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Asymmetric Hetero-Diels–Alder Reaction of Danishefsky's Dienes with α-Carbonyl Esters Catalyzed by an Indium(III)–PyBox Complex

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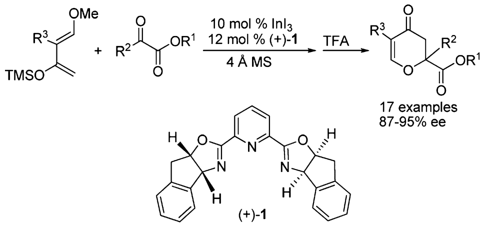
ABSTRACT



An efficient catalytic enantioselective hetero-Diels–Alder reaction of Danishefsky's dienes with α-carbonyl esters using a chiral In(III)–pybox complex has been demonstrated. This protocol offers several advantages, including mild reaction conditions, relatively low catalyst loading, and good to excellent enantioselectivities. Furthermore, the absolute configurations of the new alkynyl-containing products were determined by CD spectra in combination with TD-DFT calculations.

The asymmetric hetero-Diels–Alder (HDA) cycloaddition of Danishefsky type dienes with aldehydes is an attractive and well-investigated reaction in organic synthesis.[1] Since the enantioenriched oxygen-containing heterocycles generated by this reaction are versatile building blocks for the syntheses of numerous biologically active compounds,[2] the development of chiral catalysts for this asymmetrical HDA reaction is of great synthetic importance. Danishefsky et al. initiated the use of chiral Lewis acid catalysts to accelerate the highly enantioselective preparation of six-membered heterocycles.[3] Since then, several efficient metal-assisted[4] and metal-free[5] chiral Lewis acids have been developed for this powerful reaction. To our surprise, while many catalytic systems give good yields and enantioselectivities in the asymmetric HDA reactions of Danishefsky type dienes with aldehydes, only several efficient methods dealing with the [4 + 2] cycloaddition of Danishefsky's dienes with bidentate dienophiles, such as glyoxylate esters[6] and α-keto esters,[7] have been developed so far. In this context, the catalysts developed by Jørgensen's group,[7b] Ghosh's group,[7c] and Inanaga's group[7d,e] deserve special mention, as enantioselectivities of up to 99% have been obtained for the cycloaddition of α-keto esters to Danishefsky's diene.

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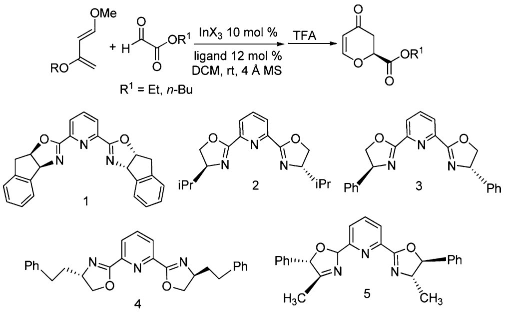
Our group and others have successfully employed In and In(III) salts in asymmetric synthesis for several years.[4t,u,8] In the course of our effort to apply chiral indium complexes in asymmetric synthesis, we discovered that In(III)−pybox complexes are efficient catalysts for asymmetric carbonyl-ene reactions of polymeric glyoxylates and trifluoropyruvates.[9] Recently, we successfully employed an In(III)−pybox complex to catalyze enantioselective Mukaiyama aldol reactions between polymeric or hydrated glyoxylates and enolsilanes, in which excellent enantioselectivities and yields were obtained with a broad substrate scope.[10] We hypothesized that this strategy could also be applied to the more challenging asymmetric HDA reaction between α-carbonyl esters and Danishefsky's diene, which had been shown to undergo both Mukaiyama aldol and hetero-Diels−Alder reactions,[4f,6e,7c] and the promising products could be used in Mukaiyamae−Michael addition to afford the corresponding 2,6-*anti*-tetrahydropyran adducts.[11]

Table 1. Screening of Indium Salts, Chiral Ligands, and Dienes[a]



entry	R^1	R	InX_3	ligand	time (h)	yield (%)[b]	ee (%)[c]
1	Et	TMS	$In(OTf)_3$	**1**	24	26	12
2	Et	TMS	InF_3	**1**	36	48	7
3	Et	TMS	$InCl_3$	**1**	18	33	45
4	Et	TMS	$InBr_3$	**1**	24	30	52
5	Et	TMS	InI_3	**1**	18	60	63
6	Et	TMS	$In(CF_3COO)_3$	**1**	40	28	7
7	*n*-Bu	TMS	InI_3	**1**	18	80	61
8	*n*-Bu	TMS	InI_3	**2**	24	51	31
9	*n*-Bu	TMS	InI_3	**3**	24	63	5
10	*n*-Bu	TMS	InI_3	**4**	20	68	21
11	*n*-Bu	TMS	InI_3	**5**	20	76	29
12	*n*-Bu	TIPS	InI_3	**1**	42	52	60
13	*n*-Bu	TBS	InI_3	**1**	42	60	50
14	*n*-Bu	TES	InI_3	**1**	24	48	63

[a] Reactions were carried out on a 0.5 mmol scale with 1.5 equiv of Danishefsky's diene in 5.0 mL of anhydrous DCM at room temperature, unless noted otherwise. TFA = trifluoroacetic acid. [b] Isolated yield. [c] The ee values were determined by chiral-phase HPLC analysis.

Unfortunately, when we used chiral $In(OTf)_3$-(+)-**1** in the reaction of commercially available ethyl glyoxylate (50% in toluene) and Danishefsky's diene in the presence of 4 Å molecular sieves, the desired product was obtained in very low ee.

After six different commercially available In(III) Lewis acids, five chiral pybox compounds, and four different siloxy-substituted Danishefsky dienes were screened, InI_3-(+)-**1** gave the best result with good yield and satisfactory enantioselectivity (Table 1, entry 7).

Using this catalytic system, we investigated the steric bulk effect of glyoxylate esters, with the hope of achieving better enantioselectivity. A series of glyoxylate esters with

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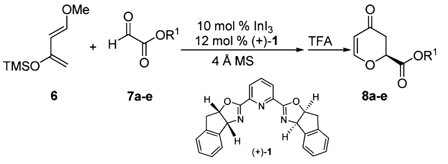
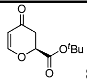
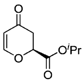
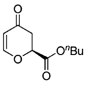
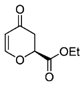
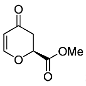
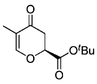
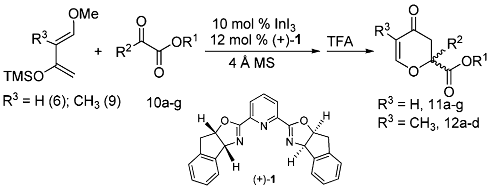
Table 2. Screening of the Glyoxylate Esters[a]

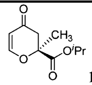
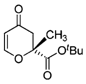
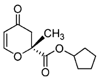
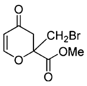
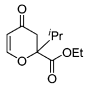
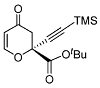
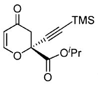
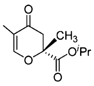
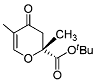
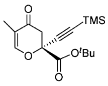
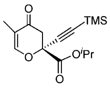


entry	product	time (h)	yield (%)[b]	ee (%)[c]	config[c]
1	 **8a**	18	59	92	*S*
2	 **8b**	20	65	70	*S*
3	 **8c**	18	80	61	*S*
4	 **8d**	18	60	63	*S*
5	 **8e**	20	61	50	*S*
6[d]	 **8f**	24	70	93	*S*

[a] Reactions were carried out on a 0.5 mmol scale with 1.5 equiv of Danishefsky's diene in 5.0 mL of anhydrous DCM at room temperature, unless noted otherwise. TFA = trifluoroacetic acid. [b] Isolated yield. [c] The ee values were determined by chiral-phase HPLC analysis, and the absolute configuration of the major products is *S*, assigned by comparing HPLC data with literature data. [d] The starting diene was (*E*)-1-methoxy-2-methyl-3-trimethylsiloxy-1,3-butadiene.

Table 3. In(III)–pybox Complex Catalyzed Asymmetric HDA Reactions of Danishefsky Type Dienes[a]



entry	product	time (h)	yield (%)[b]	ee (%)[c]	config[c]
1	 **11a**	24	84	94	*S*
2	 **11b**	20	61	90	*R*
3	 **11c**	24	67	91	*R*
4	 **11d**	24	48	30	nd
5	 **11e**	24	10	30	nd
6	 **11f**	20	64	93	*R*
7	 **11g**	24	80	93	*R*
8	 **12a**	24	77	95	*R*
9	 **12b**	20	52	89	*R*
10	 **12c**	20	59	89	*R*
11	 **12d**	24	52	87	*R*

[a] Reactions were carried out on a 0.5 mmol scale with 1.5 equiv of Danishefsky's diene in 5.0 mL of anhydrous DCM at room temperature, unless noted otherwise. TFA = trifluoroacetic acid. nd = not detected. [b] Isolated yield. [c] The ee values were determined by chiral-phase HPLC analysis, and the absolute configurations of the major products were assigned by comparing HPLC data with literature data.[7c]

different ester groups were prepared according to the reported method.[12]

Substantial improvement in the enantioselectivity was realized with increasing steric bias of the ester groups, as shown in Table 2. The highest ee (92%) could be achieved when *tert*-butyl glyoxylate was used as the dienophile. We then evaluated the effect of solvent, temperature, and catalyst loading. As expected, this reaction is sensitive to the solvent, where dichloromethane (DCM) proved to be the optimum choice of solvent and the catalyst loading could be reduced to 10 mol %. It is noteworthy that the enantiomeric excess is considered high at room temperature for this HDA reaction.[13]

With this promising result in hand, we turned to the more challenging cycloaddition between α-carbonyl esters and Danishefsky's diene. First, some synthetically useful methods for a reasonable number of α-keto esters were modified on consulting the published processes.[14] The catalytic results employing the preprepared chiral catalyst InI$_3$-(+)-**1** are summarized in Table 3. It was found that the alkyl groups directly attached to the α-position of carbonyl groups had great effects on the reaction efficiency. For example, the best result, up to 94% ee value and 84% yield, could be obtained when isopropyl pyruvate was used as the

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dienophile (Table 3, entry 1). The identity of the alkoxy groups had only slight effects on the reaction, with isopropyl, *tert*-butyl, and cyclopentyl pyruvates giving moderate yields and high ee values (Table 3, entries 1−3). However, the yield and enantioselectivity were significantly decreased when the substituents at the α-position of carbonyl groups were bromomethyl and isopropyl (Table 3, entries 4 and 5). There was no reaction observed when ethyl 2-oxo-2-phenylacetate or methyl 3,3,3-trifluoro-2-oxopropanoate was used as the substrate. Presumably steric hindrance in the transition state influences the reaction efficiency substantially. This hypothesis was proven when we used linear trimethylsilyl acetyl to replace the bulky aliphatic or aromatic substituents at the α-position of the carbonyl group. The yields were moderate and enantioselectivities were excellent as expected (Table 3, entries 6 and 7). High ee values can be also achieved using the Danishefsky type diene (*E*)-1-methoxy-2-methyl-3-trimethylsiloxy-1,3-butadiene as the substrate (Table 2, entry 6, and Table 3, entries 8−11).

Furthermore, the absolute configuration (AC) of the novel alkynyl-containing products was determined by means of chiroptical methods.[15] For further discussion, ECD spectra were also calculated by the TD-DFT method, which has been proven to be useful in predicting ECD spectra and assigning the AC of organic molecules.[16] Calculations of the ECD spectra of (*R*)- and (*S*)-**11f** were carried out using the TD-DFT-B3LYP/6-31G(d) level with Gaussian 03.[13,17] All conformations were calculated at the same level to confirm their stability (no imaginary frequencies). Electronic excitation energies (nm) and rotational strengths (Δ*ε*) were calculated for **11f**. In order to cover the 180−400 nm range, 30 transitions were calculated. In Figure 1, the simulated spectrum is in good agreement with the experimental spectral data, and the *R* configuration could be reliably assigned to **11f**.

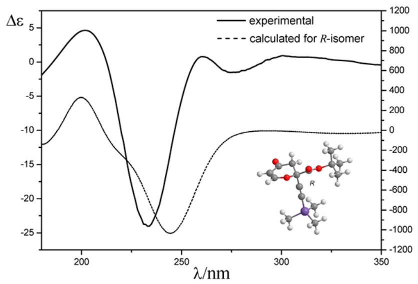
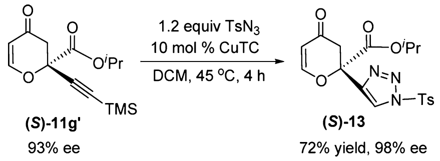


Figure 1. Experimental ECD spectrum (full trace) and simulated spectrum (dashed trace), proving the (*R*)-**11f** absolute configuration.

Finally, to get an insight into the importance of the alkynyl functionality, a classical click reaction was performed in the presence of copper(I) thiophene-2-carboxylate (CuTC). As expected, the desired 1,2,3-triazole (*S*)-**13** was obtained in good yield and excellent ee.



In conclusion, we have presented an efficient catalytic enantioselective HDA reaction of Danishefsky type dienes with α-carbonyl esters using a chiral In(III)−pybox complex, which is easily prepared from commercially available InI_3 and pybox **1**. The absolute configurations of novel alkynyl-containing products were determined by CD spectra in combination with TD-DFT calculations. This protocol offers several advantages, including mild reaction conditions, relatively low catalyst loading, and good to excellent enantioselectivities. In addition, the method grants important enantioselective access to the chiral center bearing an alkynyl group, which allows for further functional transformations, including click chemistry, metathesis, cyclization, and so on.

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Supporting Information Available. Text, figures, and a table giving additional experimental procedures and full spectroscopic data for all of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

[15] For a perspective on chiroptical methods, see a dedicated issue:-Polavarapu, P. L.; Nafie, L. A., Beova, N. Eds. *Chirality*, 2009, *21*, E1.

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