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Asymmetric 1,3-Dipolar Cycloaddition of Nitrile Oxides to New Chiral Acrylamides Derived from (S)-Indoline-2-Carboxylic Acid

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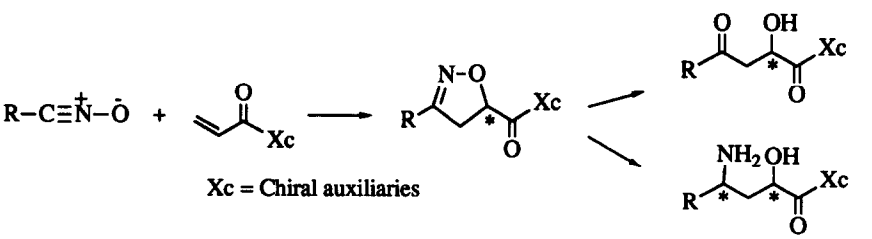
Abstract: Asymmetric 1,3-dipolar cycloaddition of nitrile oxides to new chiral acrylamides (**3a-c**) is reported to give the chiral Δ^2-isoxazolines with the high diastereoselectivity (up to 95 : 5).

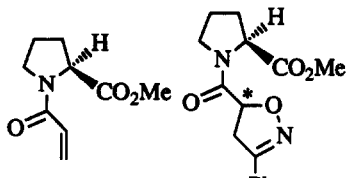
Several papers have been reported to the optically active isoxazolines by the asymmetric cycloaddition of nitrile oxides to the chiral acrylates[1], acrylamides[2], and acryloyl sultams.[3] The Δ^2-isoxazolines, obtained by 1,3-dipolar cycloaddition of nitrile oxides with the olefins, are of great importance as intermediates in the synthesis of β-hydroxy carbonyl compounds and γ-amino alcohols as shown below.[4]



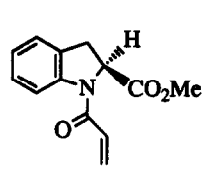
Recently, Curran and his co-workers have reported that the acrylamides derived from the Kemp's triacid show high diastereoselectivities in nitrile oxide cycloadditions.[5] Since there are several reports that provide exceptionally high levels of asymmetric induction using chiral auxiliaries derived from L-proline[6], the chiral acrylamide **1** was prepared for the use of 1,3-dipolar cycloaddition. But we have found that cycloaddition of **1** with benzonitrile oxide gave a disappointing 64 : 36 ratio of diastereomeric cycloadducts **2**. It is considered that this poor selectivity was due not only to insufficient conformational control but also to insufficient face shielding of the olefin by the chiral auxiliary.

Thus, new chiral acrylamide derivatives (**3a-c**) with improved face-shielding ability were readily prepared[7] and examined in 1,3-dipolar cycloaddition with various nitrile oxides. The dipolarophiles (**3a-c**) were prepared by the acylation of the corresponding (*S*)-indoline-2-carboxylic acid derivatives[8] with acryloyl chloride in the presence of Et_3N in CH_2Cl_2 at 0 °C. The new three chiral acrylamides have their own different

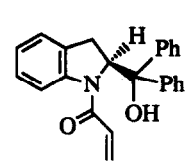
steric effects. The tertiary alcohol moiety of **3b** has the larger steric effects of two bulky phenyl rings, while the rigid molecule **3c** is expected to have different steric effects of cyclohexyl ring having the chair form.



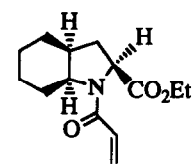
1 **2**



3a



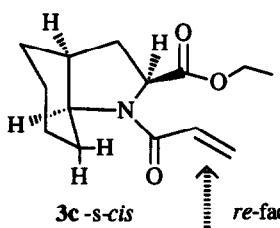
3b



3c

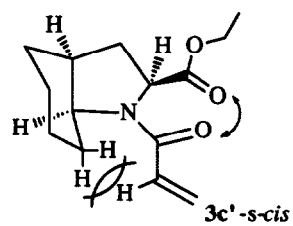
Arylnitrile oxides were generated by the Huisgen method[9], and alkylnitrile oxides were prepared by the Mukaiyama reaction.[10] The results obtained by the asymmetric cycloaddition of **3a** with benzonitrile oxide are listed in Table 1 (Run 2-8). The asymmetric cycloaddition gave the highest diastereoselectivity in Et_2O solvent at -78 °C (Run 8). These conditions were chosen to examine the reaction of various nitrile oxides and chiral acrylamides.[11] Chiral acrylamide **3c** gave the highest diastereoselectivity of isoxazoline cycloadduct (Table 2). It is considered that the structure of **3c** plays an important role in controlling the asymmetric induction.

In the cycloaddition reactions with chiral acrylamide derivatives, both the direction of attack of a reagent and the rotameric preference of the acrylamide must be controlled to give high diastereoselectivity .[3a] Recently, we have found that the acrylamide **3b** containing tertiary alcohol moiety instead of ester group is outstanding chiral auxiliary for Lewis acid promoted Diels-Alder reactions[12], yet cycloaddition of **3b** with benzonitrile oxide gave a disappointing 72 : 28 ratio of diastereomeric cycloadducts (Run 13 in Table 1). This may be due to insufficient conformer control[5] by the weak interaction (repulsion) between the amide carbonyl and the alcohol moiety in comparison with the repulsion of the dipoles in the two carbonyls of amide and ester in **3a** and **3c**.



3c -s-*cis* *re*-face attack

favorable

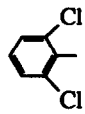
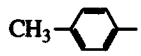


3c' -s-*cis*

unfavorable

The direction of attack is controlled by the auxiliary (Xc). Even though the direction of attack of a nitrile oxide may be well controlled, a low diastereoselectivity can also be resulted from the competition of s-*cis* with s-*trans* rotamer. Planar s-*trans* rotamers are well discussed to be strongly disfavored.[3a] Of the two *cis* conformations (**3c** and **3c'**), **3c'** is unlikely to be energetically significant in the ground state or the transition state due to either unfavorable dipole-dipole interactions or steric destabilization. Thus, **3c**-s-*cis* conformer is favorable. A chair form of the cyclohexane ring may also contribute to promote the facial shielding effect in the cycloaddition. The major product results from the "bottom-side" attack of the incoming nitrile oxide. This

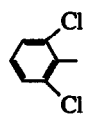
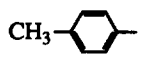
Table 1. Asymmetric Nitrile Oxides Cycloaddition with Chiral Acrylamides **3a-b**

Run	Acrylamide	R	Solvent	Temp. (°C)	Yield[a] (%)	Diastereomer ratio[b]
1	**1**	Ph	Et_2O	25	70	64 : 36
2	**3a**	Ph	Toluene	25	70	72 : 28
3	**3a**	Ph	Benzene	25	72	70 : 30
4	**3a**	Ph	CH_2Cl_2	25	67	71 : 29
5	**3a**	Ph	n-Hexane	25	32	73 : 27
6	**3a**	Ph	Et_2O	25	73	75 : 25
7	**3a**	Ph	Et_2O	0	74	78 : 22
8	**3a**	Ph	Et_2O	-78	76	83 : 17
9	**3a**		Et_2O	-78	75	87 : 13
10	**3a**		Et_2O	-78	72	85 : 15
11	**3a**	CH_3-	Benzene	25	68	74 : 26
12	**3a**	CH_3CH_2-	Benzene	25	70	73 : 27
13	**3b**	Ph	Et_2O	-78	68	72 : 28
14	**3b**	CH_3-	Benzene	25	63	70 : 30

[a] Isolated Yield

[b] Determined by HPLC Analysis

Table 2. Asymmetric Nitrile Oxides Cycloaddition with Chiral Acrylamide **3c**

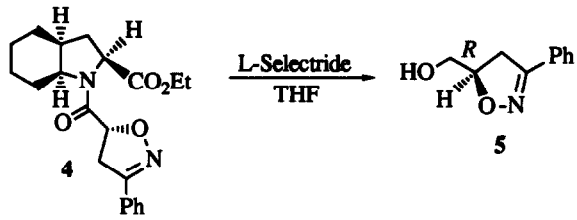
Run	Acrylamide	R	Solvent	Temp. (°C)	Yield[a] (%)	Diastereomer ratio[b]
1	**3c**	Ph	Et_2O	-78	74	95 : 5
2	**3c**		Et_2O	-78	75	94 : 6
3	**3c**		Et_2O	-78	74	92 : 8
4	**3c**	CH_3-	Benzene	25	69	88 : 12

[a] Isolated Yield

[b] Determined by HPLC Analysis

paper may contribute to understand 1,3-dipolar cycloaddition mechanism and to design useful chiral auxiliaries of acrylamides.

The major cycloadduct **4** was converted to isoxazoline **5** by reductive cleavage with L-Selectride™.[13] The absolute configuration of **5** was confirmed by comparing the $[\alpha]_D$ value with that reported.[3]



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3. (a) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555-3558. (b) Oppolzer, W.; Kingma, A. J.; Pillai, S. K. *Tetrahedron Lett.* **1991**, *32*, 4893-4896.
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6. Coppola, G. M.; Schuster, H. F. In *Asymmetric Synthesis : Construction of Chiral Molecules Using Amino Acids*, Ed.; John Wiely & Sons, Inc.: New York, 1987; pp. 267-345.
7. Acrylamide **3c** was prepared by esterification of (*S*)-indoline-2-carboxylic acid ($SOCl_2$, EtOH, 95%), hydrogenation (H_2, PtO_2, 90%), and acylation (acryloyl chloride, Et_3N, 83%).
8. Kim, Y. H.; Park, D. H.; Byun, I. S. *Heteroatom Chem.* **1992**, *3*, 51-54.
9. Huisgen, R. *Angew. Chem. Inter. Ed.* **1963**, *2*, 565-598.
10. Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339-5342.
11. A typical experimental procedure is as follows: To a solution of the chiral acrylamide **3a-c** (1.0 mmol) and arylhydroximinoyl chloride (2.0 mmol) in ether was added Et_3N (2.0 mmol) dropwise at -78 °C. The reaction mixture was stirred for 8h and then filtered. The filtrate was poured into water (saturated NaCl). The product was extracted with ether, dried over $MgSO_4$, and concentrated to give the crude diastereomeric mixture. The diastereomeric ratio was determined by HPLC (SiO_2, ethyl acetate : n-hexane (v/v) = 1 : 5). The diastereomers were separated by preparative TLC.
12. Kim, Y. H.; Kim, S. H.; Kim, J. D.; Park, D. H. unpublished data.
13. To a solution of cycloadduct **4** (0.108 mmol) and THF (7 ml) at 25 °C under N_2 was added a 1M solution of L-Selectride in THF (0.432 mmol). After stirring for 1h, the reaction mixture was quenched slowly with H_2O. Aqueous NaOH was added followed by 30% H_2O_2. The solution was diluted with EtOAc and then dried over $MgSO_4$. The residue was concentrated under reduced pressure and separated by column chromatography (SiO_2, ethyl acetate : n-hexane (v/v) = 1 : 1) to give **5** (60%) together with the recovery of the chiral auxiliary of 2-hydroxymethyloctahydroindoline (85%).

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