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Enantioselective Diels–Alder reactions of 3-(acyloxy)acrylates ☆

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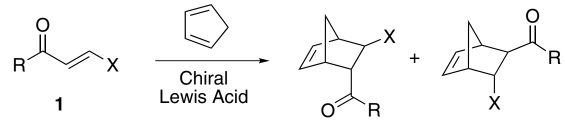
Abstract—Diels-Alder reactions with 3-(acyloxy)acrylates using chiral Lewis acid catalysts have been successfully carried out. These reactions proceed with high enantioselectivity when a chiral Lewis acid derived from $Cu(OTf)_2$ and a bisoxazoline is used. The facility of the reaction is dependent on the nature of the acyloxy group in the dienophile.

Enantioselective construction of carbon–carbon bonds has been a major area of inquiry in synthetic chemistry. One transformation of significance is the Diels–Alder (DA) reaction, where one can establish up to four adjacent chiral centers in a single synthetic operation.[1] The construction of multi-functionalized DA adducts is significant since this will allow for the preparation of key intermediates for complex molecule synthesis. A great majority of enantioselective DA reactions employ simple alkyl or aryl substituted dienophiles.[2] In contrast, heteroatom functionalized dienophiles have received less attention.[3] These substrates provide access to functionalized DA adducts directly. There is only one report by Narasaka and co-workers[4] on the use of 3-acetoxy acrylate as a dienophile in enantioselective DA reaction (Eq. 1). In their work, the dienophile proved to be inefficient (~11% yield for **1** R = oxazolidinone, X = OAc, with isoprene as a diene). To overcome this problem, they employed 3-borylpropenoyl moieties (**1** R = oxazolidinone, $X = B(OR)_2$) as 3-hydroxypropenoic acid equivalent to afford the desired cycloadducts in good yields and optical purity. This alternate protocol requires an oxidation step to convert the boronate in the Diels–Alder adduct to a hydroxy group. Exploration of 3-(acyloxy)acrylic acid derivative should be ideal to open up new methodology for asymmetric DA reactions. In this paper, we describe the first examples of highly enantioselective DA reactions with 3-(acyloxy)acryloyl dienophiles.



1 **2** endo adduct **3** exo adduct (1)

R = OR, Oxazolidinone
$X = OCOR, B(OR)_2, NR_2$

Based on the reported sluggish reactivity of acyloxy acrylates as dienophiles, we surmised that a relatively electron poor substrate with additional activation by a strong Lewis acid could allow for efficient DA reactions. To this end we investigated dienophiles with two achiral templates appended with four different acyloxy groups (**4a–d**, **6a–d**). Reaction with cyclopentadiene using ytterbium triflate as a Lewis acid was carried out to arrive at a dienophile with the best reactivity (Table 1, Eq. 2).[5] Of the two templates evaluated, the pyrrolidinone derived substrates showed superior reactivity (compare entries 1–4 with 5–8).[6] Benzoates showed higher reactivity than acetates (compare entry 1 with 2 and 1 with 3 or 4 in the pyrrolidinone series; 5 with 6 and 5 with 7 or 8 in the oxazolidinone series). Of the aroyl groups evaluated, the (4-trifluoromethyl)benzoyl moiety gave the highest yield of the DA adduct (entry 4). Hence, we chose compound **4d** as the substrate for the asymmetric DA reaction in the presence of chiral Lewis acids.

With a fairly reactive dienophile at hand, we investigated enantioselective DA cycloaddition of **4d** with cyclopentadiene. Chiral Lewis acids derived from

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Keywords: Diels–Alder; Chiral Lewis acid; β-Acyloxy acrylates.

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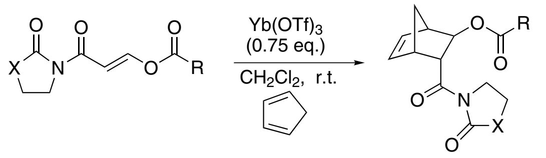
Table 1. Optimization of the 3-(acyloxy)acrylate dienophile for DA reactions[a]



4 X= CH_2
6 X = O

5 X = CH_2
7 X = O

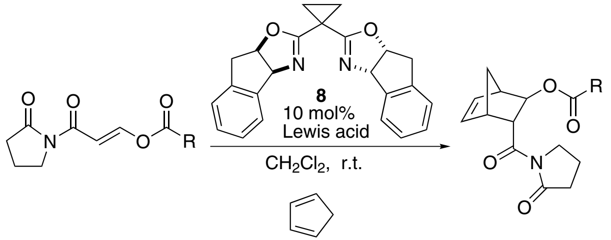
(2)

Entry	SM	R	Prod	Time (min)	Yield (%)[a]	*endo*:*exo*[b]
1	**4a**	Me	**5a**	30	59	83:17
2	**4b**	Ph	**5b**	15	55	84:16
3	**4c**	4-F–C_6H_4	**5c**	15	65	83:17
4	**4d**	4-CF_3–C_6H_4	**5d**	15	76	80:20
5	**6a**	Me	**7a**	30	5	80:20
6	**6b**	Ph	**7b**	30	21	80:20
7	**6c**	4-F–C_6H_4	**7c**	30	21	78:22
8	**6d**	4-CF_3–C_6H_4	**7d**	30	26	75:25

[a] NMR yields.

[b] Diastereomer ratio determined by ^1H NMR (500 MHz).

Table 2. Asymmetric Diels–Alder reaction in the presence of various Lewis acids



4d R = 4-CF_3-C_6H_4

5d R = 4-CF_3-C_6H_4

(3)

Entry	Lewis acid	Time (h)	Yield (%)[a]	*endo*:*exo*[b]	*endo* ee (%)[c]
1	$Cu(OTf)_2$	3	99	90:10	90
2[d]	$Cu(OTf)_2$	3	99	92:8	50
3	$Cu(ClO_4)_26H_2O$	7	99	87:13	85
4[d]	$Cu(ClO_4)_26H_2O$	5	99	90:10	37
5	$Cu(SbF_6)_2$	1.5	99	88:12	91
6[d]	$Cu(SbF_6)_2$	1	99	91:9	90
7[e]	$Cu(SbF_6)_2$	5	99	91:9	94
8	MgI_2	24	87	81:19	−28
9	$Mg(ClO_4)_2$	24	97	80:20	29
10	$Mg(NTf_2)_2$	24	75	77:23	−15
11	$Fe(ClO_4)_3$	24	76	84:16	6

[a] Isolated yields. 10 mol% of Lewis acid was used.

[b] Diastereomer ratio determined by ^1H NMR (500 MHz) and/or by HPLC.

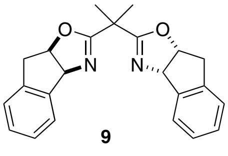
[c] Determined by chiral HPLC.

[d] MS4 Å was added.

[e] Reaction was performed at 0 °C.

bisoxazoline **8** and copper, magnesium, and iron Lewis acids were evaluated (Table 2, Eq. 3). Of the Lewis acids examined, copper salts gave the highest ee for the DA adduct (compare entries 1–7 with 8–11). In reactions with different copper salts, the use of strongly Lewis acidic $Cu(SbF_6)_2$ led to higher rate and higher ee for the *endo* adduct (compare entries 5 and 6 with 1). Decreasing the reaction temperature to 0 °C gave the highest ee value (compare entry 5 with 7). These results clearly demonstrate that β-acyloxy acrylates can function as dienophiles in enantioselective DA reactions providing adducts in high yield and selectivity. It is interesting to note that $Cu(ClO_4)_2$, which is a stronger Lewis acid than $Cu(OTf)_2$, took longer reaction time and gave the *endo* adduct with lower selectivity (entries 1 and 3). The use of molecular sieves as an additive led to an erosion of enantioselectivity (compare entry 1 with 2 and 3 with 4). The absolute configuration of the cycloadduct **5d** was determined as (2*R*,3*R*) by converting it to a compound of known configuration (vide infra).

Table 3. Evaluation of ligands for reaction of **4d** with cyclopentadiene using $\mathrm{Cu(OTf)_2}$[a]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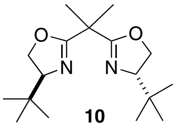
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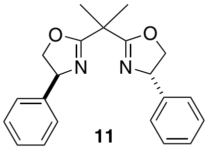

11

Entry	Ligand	Time (h)	Yield (%)[b]	*endo*:*exo*[c]	*endo* ee (%)[d]
1	**8**	3	99	90:10	90
2	**9**	8	99	90:10	83
3	**10**	72	99	90:10	54
4	**11**	2	99	94:6	−89

[a] 10 mol% of the chiral Lewis acid was used.

[b] Isolated yield.

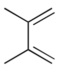
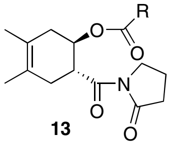
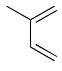
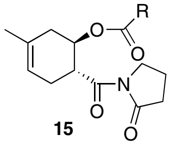
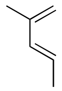
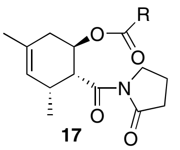
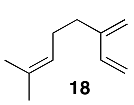
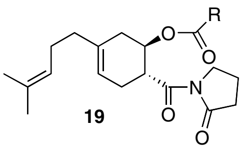
[c] Diastereomer ratio determined by ^{1}H NMR (500 MHz) and/or by HPLC.

[d] Determined by chiral HPLC.

Optimization of the chiral Lewis acid was also undertaken. Four box ligands in combination with $\mathrm{Cu(OTf)_2}$ were chosen and evaluated (Table 3).[7] Ligand **8**, containing an indan moiety and cyclopropyl bridgehead showed good ee value (entry 1). Ligand **9**, with an identical scaffold as **8**, but with an isopropylidene bridgehead, took longer time and gave lower enantioselectivity (compare entry 1 with 2). Unexpectedly, the *t*-Bubox ligand **10**, which has proven to be very effective in DA reactions using acrylates,[8] gave sluggish reaction and moderate selectivity (entry 3). Interestingly, phenylbox ligand **11** gave excellent ee value with opposite configuration (entry 4).[9] It is also interesting to note that reaction using **11** was very fast and gave the DA adduct in high yield.

To show the versatility of the new methodology, DA reactions of **4d** with four different dienes were examined (Table 4). Thus, reaction of **4d** with acyclic dienes **12**, **14**, **16**, and **18** in the presence of chiral Lewis acid [75 mol% of $\mathrm{Cu(SbF_6)_2}$ and ligand **8**] gave the desired cycloadducts in moderate to good yields and moderate ee values.[10] The reactions were slow and took days to reach completion. Small improvements in enantioselectivity could be achieved by cooling the reaction to 0 °C. However, the reactions were less efficient leading to lower chemical yields (see table). These results show the possibility of a moderately efficient procedure for the construction of chiral hydroxy-functionalized [4 + 2] cycloadducts in a single step.

Table 4. Asymmetric Diels–Alder reaction of **4d** with various dienes[a]

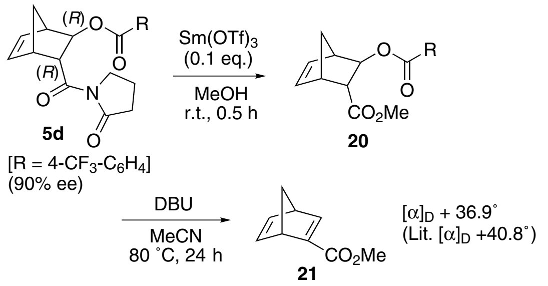
Entry	Diene	Temp (°C)	Time (d)	Product	Yield (%)[b]	ee (%)[c]
1	 **12**	rt	4	 **13**	100	59
2		0	11		81	65
3	 **14**	rt	1	 **15**	97	61
4	 **16**	0	4	 **17**	88	67
5[d]		rt	6		79	54
6	 **18**	0	11	 **19**	32	62
7		rt	6		85	61
8		0	11		36	66

[a] 75 mol% of the chiral Lewis acid [$\mathrm{Cu(SbF_6)_2}$ and ligand **8**] was used.

[b] Isolated yield.

[c] Determined by chiral HPLC.

[d] ~3% of a minor diastereomer was also obtained.



Scheme 1.

The absolute configuration of the cycloadduct **5d** was determined as follows (Scheme 1). Selective exocyclic cleavage of pyrrolidinone template was carried out by treatment with catalytic amount of $Sm(OTf)_3$ in methanol to afford methyl ester **20** in quantitative yield,[11] which was converted to 2-(methoxycarbonyl)norbornadiene **21** by heating in the presence of DBU. Comparison of the optical rotation of **21** with that in the literature[12] showed the absolute configuration of **5d** to be (2*R*,3*R*). This result was consistent with the prediction that cyclopentadiene preferentially attacks the dienophile from *re*-face when ligand **8** was used.

We propose two models for the observed stereochemistry with ligands **8** and **11**. This is based on observations in the literature on stereochemical reversal using bisoxazoline ligands that have identical configuration at C4.[13] We have also noted similar reversal in stereochemistry in radical reactions.[14] In model A, the substrate–CuX_2–ligand **8** complex adopts a distorted square-planar geometry (Fig. 1, structure **A**).[15] The tilt of the substrate is similar to the one proposed by Evans et al. with *t*-butyl bisoxazoline and copper triflate.[9b] The observed stereochemistry for **5d** is consistent with cyclopentadiene preferentially approaching the s-*cis* conformer of the dienophile from the less hindered *re*-face.

Reaction using ligand **11**, in contrast to reaction with ligand **8**, led to an enantiomeric product. It has been established in the literature that ligand **11** and copper(II) salts also adapt a slightly distorted square-planar geometry.[9b] However, the tilt of the substrate is in the opposite direction to that observed with *t*-butyl or *i*-propyl bisoxazolines.[9b] The reversal of face selectivity using ligand **11** can be accounted for by structure **B**, Figure 1. In this model, reaction occurs with diene approaching the *si*-face of the dienophile to give the adduct **5d** with opposite stereochemistry.

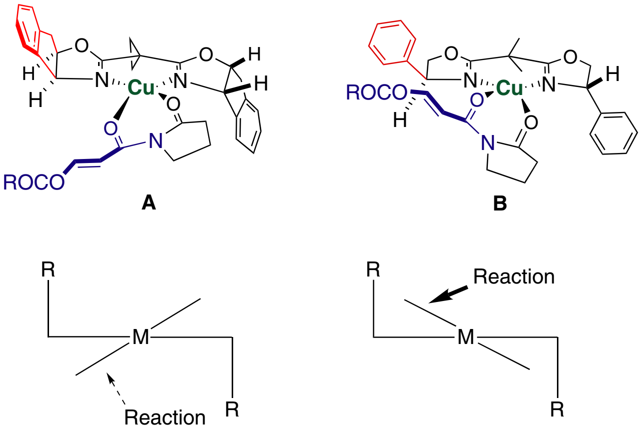


Figure 1. Plausible coordination model of the substrate (R = 4-CF_3–C_6H_4), $Cu(OTf)_2$, and ligand **8** (structure **A**) or **11** (structure **B**).

In conclusion, we have demonstrated the first successful examples of highly enantioselective Diels–Alder cycloadditions with β-acyloxy acrylates. This methodology allows for the construction of chiral hydroxy-functionalized [4 + 2] cycloadducts in a single step. Studies are underway to broaden the utility of the new methodology in the preparation of more complex adducts.

Acknowledgements

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5. The mixture of β-acyloxy acrylate substrate (0.08 mmol), Yb(OTf)$_3$ (37.2 mg, 0.06 mmol), cyclopentadiene (0.07 mL, 0.8 mmol) in CH_2Cl_2 (2.4 mL) was stirred at room temperature in a nitrogen atmosphere for 15 or 30 min. Usual work-up followed by chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/EtOAc (20:1)) yielded the mixture of *endo*- and *exo*-cyclo products and starting material. Chemical yields of the cyclo adducts and *endo*/*exo* ratios were calculated by ^{1}H NMR (500 or 400 MHz). The relative configuration of *endo*- and *exo*-cyclo adducts, *endo*-**7** (R = Me) and *exo*-**7** (R = Me), separated by chromatography on silica gel, were determined by NOESY analysis.
6. Preparation of **4** and **6**: A mixture of 1-(3-chloroacryloyl)-2-oxazolidinone (or pyrrolidinone) (10 mmol), carboxylic acid (11 mmol), and *N*-methylmorpholine (100 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 24 h. Concentration in vacuo followed by chromatography on silica gel (hexane/EtOAc (8:2 to 7:3)) yielded β-acyloxy acrylate.
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15. We have no crystallographic evidence for this assertion. The complex in principle could also be square-planar. The face selectivity will be the same from either model.