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Diastereoselective [3+2] cycloadditions of a camphor-derived chiral *N*-acryloylhydrazide with nitrile oxides: the preparation of optically pure Δ^2 -isoxazolines

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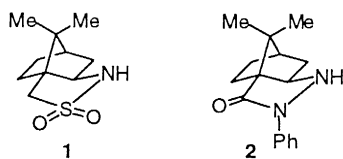
Abstract

Reaction of a novel chiral *N*-acryloylhydrazide with various nitrile oxides proceeded smoothly to afford the cycloadduct with high diastereoselectivity (99:1). The auxiliary can be easily removed from the cycloadducts under mild conditions. © 2000 Elsevier Science Ltd. All rights reserved.

Dipolar cycloadditions constitute one of the most powerful classes of reactions for the construction of useful and versatile synthetic intermediates in organic synthesis.¹ In particular, cycloadditions involving nitrile oxides as dipoles have been extensively examined and applied towards the total synthesis of many biologically active natural products.^{2a–g} The development of an efficient route to an optically active isoxazoline ring system is important because its reaction with an appropriate reagent provides a strategic alternative to β -hydroxy carbonyls, γ -amino-alcohols, etc.^{3a–i} Among the many strategies, the reaction of achiral nitrile oxides with chiral acryloyl esters or acrylamides is a conventional approach. The development of novel chiral auxiliaries that provide a face-shielding capability in cycloaddition of nitrile oxides is still of great importance.

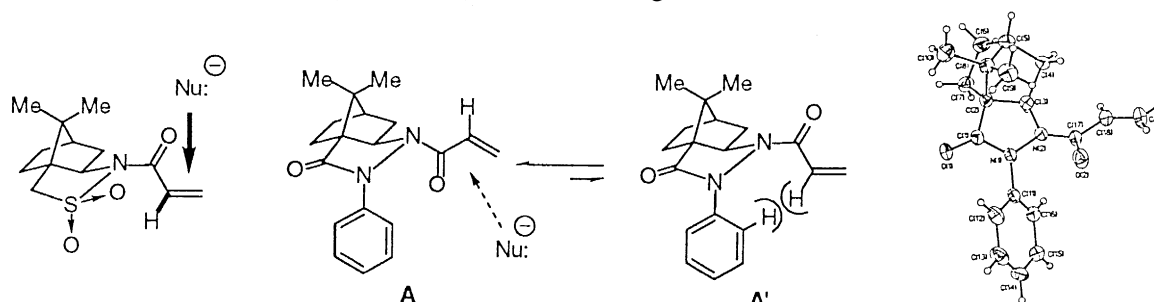
The Oppolzer camphor sultam **1** is among the most promising chiral auxiliaries presently available in asymmetric cycloaddition reactions.⁴ However, moderate to high diastereomeric ratios were obtained when *N*-acryloylsultam was reacted with various nitrile oxides.⁵ The design and synthesis of structural related auxiliaries for asymmetric synthesis has been rare, especially the functional group modifications at the C10 position.⁶ We have recently developed an efficient route for the preparation of a novel camphor-based auxiliary **2**.⁷ Compound **2** can easily be prepared in 88% overall yield from the known (+)-ketopinic acid in three steps. Herein, we wish to report the use of **2** as a highly efficient chiral auxiliary for the asymmetric induction of nitrile oxide cycloadditions.

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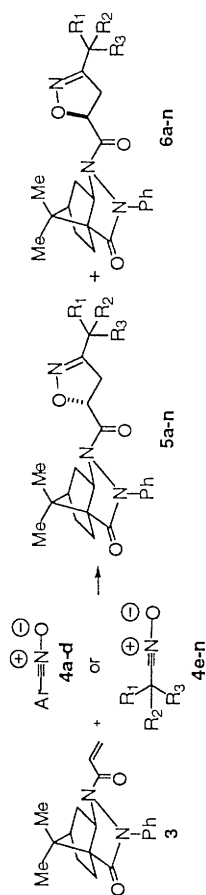
Chiral acryloylhydrazide **3** can be easily prepared from **2** (acryloyl chloride, Et₃N, CH₂Cl₂, 0°C, 96%). Cycloaddition of **3** with benzonitrile oxide **4a** in THF provided a disappointingly low diastereomeric ratio in a total of 92% yield (Table 1, entry 1). The diastereoselectivity was readily ascertained from ¹H NMR spectroscopic analysis on the crude product. High diastereoselectivity with excellent chemical yield was obtained when the reaction was carried out in CH₂Cl₂ (Table 1, entry 2). The structure of **5a** was characterized by ¹H, ¹³C NMR, HRMS, EA analyses and the absolute stereochemistry was assigned unambiguously by X-ray crystallographic analysis. The series of examples demonstrate the generality of this procedure (entries 3–15). High diastereomeric ratios were generally observed regardless of the substituent on the nitrile oxide. Careful examination of ¹H NMR spectra of the cycloadducts **5a–n** indicates that the C2 methine proton (camphor numbering) appears consistently at a range of 4.40–4.62 ppm. On the other hand, the corresponding methine of **6a**, **6e** and **6l** shows up at 4.13, 4.12 and 4.10 ppm, respectively. This characteristic feature allows the assignment of stereochemistry of the newly generated stereogenic center of other cycloadducts. The levels of facial selectivity obtained are comparable with the highest levels of diastereoselectivity reported in [3+2] nitrile oxide cycloadditions.^{3c,d} Sufficient face shielding of the alkene by the chiral auxiliary might account for the results.

The origin of diastereoselectivity in the nitrile oxide cycloadditions with Oppolzer camphor sultam has been proposed.^{5,10} Although the stereochemical outcome of the present study remains unclear, the preferential formation of configurations may be rationalized as follows. The alkene and the carbonyl group in **3** may exist as a planar *s-cis* rotamers. These are believed to be energetically favored over those of *s-trans*. However, *s-cis* acryloylhydrazide may have two low energy rotamers about the C–N bond which would give rise to two diastereomeric products if a reagent attacks from the same face. Unlike the planar conformation of chiral camphor sultam with the Cα proton oriented toward the sulfone oxygens, the rotamer A is likely to be energetically significant over A' in the transition state. This may be due to the unfavorable steric interactions between the Cα proton and the *N*-phenyl substituent in A'. The X-ray crystal structure of **3** indeed favors this conformer in the solid state. The incorporation of the 2'-phenyl pyrazolidin-3'-one system into the camphor skeleton results in the conformation change that causes the C8 methyl group to effectively shield the approach of dipole from the top face. The major product results from the 'bottom side' attack (Cα *re* face) of the incoming nitrile oxide.



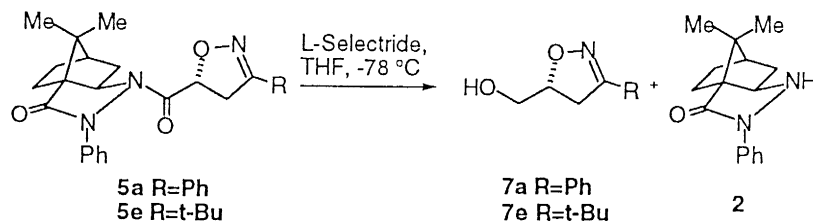
To complete one cycle of the chiral auxiliary, cycloadducts **5a** and **5e** were reduced with L-Selectride in THF at –78°C separately to provide essentially optically pure Δ²-isoxazolines **7a** (53%) and **7e** (75%). Excellent enantiomeric excess (99% ee) was obtained by means of optical rotation comparison (**7a**: [α]_D²⁵ –177 (c 0.7, CHCl₃); lit.⁵ [α]_D²⁵ –179 (c 1.0, CHCl₃); **7e**: [α]_D²⁵ –140 (c 1.0, CHCl₃); lit.⁵ [α]_D²⁵ –141 (c 1.0, CHCl₃)). The auxiliary **2** was recovered in high material yield (92 and 89%).

Table 1
Cycloadditions of various nitrile oxides with chiral acryloylhydrazide **3**



entry	nitrile oxide	solvent	ratio ^a	product	yield(%) ^b
1	4a Ar=C ₆ H ₅ ^c	THF	77:23	5a/6a	92
2	4a Ar=C ₆ H ₅ ^c	CH ₂ Cl ₂	99:1	5a/6a	97
3	4b Ar= <i>p</i> -MeOC ₆ H ₄ ^c	CH ₂ Cl ₂	99:1	5b/6b	95
4	4c Ar= <i>p</i> -NO ₂ C ₆ H ₄ ^c	CH ₂ Cl ₂	98:2	5c/6c	78
5	4d Ar= <i>p</i> -NCC ₆ H ₄ ^c	CH ₂ Cl ₂	98:2	5d/6d	75
6	4e R ₁ =R ₂ =R ₃ =Me ^c	CH ₂ Cl ₂	99:1	5e/6e	96
7	4f R ₁ =R ₂ =R ₃ =H ^c	CH ₂ Cl ₂	99:1	5f/6f	85
8	4g R ₁ =R ₂ =H R ₃ =Me ^c	CH ₂ Cl ₂	98:2	5g/6g	92
9	4h R ₁ =H R ₂ =R ₃ =Me ^c	CH ₂ Cl ₂	99:1	5h/6h	92
10	4i R ₁ =R ₂ =Ph, R ₃ =c-C ₆ H ₁₁ ^d	CH ₂ Cl ₂	99:1	5i/6i	88
11	4j R ₁ =R ₂ =Ph, R ₃ =n-Pr ^d	CH ₂ Cl ₂	98:2	5j/6j	90
12	4k R ₁ =R ₂ =Ph, R ₃ =n-Bu ^d	CH ₂ Cl ₂	98:2	5k/6k	92
13	4l R ₁ =R ₂ =Ph, R ₃ =Bn ^d	CH ₂ Cl ₂	99:1	5l/6l	90
14	4m R ₁ =R ₂ =Ph, R ₃ =i-Pr ^d	CH ₂ Cl ₂	98:2	5m/6m	92
15	4n R ₁ =R ₂ =Ph, R ₃ =t-Bu ^d	CH ₂ Cl ₂	99:1	5n/6n	89

^aRatios determined by 200 MHz ¹H NMR analyses of relevant signals. ^bIsolated yield. ^cGenerated in situ from the corresponding oximes in the presence of Et₃N and NBS.^{3c,8} ^dIsolated nitrile oxide.⁹



In summary, compound **2** has been successfully used as a novel camphor-derived auxiliary for the [3+2] nitrile oxide cycloadditions to achieve high stereoselection. The efficient synthesis of **2** and the mild conditions for the removal of the auxiliary make this methodology attractive. Further studies using this chiral auxiliary to investigate its general utility for asymmetric synthesis are underway.

Acknowledgements

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