

Highly Regio- and Diastereoselective Oxazol-5-one Addition to Nitrostyrenes

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A convenient and novel oxazol-5-one addition to nitrostyrenes is reported. The reaction is catalyzed by tertiary amines and yields the corresponding adducts with total regio- and diastereoselectivity. The addition exclusively takes place at

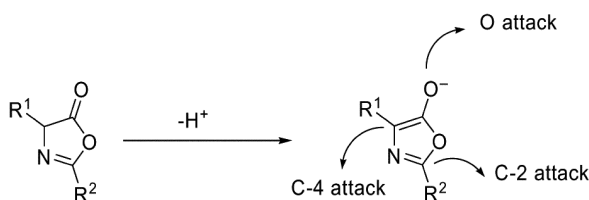
the C-2 position of oxazol-5-ones, furnishing diastereopure N,O-aminals.

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Introduction

The discovery of new reactions that allow us to build complex molecular scaffolds in an efficient way from readily available starting materials remains a challenging goal in chemical synthesis. The stereocontrolled construction of quaternary stereocenters is one of the most difficult challenges for synthetic chemists nowadays. Consequently, asymmetric processes that are able to build quaternary carbons have been the subject of intense research in recent years.^[1]

The use of oxazol-5-ones as nucleophilic reactants in Michael additions has hitherto hardly been studied. Since oxazol-5-one anions are ambifunctional (Scheme 1), they can react with activated electrophilic compounds either at C-2, at C-4 or at the exocyclic oxygen.



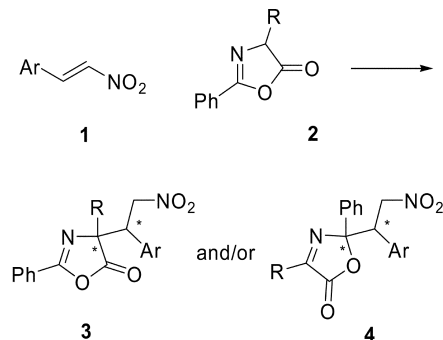
Scheme 1. Deprotonated oxazol-5-one.

The most common way to react is at C-4 of the oxazol-5-one.^[2] However, as is already known, the site of the reaction is determined primarily by the kind of activated double bond.^[3] In fact, the nature of oxazol-5-one has little influ-

ence at the position that undergoes the addition; only when strong electron-withdrawing groups are present in position 2 of the oxazol-5-one ring, such as a trifluoromethyl group, the addition predominantly occurs in position 2.^[4]

During the preparation of this work, Jørgensen reported a very elegant synthesis of α,α -disubstituted amino acid derivatives that relies on the racemic oxazol-5-ones Michael addition to α,β -unsaturated aldehydes, catalyzed by chiral secondary amines.^[5] In this case, the reaction is C-4-specific.

On the other hand, when extremely electron-poor Michael acceptors such as acrylonitrile, fumaric and maleic esters and the corresponding dinitriles are used, exclusively C-2 of 2,4-disubstituted oxazol-5-ones reacts. Surprisingly, to the best of our knowledge, there are no examples of oxazol-5-one additions to nitrostyrenes in the literature. With this chemo-information in mind, we decided to study the addition of oxazol-5-ones **2** to nitrostyrenes **1**^[6] in order to evaluate the regioselectivity and diastereoselectivity of the process (Scheme 2).



Scheme 2. Oxazol-5-one addition to nitrostyrenes.

When the attack takes place at C-2 the obtained compound **4** is a N,O-aminal. These compounds are structural motifs found in a number of interesting natural products

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and pharmaceuticals. For example, chiral N,O-subunits are found in important natural products like zampanolide,^[7] echinocandin B, spergualin, tallysomylin, mycalamalde A,^[8] and other compounds in the peredin^[9] family along with important targets like psymberin^[10] The stereochemical relevance of this motif to biological activity is significant and well-known as evidenced through cytotoxicity studies against various human tumor cell lines by De Brabander with psymberin and by others in the pederin/mycalamide series.^[11]

Another important aspect of the chiral N,O-aminal subunit is that it represents a particularly difficult synthetic challenge that had to be addressed in the previous preparative studies.^[9]

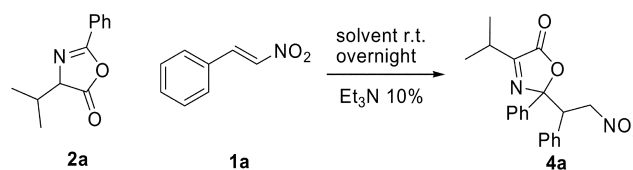
Although some elegant methods were developed to construct N,O-aminals, the preparation of chiral N,O-aminals via asymmetric catalysis is practically unknown. Only very recently Antilla and co-workers reported an elegant alcohol addition to imines, catalyzed by chiral phosphoric acids.^[12]

Herein, we will report a new organocatalytic approach to the diastereoselective addition of oxazol-5-ones to nitrostyrenes, showing that racemic 4-alkyl-2-phenyloxazol-5-ones only react at position C-2, giving the corresponding pseudooxazol-5-ones **4** in high yields.

In initial experiments, we screened different bases for the reaction between β -phenylnitrostyrene **1a** and oxazol-5-one **2a**.^[13] To our delight, when we carried out the reaction with Et₃N in CH₂Cl₂, we achieved high yield, regioselectivity and diastereoselectivity (entry 1, Table 1). The only isolated

compound from the reaction was the product obtained by the addition at C-2 of the oxazol-5-one ring, according to his spectral properties. Remarkably, no addition at C-4 was detected by NMR of the crude reaction, showing the total regioselectivity of the process. The reaction does not work without base or with inorganic bases such as NaHCO₃,

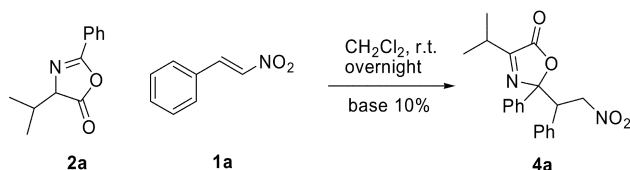
Table 2. Solvent screening.^[a]



Entry	Solvent	Conversion ^[b]	d.r. ^[c]
1	CHCl ₃	100%	13:1
2	AcOEt	100%	>25:1
3	THF	100%	>25:1
4	toluene	100%	>25:1
5	MeOH	0	–

[a] Experimental conditions: A mixture of **2a** (0.30 mmol), Et₃N (0.025 mmol) and **1a** (0.25 mmol) in the desired solvent (5 mL) was stirred at room temperature overnight. Crude product **4a** was purified by column chromatography. [b] Determined by NMR analysis of crude reaction. [c] Determined by NMR analysis of crude reaction.

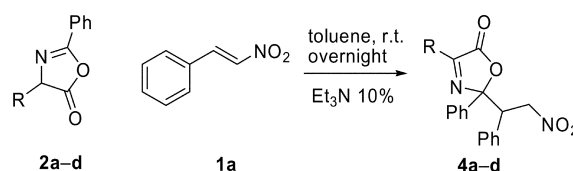
Table 1. Base screening.^[a]



Entry	Base	Conversion ^[b]	d.r. ^[c]
1	Et ₃ N	100%	13:1
2	–	0	–
3	NaHCO ₃	0	–
4	K ₂ CO ₃	traces	–
5	KOAc	0	–
6	(–)-cinchonidine	100%	10:1
7	DABCO	100%	9:1

[a] Experimental conditions: A mixture of **2a** (0.30 mmol), base (0.025 mol), **1a** (0.25 mmol) in CH₂Cl₂ (5 mL) was stirred at room temperature overnight. Crude product **4a** was purified by column chromatography. [b] Determined by NMR analysis of crude reaction. [c] Determined by NMR analysis of crude reaction.

Table 3. Oxazol-5-one scope.^[a]



Entry	R	Product	Yield ^[b]	d.r. ^[c]
1	<i>i</i> Pr	4a	95%	>25:1
2 ^[d]	Me	4b	97%	13:1
3	<i>t</i> Bu	4c	93%	>25:1
4	<i>i</i> Bu	4d	95%	>25:1

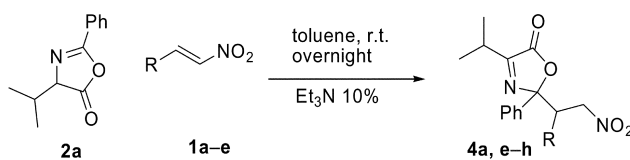
[a] Experimental conditions: A mixture of **2a–d** (0.30 mmol), Et₃N (0.025 mmol) and **1a** (0.25 mmol) in toluene (5 mL) was stirred at room temperature overnight. Crude product **4a–d** was purified by column chromatography. [b] Isolated yield. [c] Determined by NMR analysis of crude reaction. [d] Reaction run in AcOEt.


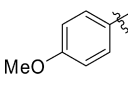

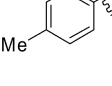

K_2CO_3 or KOAc (entries 2, 3, 4 and 5, Table 1). With bulkier organic bases such as cinchonidine^[14] or DABCO, the diastereoselectivity decreases but the regioselectivity is absolute (entries 6 and 7; Table 1).

Next, we decided to screen different solvents in order to increase the diastereoselectivity of the process; as the base catalyst we choose Et_3N , which gave the best results. Interestingly enough, when the reaction was performed in toluene, THF and AcOEt (entries 2, 3 and 4; Table 2) we could only detect one diastereomer by NMR spectroscopy. As expected, when the reaction was carried out in MeOH the addition did not take place because of extensive decomposition of the oxazol-5-one **2a**.

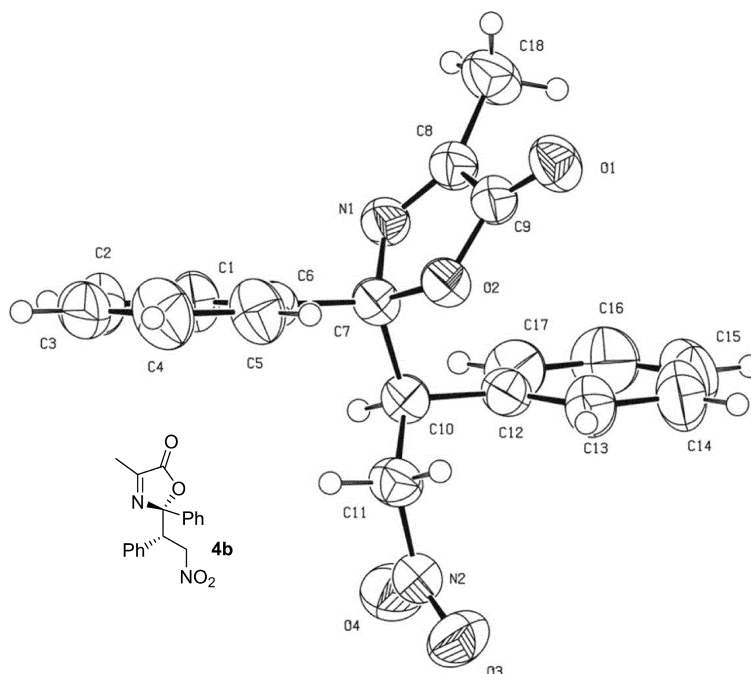
Then, we decided to study the scope of the reaction using different oxazol-5-ones **2a–d**. We decided to run the reaction in toluene and using triethylamine as a base catalyst. Fortunately, we achieved high levels of diastereoselectivity and excellent yields in all the entries. When oxazol-5-ones with $R = iPr$, iBu or tBu were used (entries 1, 3 and 5; Table 3), the reaction afforded only one diastereomer by NMR spectroscopy. Only when the methyl-substituted oxazol-5-one **2b** was used, the diastereomeric ratio decreased to 13:1.

Next, we studied the scope of the reaction using different nitrostyrenes. To our delight, when oxazol-5-one **2a** was treated with nitrostyrenes **1a–e** in toluene using 10 mol-% of Et_3N , in the whole set of examples, we only obtained one diastereomer, with total regioselectivity and in excellent yields. Remarkably, the use of different substituents in the phenyl ring does not affect the outcome of the reaction. Moreover, the presence of electron-withdrawing groups such as fluoro (entries 3 and 5; Table 4) or of electron-

Table 4. Nitrostyrene scope.^[a]


Entry	R	Product	Yield ^[b]	d.r. ^[c]
1		4a	95%	>25:1
2		4e	94%	>25:1
3		4f	97%	>25:1
4		4g	92%	>25:1
5		4h	91%	>25:1

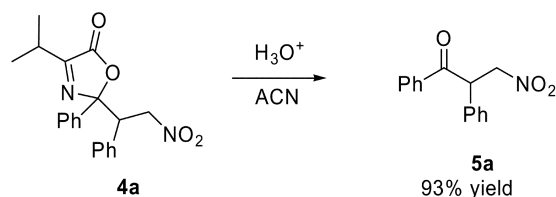
[a] Experimental conditions: A mixture of **2a** (0.30 mmol), Et_3N (0.025 mmol) and nitrostyrene **1a–e** (0.25 mmol) in toluene (5 mL) was stirred at room temperature overnight. Crude product **4a, e–h** was purified by column chromatography. [b] Isolated yield. [c] Determined by NMR analysis of crude reaction.

Figure 1. X-ray structure of the major diastereomer of **4b**.

donating groups like methoxy or methyl (entries 2 and 4) does not have any influence on the diastereoselectivity or yield of the reaction.

In order to confirm the regioselectivity and to ascertain the stereochemistry of the nitro compounds obtained, an X-ray diffraction of the major isomer of **4b** was performed.^[15] As shown in Figure 1, the crystal structure of this compound confirms the previously assigned regiochemistry and shows that the relative configuration is *S**,*S**.

Finally, acidic hydrolysis of compound **4a** furnishes the ketone **5a**^[16] (Scheme 3) in excellent yield. This reaction can be used as a 2C-homologation of nitro compounds. The preparation of 1-nitro-3-keto compounds represents formally an umpolung reaction between benzoyl chloride and nitroalkenes that is fairly difficult to achieve.



Scheme 3. Hydrolysis of compound **4a**.

A working mechanistic hypothesis that can account for the observed regio- and diastereoselectivity of the process is depicted on Figure 2, and involves the formation of a hydrogen bond between the oxazol-5-one carbonyl oxygen and the nitro group.

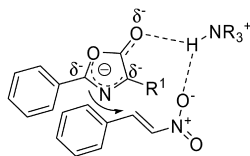


Figure 2. Proposed transition state for oxazol-5-one addition.

In summary, we have developed a highly chemo-, regio- and diastereoselective addition of oxazol-5-ones to nitrostyrenes. The reaction is efficiently catalyzed by commercially available tertiary amines and gives the corresponding pseudooxazol-5-ones **4** in high yields and with up to >25:1 diastereomer ratio. Mechanistic studies, synthetic applications, a suitable chiral version of this new methodology and the discovery of new reactions based on this concept are ongoing in our laboratory.

Supporting Information (see also the footnote on the first page of this article): Experimental procedure and crystallographic data of **4b**.

Acknowledgments

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- [14] In an initial experiment (–)-cinchonidine catalyzed the organocatalytic addition of oxazol-5-one **2a** to nitrostyrene **1a** in 94% yield; diastereoselective ratio 10:1, *ee* = 30%.
- [15] X-ray diffraction of **4b**: A prismatic crystal (0.1 × 0.1 × 0.2 mm) was selected and mounted on a MAR345 diffractometer with an image plate detector. Unit-cell parameters were determined from 209 reflections (3 < θ < 31°) and refined by least-squares method. Intensities were collected with graphite-monochromatized Mo- K_{α} radiation. 12257 reflections were measured in the range 2.59° ≤ θ ≤ 30.29°. 4033 of which were non-equivalent by symmetry [$R_{int}(on I)$ = 0.046]. 3412 reflections were assumed as observed applying the condition $I > 2\sigma(I)$. Lorentz polarization but no absorption corrections were made. The structure was solved by Direct methods, using SHELXS computer program (G. M. Sheldrick, *A program for automatic solution of crystal structure*, University of Göttingen, Germany, **1990**) and refined by full-matrix least-squares method with SHELX97 computer program (G. M. Sheldrick, *A program for crystal structure refinement*, University of Göttingen, Germany, **1997**), using 12257 reflections, (very negative intensities were not assumed). The function minimized was $\sum w||F_o|^2 - |F_c|^2|$, where $w = [\sigma^2(I) + (0.0857P)^2 + 0.0102P]^{-1}$, and $P = (|F_o|^2 + 2|F_c|^2)/3$, f , f' and f'' were taken from International Tables of X-ray Crystallography (*International Tables of X-ray Crystal-*

lography, Kynoch Press, **1974**, vol. IV, pp. 99–100 and 149). All H atoms were computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 time the equivalent temperature factor of the atom which are linked. The final $R(\text{on } F)$ factor was 0.056, $wR(\text{on } |F|^2)$ was 0.063 and goodness of fit was 1.139 for all observed reflections. The number of refined parameters was 219; max. shift/esd = 0.00, mean shift/esd = 0.00; max. and min. peaks in final difference synthesis was 0.373 and $-0.264 \text{ e } \text{\AA}^{-3}$, respectively. CCDC-

705916 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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