cis-2-Amino-3,3-dimethyl-1-indanol: Application as a Highly Efficient Chiral Auxiliary for the Diels-Alder Reaction

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(Received October 9, 1996)

The chiral oxazolidinone, derived from *cis*-2-amino-3,3-dimethyl-1-indanol, was found to be an efficient chiral auxiliary in the asymmetric Diels-Alder reaction.

The asymmetric Diels-Alder reaction is one of the most useful methods for stereoselectively creating multiple chiral centers in a single step.[1] Among the various kinds of asymmetric Diels-Alder reaction, utilization of Evans' chiral oxazolidinone[2] as a chiral auxiliary is known as a useful and reliable method. Therefore several oxazolidinone-type auxiliaries have been developed in order to accomplish complete selectivity in the asymmetric Diels-Alder reaction.[3]

During our investigation concerning the development of new chiral auxiliaries via optical resolution of racemates,[4] *cis*-2-amino-3,3-dimethyl-1-indanol (**1**) was easily synthesized and optically resolved into its both enantiomers, and **1**-derived oxazolidinone was found to be a highly effective chiral auxiliary in the reactions of the corresponding imide enolates with various electrophiles.[5] The supposed structure of the imide enolate **2** is shown in Figure 1. By analogy, we expected that high level of diastereofacial discrimination could be accomplished in the reaction of chiral dienophile-Lewis acid complex **3** with diene. Based on this hypothesis we investigated application of the **1**-derived oxazolidinone as an auxiliary in the asymmetric Diels-Alder reaction.

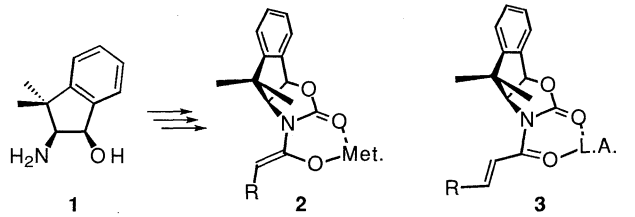
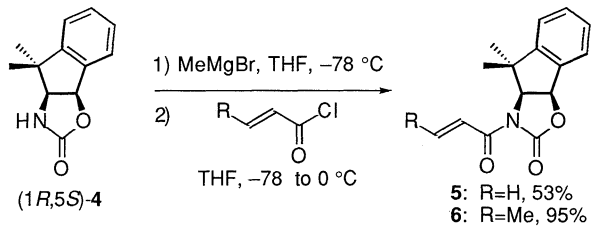


Figure 1. The supposed structures of the imide-enolate **2** and the dienophile-Lewis acid complex **3**.

Substrates **5** and **6** were easily prepared by acylation of (1*R*,5*S*)-**4** with the corresponding α,β-unsaturated carboxylic acid chlorides according to the standard method (Scheme 1).[2]

Scheme 1.



The Diels-Alder reaction was performed under standard reaction conditions (Scheme 2);[2] Et_2AlCl (1.4 equivalent to the substrate) and CH_2Cl_2 were used as activator and solvent, respectively. The results are listed in Table 1.

Excellent diastereofacial selectivity and *endo*/*exo* selectivity (or regio selectivity) were achieved. It is noteworthy that the diastereofacial selectivities were excellent even in the reactions of *N*-acryloyloxazolidinone **5** (entries 1,3,5,7) Furthermore, the diastereofacial selectivities were also excellent in the reactions with acyclic dienes (entries 5-7).

Scheme 2.

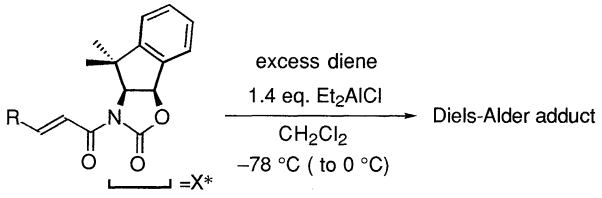
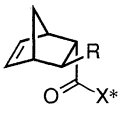
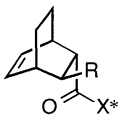
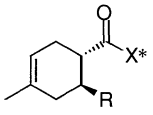
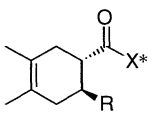


Table 1. The diastereoselective Diels-Alder reaction of *N*-(α,β-unsaturated acyl)oxazolidinones **5** and **6** with various dienes

entry	diene	major diastereomer	R	yield/%	*endo* :*exo*[a]	d.r.[a]
1			H	75	97:3	98:2[b]
2			Me	97	99:1	>99:1[b]
3			H	44	99:1	99:1[b]
4[c]			Me	58	98:2	96:4[b]
5[c]			H	76	–[d]	>99:1
6[c]			Me	65	–[d]	>99:1
7[c]			H	33	–	98:2
8[c]			Me	0[e]	–	–

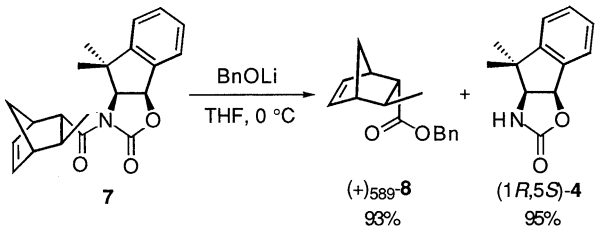
[a] Determined by HPLC. [b] D.r. of the *endo*-adduct.
[c] The reaction temperature was allowed to raise to 0 °C.
[d] The regio-isomeric ratio, determined by HPLC analysis, was >99:1. [e] The products were complicated.

The reaction with a relatively less reactive diene required raising the temperature to 0 °C (entries 4-8), which led to formation of some polymeric substances as by-products, along with the desired product. The cycloadduct of **6** with 2,3-dimethylbutadiene was not obtained even when the reaction was carried out at 0 °C for 5 h (entry 8).

All of the adducts obtained in the present reactions were crystalline due to the high crystallizability of the auxiliary part. This enabled us to obtain the products diastereomerically pure after a single recrystallization. For example, recrystallization of the diastereomeric mixture, obtained by the reaction of **6** with cyclohexadiene (entry 4), from hexane gave the corresponding diasteromerically pure cycloadduct in 73% yield.

Removal of the auxiliary was easily accomplished by alcoholysis of the product (Scheme 3). For example, treatment of diastereomerically pure **7** with lithium phenylmethoxide[2] in THF gave the corresponding ester (+)$_{589}$-**8**[6] and the oxazolidinone-auxiliary in excellent yields.

Scheme 3.



7 (+)$_{589}$-**8** 93% (1*R*,5*S*)-**4** 95%

The absolute configuration of (+)$_{589}$-**8** was determined by a comparison of its specific rotation with the value in the literature.[2] The absolute configuration of **7** was determined on the basis of the absolute configuration of (+)$_{589}$-**8**, and those of the other major products of the present reactions were correlated with that of **7** by comparing their ^{1}H-NMR spectral and HPLC data.

A representative procedure for the cycloaddition of *N*-crotonoyloxazolidinone **6** and cyclopentadiene is as follows. To a stirred solution of **6** (198 mg, 0.731 mmol) in a mixture of cyclopentadiene (1.5 mL, freshly distilled) and CH_2Cl_2 (2.0 mL) was added Et_2AlCl (1.2 mL, 1.0 mmol; 0.86 M hexane solution) at –78 °C under an argon atmosphere. After the mixture was stirred for 30 min at –78 °C, saturated aqueous ammonium chloride (5 mL) was added to the reaction mixture. After usual workup and successive removal of the highly polar by-products by short column chromatography (hexane/ethyl acetate (1/1)), HPLC analysis of the crude mixture was performed in order to determine the diastereoselectivity, for which an authentic sample was prepared by the reaction of the lithium salt of racemic **4** with the corresponding racemic carboxylic acid chloride. Purification by column chromatography (hexane/ethyl acetate (9/1)) gave the corresponding cycloadduct **7** (239 mg, 0.707 mmol, 97%) as colorless crystals.

In summary, the chiral oxazolidinone, derived from *cis*-2-amino-3,3-dimethyl-1-indanol, was found to be a highly effective chiral auxiliary in the asymmetric Diels-Alder reaction.

The present work was supported by Grants-in-Aid for Scientific Research (No. 08245215) from the Ministry of Education, Science, Sports and Culture of Japan.

References and Notes

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6 The specific rotation of (+)$_{589}$-**8**: $[\alpha]^{22.4}_{589}$ +127° (*c* 3.30, $CHCl_3$) (lit. $[\alpha]_{589}$ +130° (*c* 2.08, $CHCl_3$)).[2]