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Diastereoselective conjugate addition of 1-(α,β-unsaturated acyl)hydantoin with nucleophiles

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Abstract—A diastereomeric conjugate addition of dialkylaluminum chloride to 1-(α,β-unsaturated acyl)hydantoin provided the corresponding alkyl adduct with inducted chirality in the β-position. Treatment of 1-(α,β-unsaturated acyl)hydantoin with Gilman reagent in the presence of Lewis acid also gave the same product. In this reaction, diethylaluminum chloride was the most effective Lewis acid and the absolute configuration of the major adduct at the β-position of acyl group depended on the kinds of existing metals.

A methodology for the synthesis of optically active compounds has been developed based on the use of chiral auxiliaries. Among them, five-membered heterocycles containing a nitrogen atom such as 2-oxazolidinone[1] or 2-imidazolidinone[2] are the most widely used. In many diastereoselective syntheses utilizing a chiral auxiliary, although reactions inducing a chiral center at the α- position of the acyl group gives the corresponding chiral compounds in excellent diastereoselectivity (>98% de), it has been known that diastereoselectivities of compounds having a chiral center at the β-position in the reaction of conjugate addition of (α,β-unsaturated acyl)chiral auxiliary are relatively low (ca. >75% de). Therefore, development of a new and convenient chiral auxiliary is still required for synthesizing new optically active compounds at the β-position of the acyl group utilizing a conjugate addition system, in excellent diastereoselectivity. Recently, we reported a facile preparation of optically active hydantoin from amino acid amide without racemization.[3] Hydantoin resembles 2-oxazolidinone or 2-imidazolidinone, so that it is expected that hydantoin will be utilized as a chiral auxiliary (Fig. 1). In this letter, we wish to report that conjugate addition of 1-(α,β-unsaturated acyl)hydantoin **1** with dialkylaluminum chloride or a Gilman reagent–Lewis acid complex provides the corresponding alkyl adduct **2** with induced chirality at the β-position (Scheme 1).

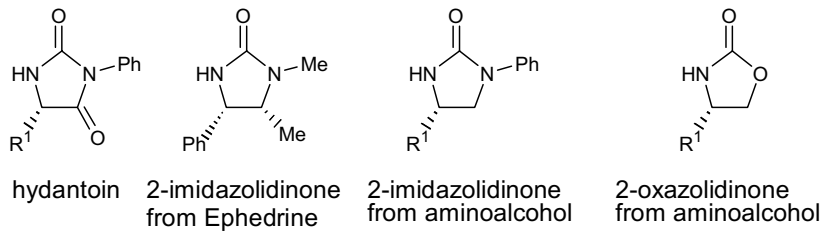

Figure 1.

Keywords: Hydantoin; Chiral auxiliary; Conjugate addition; Alkylaluminum; Alkylcuprate; Asymmetric addition.
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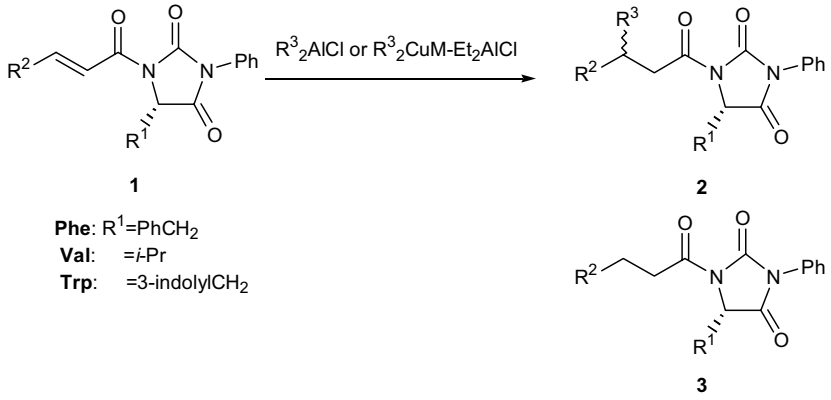


Scheme 1. Diastereomeric conjugate addition of some nucleophiles to **1**.

The starting material **1** was prepared by the reaction of hydantoin with carboxylic acid anhydride in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in DMF at room temperature. Initially, we examined the treatment of **1-Phe** ($R^2 = Ph$) with ethylaluminum in CH_2Cl_2, and the results are shown in Table 1. Among the attempts with three types of ethylaluminum, diethylaluminum chloride gave the best result in ethyl addition to **1-Phe** (Run 2). Other hydantoins derived from valine and tryptophan were also examined. In the present reaction systems, the R^1 group was not a significant factor in determination of diastereoselectivity of **2** (Runs 2, 4 and 5).

Next, alkyl addition of various **1-Phe** using some dialkylaluminum chlorides, which were commercially available, was performed (Table 2). Generally, ethyl addition of an equimolar amount of diethylaluminum chloride smoothly proceeded to form the corresponding ethyl adduct **2** (Runs 1 and 2). In contrast, 2–3 equimolar amounts of dimethyl- or diisobutylaluminum chloride were necessary to complete consumption of **1** (Runs 3–6). The rate of addition of an isobutyl group to 1-(4-chlorocinnamoyl)hydantoin was slow, so that the reduced compound **3** was mainly isolated (Run 6).

Concerning the first report on conjugate addition of organoaluminum to α,β-unsaturated carboxylic acid derivatives, Kunz and co-workers reported asymmetric conjugate addition of dialkylaluminum chloride to 3-(α,β-unsaturated acyl)-oxazolidinone.[4] However, 4 equimolar amounts of dialkylaluminum chloride such as ethyl, methyl and isobutyl were used in all reactions. Further, addition of an equimolar amount of dimethylaluminum chloride is necessary for isobutyl addition using isobutylaluminum chloride, and methyl addition using dimethylaluminum chloride proceeds under irradiation only. In contrast, the present reaction smoothly proceeded without an additive and irradiation to give **2** to completion.

Table 1. Effect of ethylaluminums on ethyl addition of **1-Phe** ($R^2 = Ph$)

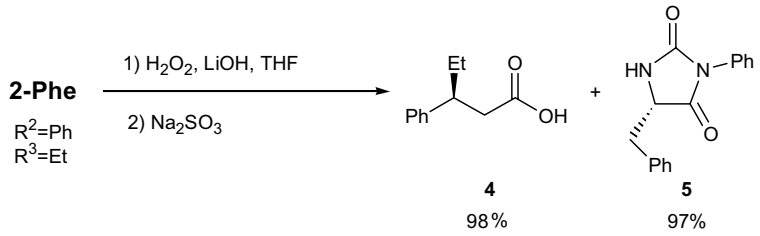
Run	**1**	Et_mAlCl_n[a]	Temp./°C	Time/h	Yield/%	(*S*):(*R*)[b]
1	Phe	$EtAlCl_2$	−40 to −20	24	8	85:15
2	Phe	Et_2AlCl	−50 to −20	3	97	94:6
3	Phe	Et_3Al[c]	−40 to −20	20	Complicated	
4	Val	Et_2AlCl	−50 to 0	5	97	90:10
5	Trp	Et_2AlCl	−50 to −40	19	78	88:12

[a] Ethylaluminum (1.1 equiv) was used except for Run 3.
[b] Product ratios were determined by integration of diastereomeric α-methine signals of hydantoin in ^1H NMR spectra.
[c] Et_3Al (2.2 equiv) was used.

Table 2. Diastereoselective conjugate addition of dialkylaluminum chloride to **1-Phe** ($R^1 = PhCH_2$)

Run	R^2	R^3 (equiv)	Temp./°C	Time/h	Yield/%	(*S*):(*R*[a])
1	4-ClC_6H_4	Et (1.2)	−40 to −10	20	83	91:9
2	Me	Et (1.2)	−50 to −15	0.5	91	—[b]
3	Ph	Me (3.0)	−40 to −15	14	79	76:24
4	4-ClC_6H_4	Me (2.2)	−40 to −20	18	85	77:23
5	Ph	*i*-Bu (2.5)	−50 to −40	19	78	88:12
6	4-ClC_6H_4	*i*-Bu (2.5)	−40 to −20	24	16[c]	89:11

[a] Product ratios were determined by integration of diastereomeric α-methine signals of hydantoin in ^1H NMR spectra.
[b] Determination of diastereomeric ratio was impossible by ^1H NMR spectra and HPLC analysis.
[c] The reduced compound **3** was isolated in 71% yield.



Scheme 2. Removal of hydantoin.

We examined the removal of the chiral auxiliary and determination of the absolute configuration at the β-position of the acyl group of **2**. Since separation of each diastereomer of the ethyl or isobutyl adduct was possible by preparative TLC, the major diastereomer of the ethyl adduct was isolated. Scheme 2 gives the result of removal of the chiral auxiliary by the use of lithium hydroperoxide as a cleavage agent. The corresponding carboxylic acid **4** was separated from chiral auxiliary **5**, which was recovered in excellent yield. The value of the specific rotation of the synthesized **4** was the same as that of the reported value.[5] Thus, its absolute configuration at the β-position was determined to be (*S*)-form.

From the above results, it was found that hydantoin has a capacity as a chiral auxiliary. The next aim was conjugate addition of another nucleophile to 1-(α,β-unsaturated acyl)hydantoin. For example, diastereo-selective conjugate addition of an alkylmetal compound to *N*-(α,β-unsaturated acyl)chiral pyrrolidone in the presence of additive has been reported.[6] Among many nucleophiles, organocopper reagents are the most versatile reagents available for conjugate addition reactions, so that we examined treatment of **1** with the Gilman reagent prepared from 2 equimolar amounts of butyllithium and copper(I) iodide. Unfortunately, the reaction was complicated and none of the corresponding butyl adducts were given (Table 3, Run 1). Since hydantoin was generally unstable under basic conditions, it was suspected that the basicity of the Gilman reagent would decompose the hydantoin moiety of **1**. When the reaction system using the Gilman reagent is performed under neutral or acidic conditions, decomposition of **1** will be suppressed and the corresponding adduct **3** can be obtained in high yield. It is well known that a complex composed of the Gilman reagent and a Lewis acid such as BF_3 etherate or $AlCl_3$ had high potential as a Michael donor,[7] and the use of Lewis acid would decrease the basicity of the reaction system. BF_3 etherate was a powerful additive for suppressing decomposition of **1** and the butyl adduct was isolated in moderate yield and diastereoselectivity (Run 3). After several attempts, conjugate addition of the Gilman reagent to **1-Val** derived from valine in the presence of Et_2AlCl gave the best yield and diastereoselectivity (Run 6). Although the reaction of **1-Trp** derived from tryptophan afforded the butyl adduct in moderate yield, its stereoselectivity showed to be the highest of all (Run 7).

Bergdahl and co-workers reported a similar examination when 2-oxazolidinone was used as a chiral auxiliary.[8] In conjugate additions employing the BuLi–CuI–Me_3SiI (TMSI) system, the absolute configuration of the major product was (*S*)-form. The absolute configuration of **2** synthesized from the present reaction at the β-position was determined by HPLC analysis of the benzyl ester obtained after removal of hydantoin using lithium benzyloxide, and the major absolute configuration of benzyl 3-methylheptanate prepared by the present reaction system was (*R*)-form.[9]

Further conjugate addition was also performed under different reaction conditions (Table 4). Interestingly, the diastereoselectivity of the butyl adduct **2** depended on the existing metals in the reaction mixture. Although the conjugate addition using the butyllithium-derived reagent resulted in (*S*)-adduct as the main product (Table 4, Run 1),[10] a similar addition using a Grignard reagent instead of organolithium gave the opposite major diastereomer, namely, (*R*)-form, predominantly (Table 4, Run 2). Concerning conjugate addition using *N*-(α,β-unsaturated acyl)-oxazolidinone in the LiRCuI–TMSI

Table 3. Conjugate addition of **1** using Gilman reagent–Lewis acid complex

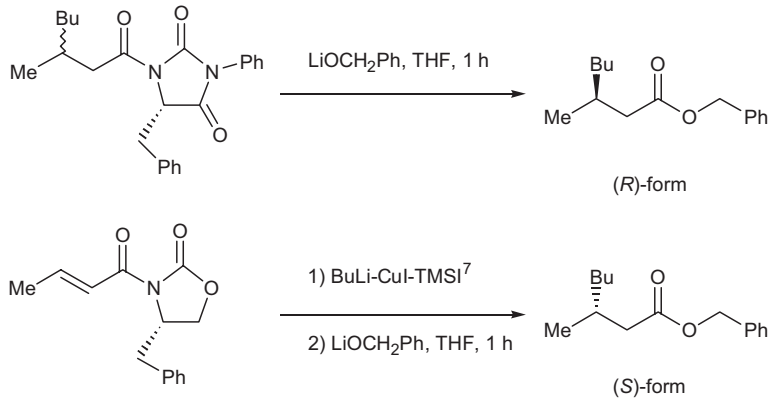
Run[a]	**1**	Lewis acid	Temp./°C	Yield/%[b]	(*S*):(*R*)[c]
1[d]	Phe	None	−50 to rt	—[e]	—
2	Phe	$SnCl_4$	−78	Trace	—
3	Phe	BF_3 etherate	−78	85	32:68
4	Phe	$EtAlCl_2$	−78	74	20:80
5	Phe	Et_2AlCl	−78	86	8:92
6	Val	Et_2AlCl	−78	88	9:91
7	Trp	Et_2AlCl	−78	65	3:97

[a] All reactions were performed for 3 h.
[b] Isolated yield.
[c] Product ratios were determined by integration of diastereomeric α-methylene signals of acyl group in ^1H NMR spectra.
[d] The reaction was performed for 16 h.
[e] The reaction was complicated.

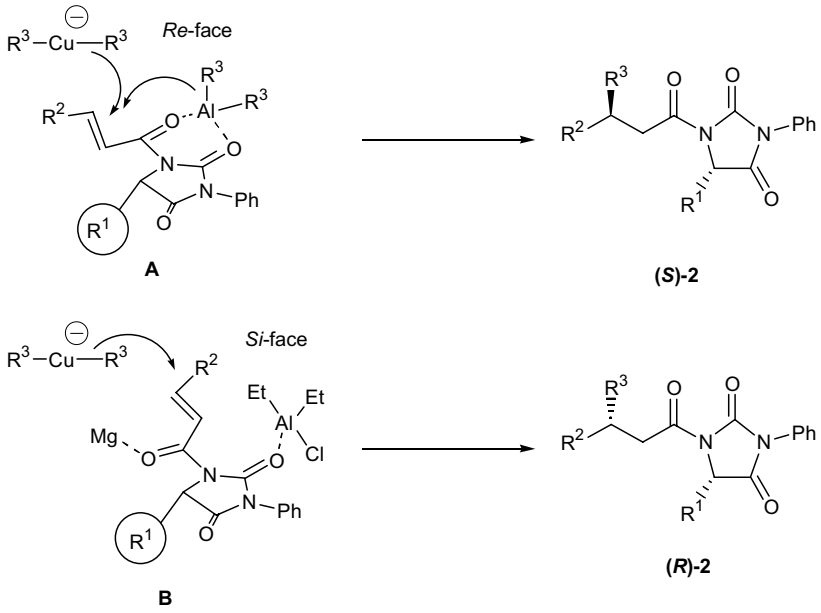
Table 4. Conjugate addition of some R^3M to **1-Val** ($R^2 = Me$)

Run	R^3M	Solvent	Yield/%	(*S*):(*R*)[a]
1	BuLi	THF	93	95:5
2	BuMgBr	THF	76	14:86
3	BuLi	Et_2O	88	92:8
4	BuMgBr	Et_2O	84	46:54
5[b]	BuLi	THF	26[c]	12:88

[a] Product ratios were determined by integration of diastereomeric α-methylene signals of acyl group in ^1H NMR spectra.
[b] The reaction was performed in the BuLi–CuI–TMSI system.[8]
[c] The starting material was recovered in 65% yield.



Scheme 3. Conversion of butyl adducts to benzyl 3-methylheptanate.



Scheme 4. Proposed reaction pathway.

system, the absolute configuration of the adduct at the β-position depended on not only the presence or absence of a magnesium ion but also the solvent. Contrarily, the absolute configuration of **2** at the β-position was independent of the solvent in the present reaction system (Runs 2 and 4) (Scheme 3).

Scheme 4 shows the proposed reaction pathway. In the conjugate addition using $R^3{}_2AlCl$ or $R^3{}_2CuLi$–Et_2AlCl system, since **1** will be fixed conformationally upon complexation with the dialkylaluminum chloride, addition or migration of the alkyl group should occur from the *Re*-face of intermediate A, leading to (*S*)-form adduct. On the other hand, the presence of an Mg ion in the present reaction is crucial for giving the (*R*)-form adduct via attack of the alkyl group from the *Si*-face of intermediate B.

In conclusion, hydantoin has the capacity as a chiral auxiliary and has some unique contribution in comparison with conventional chiral auxiliaries. Further study on new reactions, new cleavage methods, and unique utilization by taking advantage of the characteristics of hydantoin are now in progress.

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9. Conditions: column, Chiralpak OB-H (Daicel Chemical Industries, Ltd.) 1 mL/min of hexane/2-propanol = 99:1, detection 254 nm, (*R*)-form; 7.10 min, (*S*)-form, 8.10 min.
10. Method for preparation of organocuprate; To a THF suspension of copper(I) iodide was added 2 equimolar amounts of butyllithium in hexane or butylmagnesium bromide in THF at −78 °C and the reaction mixture was stirred for 20 min at −20 °C. An equimolar amount of Et_2AlCl in hexane was added to the reaction mixture at −78 °C.