Ph), 4.56 - 4.51 (1 H, m, C*H*-N), 3.64 (1 H, dd, *J* 9.1, 3.5, one of C$H_2$O), 3.49 (1 H, apparent t, *J* 9.1, one of C$H_2$O), 3.29 (1 H, d, *J* 11.4, one of C$H_2$S), 3.17 (1 H, dd, *J* 11.4, 7.1, one of C$H_2$S), 2.34 (3 H, s, C$H_3$), 2.27 (3 H, s, C$H_3$) and 0.93 (21 H, m, *i*Pr$_3$Si).

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