A Highly Stereoselective Diels−Alder Cycloaddition of Enones with Chiral Cyclic 2-Amidodienes Derived from Allenamides
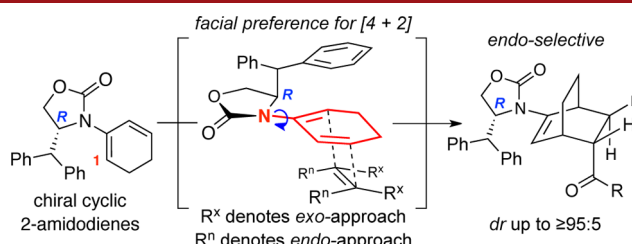
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ABSTRACT

facial preference for [4 + 2]

endo-selective

chiral cyclic 2-amidodienes

Rˣ denotes *exo*-approach
Rⁿ denotes *endo*-approach

dr up to ≥95:5

Lewis acid promoted Diels−Alder cycloadditions of a series of *de novo* chiral cyclic 2-amidodienes are described. These cyclic 2-amidodienes are derived from chiral α-allyl allenamides via a sequence of *E*-selective 1,3-H shift and 6π-electron pericyclic ring closure. With enones serving as effective dienophiles, these cycloadditions can be highly diastereoselective depending upon the chiral amide substituent, thereby representing a facile entry to optically enriched [2.2.2]bicyclic manifolds.

We recently reported[1] a highly stereoselective 1,3-hydrogen shift involving allenamides[2−4] that proves to be a facile entry to valuable dienamides or trienamides [**1**→**2** in Scheme 1].[5−7] With the *E*-selectivity in this acid or thermally promoted 1,3-H shift, the resulting 2-amidotrienes **2**

are perfectly set up to undergo a 6π-electron pericyclic ring closure[8] to give chiral cyclic 2-amidodienes **3**.[1] While 2-amino- or 2-amidodienes can find sufficient precedents,[9−11] cyclic 2-amidodienes **3** represent rare cyclic dienes.[12] While Diels−Alder cycloadditions of amino- and amido-dienes are known,[6−13] cycloadditions of respective cyclic dienes are much less known.[12] To the best of our

Scheme 1. Cyclic 2-Amidodienes in [4 + 2] Cycloadditions

1: α-allyl-allenamides

Δ or acid: *1,3-H-shift*

2: 3-amidotrienes

pericyclic ring-closure

3: chiral cyclic 2-amidodienes

dienophiles | R = Bn

Rˣ: *exo*-selective
Rⁿ: *endo*-selective

5: *endo/exo*

[4 + 2]

4: *endo/exo-I*

facial preference

4': *endo/exo-II*

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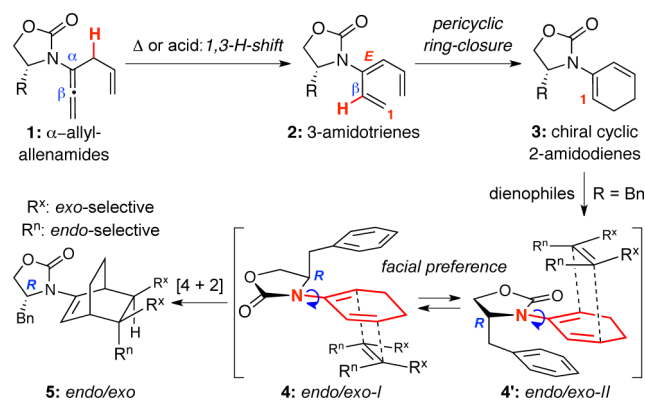
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(5) For reviews on chemistry of dienamides, see: (a) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. (b) Petrzilka, M. *Synthesis* **1981**, 753. (c) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421. (d) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1582. (e) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023.

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knowledge cycloaddition of dienes such as **3** has not been explored in a systematic manner.[14] Cyclic dienes **3** are unique, as they contain a chiral amino auxiliary at the C2-position. However, the rotation along the C−N bond potentially poses two possible coplanar conformations that could present a significant challenge in controlling the facial preference for the approaching dienophile [**4** versus **4′**]. We wish to report here our efforts in developing stereoselective Diels−Alder cycloadditions of these chiral cyclic 2-amidodienes.

Table 1. Identification of a Suitable Lewis Acid
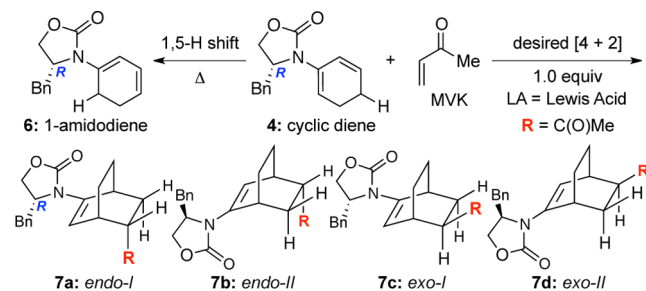
entry	LA	additive	solvent	temp [°C]	temp [h]	yield [%][a]	dr ratio[b]
1	TiCl$_4$	–	CH$_2$Cl$_2$	−78	1	50	75:25
2	AlCl$_3$	–	CH$_2$Cl$_2$	−78	1.5	19	66:37
3	EtAlCl$_2$	–	CH$_2$Cl$_2$	−78 to 0	2.5	0[c]	–
4	Et$_2$AlCl	–	CH$_2$Cl$_2$	−78 to 0	2.5	0[c]	–
5	SnCl$_4$	–	CH$_2$Cl$_2$	−78	1	75	88:12
6	SnCl$_4$	4 Å MS	CH$_2$Cl$_2$	−78	1	86	83:17
7	SnCl$_4$[d]	4 Å MS	CH$_2$Cl$_2$	−78	1	46	83:17
8	SnCl$_4$[e]	4 Å MS	CH$_2$Cl$_2$	−78	1	30	83:17
9	TMSOTf	–	CH$_2$Cl$_2$	−78	1	30	N.D.[f]
10	Sc(OTf)$_3$	–	CH$_2$Cl$_2$	0	1.5	0[c]	–
11	Yb(OTf)$_3$	–	CH$_2$Cl$_2$	rt	2	25	N.D.
12	lnCl$_3$	–	CH$_2$Cl$_2$	rt	6	30	N.D.
13	MgBr$_2$	–	THF	rt	12	no rxn[g]	–
14	LiClO$_4$	–	Et$_2$O	rt	12	no rxn	–

[a] Isolated yields; in all cases 1.0 equiv of Lewis acid was used with exceptions of entries 7 and 8. [b] Ratios determined using ^{1}H and/or ^{13}C NMR. [c] A complex mixture likely resulting from decomposition of **6** was obtained with no observable desired cycloadduct. [d] 0.50 equiv of SnCl$_4$ was used. [e] 0.25 equiv of SnCl$_4$ was used. [f] N.D. = Not Determined. [g] Complete recovery of starting diene **6**.

Given our prior experience with a 1,5-H shift that had led to the formation of thermodynamically more favorable cyclic 1-amidodienes [see **6**],[1b] our first challenge was to ensure that cycloadditions of these cyclic 2-amidodienes can take place competitively without the interference of a 1,5-H shift. Toward that goal, we screened a variety of Lewis acids in an attempt to lower the activation barrier for the cycloaddition. As shown in Table 1, the reaction of diene **4** with methyl vinyl ketone [MVK] was carried out with a series of Lewis acids, and we found that SnCl$_4$ is the most effective in promoting the cycloaddition, leading to cycloadduct **7a** and **7b** as an isomeric mixture in 86% yield when also using 4 Å MS [entry 6].[15] On the other hand, TiCl$_4$, AlCl$_3$, TMSOTf, Yb(OTf)$_3$, and InCl$_3$ [entries 1, 2, 9, 11, and 12, respectively] are met with marginal success, while EtAlCl$_2$, Et$_2$AlCl, Sc(OTf)$_3$, MgBr$_2$, and LiClO$_4$ did not work with no observable reactions taking place in the last two cases [entries, 3, 4, 10, 13, and 14, respectively].

When using less than 1.0 equiv of SnCl$_4$, the reaction gave lower yields [entries 7 and 8]. It is noteworthy that while the diastereomeric ratio was moderate, under these conditions, the reaction was quite facile even at −78 °C, thereby suppressing the thermally driven 1,5-H shift. Although stereochemical assignment was confirmed later with another cyclic diene [*vide infra*], both isomers are shown to be *endo* cycloadducts with the major isomer being **7a** and the minor being **7b**.

We quickly found that enones such as ethyl and aryl vinyl ketone could also serve as useful dienophiles when reacting with diene **4** [Table 2]. Yields in these reactions are moderate, but the diastereoselectivity was improved when using ethyl vinyl ketone [see **8**] under the conditions of 1.0 equiv of SnCl$_4$ and 4 Å MS, albeit with only a 55% yield. Unfortunately, for reasons that are currently not clear to us, other enones including 2-cyclohexenone and ynone as well as unsaturated esters were not suitable as dienophiles under these conditions. Instead, we observed a significant substrate decomposition of the starting diene **4**. Intriguingly, when using *p*-benzoquinone, we observed

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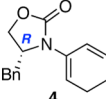
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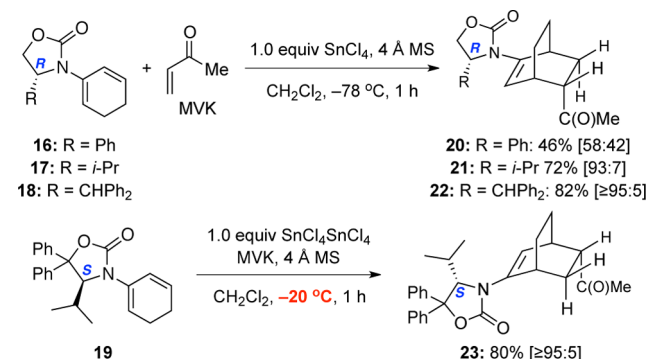
(15) See Supporting Information.

an entirely different pathway that led to a benzofuran product.[16]

cyclic diene	dienophiles	yield [%] and *dr*	unsuccessful dienophiles[c,d]
4		**8**: 55 [≥95:5]	
		9: 47 [75:25]	
		10: R = MeO [48; 66:34]	
		11: R = Me [37; 75:25]	
		12: R = Br [64; 75:25]	
		13: R = Cl [43; 66:34]	
		14: R = F [50; 66:34]	
		15: R = NO$_2$ [47; 52:48]	R = H or CO$_2$Me

[a] For each reaction, conditions would follow those described for entry 6 in Table 1. All are isolated yields. [b] Ratios denote *endo-I* to *endo-II* and are determined using ^{1}H and/or ^{13}C NMR. [c] For 3-butyne-2-one: ZnCl$_2$ in CH$_2$Cl$_2$ at 0 °C to rt was also examined. [d] For 2-cyclohexenone: AlCl$_3$ in toluene as well as TfOH in CH$_2$Cl$_2$ at 0 °C to rt was also examined.

Scheme 2. Effect of the Chiral Auxiliary on Selectivity

16: R = Ph
17: R = *i*-Pr
18: R = CHPh$_2$

20: R = Ph: 46% [58:42]
21: R = *i*-Pr 72% [93:7]
22: R = CHPh$_2$: 82% [≥95:5]

23: 80% [≥95:5]

On the other hand, we found that when using cyclic 2-amidodienes with other chiral amide auxiliaries, both stereoselectivity and efficiency could be drastically improved. As shown in Scheme 2, although using the Ph-substituted Evans auxiliary, cycloaddition with MVK led to cycloadduct **20** with diminished selectivity, diene **17** with the *i*-Pr-substituted Evans auxiliary gave **21** in 72% yield with a 93:7 ratio. Cyclic 2-amidodienes **18** and **19**

(16) When using *p*-benzoquinone, tetrahydro-dibenzofuran **i** was found in 47% yield, thereby constituting a [3 + 2] annulation process. The stereochemistry of **i** is tentatively assigned based on an *endo* approach of *p*-benzoquinone similar to the Diels−Alder transition state.

(17) For some examples of related annulations, see: (a) Brannock, K. C.; Brupitt, R. D.; Davis, H. E.; Pridgen, H. S.; Thweatt, J. G. *J. Org. Chem.* **1964**, *29*, 2579. (b) Duthaler, R. O.; Lyle, P. A.; Heuberger, C. *Helv. Chim. Acta* **1984**, *67*, 1406. (c) Hilgeroth, A.; Brachwitz, K.; Baumeister, U. *Heterocycles* **2001**, *55*, 661.

(18) (a) Sibi, M. P.; Ji, J. G. *Angew. Chem., Int. Ed.* **1996**, *35*, 190. (b) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (c) Sibi, M. P.; Soeta, T.; Jasperse, C. P. *Org. Lett.* **2009**, *11*, 5366.

substituted with the Sibi[18] and Seebach auxiliary,[19] respectively, afforded **22** and **23** in 82% and 80% yield essentially as a single isomer, thereby establishing a facile entry to optically enriched [2.2.2]bicyclic manifolds. The single crystal X-ray structure of **22a** provided unambiguous confirmation of the *endo-I* selectivity [left Figure 1].[20,21]
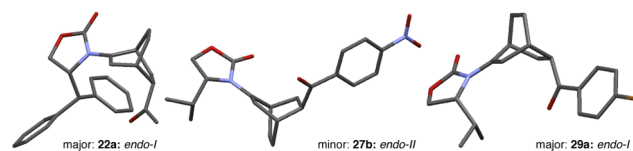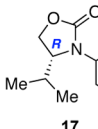

major: **22a**: *endo-I*   minor: **27b**: *endo-II*   major: **29a**: *endo-I*
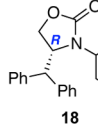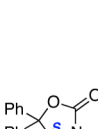
Figure 1. X-ray structures of **22a**, **27b**, and **29a**.

Table 3. A Highly Stereoselective [4 + 2] Cycloaddition[a,b]

| cyclic dienes	dienophiles	yield [%] and *dr*	dienophiles	yield [%] and *dr*
17		**24**: 76 [≥95:5]		**25**: 53 [≥95:5]
		26: 64 [≥95:5]		**27**: 73 [66:34]
		28: 59 [71:29]		**29**: 48 [75:25]
18		**30**: 82 [≥95:5]		**31**: 52 [≥95:5]
		32: 64 [≥95:5]		**33**: 82 [75:25]
		34: 79 [91:9]		**35**: 70 [83:17]
19		**36**: 71 [≥95:5] at −20 °C		**37**: 77 [≥95:5] at 0 °C
		38: 66 [≥95:5] at 0 °C		**39**: 72 [50:25:25][c] at 0 °C
		40: 50 [34:33:33][c] at 0 °C		**41**: 54 [50:33:17][c] at 0 °C

[a] Reactions conditions followed those described for entry 6 in Table 1. All are isolated yields. [b] Ratios denote *endo-I* to *endo-II* and are determined using ^{1}H and/or ^{13}C NMR. [c] The two minor isomers appear to be *exo-I* and *exo-II* (see ref 20).
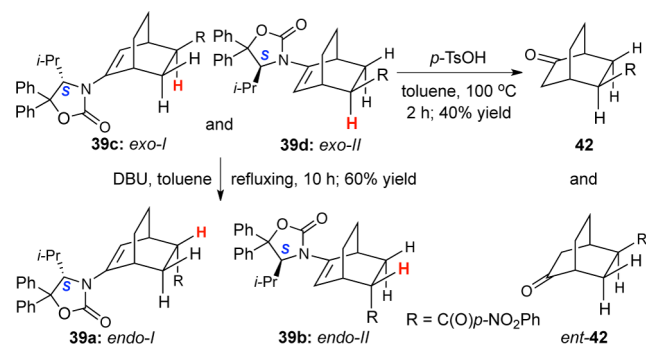
Success in finding chiral amides that can provide a high level of diastereoselectivity allowed us to broaden the scope

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of this cycloaddition significantly as shown in Table 3. Several key features are as follows: (a) substitutions at the α-position of the enone are feasible; (b) while aryl vinyl ketones in general are less selective than alkyl vinyl ketones, diene **18** with the Sibi auxiliary proves to be useful for aryl vinyl ketones in both yields and diastereoselectivity; (c) X-ray structures of cycloadducts **27b** and **29a** provide further confirmation that the major isomer is *endo-I* and the minor is *endo-II* [center and right, respectively, in Figure 1]; and (d) when using diene **19** with the Seebach auxiliary and aryl vinyl ketones, we found three isomers for the first time [see **39**−**41**]. The two minor isomers of **39**−**41** are inseparable and have been assigned as a mixture of *exo-I* and *exo-II* isomers based on the following experiments.

Hydrolysis of the minor cycloadducts of **39** with *p*-TSA gave ketone **42** as a single isomer [Scheme 3]. This result suggests that, after removal of the chiral amide, the *exo-I* and *exo-II* isomeric pair would lead to **42** and *ent-42*, respectively, which are indistinguishable spectroscopically. When using DBU in refluxing toluene to equilibrate the minor isomers, two new cycloadducts were found with one matching the major *endo-I* isomer, thereby further confirming that the minor isomers are *exo-I* and *exo-II*.[22]

Scheme 3. Assignment of Possible *exo*-Cycloadducts

To probe whether this cycloaddition is reversible, the minor cycloadduct **15b** was resubjected to the same reaction conditions, and we observed no corresponding major isomer **15a** with complete recovery of **15b**. Furthermore, when a 1:1 mixture of minor cycloadducts **13b** and **27b** were resubjected to the same conditions, no crossover

Figure 2. Different facial preference of chiral amides.

products were found with again complete recovery of both **13b** and **27b**. These results suggest that no retro-cycloaddition and equilibration took place under these reactions conditions and that the observed diastereoselectivity is likely a kinetic one.[23]

With that, a proposed explanation on various degrees in the ability of different chiral amides in inducing diastereoselectivity is shown in Figure 2. Given the assumption that the oxazolidinone ring is coplanar with the diene motif to allow for maximum delocalization of the nitrogen lone pair, the assignment of *endo-I* being the major cycloadduct would suggests that dienophiles approach from the bottom face because of shielding of the top face by the substituent on the chiral oxazolidinone auxiliary [−Ph, −Bn, −CHPh₂].

With this assumption in hand, it may be rationalized that diene **16** with the Ph-substituted Evans auxiliary would contribute the least amount of facial bias. On the other hand, diene **18** [or, **17** as well as **19**] could provide the most facial differentiation because unlike in diene **4** where the Bn group can still rotate away, leading to insufficient shielding, the diphenyl methyl motif can enhance the shielding through one of the two Ph rings. These are only preliminary analyses, and thus, efforts to improve our mechanistic understanding of this cycloaddition through more thorough calculations are ongoing.

We have described here a Lewis acid promoted Diels−Alder cycloaddition using *de novo* chiral cyclic 2-amidodienes. Under these conditions, enones prove to be the most suitable dienophiles, leading to optically enriched [2.2.2]bicyclic manifolds in a highly regio- and diastereoselective manner. Its applications in natural product synthesis are currently underway.

Supporting Information Available. Experimental procedures as well as NMR spectra, characterizations, and X-ray structural files. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Preliminary X-ray structure of cycloadduct **23a** was also obtained to avoid surprises that we had when using Seebach's chiral auxiliary in diastereoselective (4 + 3) cycloadditions where CH−π interactions reversed the stereochemical outcome [see ref 21]. However, the resolution of this structure, while sufficient for unambiguous stereochemical assignment, is not suitable for publication at the present state. Thus, the structural representation is shown in the Supporting Information, but the CIF file is not submitted.

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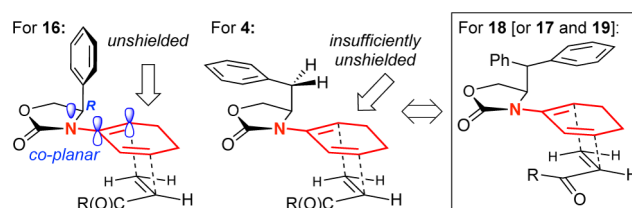(22) We obtained similar results when using a 2:1 mixture of the minor isomers from **41**.

(23) We thank one of the referees for suggesting these control studies.

The authors declare no competing financial interest.