ARTICLE

OBC
www.rsc.org/obc

The first catalytic inverse-electron demand hetero-Diels–Alder reaction of nitroso alkenes using pyrrolidine as an organocatalyst

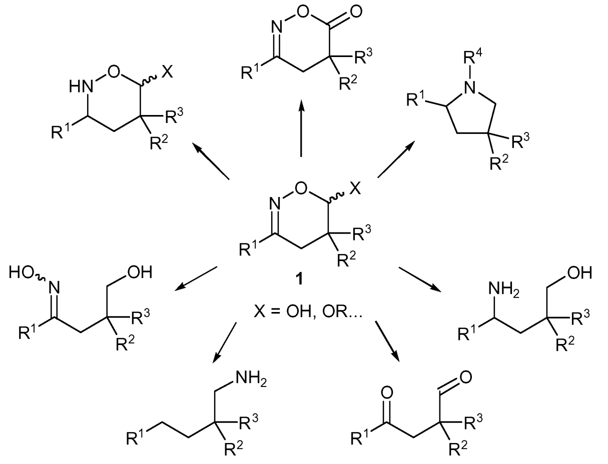
Tobias C. Wabnitz, Steen Saaby and Karl Anker Jørgensen*
The Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, 8000 Aarhus C, Denmark. E-mail: kaj@chem.au.dk;
Fax: (+45) 8619-6199; Tel: (+45) 8942-3910

Received 17th December 2003, Accepted 29th January 2004
First published as an Advance Article on the web 16th February 2004

The first catalytic inverse-electron demand hetero-Diels–Alder reaction of nitroso alkenes has been developed. Nitroso alkenes were generated *in situ* from α-halooximes and underwent [4 + 2]-cycloadditions with enamines as dienophiles formed from aldehydes and pyrrolidine (10 mol%) as an organocatalyst. The presence of a suitable heterogeneous buffer system was found to be essential and best results were obtained with sodium acetate trihydrate. The resulting 5,6-dihydro-4*H*-oxazines were obtained in moderate to good yields under mild reaction conditions. A catalytic cycle has been proposed and evidence for the cycloaddition mechanism has been obtained. Moderate asymmetric induction (42% ee) was observed when a chiral secondary amine was used.

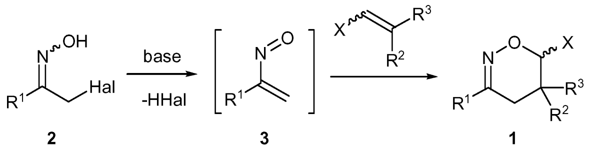
Introduction

Over the last years, 5,6-dihydro-4*H*-oxazines have been shown to be versatile synthetic intermediates for the preparation of a large number of diverse products. It has been demonstrated in several reports that these oxazine derivatives of the generalised structure **1** can be readily converted into oxazinones, pyrrolidines, pyrroles, amino alcohols, amines, 1,3-dicarbonyl compounds and other products *via* simple oxidations, reductions or hydrolysis reactions (Scheme 1).[1]



Scheme 1 Transformations of 5,6-dihydro-4*H*-oxazines **1**.

As outlined in Scheme 2, the oxazines **1** are in turn easily accessible from α-halooximes **2** and olefinic substrates such as enol ethers, enamines, alkenes or allenes. Owing to the fundamental studies of Gilchrist *et al.* and the thorough investigations performed by Reißig and coworkers, these processes have been identified as hetero-Diels–Alder reactions with inverse-electron demand involving transient nitroso alkenes **3**.[2,3] These highly reactive intermediates can be generated through base-mediated dehydrohalogenations of the readily available α-halooximes and furnish the cycloadducts **1** in a highly regioselective fashion.



Scheme 2 Synthesis of 5,6-dihydro-4*H*-oxazines **1** *via* hetero-Diels–Alder reactions involving transient nitroso alkenes.

Although numerous applications of this reaction have been reported, severe restrictions have remained in place. Due to their high reactivity, only very few, sterically encumbered nitroso alkenes have been isolated and characterised.[4] It is also known that processes involving these intermediates are prone to side reactions such as polymerisations. Similarly, long reaction times of up to 10 days are necessary to minimise the concentration of free nitroso alkenes and large excesses of the dienophiles are required in order to obtain acceptable yields. Furthermore, the requirement to preform reactive dienophiles such as enol ethers has limited the practicability of this otherwise very useful conversion.

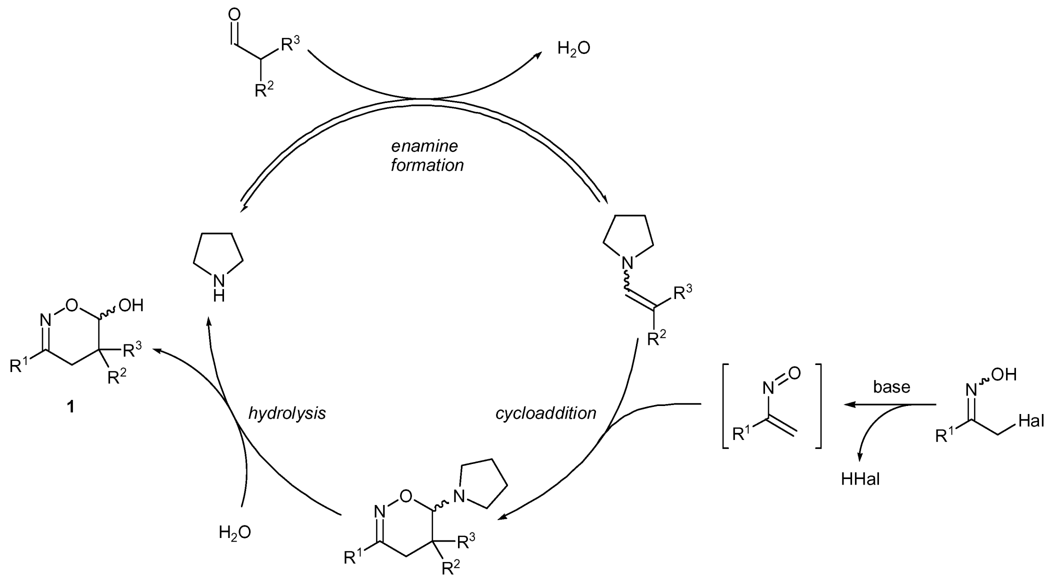
In order to increase the reaction scope and enable its application to a large number of substrates, our investigations focused on the development of a catalytic hetero-Diels–Alder reaction of nitroso alkenes using inexpensive and readily available reagents and catalysts, with possible extensions to enantioselective variants. The results of these investigations are presented in this article.

Results and discussion

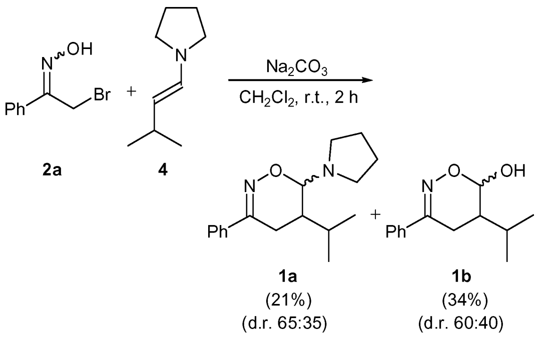
Lewis acid catalysts need to be avoided in processes involving nitroso alkenes as they are known to increase the high reactivity of these species even further and lead to the formation of undesired dimerisation products and polymers.[5] Encouraged by recent advances in organocatalytic cycloaddition reactions, we decided to pursue such an approach.[6] Mixtures of aldehydes and catalytic amounts of secondary amines such as pyrrolidine can reversibly generate electron-rich enamines. These compounds are suitable dienophiles for cycloadditions with inverse electron demand. The envisaged catalytic cycle is shown in Scheme 3.

Initial experiments with the preformed enamine **4**, formed from isovaleraldehyde and pyrrolidine, and α-bromoacetophenone oxime (**2a**) revealed that both the anticipated aminoacetal **1a** as well as the desired dihydro oxazine **1b** were formed in this reaction (Scheme 4). Both products **1a** and **1b** could be isolated as mixtures of diastereomers. However, low yields and the formation of several unidentified by-products indicated that there were several challenges inherent to this reaction sequence which needed to be addressed.

DOI: 10.1039/b316518c

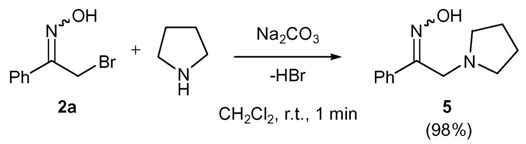


Scheme 3 Catalytic cycle of the pyrrolidine-mediated hetero-Diels–Alder reaction of nitroso alkenes with enamines leading to 5,6-dihydro-4*H*-oxazines.



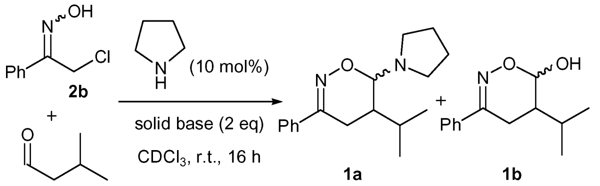
Scheme 4 Reaction of α-halooximes with preformed enamines.

It is well known that nitroso alkenes are highly susceptible to conjugate additions of heteroatom nucleophiles, especially amines.[4] It was confirmed in the present case that an instantaneous addition of pyrrolidine to α-bromoacetophenone oxime (**2a**) took place at room temperature and the resulting tertiary amine **5** was isolated in high yield (Scheme 5).[7] However, this side reaction could be completely suppressed when the oxime was added as the last reaction component to a solution containing the amine catalyst and an excess of the aldehyde, thereby shifting the initial equilibrium towards the enamine (see Scheme 3).



Scheme 5 Reaction of α-bromoacetophenone oxime with pyrrolidine.

Table 1 Effect of solid bases/buffers on catalytic turnover



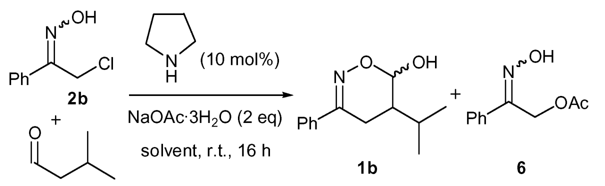
Entry	Base	Conversion (%)	Ratio **1a** : **1b**
1	*No base*	30	30 : 70
2	Na_2CO_3	—[a]	(100 : 0)
3	$Na_2CO_3{\cdot}H_2O$	—[a]	(100 : 0)
4	$Na_2CO_3{\cdot}10H_2O$	—[a]	(100 : 0)
5	$NaHCO_3$	50	20 : 80
6	KH_2PO_4	30	30 : 70
7	$Na_2HPO_4{\cdot}2H_2O$	40	20 : 80
8	$Na_2C_2O_4$	30	30 : 70
9	$Na_3C_6H_5O_7{\cdot}2H_2O$	30	30 : 70
10	NaOAc	80	10 : 90
11	$NaOAc{\cdot}3H_2O$	95	5 : 95
12	$NaOAc{\cdot}3H_2O$[b]	—[c]	—

[a] Decomposition. [b] No pyrrolidine added. [c] No conversion.

Although pyrrolidine, or the corresponding enamines, were sufficiently basic to induce dehydrohalogenation of the α-halooxime, one equivalent of acid liberated in this process has to be neutralised in order to achieve catalytic turnover and the presence of a base is therefore necessary. In contrast, the hydrolytic cleavage of the intermediate aminoacetal to release the amine catalyst (see Scheme 3) calls for a slightly acidic medium.[6a] In order to balance these apparently irreconcilable requirements we decided to employ heterogeneous buffer systems in order to keep the proton concentration in solution approximately constant throughout the reaction.[8] Various buffers were examined for their ability to neutralise acid and enhance hydrolytic cleavage in the model reaction comprising α-chloroacetophenone oxime (**2b**), isovaleraldehyde and catalytic amounts of pyrrolidine (10 mol%). The results of these studies are summarised in Table 1.

As expected, only moderate amounts of the hetero-Diels–Alder adducts were observed in the absence of base and conversion ceased after approximately 30% of the starting material had been consumed (Table 1, entry 1).[9] Sodium carbonate (Na_2CO_3) and hydrates thereof ($Na_2CO_3{\cdot}nH_2O$), which are the most commonly used bases for dehydrohalogenations of α-halooximes, were employed in initial experiments but were found to induce serious decomposition reactions and could not be used. Only traces of the aminoacetal **1a** were detected in these cases (entries 2–4). In the presence of the less basic sodium hydrogen carbonate ($NaHCO_3$), conversion to the desired products was slightly enhanced (entry 5). In contrast, phosphate, oxalate and citrate salts turned out to be unsuitable buffers and virtually identical conversions compared to the base-free reaction were detected (entries 6–9). Sodium acetate (NaOAc), on the other hand, dramatically accelerated catalytic turnover to the desired hemiacetal **1b** (entry 10) and an even more rapid reaction took place when sodium acetate trihydrate ($NaOAc{\cdot}3H_2O$) was used (entry 11).[10] It is likely that the acetate

Table 2 Effect of different solvents on catalytic turnover

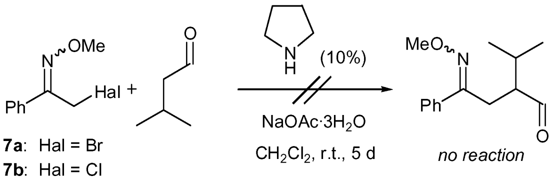


Entry	Solvent	Conversion (%)	Ratio **1b** : **6**
1	CH_2Cl_2	95	100 : 0
2	$CHCl_3$	95	100 : 0
3	Et_2O	20	75 : 25
4	$PhCH_3$	70	90 : 10
5	THF	100	10 : 90
6	CH_3CN	100	5 : 95
7	CH_3NO_2	100	0 : 100

buffer provides the correct combination of basicity/acidity as well as low nucleophilicity. A control experiment also confirmed that the role of $NaOAc{\cdot}3H_2O$ was indeed solely as a buffer as no product formation was observed in the absence of pyrrolidine (entry 12).

With a suitable buffer system in hand, further studies aimed at finding the optimum reaction conditions for the hetero-Diels–Alder reaction of the nitroso alkene generated from the α-chlorooxime **2b** were carried out (Table 2). While the reaction proceeded rapidly in dichloromethane and chloroform (entries 1,2), slower conversion and formation of the undesired ester **6** were observed in ether and toluene (entries 3,4). When more polar solvents such as THF, acetonitrile or nitromethane were used, **6** turned out to be the main product (entries 5–7). In these cases, the ester **6** is either formed *via* conjugate addition of acetate to the transient nitroso alkene or *via* a nucleophilic substitution pathway which is expected to be facilitated in dipolar aprotic solvents.[11]

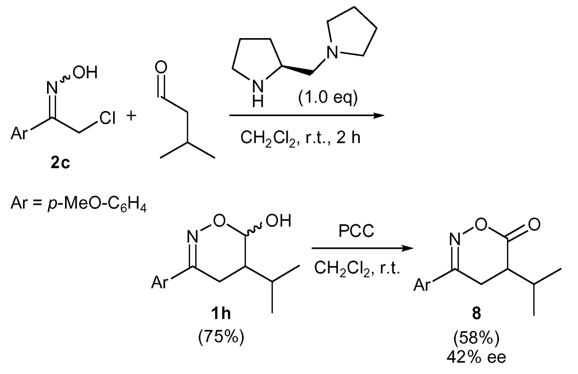
Although Gilchrist and Reißig and their coworkers presented compelling evidence for the electrocyclic nature of oxazine formation from α-halooximes (as a source of transient nitroso alkenes) and dienophiles, these findings cannot be transferred directly to reactions of enamines as these compounds are known to be strongly polarised and highly nucleophilic.[2,3] To assess the ease of nucleophilic substitution reactions in the present system, the α-bromo- and α-chloro-*O*-methyloximes **7a** and **7b** were synthesised and employed under the established reaction conditions (Scheme 6). These α-halooximes are unable to generate nitroso alkenes *via* dehydrohalogenation, hence additions of enamines to these compounds have to proceed through substitution mechanisms. No products were detected after 5 days, confirming the involvement of intermediate nitroso alkenes and pointing towards a hetero-Diels–Alder cycloaddition pathway when the non-*O*-alkylated α-halooximes **2** are employed as substrates.[12–14]



Scheme 6 Reaction of *O*-methylated α-halooximes **7** with enamines.

Based on these results, the scope of the newly developed organocatalytic hetero-Diels–Alder reaction of nitroso alkenes was investigated using $NaOAc{\cdot}3H_2O$ as a heterogeneous buffer in dichloromethane (Table 3). Good yields of the cycloaddition products were obtained when α-chloroacetophenone oxime (**2b**) and α-unbranched aldehydes were used (entries 1–6). In this category, only acetaldehyde turned out to be an unsuitable dienophile precursor due to rapid condensation reactions in the presence of pyrrolidine (entry 7).[15] Both the α-chlorooxime **2b** and the analogous bromooxime **2a** could be used and very similar yields were obtained (entry 1 *vs.* 8). Aldehydes bearing additional substituents in the α-position such as isobutyraldehyde and 2,2-diphenylacetaldehyde did not lead to the formation of the desired oxazine hetero-Diels–Alder adducts, probably due to increased steric demand and decreased reactivity of the corresponding enamines (entries 9,10). Similarly, electron-rich nitroso alkenes are known to be much less reactive than those bearing electron-withdrawing groups.[1j] Therefore, it was not surprising when no conversion was observed with α-chloro-4-methoxyacetophenone oxime (**2c**) under the standard reaction conditions (entries 11,12). However, the desired product could be obtained when stoichiometric amounts of pyrrolidine were used (entry 13). In contrast, the electron-poor α-bromo-4-nitroacetophenone oxime (**2d**) was found to be highly reactive and the oxazines **1i**–**1k** were obtained in reduced reaction times (entries 14–16). In a similar manner, reactions with 3-bromopyruvate oxime (**2e**) furnished the hetero-Diels–Alder adducts within 24 h, but yields were lower than expected due to side reactions of the starting material (entries 17–20). In addition, $NaOAc{\cdot}3H_2O$ could not be used as a buffer in these cases because of competitive reactions of the starting material with acetate and a $NaHCO_3$-based buffer had to be used instead.[16]

It is to be expected that the studies presented herein will greatly facilitate the development of a corresponding enantioselective access to oxazine derivatives. Initial experiments along this route were carried out using stoichiometric amounts of the chiral amine (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine and first results are promising as the oxazinone **8** could be obtained with 42% ee after oxidation of the hemiacetal **1h** with pyridinium chlorochromate(VI) (PCC) (Scheme 7). Preliminary studies on catalytic enantioselective reactions revealed that such processes are possible, but due to slower rates of the enamine formation and cycloaddition steps (see Scheme 3) yields were low and substantial amounts of by-products were formed. These drawbacks will be addressed in further studies.

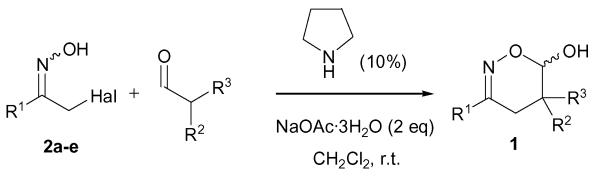


Scheme 7 Formation of oxazine derivatives mediated by a chiral secondary amine.

Conclusion

In summary, the first catalytic hetero-Diels–Alder reaction of nitroso alkenes using simple and inexpensive catalysts and reagents such as pyrrolidine, aldehydes and $NaOAc{\cdot}3H_2O$ has been developed. Underlying mechanistic principles and key stages in the catalytic cycle as well as potential side reactions have been identified and a number of 5,6-dihydro-4*H*-oxazines have been prepared in moderate to good yields in one step from α-halooximes under mild reaction conditions. Preliminary results indicate that a catalytic enantioselective reaction is possible.

Table 3 Organocatalytic synthesis of oxazine derivatives from α-halooximes and aldehydes



Entry	Oxime	R^1	Hal	R^2	R^3	*t*/h	Product	Yield (%)
1	**2b**	Ph	Cl	^{i}Pr	H	72	**1b**	81
2	**2b**	Ph	Cl	Me	H	72	**1c**	69
3	**2b**	Ph	Cl	Et	H	72	**1d**	89
4	**2b**	Ph	Cl	^{n}Pr	H	72	**1e**	77
5	**2b**	Ph	Cl	Ph	H	72	**1f**	87
6	**2b**	Ph	Cl	Bn	H	72	**1g**	68
7[a]	**2b**	Ph	Cl	H	H	24	–	–[b]
8	**2a**	Ph	Br	^{i}Pr	H	72	**1b**	75
9	**2b**	Ph	Cl	Me	Me	72	–	–[c]
10	**2b**	Ph	Cl	Ph	Ph	72	–	–[c]
11	**2c**	*p*-MeO–C_6H_4	Cl	^{i}Pr	H	72	–	–[c]
12	**2c**	*p*-MeO–C_6H_4	Cl	Bn	H	72	–	–[c]
13[d]	**2c**	*p*-MeO–C_6H_4	Cl	^{i}Pr	H	2	**1h**	58
14	**2d**	*p*-NO_2–C_6H_4	Br	^{i}Pr	H	24	**1i**	59
15	**2d**	*p*-NO_2–C_6H_4	Br	Bn	H	24	**1j**	68
16	**2d**	*p*-NO_2–C_6H_4	Br	Me	H	24	**1k**	52
17[e]	**2e**	EtO_2C	Br	^{i}Pr	H	24	**1l**	48
18[e]	**2e**	EtO_2C	Br	^{c}Pr	H	24	**1m**	50
19[e]	**2e**	EtO_2C	Br	Et	H	24	**1n**	44
20[e]	**2e**	EtO_2C	Br	Bn	H	24	**1o**	57

[a] Reaction at 5 °C. [b] Decomposition. [c] No reaction. [d] Pyrrolidine (1.0 equiv.) was used. [e] $NaHCO_3$ (2.0 equiv.) and TFA (0.2 equiv.) were used as buffer.

Experimental

General details

NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 MHz (^{1}H) or 100 MHz (^{13}C), respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals. The multiplicities of ^{1}H signals are designated by the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; br = broad; m = multiplet, app = apparent. All coupling constants, *J*, are reported in Hertz. ^{13}C NMR spectra were acquired on a broad band decoupled mode and the multiplicities were obtained using DEPT sequences. The following symbolisms are used for the multiplicities in ^{13}C spectra: q = primary methyl; t = secondary methylene; d = tertiary methine; s = quaternary. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES$^+$) ionisation techniques or on a Kratos MS890MS using electron ionisation (EI$^+$) techniques. Flash column chromatography was carried out using Fluka Kieselgel 60 (230–400 mesh). Analytical thin layer chromatography (TLC) was performed using precoated aluminium-backed plates (Merck Kieselgel 60 F254) and visualised by ultraviolet irradiation or vanillin dip. Analytical grade solvents were used. All commercially available reagents were used as received. The α-halooximes **2a**–**e** and the enamine **4** were prepared according to literature procedures.[2b,12,17] The ester **6** was identified through comparison with data reported in the literature.[18] The methylene protons of **6** at δ_H 4.98 and 5.31 (for *trans*- and *cis*-isomers, respectively) and the hemiacetal methine protons of the dihydro oxazines **1** were used to estimate conversion by ^{1}H NMR of crude reaction mixtures.

General procedure for the preparation of 5,6-dihydro-4*H*-oxazines. Pyrrolidine (4 µl, 0.05 mmol) and the aldehyde (1.5 mmol) were added to a suspension of NaOAc·3H_2O (136 mg, 1.00 mmol) in CH_2Cl_2 and stirred for 5 min at ambient temperature. The α-halooxime (0.5 mmol) was added to this mixture and the reaction was monitored by TLC. Where applicable, conversion was determined by NMR analysis of a filtered aliquot of the reaction mixture. Upon complete conversion of the α-halooxime, the mixture was adsorbed to silica gel (*ca.* 1.5 g) and the solvent was evaporated *in vacuo*. The product was purified by column chromatography. Diastereomeric ratios were estimated from the ^{1}H NMR signals of the hemiacetal methine protons of the products.[19] Deviations from this procedure are noted with the individual experiments.

5-Isopropyl-3-phenyl-6-(pyrrolidin-1-yl)-5,6-dihydro-4*H*-[1,2]-oxazine (1a). α-Bromoacetophenone oxime (**2a**) (214 mg, 1.00 mmol) was dissolved in a suspension of Na_2CO_3 (159 mg, 1.50 mmol) in CH_2Cl_2 (3 ml). The enamine 1-((*E*)-3-methylbut-1-enyl)-pyrrolidine (**4**) (328 µl, 2.00 mmol) was added dropwise at ambient temperature. After 2 h, the starting material had been completely consumed and the reaction products were separated by column chromatography. Apart from compound **1b** (75 mg, 34%), two diastereomers of compound **1a** were obtained as colourless oils (*major diastereoisomer*: 35 mg, 13%, *minor diastereoisomer*: 22 mg, 8%). *Major diastereoisomer: R_f* 0.60 (1 : 3 pentane : ether); δ_H (400 MHz, $CDCl_3$) 0.80 (3H, d, *J* 7.0, C*H*$_3$), 0.91 (3H, d, *J* 7.0, C*H*$_3$), 1.66–1.78 (4H, m, 2 × C*H*$_2$), 1.90–2.16 (2H, m, 2 × C*H*), 2.34 (1H, dd, *J* 17.8, 11.2, N=CC*H*H), 2.59 (1H, dd, *J* 17.8, 7.4, N=CCH*H*), 2.84–3.02 (4H, m, 2 × NC*H*$_2$), 4.48 (1H, d, *J* 10.0, OC*H*), 7.24–7.31 (3H, m, Ar*H*), 7.62 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 16.1 (q), 20.6 (q), 23.8 (t), 25.2 (t), 26.9 (d), 38.2 (d), 47.0 (t), 92.5 (d), 125.5 (d), 128.6 (d), 129.4 (d), 136.2 (s), 155.1 (s); *m*/*z* (ES$^+$) 273 (100%, MH$^+$) [Found: (MH$^+$) 273.1970. $C_{17}H_{25}N_2O$ requires *M*H, 273.1967]. *Minor diastereoisomer: R_f* 0.21 (1 : 3 pentane : ether); δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.8, C*H*$_3$), 1.02 (3H, d, *J* 6.8, C*H*$_3$), 1.75–1.91 (5H, m, 2 × C*H*$_2$, C*H*), 2.03–2.10 (1H, m, $(CH_3)_2$C*H*), 2.62 (1H, dd, *J* 17.2, 6.1, N=CC*H*H), 2.80–2.89 (2H, m, NC*H*$_2$), 3.08 (1H, dd, *J* 17.2, 9.1, N=CCH*H*), 3.38–3.42 (2H, m, NC*H*$_2$), 4.98 (1H, d, *J* 6.7, OC*H*), 7.38–7.48 (3H, m, Ar*H*), 8.35–8.41 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 19.4 (q), 20.3 (q), 24.9 (t), 31.2 (t), 31.5 (t), 41.4 (d), 47.9 (t), 93.3 (d), 127.3 (d), 128.6 (d), 130.2 (d), 138.8 (s), 155.6 (s); *m*/*z* (ES$^+$) 273 (100%, MH$^+$) [Found: (MH$^+$) 273.1974. $C_{17}H_{25}N_2O$ requires *M*H, 273.1967].

5-Isopropyl-3-phenyl-5,6-dihydro-4*H*-[1,2]oxazin-6-ol (1b). Compound **1b** was prepared according to the general procedure and after 72 h the product was isolated as a yellow solid (88 mg, 81%). R_f 0.50 (1 : 3 pentane : ether); δ_H (400 MHz, acetone-d_6, *ca.* 60 : 40 mixture of diastereomers) 0.94–1.06 (6H, m, 2 × C*H*$_3$), 1.43–1.83 (2H, m, 2 × C*H*), 2.33 (0.6H, dd, *J* 17.6, 12.5, N=CC*H*H), 2.54 (0.4H, dd, *J* 18.0, 4.5, N=CC*H*H), 2.70 (0.6H, dd, *J* 17.6, 6.0, N=CCH*H*), 2.79 (0.4H, dd, *J* 18.0, 6.4, N=CCH*H*), 5.46 (0.6H, br d, *J* 4.0, O$_2$C*H*), 5.83 (0.4H, br d, *J* 4.0, O$_2$C*H*), 7.26–7.42 (3H, m, Ar*H*), 7.70–7.81 (2H, m, Ar*H*); δ_C (100 MHz, acetone-d_6) 18.9 (q), 19.3 (q), 19.8 (q), 20.0 (q), 21.1 (t), 21.8 (t), 27.9 (d), 29.9 (d), 39.9 (d), 40.0 (d), 90.8 (d), 93.5 (d), 125.5 (d), 125.6 (d), 128.5 (2 × d), 129.3 (d), 129.4 (d), 136.8 (2 × s), 154.2 (2 × s); *m*/*z* (ES$^+$) 242 (100%, MNa$^+$) [Found: (MNa$^+$) 242.1156. $C_{13}H_{17}NaNO_2$ requires *M*Na, 242.1157].

5-Methyl-3-phenyl-5,6-dihydro-4*H*-[1,2]oxazin-6-ol (1c). Compound **1c** was prepared according to the general procedure and after 72 h the product was isolated as a dark yellow solid (66 mg, 69%). R_f 0.38 (3 : 1 pentane : THF); δ_H (400 MHz, acetone-d_6, *ca.* 60 : 40 mixture of diastereomers) 1.02 (1.2H, d, *J* 7.0, C*H*$_3$), 1.10 (1.8H, d, *J* 7.0, C*H*$_3$), 2.05–2.20 (1H, m, C*H*), 2.31 (0.6H, dd, *J* 17.6, 12.0, N=CC*H*H), 2.34 (0.4H, dd, *J* 18.0, 4.2, N=CC*H*H), 2.61 (0.6H, dd, *J* 17.6, 6.4, N=CCH*H*), 2.86 (0.4H, dd, *J* 18.0, 6.8, N=CCH*H*), 5.06 (0.4H, br d, *J* 3.8, O$_2$C*H*), 5.30 (0.6H, br d, *J* 2.0, O$_2$C*H*), 7.31–7.45 (3H, m, Ar*H*), 7.66–7.79 (2H, m, Ar*H*); δ_C (100 MHz, acetone-d_6) 16.2 (q), 24.6 (t), 25.4 (t), 28.2 (d), 28.4 (d), 30.1 (q), 92.9 (d), 95.3 (d), 125.4 (2 × d), 128.5 (2 × d), 129.3 (d), 129.4 (d), 136.7 (s), 136.9 (s), 153.5 (s), 154.0 (s); *m*/*z* (ES$^+$) 214 (100%, MNa$^+$) [Found: (MNa$^+$) 214.0844. $C_{11}H_{13}NaNO_2$ requires *M*Na, 214.0844].

5-Ethyl-3-phenyl-5,6-dihydro-4*H*-[1,2]oxazin-6-ol (1d). Compound **1d** was prepared according to the general procedure and after 72 h the product was isolated as a yellow solid (91 mg, 89%). R_f 0.41 (3 : 1 pentane : THF); δ_H (400 MHz, acetone-d_6, *ca.* 60 : 40 mixture of diastereomers) 0.98 (1.2H, t, *J* 7.4, C*H*$_3$), 1.03 (1.8H, t, *J* 7.4, C*H*$_3$), 1.42–1.66 (2H, m, C*H*$_2$CH$_3$), 1.81–1.96 (1H, m, C*H*), 2.31 (0.6H, dd, *J* 17.6, 12.5, N=CC*H*H), 2.40 (0.4H, dd, *J* 18.0, 3.9, N=CC*H*H), 2.65 (0.6H, dd, *J* 17.6, 6.1, N=CCH*H*), 2.84 (0.4H, dd, *J* 18.0, 6.8, N=CCH*H*), 5.08 (0.4H, br d, *J* 3.8, O$_2$C*H*), 5.38 (0.6H, br d, *J* 2.0, O$_2$C*H*), 7.38–7.42 (3H, m, Ar*H*), 7.66–7.80 (2H, m, Ar*H*); δ_C (100 MHz, acetone-d_6) 10.4 (q), 10.8(q), 22.9 (t), 23.2 (t), 24.0 (t), 24.8 (t), 34.9 (d), 35.3 (d), 91.8 (d), 94.1 (d), 125.4 (2 × d), 128.5 (2 × d), 129.2 (d), 129.3 (d), 136.8 (s), 136.9 (s), 153.8 (s), 154.0 (s). *m*/*z* (ES$^+$) 228 (100%, MNa$^+$) [Found: (MNa$^+$) 228.0994. $C_{12}H_{15}NaNO_2$ requires *M*Na, 228.1000].

5-Propyl-3-phenyl-5,6-dihydro-4*H*-[1,2]oxazin-6-ol (1e). Compound **1e** was prepared according to the general procedure and after 72 h the product was isolated as a yellow solid (84 mg, 77%). R_f 0.38 (3 : 1 pentane : THF); δ_H (400 MHz, acetone-d_6, *ca.* 60 : 40 mixture of diastereomers) 0.94–0.99 (3H, m, C*H*$_3$), 1.40–1.58 (4H, m, 2 × C*H*$_2$), 1.89–1.99 (1H, m, C*H*), 2.30 (0.6H, dd, *J* 17.6, 12.5, N=CC*H*H), 2.39 (0.4H, dd, *J* 18.0, 3.2, N=CC*H*H), 2.61 (0.6H, dd, *J* 17.6, 6.0), 2.84 (0.4H, dd, *J* 18.0, 6.6, N=CCH*H*), 5.14 (0.4H, br d, *J* 3.8, O$_2$C*H*), 5.38 (0.6H, br d, *J* 2.8, O$_2$C*H*), 7.35–7.46 (3H, m, Ar*H*), 7.70–7.81 (2H, m, Ar*H*); δ_C (100 MHz, acetone-d_6) 13.8 (q), 13.9 (q), 19.4 (t), 19.8 (d), 23.1 (t), 23.5 (t), 33.0 (d), 33.4 (d), 33.5 (t), 34.2 (t), 92.0 (d), 94.3 (d), 125.4 (2 × d), 128.5 (2 × d), 129.2 (d), 129.3 (d), 136.8 (s), 136.9 (s), 153.9 (s), 154.1 (s); *m*/*z* (ES$^+$) 242 (100%, MNa$^+$) [Found: (MNa$^+$) 242.1150. $C_{13}H_{17}NaNO_2$ requires *M*Na, 242.1157].

5-Phenyl-3-phenyl-5,6-dihydro-4*H*-[1,2]oxazin-6-ol (1f). Compound **1f** was prepared according to the general procedure and after 72 h the product was isolated as a yellow solid (110 mg, 87%). R_f 0.35 (3 : 1 pentane : THF); δ_H (400 MHz, acetone-d_6, *ca.* 60 : 40 mixture of diastereomers) 2.82 (0.6H, dd, *J* 17.4,5.5, N=CC*H*H), 2.84 (0.4H, dd, *J* 18.2, 5.5, N=CC*H*H), 3.05 (0.6H, dd, *J* 17.4, 13.1, N=CCH*H*), 3.16 (0.4H, dd, *J* 18.2, 7.4, N=CCH*H*), 3.24–3.32 (1H, m, C*H*), 5.40 (0.4H, br d, *J* 4.6, O$_2$C*H*), 5.56 (0.6H, br d, *J* 2.3, O$_2$C*H*), 7.20–7.54 (8H, m, Ar*H*), 7.77–7.83 (2H, m, Ar*H*); δ_C (100 MHz, CDCl$_3$) 23.7 (t), 24.9 (t), 39.5 (d), 39.6 (d), 92.8 (d), 94.5 (d), 125.9 (2 × d), 127.6 (d), 127.7 (d), 127.9 (d), 128.6 (2 × d), 128.8 (d), 128.9 (2 × d), 130.0 (d), 130.2 (d), 135.5 (s), 135.6 (s), 139.4 (s), 140.5 (s), 156.2 (s), 156.9 (s); *m*/*z* (ES$^+$) 276 (100%, MNa$^+$) [Found: (MNa$^+$) 276.1007. $C_{16}H_{15}NaNO_2$ requires *M*Na, 276.1000].

5-Benzyl-3-phenyl-5,6-dihydro-4*H*-[1,2]oxazin-6-ol (1g). Compound **1g** was prepared according to the general procedure and after 72 h the product was isolated as a yellow solid (91 mg, 68%). R_f 0.38 (3 : 1 pentane : THF); δ_H (400 MHz, CDCl$_3$, *ca.* 60 : 40 mixture of diastereomers) 2.24–2.58 (3H, m, C*H*, PhC*H*$_2$), 2.71–2.90 (2H, m, N=CC*H*$_2$), 5.25 (0.4H, br d, *J* 2.8, O$_2$C*H*), 5.32 (0.6H, br d, *J* 2.8, O$_2$C*H*), 7.09–7.41 (8H, m, Ar*H*), 7.62–7.70 (2H, m, Ar*H*); δ_C (100 MHz, CD$_3$NO$_2$, 60 °C) 22.6 (t), 23.1 (t), 35.1 (d), 35.2 (d), 36.9 (t), 37.6 (d), 91.9 (d), 93.8 (d), 125.5 (2 × d), 126.4 (2 × d), 128.2 (2 × d), 128.5 (2 × d), 129.2 (d), 129.3 (d), 129.5 (d), 129.6 (d), 136.4 (s), 136.6 (s), 139.5 (2 × s), 155.3 (s), 155.5 (s); *m*/*z* (ES$^+$) 290 (100%, MNa$^+$) [Found: (MNa$^+$) 290.1162. $C_{17}H_{17}NaNO_2$ requires *M*Na, 290.1157].

5-Isopropyl-3-(4-methoxyphenyl)-5,6-dihydro-4*H*-[1,2]oxazin-6-ol (1h). Compound **1h** was prepared according to the general procedure in the absence of NaOAc·3H$_2$O, using a stoichiometric amount of pyrrolidine (42 µl, 0.5 mmol). The product was isolated as a colourless solid after 2 h (72 mg, 58%). R_f 0.43 (4 : 1 CH$_2$Cl$_2$: ether); δ_H (400 MHz, CDCl$_3$, *ca.* 75 : 25 mixture of diastereomers) 0.93 (0.75H, d, *J* 6.0, C*H*$_3$), 0.98–1.01 (5.25H, m, C*H*$_3$), 1.54–1.80 (2H, m, 2 × C*H*), 2.35 (0.75H, dd, *J* 17.6, 12.4, N=CC*H*H), 2.42 (0.25H, dd, *J* 17.6, 3.6, N=CC*H*H), 2.60 (0.75H, dd, *J* 17.6, 3.4, N=CCH*H*), 2.76 (0.25H, dd, *J* 18.0, 6.8, N=CCH*H*), 3.82 (3H, s, OC*H*$_3$), 5.39 (0.25H, d, *J* 2.8, O$_2$C*H*), 5.55 (0.75H, d, *J* 2.4, O$_2$C*H*), 6.86–6.92 (2H, m, Ar*H*), 7.63–7.69 (2H, m, Ar*H*); δ_C (100 MHz, CDCl$_3$) 19.6 (2 × q), 20.1 (q), 20.3 (q), 20.8 (t), 21.9 (t), 28.0 (d), 29.6 (d), 39.5 (d), 39.8 (d), 55.3 (2 × q), 90.8 (d), 93.2 (d), 113.7 (2 × d), 126.8 (d), 126.9 (d), 128.1 (s), 128.2 (s), 155.3 (s), 156.6 (s), 160.6 (s), 160.7 (s); *m*/*z* (ES$^+$) 272 (100%, MNa$^+$) [Found: (MNa$^+$) 272.1262. $C_{14}H_{19}NNaO_3$ requires *M*Na, 272.1263].

5-Isopropyl-3-(4-nitrophenyl)-5,6-dihydro-4*H*-[1,2]oxazin-6-ol (1i). Compound **1i** was prepared according to the general procedure and after 24 h the product was isolated as a yellow oil (78 mg, 59%). R_f 0.32 (3 : 1 pentane : THF); δ_H (400 MHz, CDCl$_3$, *ca.* 75 : 25 mixture of diastereomers) 0.95–1.03 (6H, m, 2 × C*H*$_3$), 1.58–1.85 (2H, m, 2 × C*H*), 2.42 (0.75H, dd, *J* 17.6, 12.1, N=CC*H*H), 2.48 (0.25H, dd, *J* 18.0, 3.0, N=CC*H*H), 2.62 (0.75H, dd, *J* 17.6, 5.9, N=CCH*H*), 2.83 (0.25H, dd, *J* 18.0, 7.0, N=CCH*H*), 5.43 (0.25H, br d, *J* 2.6, O$_2$C*H*), 5.60 (0.75H, br d, *J* 2.0, O$_2$C*H*), 7.82–7.90 (2H, m, Ar*H*), 8.18–8.26 (2H, m, Ar*H*); δ_C (100 MHz, CDCl$_3$) 19.8 (q), 20.0 (q), 20.3 (q), 20.6 (q), 20.9 (t), 22.2 (t), 28.0 (d), 29.8 (d), 39.1 (d), 39.4 (d), 91.6 (d), 93.4 (d), 123.9 (d), 124.0 (d), 126.6 (2 × d), 141.8 (s), 141.9 (s), 148.5 (2 × s), 154.4 (s), 154.8 (s); *m*/*z* (EI$^+$) 264 (36%, M$^+$) [Found: (M$^+$) 264.1108. $C_{13}H_{16}N_2O_4$ requires *M*, 264.1110].

5-Benzyl-3-(4-nitrophenyl)-5,6-dihydro-4*H*-[1,2]oxazin-6-ol (1j). Compound **1j** was prepared according to the general procedure and after 24 h the product was isolated as a yellow oil (106 mg, 68%). R_f 0.34 (3 : 1 pentane : THF); δ_H (400 MHz,

$CDCl_3$, *ca.* 60 : 40 mixture of diastereomers) 2.28–2.58 (3H, m, C*H*, ArC*H*$_2$), 2.71–2.93 (2H, m, N=CC*H*$_2$), 5.29 (0.4H, br d, *J* 2.6, O_2C*H*), 5.36 (0.6H, br d, *J* 2.2, O_2C*H*), 7.18–7.38 (5H, m, Ar*H*), 7.80–7.88 (2H, m, *p*-NO_2–Ar*H*), 8.18–8.26 (2H, m, *p*-NO_2–Ar*H*); δ_C (100 MHz, $CDCl_3$) 22.0 (t), 23.3 (t), 34.0 (d), 34.7 (d), 37.2 (t), 38.0 (t), 92.0 (d), 93.2 (d), 123.9 (d), 124.0 (d), 126.5 (d), 126.6 (d), 126.9 (2 × d), 128.9 (2 × d), 129.2 (d), 129.3 (d), 138.3 (s), 138.4 (s), 141.6 (s), 141.8 (s), 148.6 (2 × s), 154.1 (s), 154.6 (s); *m*/*z* (EI$^+$) 312 (15%, M$^+$) [Found: (M$^+$) 312.1111. $C_{17}H_{16}N_2O_4$ requires *M*, 312.1110].

5-Methyl-3-(4-nitrophenyl)-5,6-dihydro-4*H*-[1,2]oxazin-6-ol (1k). Compound **1k** was prepared according to the general procedure and after 24 h the product was isolated as a yellow oil (61 mg, 52%). R_f 0.30 (3 : 1 pentane : THF); δ_H (400 MHz, $CDCl_3$, *ca.* 60 : 40 mixture of diastereomers) 1.05 (1.2H, d, *J* 6.8, C*H*$_3$), 1.15 (1.8H, d, *J* 6.8, C*H*$_3$), 2.08–2.18 (1.8H, m, C*H*), 2.23–2.34 (1.2H, m, C*H*), 2.30 (0.4H, dd, *J* 18.0, 3.2, N=CC*H*H), 2.44 (0.6H, dd, *J* 17.6, 11.9, N=CC*H*H), 2.54 (0.6H, dd, *J* 17.6, 6.5, N=CCH*H*), 2.92 (0.4H, dd, *J* 18.0, 7.6, N=CCH*H*), 5.23 (0.4H, br d, *J* 3.0, O_2C*H*), 5.42 (0.6H, br d, *J* 2.5, O_2C*H*), 7.82–7.90 (2H, m, Ar*H*), 8.18–8.24 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 16.6 (q), 16.8 (q), 24.8 (t), 24.9 (t), 27.3 (d), 27.7 (d), 93.6 (d), 95.2 (d), 123.9 (2 × d), 126.5 (2 × d), 141.7 (s), 142.0 (s), 148.5 (2 × s), 153.5 (s), 154.2 (s); *m*/*z* (EI$^+$) 236 (43%, M$^+$) [Found: (M$^+$) 236.0794. $C_{11}H_{12}N_2O_4$ requires *M*, 236.0797].

6-Hydroxy-5-isopropyl-5,6-dihydro-4*H*-[1,2]oxazine-3-carboxylic acid ethyl ester (1l). Compound **1l** was prepared according to the general procedure (with $NaHCO_3$ (84 mg, 1 mmol) and CF_3CO_2H (8 μl, 0.1 mmol) as a buffer) and after 24 h the product was isolated as a colourless oil (52 mg, 48%). R_f 0.25 (1 : 1 pentane : ether); δ_H (400 MHz, $CDCl_3$, *ca.* 70 : 30 mixture of diastereomers) 0.90 (0.9H, d, *J* 6.7, CHC*H*$_3$), 0.95 (0.9H, d, *J* 6.7, CHC*H*$_3$), 0.96 (2.1H, d, *J* 6.7, CHC*H*$_3$), 0.99 (2.1H, d, *J* 6.7, CHC*H*$_3$), 1.33 (3H, app t, *J* 7.2, CH_2C*H*$_3$), 1.35–1.72 (2H, m, 2 × C*H*), 2.11 (0.7H, dd, *J* 18.8, 12.8, N=CC*H*H), 2.45 (0.3H, dd, *J* 19.1, 3.6, N=CC*H*H), 2.56 (0.3H, dd, *J* 19.1, 6.8, N=CCH*H*), 2.63 (0.7H, dd, *J* 18.8, 6.1, N=CCH*H*), 4.31 (2H, app q, *J* 7.2, C*H*$_2$CH$_3$), 5.41 (0.3H, br d, *J* 3.1, O_2C*H*), 5.56 (0.7H, br d, *J* 2.2, O_2C*H*); δ_C (100 MHz, $CDCl_3$) 14.3 (2 × q), 19.5 (t), 19.8 (q), 19.9 (q), 20.3 (q), 20.5 (q), 20.7 (t), 27.7 (d), 29.6 (d), 38.3 (d), 38.9 (d), 62.3 (2 × t), 92.2 (d), 93.8 (d), 150.9 (s), 151.2 (s), 163.5 (2 × s); *m*/*z* (ES$^+$) 238 (100%, MNa$^+$) [Found: (MNa$^+$) 238.1056. $C_{10}H_{17}NaNO_4$ requires *M*Na, 238.1055].

6-Hydroxy-5-propyl-5,6-dihydro-4*H*-[1,2]oxazine-3-carboxylic acid ethyl ester (1m). Compound **1m** was prepared according to the general procedure (with $NaHCO_3$ (84 mg, 1 mmol) and CF_3CO_2H (8 μl, 0.1 mmol) as a buffer) and after 24 h the product was isolated as a colourless oil (54 mg, 50%). R_f 0.25 (1 : 1 pentane : ether); δ_H (400 MHz, $CDCl_3$, *ca.* 60 : 40 mixture of diastereomers) 0.90 (1.2H, t, *J* 7.0, CH_2C*H*$_3$) 0.92 (1.8H, t, *J* 7.0, CH_2C*H*$_3$), 1.29–1.50 (7H, m, C*H*$_2$CH$_2$, CH$_2$C*H*$_2$, CH$_2$C*H*$_3$), 1.81–1.90 (0.6H, m, C*H*), 1.96–2.06 (0.4H, m, C*H*), 2.12 (0.6H, dd, *J* 18.8, 12.8, N=CC*H*H), 2.32 (0.4H, dd, *J* 19.1, 2.5, N=CC*H*H), 2.53 (0.6H, dd, *J* 18.8, 6.0, N=CCH*H*), 2.60 (0.4H, dd, *J* 19.1, 7.1), 4.32 (2H, app q, *J* 7.2, OCH$_2$C*H*$_3$), 5.26 (0.4H, br d, *J* 2.8, O_2C*H*) 5.42 (0.6H, br d, *J* 2.1, O_2C*H*); δ_C (100 MHz, $CDCl_3$) 14.2 (q), 14.3 (q), 14.4 (2 × q), 19.5 (t), 19.9 (t), 21.5 (t), 21.9 (t), 31.5 (d), 31.8 (d), 32.8 (t), 33.5 (t), 62.3 (t), 62.4 (t), 93.2 (d), 94.7 (d), 150.5 (s), 151.1 (s), 163.4 (s), 163.5 (s); *m*/*z* (ES$^+$) 238 (100%, MNa$^+$) [Found: (MNa$^+$) 238.1056. $C_{10}H_{17}NaNO_4$ requires *M*Na, 238.1055].

6-Hydroxy-5-ethyl-5,6-dihydro-4*H*-[1,2]oxazine-3-carboxylic acid ethyl ester (1n). Compound **1n** was prepared according to the general procedure (with $NaHCO_3$ (84 mg, 1 mmol) and CF_3CO_2H (8 μl, 0.1 mmol) as a buffer) and after 24 h the product was isolated as a colourless oil (44 mg, 44%). R_f 0.16 (1 : 1 pentane : ether); δ_H (400 MHz, $CDCl_3$, *ca.* 60 : 40 mixture of diastereomers) 0.93 (1.2H, t, *J* 7.6, CH_2C*H*$_3$), 0.96 (1.8H, *J* 7.6, CH_2C*H*$_3$), 1.33 (3H, app t, *J* 7.2, OCH$_2$C*H*$_3$), 1.35–1.56 (2H, m, C*H*$_2$CH$_3$), 1.66–1.76 (0.6H, m, C*H*), 1.83–1.92 (0.4H, m C*H*), 2.13 (0.6H, dd, *J* 18.8, 12.7, N=CC*H*H), 2.32 (0.4H, dd, *J* 19.1, 2.8, N=CC*H*H), 2.53 (0.6H, dd, *J* 18.8, 6.0, N=CCH*H*), 2.59 (0.4H, dd, *J* 19.1, 7.1, N=CCH*H*), 4.29 (2H, app q, *J* 7.2, OC*H*$_2$CH$_3$), 5.29 (0.4H, br d, *J* 2.0, O_2C*H*), 5.44 (0.6H, br d, *J* 1.4, O_2C*H*); δ_C (100 MHz, $CDCl_3$) 11.0 (q), 11.4 (q), 14.3 (2 × q), 21.4 (t), 21.8 (t), 23.7 (t), 24.4 (t), 33.6 (d), 33.8 (d), 62.3 (2 × t), 93.1 (d), 94.6 (d), 150.4 (s), 150.9 (s), 163.5 (s), 163.6 (s); *m*/*z* (ES$^+$) 224 (100%, MNa$^+$) [Found: (MNa$^+$) 224.0900. $C_9H_{15}NaNO_4$ requires *M*Na, 224.0899].

6-Hydroxy-5-benzyl-5,6-dihydro-4*H*-[1,2]oxazine-3-carboxylic acid ethyl ester (1o). Compound **1o** was prepared according to the general procedure (with $NaHCO_3$ (84 mg, 1 mmol) and CF_3CO_2H (8 μl, 0.1 mmol) as a buffer) and after 24 h the product was isolated as a colourless oil (75 mg, 57%). R_f 0.13 (1 : 1 pentane : ether); δ_H (400 MHz, $CDCl_3$, *ca.* 60 : 40 mixture of diastereomers) 1.31 (1.8H, t, *J* 7.2, CH_2C*H*$_3$), 1.34 (1.2H, t, *J* 7.2, CH_2C*H*$_3$), 2.09–2.82 (5H, m, C*H*, N=CC*H*$_2$, ArC*H*$_2$), 4.28 (1.2H, q, *J* 7.2, C*H*$_2$CH$_3$), 4.31 (0.8H, q, *J* 7.2, C*H*$_2$CH$_3$), 5.23 (0.4H, br d, *J* 2.5, O_2C*H*), 5.32 (0.6H, br d, *J* 2.0, O_2C*H*), 7.15–7.34 (5H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 14.3 (2 × q), 21.3 (t), 22.0 (t), 33.6 (d), 34.3 (d), 37.0 (t), 37.7 (t), 62.3 (t), 62.4 (t), 92.6 (d), 93.7 (d), 126.8 (2 × d), 128.8 (d), 128.9 (d), 129.2 (d), 129.4 (d), 138.3 (s), 138.4 (s), 150.2 (s), 150.8 (s), 163.3 (s), 163.5 (s); *m*/*z* (ES$^+$) 286 (100%, MNa$^+$) [Found: (MNa$^+$) 286.1052. $C_{14}H_{17}NaNO_4$ requires *M*Na, 286.1055].

1-Phenyl-2-(pyrrolidin-1-yl)ethanone oxime (5). Pyrrolidine (42 μl, 0.5 mmol) was added to a solution of α-bromoacetophenone oxime (**2a**) (53 mg, 0.25 mmol) in CH_2Cl_2 (1 ml) and the solution was stirred at ambient temperature. TLC analysis immediately after addition of pyrrolidine revealed complete conversion of **2a**. Compound **5** was isolated as a colourless oil after column chromatography (50 mg, 98%). R_f 0.10 (1 : 1 pentane : ether); δ_H (400 MHz, $CDCl_3$) 1.62–1.69 (4H, m, 2 × C*H*$_2$), 2.42–2.52 (4H, 2 × NC*H*$_2$), 3.43 (2H, s, N=CCH$_2$), 7.23–7.34 (3H, m, Ar*H*), 7.46–7.51 (2H, m, Ar*H*), 9.8 (1H, br s, O*H*); δ_C (100 MHz, $CDCl_3$) 23.7 (t), 54.3 (t), 59.9 (t), 128.3 (d), 128.5 (d), 129.2 (d), 133.1 (s), 155.2 (s); *m*/*z* (ES$^+$) 205 (100%, MH$^+$) [Found: (MH$^+$) 205.1348. $C_{12}H_{17}N_2O$ requires *M*H, 205.1341].

2-Bromo-1-phenylethanone *O*-methyl-oxime (7a). α-Bromoacetophenone (3.98 g, 20.0 mmol) and *O*-methyl hydroxylamine hydrochloride (2.50 g, 30.0 mmol) were dissolved in ethanol (50 ml) containing one drop of concentrated sulfuric acid. The mixture was stirred at ambient temperature for 2 h. The solvent was evaporated *in vacuo* to near dryness. Ether (50 ml) was added and the solution was washed with 1 M aqueous $KHSO_4$ (2 × 20 ml), saturated aqueous $NaHCO_3$ (20 ml) and water (20 ml). The organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. Filtration of the crude product (dissolved in 3 : 1 pentane : CH_2Cl_2) through a short pad of silica gel and evaporation of the solvents *in vacuo* afforded the product as a colourless liquid (3.40 g, ≈75%).[20] R_f 0.40 (3 : 1 pentane : CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 4.13 (3H, s, C*H*$_3$), 4.37 (2H, s, C*H*$_2$), 7.40–7.48 (3H, m, Ar*H*), 7.72–7.78 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 18.3 (t), 63.1 (q), 126.4 (d), 128.9 (d), 129.9 (d), 133.7 (s), 152.9 (s); *m*/*z* (ES$^+$) 228 (88%, MH$^+$) [Found: (MH$^+$) 228.0050. $C_9H_{11}BrNO$ requires *M*H, 228.0024].

2-Chloro-1-phenylethanone *O*-methyl-oxime (7b). Compound **7b** was prepared from α-chloroacetophenone (1.54 g, 10.0

mmol) and *O*-methyl hydroxylamine hydrochloride (1.25 g, 15.0 mmol), following an analogous procedure as described for compound **7a**. The product was obtained as a colourless liquid (1.65 g, 90%). R_f 0.56 (1 : 1 pentane : CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 4.08 (3H, s, C*H*$_3$), 4.53 (2H, s, C*H*$_2$), 7.38–7.42 (3H, m, Ar*H*), 7.69–7.73 (2H, m, Ar*H*); δ_C (100 MHz, $CDCl_3$) 32.8 (t), 63.0 (q), 126.4 (d), 128.9 (d), 129.9 (d), 133.6 (s), 152.8 (s); *m*/*z* (ES^+) 184 (100%, MH^+) [Found: (MH^+) 184.0533. $C_9H_{11}ClNO$ requires *M*H, 184.0529].

5-Isopropyl-3-(4-methoxyphenyl)-4,5-dihydro-[1,2]oxazin-6-one (8). To an ice-cooled solution of **1h** (27 mg, 0.11 mmol) in CH_2Cl_2 (1.5 ml) was added PCC (17 mg, 0.08 mmol). After stirring for 1.5 hours additional PCC (17 mg, 0.08 mmol) was added and the reaction mixture was left to warm to room temperature. After 16 hours the reaction product was separated by column chromatography (colourless oil, 16 mg, 58%). R_f 0.60 (9 : 1 CH_2Cl_2 : ether); δ_H (400 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.4, C*H*$_3$), 1.07 (3H, d, *J* 6.8, C*H*$_3$), 2.29 (1H, app oct, *J* 6.6, C*H*(CH_3)$_2$), 2.51 (1H, app dt, *J* 10.0, 5.8, C*H*CO_2), 2.87 (1H, dd, *J* 16.8, 9.8, N=CC*H*H), 2.98 (1H, dd, *J* 17.2, 6.4, N=CCH*H*), 3.86 (3H, s, OC*H*$_3$), 6.96 (2H, d, *J* 9.2, Ar*H*), 7.70 (2H, d, *J* 8.8, Ar*H*); δ_C (100 MHz, $CDCl_3$) 18.8 (q), 20.3 (q), 24.0 (t), 27.0 (d), 41.0 (d), 55.4 (q), 114.3 (d), 124.6 (s), 128.1 (d), 161.3 (s), 162.0 (s), 171.5 (s); *m*/*z* (ES^+) 248 (100%, MH^+) [Found: (MH^+) 248.1285. $C_{14}H_{18}NO_3$ requires *M*H, 248.1287]. The enantiomeric excess was determined by HPLC using Daicel Chiralpak AS columns (two columns in series) (hexane–*i*-PrOH (98 : 2); flow rate 1.0 ml min^{-1}; τ_{major} = 123 min; τ_{minor} = 116 min).

Acknowledgments

This work was made possible by a grant from The Danish National Research Foundation and EU:HMPT-CT-2001-00317.

References

1 (*a*) A. Kamimura, Y. Kaneko, A. Ohta, A. Kakehi, H. Matsuda and S. Kanemasa, *Tetrahedron Lett.*, 1999, **40**, 4349–4352; (*b*) A. Kamimura, Y. Kaneko, A. Ohta, K. Matsuura, Y. Fujimoto, A. Kakehi and S. Kanemasa, *Tetrahedron*, 2002, **58**, 9613–9620; (*c*) R. Zimmer, B. Orschel, S. Scherer and H.-U. Reißig, *Synthesis*, 2002, 1553–1563; (*d*) R. Zimmer, M. Hoffmann and H.-U. Reißig, *Chem. Ber.*, 1992, **125**, 2243–2248; (*e*) J. Angermann, K. Homann, H.-U. Reißig and R. Zimmer, *Synlett*, 1995, 1014–1016; (*f*) J. K. Gallos, V. C. Sarli, A. C. Varvogli, C. Z. Papadoyanni, S. D. Papaspyrou and N. G. Argyropoulos, *Tetrahedron Lett.*, 2003, **44**, 3905–3909; (*g*) S. Nakanishi, Y. Shirai, K. Takahashi and Y. Otsuji, *Chem. Lett.*, 1981, 869–872; (*h*) R. Zimmer and H.-U. Reißig, *J. Org. Chem.*, 1992, **57**, 339–347; (*i*) M. Buchholz, F. Hiller and H.-U. Reißig, *Eur. J. Org. Chem.*, 2002, 2838–2843; (*j*) C. Hippeli and H.-U. Reißig, *Liebigs Ann.*, 1990, 217–226; (*k*) C. Hippeli, R. Zimmer and H.-U. Reißig, *Liebigs Ann.*, 1990, 469–474; (*l*) P. Bravo, G. Gaudiano, P. P. Ponti and A. Umani-Ronchi, *Tetrahedron*, 1970, **26**, 1315–1330; (*m*) T. L. Gilchrist, G. M. Iskander and A. K. Yagoub, *J. Chem. Soc., Chem. Commun.*, 1981, 696–698; (*n*) T. L. Gilchrist, G. M. Iskander and A. K. Yagoub, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2769–2773; (*o*) C. Hippeli and H.-U. Reißig, *Liebigs Ann.*, 1990, 475–481.

2 (*a*) R. Faragher and T. L. Gilchrist, *J. Chem. Soc., Chem. Commun.*, 1976, 581–582; (*b*) D. E. Davies, T. L. Gilchrist and T. G. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1275–1281; (*c*) T. L. Gilchrist and T. G. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1283–1292; (*d*) T. L. Gilchrist, *Chem. Soc. Rev.*, 1983, 53–73.

3 (*a*) R. Zimmer and H.-U. Reißig, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1518–1519; (*b*) H.-U. Reißig, C. Hippeli and T. Arnold, *Chem. Ber.*, 1990, **123**, 2403–2411; (*c*) K. Paulini, H.-U. Reißig and P. Rademacher, *J. Prakt. Chem.*, 1995, **337**, 209–215; (*d*) D. Sperling, A. Mehlhorn, H.-U. Reißig and J. Fabian, *Liebigs Ann.*, 1996, 1615–1621; (*e*) R. Zimmer, J. Angermann, U. Hain, F. Hiller and H.-U. Reißig, *Synthesis*, 1997, 1467–1474.

4 W. Höbold, U. Prietz and W. Pritzkow, *J. Prakt. Chem.*, 1969, **311**, 260–265.

5 J. Lee, L. Chen, A. H. West and G. B. Richter-Addo, *Chem. Rev.*, 2002, **102**, 1019–1065.

6 For organocatalytic cycloadditions involving electron-rich enamines, see: (*a*) K. Juhl and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2003, **42**, 1498–1501; (*b*) D. B. Ramachary, N. S. Chowdari and C. F. Barbas III, *Angew. Chem., Int. Ed.*, 2003, **42**, 4233–4237; (*c*) D. B. Ramachary, N. S. Chowdari and C. F. Barbas, *Tetrahedron Lett.*, 2002, **43**, 6743–6746.

7 An analogous reaction took also place with α-chloroacetophenone oxime (**2b**).

8 The use of homogeneous bases such as triethylamine or Hünig's base led to immediate decomposition of the halooxime.

9 Conversion did not increase when the reaction time was extended.

10 The presence of water probably facilitates hydrolysis of **1a**.

11 Protic solvents such as ethanol cannot be used as they undergo conjugate addition reactions to nitroso alkenes.

12 These stark differences in reactivity of *O*-alkylated and non-alkylated oximes have been noticed previously, see: H. C. J. Ottenheijm, R. Plate, J. H. Noordik and J. D. M. Herscheid, *J. Org. Chem.*, 1982, **47**, 2147–2154.

13 Evidence allowing the distinction between stepwise and concerted mechanisms of the present hetero-Diels–Alder reactions was not collected.

14 Theoretical investigations predict concerted asynchronous transition structures, see: J. Liu, S. Niwayama, Y. You and K. N. Houk, *J. Org. Chem.*, 1998, **63**, 1064–1073 and references cited therein.

15 Slow homoaldol reactions were observed in some cases upon prolonged reaction times, but did not affect the reaction yield as an excess of the aldehyde component was used.

16 Reactions with $NaHCO_3$ as a buffer could be accelerated by addition of 20% trifluoroacetic acid (TFA), probably due to generation of water (which facilitates aminoacetal hydrolysis) and generation of a non-nucleophilic carboxylate anion (which can act as a proton shuttle).

17 G. B. Fisher, L. Lee and F. W. Klettke, *Synth. Comun.*, 1994, **24**, 1541–1546.

18 J. H. Smith and E. T. Kaiser, *J. Org. Chem.*, 1974, **39**, 728–730.

19 Hemiacetal diastereomers could not be separated in any case and rapid equilibration *via* an open chain aldehyde intermediate is likely.

20 Small quantities of the chlorooxime **7b** were formed through halide exchange during this procedure and could not be separated from the product.