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An Asymmetric Route to the 5,6-Dihydro-*4H*-1,3-Thiazine Skeleton via an Asymmetric Hetero Diels-Alder Reaction

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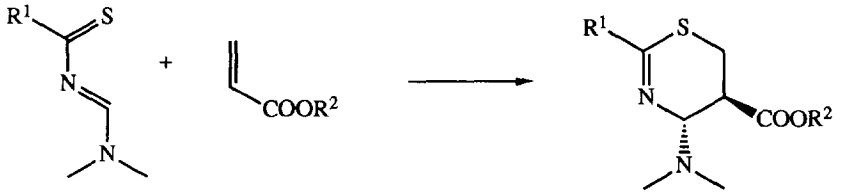
Abstract: Magnesium bromide mediated hetero Diels-Alder cycloaddition of diene **1** (R^1 = Ph) to chiral N-acryloyl-2-oxazolidinone **4b** leads to **5b** as the sole adduct formed. Chiral auxiliary removal leads to enantiomerically pure 5,6-dihydro-*4H*-1,3-thiazine **3** (R^2 = Bn). The selectivity of the cycloaddition is reversed under thermal or high pressure activation. The predominant diastereomeric adduct **6b** is isolated in pure form after flash chromatography.

For some years, studies in our laboratory have focused on the construction of the dihydro-1,3-thiazine ring, a subunit found in biologically active natural products (eg. cephamycin C) as well as in many unnatural compounds displaying a broad range of activities (medicinal drugs, herbicids, pesticids, etc). In particular it has been shown that the hetero Diels-Alder reaction of 3-aza-4-dimethylamino-1-thia-butadienes **1** with acrylates **2** induced by heating[1] or by application of high pressure[2] provides a convenient and efficient route to substituted 5,6-dihydro-*4H*-1,3-thiazines **3**, allowing for the simultaneous construction of carbon-carbon and sulfur-carbon bonds and installation of two contiguous stereogenic centers (Scheme 1).



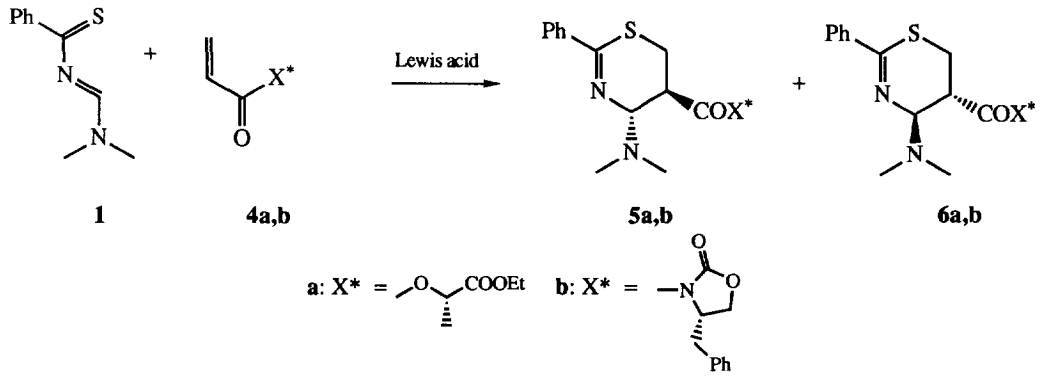
1 **2** **3**

Scheme 1

In continuation of this work we have now considered the possibility that acrylates bearing a chiral substituent might provide ready access to optically active **3** and we report herein our preliminary results which have culminated with the first asymmetric synthesis of the substituted 5,6-dihydro-*4H*-1,3-thiazine **3** in the case where R^1 = Ph and R^2 = Bn.

The chiral dienophiles selected for study were the known acrylate **4a** and N-acryloyl-2-oxazolidinone **4b**. Although both of them have been widely used in asymmetric Diels-Alder reactions, there is no report of their use in hetero Diels-Alder reactions involving an heterodiene[3]. The cycloaddition of acrylate **4a** with cyclopentadiene has been previously reported by Helmchen et al[4]. These authors have observed a remarkable reversal of selectivity of the addition process depending on the Lewis acid utilized ($TiCl_4$ versus $EtAlCl_2$).

With this result in mind we first studied the reaction of heterodiene **1** (R^1 = Ph) with acrylate **4a** in the presence of Lewis acid catalysts. As can be seen from the data in Table 1 such a dichotomy is no longer found in the present reaction.



Scheme 2

Table 1 : Hetero Diels-Alder reaction of diene **1** with acrylate **4a** and N-acryloyl-2-oxazolidinone **4b**.

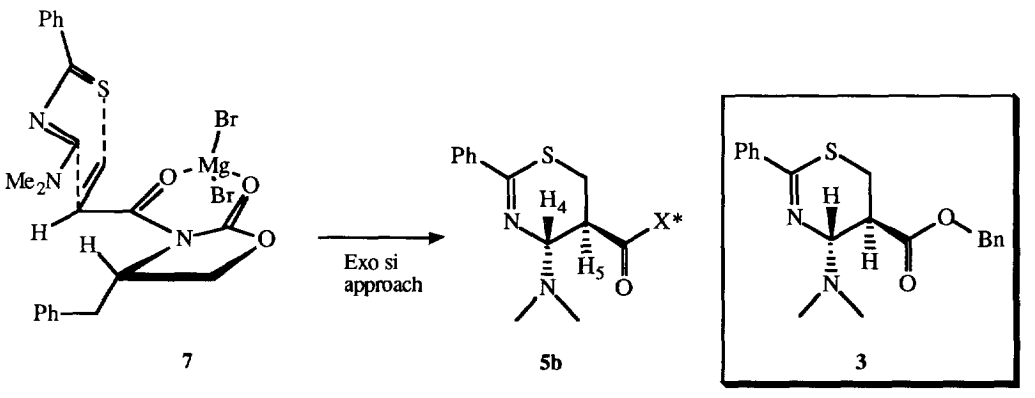
Entry	Dienophile	Experimental Conditions[a] Lewis acid (eq./eq.**4**)	temp.(°C)	time (h)	Yield %	Diastereoselection[b] **5/6**
1	**4a**	none	20	3	72	50/50
2	**4a**	$TiCl_4$ (1)	-78 to -20	3	80	60/40
3	**4a**	$TiCl_2(OiPr)_2$ (2)	-78 to -20	3	58	65/35
4	**4a**	$EtAlCl_2$ (1)	-78 to -30	3	86	65/35
5	**4a**	Et_2AlCl (1)	-20	3	90	70/30
6	**4a**	Et_2AlCl (1)	-60	3	90	70/30
7	**4a**	$MgBr_2$ (1.5)	20	1.5	90	65/35
8	**4b**	none	110	20	75	20/80
9	**4b**	none (10Kbar)	20	40	95	16/84
10	**4b**	$MgBr_2$ (1)	0	3	95	100/0

[a]Lewis acid catalyzed reactions were conducted in CH_2Cl_2 with molar ratio of diene:dienophile = 1:1.5 ; Reaction under thermal activation was conducted in toluene with molar ratio of diene:dienophile = 1:1.5 ; Reaction under high pressure activation was conducted in THF with molar ratio of diene:dienophile = 1:1. [b]Ratios of diastereomers were derived by integration of the NMe_2 peaks in the ^1H NMR spectra (400MHz) of the unpurified cycloaddition products.

In all cases examined the same adduct is predominant in the diastereomeric mixture. Also in sharp contrast with the Helmchen results, the diastereoselection is not very high (70/30 at best, absence of diastereoselection in the uncatalyzed reaction).

Such disappointing results prompted us next to turn our attention to the reaction of heterodiene **1** with N-acryloyl-2-oxazolidinone **4b**. As can be seen from entry 10 *the reaction catalyzed by magnesium bromide in CH_2Cl_2 as the solvent led to a single diastereomer* **5b** as judged by NMR analysis. It is worthy of note that other Lewis acid such as $TiCl_4$ and $AlEt_2Cl$, which are efficient in all carbon Diels-Alder reactions involving dienophile **4b**[5], failed to promote the present cycloaddition. Also of interest is the reversal of selectivity and the significant diastereoselection observed under thermal (entry 8) and high pressure activation (entry 9). The mixture of diastereomers formed in the latter case was easily separated by column chromatography to give a pure sample of **6b.** *Thus, depending upon the activation mode employed (Lewis acid or high pressure), either* ***5b*** *or* ***6b*** *could be obtained in optically pure form.*

The NMR coupling constants of the protons at C-4 and C-5 (10.1Hz) provide a simple means for establishing the relative *trans* configuration of the two newly created stereogenic centers in adducts **5b**[6] and **6b**[7]. The absolute configuration could be established as being *4R,5R* in diastereomer **5b** by a single crystal X-ray[8] and is in accordance with the generally observed bias of N-acryloyl-2-oxazolidinone **4b** to react on the less hindered si face[5], here via a magnesium chelated form **7**, and a cyclocondensation process occurring through an exo topology (Scheme 3). The exo addition mode is consistent with previous results in achiral series[1,2,9] and seems to be a general property of dienes **1**.



7 **5b** **3**

Scheme 3

Finally chiral auxiliary removal was effected without epimerization[10,11] by treatment of adduct **5b** with lithium benzyloxyde (1.5 eq, -78°c to 0°C, THF) to give the 5,6-dihydro-*4H*-1,3-thiazine **3** in 40% yield[12].

In summary, the magnesium bromide catalyzed hetero Diels-Alder addition of diene **1** (R^1 = Ph) to chiral N-acryloyl-2-oxazolidinone **4b** can be carried out with a very high level of diastereoselection to give, after chiral auxiliary removal, the substituted (*4R,5R*)-5,6-dihydro-*4H*-1,3-thiazine **3** which may serve as useful template for stereoselective transformations. Additional studies in order to expand the scope of this reaction to other heterodienes are currently under investigations.

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References and Notes

1 (a) Meslin, J.C.; Quiniou, H. *Bull. Soc. Chim. Fr.* **1979**, *II*, 347-349. (b) Chehna,M.; Pradère, J.P.; Quiniou, H.; Le Botlan, D.; Toupet, L. *Phosphorus Sulfur and Silicon*, **1989**, *42*, 15-19.

2 (a) Chehna, M.; Pradère, J.P.; Guingant, A. *Synthetic Comm.* **1987**, *17*, 1971-1976. (b) Cellerin,C.; Gokou Tea, C.; Pradère, J.P.; Guingant, A.; Guénot, P. *Sulfur Lett.* **1988**, *8*, 205-209.

3 For a recent review on asymmetric hetero Diels-Alder reactions, see: Waldmann, H. *Synthesis*, **1994**, 535-551.

4 Poll, T.; Metter, J.O.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 112-114. See also: Hamley, P.; Helmchen, G.; Holmes, A.B.; Marshall, D.R.; MacKinnon, J.W.M.; Smith, D.F.; Ziller, J.W. *J. Chem.; Chem.Commun.* **1992**, 786-788.

5 Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256.

6 **5b**: white solid, mp 125-126°C (diethylether-petroleum ether) ; $[\alpha]_D$ = - 65.4 (c = 0.52, $CHCl_3$) ; IR (KBr): 1762, 1692, 1616 cm^{-1} ; ^1H NMR (400 Mz,$CDCl_3$, δ): 2.47 (s, 6H), 2.88 (dd, *J* = 8.6 Hz, 13.7 Hz, 1H), 3.10 (dd, *J* = 3.7 Hz, 12.2 Hz, 1H), 3.26 (dd, *J* = 3.2 Hz, 13.7 Hz, 1H), 3.55 (dd, *J* = 12.2 Hz, 12.2 Hz, 1H), 4.20 (m, 2H), 4.38 (ddd, *J* = 3.7 Hz, 10.1 Hz, 12.2 Hz, 1H), 4.69 (d, *J* = 10.1 Hz, 1H), 4.79 (m, 1H), 7.35, (m, 8H), 7.85 (m, 2H) ; ^{13}C (100MHz, $CDCl_3$, δ): 28.3, 36.7, 37.4, 40.7, 55.3, 65.9, 80.5, 126.7, 127.4, 128.4, 129.0, 129.8, 130.8, 135.3, 138.6, 153.5, 157.5, 174.9 ; MS: m/e = 423 (M^+), 192, 159, 121, 55, 44.

7 **6b**: white solid, mp 107-108°C (diethylether-petroleum ether) ; $[\alpha]_D$ = +196.4 (c = 0.28, $CHCl_3$) ; ^1H NMR (400 Mz,$CDCl_3$, δ): 2.41 (s,6H), 2.82 (dd,*J* = 8.6 Hz, 13.7 Hz, 1H), 3.14 (dd, *J* = 3.7 Hz, 12.2 Hz, 1H), 3.30 (dd, *J* = 3.2 Hz, 13.7 Hz, 1H), 3.47 (dd, *J* = 12.2 Hz, 12.2 Hz, 1H), 4.24 (m, 2H), 4.49 (ddd, *J* = 3.7 Hz, 10.1 Hz, 12.2 Hz, 1H), 4.71 (d, *J* = 10.1 Hz, 1H), 4.79 (m, 1H), 7.32 (m, 8H), 7.85 (m, 2H).

8 Toupet, L. Université de Rennes. Details of the crystal structure of **5b** will be reported in a forthcoming full paper.

9 Additional results to be reported in a forthcoming full paper strongly suggest that **5b** is a kinetic adduct. Studies are in progress in order to best understand the origin of the exo selectivity.

10 Absence of epimerization during the auxiliary removal process could be ascertained after NMR analysis of **3** (400MHz, $CDCl_3$) using mandelic acid (1 eq.) as chiral solvating agent.

11 We have experienced considerable difficulties in removing the 2-oxazolidinone chiral auxiliary from adduct **5b** probably due to steric shielding of the exocylic carbonyl group. Transesterification with lithium benzyloxide gave no more than 40% yield of the corresponding **3**. Other protocols employing lithium hydroxide, basic hydrogen peroxide or lithium borohydride proved to be ineffective in the case at hand.

12 **3**: white solid, mp 88-89°C (diethylether-petroleum ether) ; $[\alpha]_D$ = -123.1 (c = 0.26, $CHCl_3$); IR (KBr): 1733, 1612 cm^{-1} ; ^1H NMR (400 Mz,$CDCl_3$, δ): 2.41 (s, 6H), 2.76 (ddd, *J* = 3.9 Hz, 10.1 Hz, 12.2 Hz, 1H), 3.11 (dd, *J* = 3.9 Hz, 12.2 Hz, 1H), 3.54 (dd, *J* = 12.2 Hz, *J* = 12.2 Hz, 1H), 4.45 (d, *J* = 10 Hz, 1H), (.5.20 (d, *J* = 12 4 Hz, 1H), 5.25 (d, *J* = 12.4 Hz, 1H), 7.38 (m, 3H), 7.87 (m, 2H) ; ^{13}C (100MHz, $CDCl_3$, δ): 28.3, 40.1, 40.3, 66.9, 79.2, 126.6, 128.2, 128.3, 128.4, 128.6, 130.8, 136.0, 138.5, 157.8, 173.4 ; MS: m/e =354 (M^+), 192, 159, 121, 89, 77.

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