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Asymmetric hetero Diels–Alder route to quaternary carbon centers: synthesis of (−)-malyngolide

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Abstract—Conformationally constrained chiral bis(oxazoline)-metal complex catalyzed asymmetric hetero Diels–Alder reactions of Danishefsky's diene and a variety of α-keto esters constructed quaternary carbon centers enantioselectively. The reaction was utilized in the synthesis of (−)-malyngolide. © 2001 Elsevier Science Ltd. All rights reserved.

Development of effective catalytic processes for the enantioselective hetero Diels–Alder reactions of aldehydes and dienes is of significant interest in organic synthesis.[1] The potential of chiral bis(oxazoline)-metal complexes as versatile catalysts for a variety of asymmetric transformations has been documented.[2] We recently reported conformationally constrained chiral bis(oxazoline)-metal complex catalyzed asymmetric hetero Diels–Alder reactions of Danishefsky's diene and various bidentate aldehydes including glyoxalate esters and benzyloxyacetaldehyde to form the respective cycloadduct enantioselectively.[3] The reaction proceeded through a Mukaiyama aldol reaction followed by an acid-catalyzed cyclization to provide the hetero Diels–Alder product (Fig. 1). Jørgensen and co-workers have also demonstrated that the corresponding reaction with alkyl pyruvates and Danishefsky's diene can proceed with high enantioselectivities and isolated yields.[4] The resulting cycloadduct provided important enantioselective access to quaternary chiral centers. Enantioselective synthesis of such quaternary centers is of significant interest in organic synthesis.[5] As per our continuing interest in the development of effective methodologies for quaternary chiral centers, we subsequently investigated catalytic hetero Diels–Alder reactions of a variety of α-keto esters utilizing *cis*-aminoindan-2-ol derived conformationally constrained inda-box-metal complexes.[6,7] One of the main advantages of inda-box-derived catalysts is that both enantiomers are commercially available or can be readily synthesized, providing convenient access to either enantiomer of the cycloadduct in a stereopredictable fashion.[7] Herein, we report that the inda-box derived ligand–metal complexes are effective catalysts for hetero Diels–Alder reactions of Danishefsky's diene and a number of α-keto esters. The methodology was utilized in the synthesis of the marine natural product (−)-malyngolide, an antibiotic with significant activity against *Streptococcus pyogenes* and *Mycobacterium smegmatis*.[8] Since the first synthesis by Mukaiyama,[9] a number of other syntheses of (−)-malyngolide have been reported.[10] However, only a few them utilize asymmetric catalytic methodology.[11]

As described previously, the ligand–metal complexes were prepared by reaction of an equimolar mixture of bis(oxazoline) ligand and $Cu(OTf)_2$ in dry CH_2Cl_2 at 23°C under a nitrogen atmosphere.[2] The resulting chiral catalyst (5–20 mol% to ketone) was cooled to −78°C and representative α-keto ester followed by 1.2–2 equiv. of Danishefsky's diene were added. The reaction mixture was stirred at −78°C for 12 h. After this period, the formation of the respective Mukaiyama aldol product as well as pyranone derivative **5** can be observed by

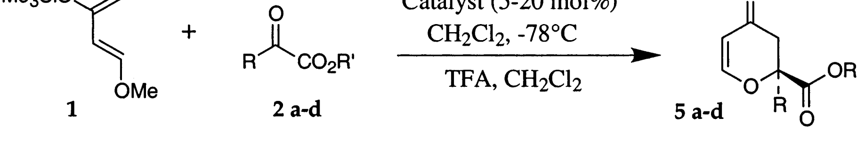

Figure 1.

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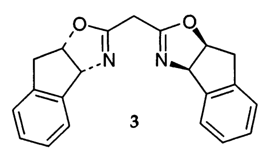
TLC. The reaction mixture was treated with an excess of trifluoroacetic acid in CH_2Cl_2 and the resulting mixture was warmed to 0°C. During a 4–8 h period, the aldol product is converted to cyclocondensation product **5**. The enantiomeric excess of various hetero Diels–Alder cycloadducts was determined by chiral HPLC analysis (using a Daicel OD column, 10% isopropanol/hexane as the eluent) of the cycloadducts or the derived secondary alcohol after reduction of the α,β-unsaturated ketone as well as by comparison of optical rotation with the authentic material.

The results of various hetero Diels–Alder reactions are summarized in Table 1. As can be seen, both the choice of ligand and the size of alkyl groups in the keto ester have relevance on the observed enantioselectivity. The reaction of methyl pyruvate and diene **1** with 10 mol% chiral catalyst derived from conformationally constrained bis(oxazoline) **3** provided near quantitative yield of cycloadduct **5a** in 87% e.e. The corresponding reaction with ethyl pyruvate furnished **5b** in 96% e.e.; however, the reaction yield was moderate. In comparison, reaction of ethyl pyruvate with *ent*-**3** ligand derived catalyst furnished *ent*-**5b** (entry 4) in 62% yield and 99% e.e. Ligand **4** derived catalyst has exhibited similar results (entry 3). The reaction of ketone containing a propenyl side chain gave 83% e.e. with ligand **3**-derived catalyst.[12] The keto ester containing a large nonyl side chain furnished cycloadduct **5d** in 73% isolated yield and 56% e.e. with ligand *ent*-**3** derived catalyst (entry 6).[13] In contrast, the reaction with ligand **4** derived catalyst afforded **5d** in lower enantioselectivity (47% e.e.). Interestingly, the reaction of **1** with benzyloxy-2-undecanone did not provide any cycloadduct.

To corroborate the stereochemical assignment of the cycloadduct derived from ethyl 2-oxoundecanate (entry 6), pyranone derivative **5d** was utilized in the synthesis of (−)-malyngolide. Reduction of **5d** with $NaBH_4$ in the presence of cerium chloride heptahydrate followed by treatment of the resulting 1,2-reduction product with K-10 and methanol furnished the Ferrier rearrangement product **6** as a 1:1 mixture of diastereomer (Scheme 1). Ethyl ester **6** was then converted to benzyl ether **7** in a three-step sequence involving: (1) $LiAlH_4$ reduction of the ester to a primary alcohol in ether at 0°C, (2) hydrogenation of the olefin with 10% Pd–C in CH_3OH and (3) protection of the free alcohol as benzyl ether by treatment with sodium hydride and benzyl bromide. Methyl acetal **7** was isolated in 56% overall yield (from **6**) after silica gel chromatography. Exposure of **7** to Jones' reagent in acetone at 23°C furnished δ-lactone **8** directly in 60% isolated yield. Methylation of **8** was accomplished by a modified Mukaiyama procedure.[9] Deprotonation of **8** with LHMDS and HMPA at −78°C

Table 1. Hetero Diels–Alder reaction of α-ketoesters and diene **1**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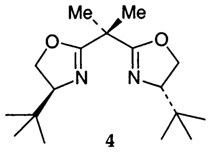

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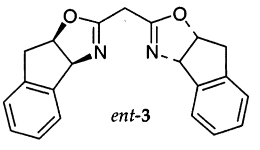
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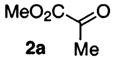
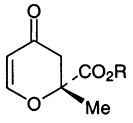
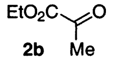
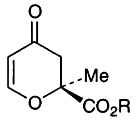
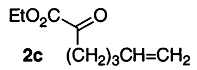
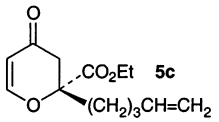
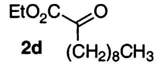
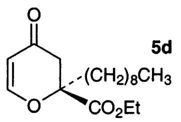
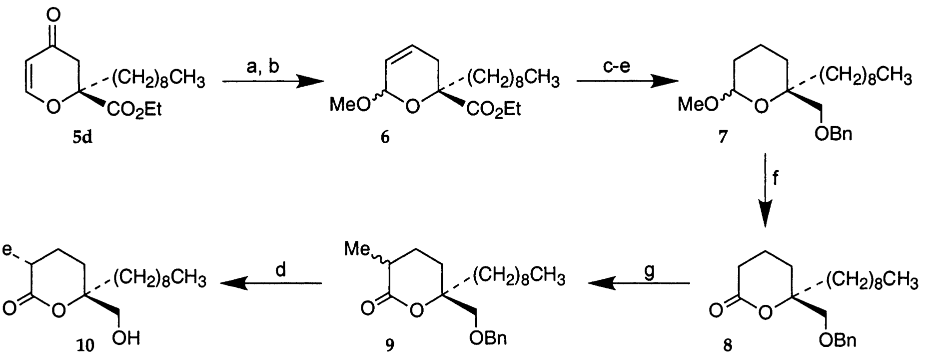
Entry	Ketoester (2)	Ligand	Cycloadduct (major)	% Yield^a	$[\alpha]_D^{23°C}$ $(CHCl_3)$	% ee^b
1.	 $MeO_2C{-}C(=O){-}Me$ **2a**	3	 **5a** R = Me	99	-150 (c 1.15)	87
2.	 $EtO_2C{-}C(=O){-}Me$ **2b**	3	**5b** R = Et	52	-145 (c 1.2)	96
3.	**2a**	4	 *ent*-**5a**	66	+171 (c 1.1)	99
4.	**2b**	*ent*-3	*ent*-**5b**	62	+161 (c 1.04)	99
5.	 $EtO_2C{-}C(=O){-}(CH_2)_3CH{=}CH_2$ **2c**	3	 **5c**	65	-50 (c 1.0)	83^c
6.	 $EtO_2C{-}C(=O){-}(CH_2)_8CH_3$ **2d**	*ent*-3	 **5d**	73	+63 (c 0.79)	56^d
7.	**2d**	4		77	+54 (c 1.4)	47^e

^{a} Isolated yield after silica gel chromatography. ^{b} Enantiomeric excess was determined by chiral HPLC (10% 2-propanol/hexane, 254 nm) and/or comparison of optical rotation. ^{c} Chiral HPLC (10% 2-propanol/hexane, 210 nm) after the derivatization. ^{d} Converted to (-)-malyngolide and compared optical rotation. ^{e}Based upon entry 6.



Scheme 1. (a) $NaBH_4$, $CeCl_3·7H_2O$, $EtOH/H_2O$, 0°C; (b) K-10, CH_3OH, 0–23°C (56%); (c) $LiAlH_4$, Et_2O, 0°C; (d) H_2, Pd–C, CH_3OH, 23°C; (e) BnBr, NaH, DMF, 0°C (56%, three steps); (f) Jones' reagent, acetone, 23°C (60%); (g) LHMDS, HMPA, CH_3I, THF, −78°C (96%).

followed by reaction with methyl iodide provided alkylation product **9** as a 1.5:1 mixture of diastereomers in 96% yield. The removal of the benzyl group by hydrogenation with 10% Pd–C afforded a mixture (1.5:1) of (−)-malyngolide **10** and its epimer which were easily separated by flash column chromatography over silica gel (30% EtOAc/hexane). Spectral data (^1H and ^{13}C NMR) for synthetic **10** ($[\alpha]_D^{23}$ −7.3° (*c* 1.1, $CHCl_3$), lit. $[\alpha]_D^{23}$ −13° (*c* 2, $CHCl_3$) are in full agreement with that reported in the literature.[9] Thus, (−)-malyngolide **10** has been synthesized in enantiomerically enriched form.[14]

In conclusion, *cis*-aminoindan-2-ol-derived conformationally constrained bis(oxazoline) complexed with $Cu(OTf)_2$ is a very effective catalyst for the hetero Diels–Alder reaction of Danishefsky's diene and alkyl 2-oxoalkanoate containing a small alkyl group. The resulting cycloadduct provided an important access to quaternary carbon centers enantioselectively. The methodology was applied to the synthesis of (−)-malyngolide. Further studies aimed at improving enantioselectivity and exploring reaction scope are in progress.

Acknowledgements

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12. Reduction with $NaBH_4/CeCl_3·7H_2O$ provided single allylic alcohol (by ^1H and ^{13}C NMR). Enantioselectivity was determined by Chiral HPLC using 10% 2-propanol/hexane as the eluent at 210 nm wavelength.
13. The use of inda-box-$Cu(SbF_6)_2$ (10 mol%) also provided **5d** in 56% e.e. and 50% isolated yield.
14. All new compounds gave satisfactory spectroscopic and analytical results.