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

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Abstract

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 γ -allyl allenamides via a sequence of *E*-selective 1,3-H shift and 6 π -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 reported¹ a highly stereoselective 1,3-hydrogen shift involving allenamides²⁻⁴ that proves to be a facile entry to valuable dienamides or trienamides [**1** $\rightarrow$ **2** in Scheme 1].⁵⁻⁷ With the *E*-selectivity in this acid or thermally promoted 1,3-H shift, the resulting 2-amido-trienes **2** are perfectly set up to undergo a 6 π -electron pericyclic ring-closure⁸ 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 knowledge cycloaddition of dienes such as **3** has not been explored in a systematic matter.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 co-planar 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.

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

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Supporting Information Available: Experimental procedures as well as NMR spectra, characterizations, and X-ray structural files are available for all new compounds and free of charge via Internet <http://pubs.acs.org>.

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 SnCl₄ 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, TiCl₄, AlCl₃, TMSOTf, Yb(OTf)₃, and InCl₃ [entries 1, 2, 9, 11, and 12, respectively] are met with marginal success, while EtAlCl₂, Et₂AlCl, Sc(OTf)₃, MgBr₂, and LiClO₄ 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 SnCl₄, 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 diastereoselectivity was improved when using ethyl vinyl ketone [see **8**] under the conditions of 1.0 equiv SnCl₄ and 4 Å MS, albeit only 55% yield. Unfortunately, for reasons that are currently not clear to us, other enones including 2-cyclohexenone and ynones as well as unsaturated esters were not suitable as dienophiles under these conditions. Instead, we observed a significant substrate decomposition of the start diene **4**. Intriguingly, when using *p*-benzoquinone, we observed an entirely different pathway that led to a benzofuran product.¹⁶

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** substituted with the Sibi¹⁸ and Seebach auxiliary,¹⁹ respectively, afforded **22** and **23** in 82% and 80% essentially as a single isomer, thereby establishing a facile entry to optically enriched [2.2.2]bicyclic manifolds. Single crystal X-ray structure of **22a** provided unambiguous confirmation of the *endo-I* selectivity [left Figure 1].^{20,21}

Success in finding chiral amides that can provide a high level of diastereoselectivity allowed us to broaden the scope of this cycloaddition significantly as shown in Table 3. Several key features are: (a) substitutions at –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 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

To probe whether this cycloaddition is reversible, the minor cycloadduct **15b** was re-subjected 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 re-subjected to the same conditions, no crossover 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 co-planar with the diene motif to allow for maximum delocalization of the nitrogen lone pair, the assignment of *endo-I* being the major cycloadduct would suggest 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Hayashi R, Hsung RP, Feltenberger JB, Lohse AG. *Org Lett.* 2009; 11:2125. [PubMed: 19371081] (b) Hayashi R, Feltenberger JB, Hsung RP. *Org Lett.* 2010; 12:1152. [PubMed: 20170149] (c) Hayashi R, Walton MC, Hsung RP, Schwab J, Yu X. *Org Lett.* 2010; 12:5768. [PubMed: 21090590] (d) Hayashi R, Feltenberger JB, Lohse AG, Walton MC, Hsung RP. *Beil J Org Chem.* 2011; 7:410.
2. For leading reviews on allenamide chemistry, see: Lu T, Lu Z, Ma ZX, Zhang Y, Hsung RP. *Chem Rev.* 2013; 130:4862. [PubMed: 23550917] Hsung RP, Wei LL, Xiong H. *Acc Chem Res.* 2003; 36:773. [PubMed: 14567711]
3. Also see: Standen PE, Kimber MC. *Curr Opin Drug Discov & Devel.* 2010; 13:645. Deagostino A, Prandi C, Tabasso S, Venturello P. *Molecules.* 2010; 15:2667. [PubMed: 20428072]

4. For general reviews on allenes, see: Krause N, Hashmi ASK. Modern Allene Chemistry. Wiley-VCH Verlag GmbH & Co. KGaA Weinheim 2004; 1 and 2
5. For reviews on chemistry of dienamides, see: Overman LE. Acc Chem Res. 1980; 13:218. Petrzilka M. Synthesis. 1981;753. Campbell AL, Lenz GR. Synthesis. 1987;421. Krohn K. Angew Chem Int Ed Engl. 1993; 32:1582. Enders D, Meyer O. Liebigs Ann. 1996:1023.
6. For a recent review on chemistry of enamides, see: Carbery DR. Org Biomol Chem. 2008; 9:3455. [PubMed: 19082143] Also see: Rappoport Z. The Chemistry of Enamines in The Chemistry of Functional Groups. John Wiley and Sons New York 1994. Whitesell JK, Whitesell MA. Synthesis. 1983:517. Hickmott PW. Tetrahedron. 1982; 38:1975–3363.
7. For a review on the synthesis of enamides, see: Tracey MR, Hsung RP, Antoline J, Kurtz KCM, Shen L, Slafer BW, Zhang Y. Weinreb, Steve M. Science of Synthesis, Houben-Weyl Methods of Molecular Transformations. Georg Thieme Verlag KG Chapter 21.4 2005;
8. For reviews, see: Marvell EN. Thermal Electrocyclic Reactions. Academic Press New York 1980. Okamura WH, de Lera AR. Trost BM, Fleming I, Paquette LA. Comprehensive Organic Synthesis. Pergamon Press New York 1991; 5:699–750.
9. For reviews on chemistry of 2-amino- or 2-amidodienes: Krohn K. Angew Chem Int Ed Engl. 1993; 32:1582. Enders D, Meyer O. Liebigs Ann. 1996:1023.
10. For leading examples of 2-amino-dienes, see: Enders D, Meyer O, Raabe G. Synthesis. 1992:1242. Barluenga J, Canteli R-M, Flrez J, Garca-Granda S, Gutierrez-Rodriguez A, Martín E. J Am Chem Soc. 1998; 120:2514. and references cited there in.
11. For leading examples of 2-amido-dienes, see: Ha JD, Kang CH, Belmore KA, Cha JK. J Org Chem. 1998; 63:3810. González-Romero C, Bernal P, Jiménez F, Cruz MC, Fuentes-Benites A, Benavides A, Bautista R, Tamariz J. Pure Appl Chem. 2007; 79:181. and references cited therein. Movassaghi M, Hunt DK, Tjandra M. J Am Chem Soc. 2006; 128:8126. [PubMed: 16787063]
12. For some rare examples cyclic amido-dienes, see: Martínez R, Jiménez-Vázquez HA, Delgado F, Tamariz J. Tetrahedron. 2003; 59:481. Wallace DJ, Klauber DJ, Chen CY, Volante RP. Org Lett. 2003; 5:4749. [PubMed: 14627431] Wabnitz TC, Yu JQ, Spencer JB. Chem Eur J. 2004; 10:484. [PubMed: 14735517]
13. (a) Terada A, Murata K. Bull Chem Soc Jpn. 1967; 40:1644. (b) Overman LE, Clizbe LA. J Am Chem Soc. 1976; 98:2352. (c) Oppolzer W, Bieber L, Francotte E. Tetrahedron Lett. 1979:4537. (d) Smith AB III, Wexler BA, Tu C-Y, Konopelski JP. J Am Chem Soc. 1985; 107:1308. (f) Schlessinger RH, Pettus TRR, Springer JP, Hoogsteen K. J Org Chem. 1994; 59:3246. (e) Kozmin SA, Rawal VH. J Am Chem Soc. 1997; 119:7165. (f) Huang Y, Iwama T, Rawal VH. J Am Chem Soc. 2002; 124:5950. [PubMed: 12022822] (g) Robiette R, Cheboub-Benchaba K, Peeters D, Marchand-Brynaert J. J Org Chem. 2003; 68:9809. [PubMed: 14656111]
14. We have examined cycloadditions of related dienes in a tandem and intramolecular mode. See: Feltenberger JB, Hsung RP. Org Lett. 2011; 13:3114. [PubMed: 21612235] Hayashi R, Ma ZX, Hsung RP. Org Lett. 2012; 14:252. [PubMed: 22149386]
15. See Supporting Information.
16. When using *p*-benzoquinone, tetrahydro-dibenzofuran **i** was found in 47% yield, thereby constituting a [3 + 2] annulation process. 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: Brannock KC, Brupitt RD, Davis HE, Pridgen HS, Thweatt JG. J Org Chem. 1964; 29:2579. Duthaler RO, Lyle PA, Heuberger C. Helv Chim Acta. 1984; 67:1406. Hilgeroth A, Brachwitz K, Baumeister U. Heterocycles. 2001; 55:661.
18. (a) Sibi MP, Ji JG. Angew Chem, Int Ed. 1996; 35:190. (b) Sibi MP, Porter NA. Acc Chem Res. 1999; 32:163. (c) Sibi MP, Soeta T, Jasperse CP. Org Lett. 2009; 11:5366. [PubMed: 19877629]
19. (a) Hintermann T, Seebach D. Helv Chim Acta. 1998; 81:2093. (b) Gaul C, Seebach D. Org Lett. 2000; 2:1501. [PubMed: 10841464] (c) Gaul C, Schweizer BW, Seiler P, Seebach D. Helv Chim Acta. 2002; 85:1546.

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-interactions reversed the stereochemical outcome [see reference 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 Supporting Information but the CIF file is not submitted.
21. (a) Krenske EH, Houk KN, Lohse AG, Antoline JE, Hsung RP. Chem Sci. 2010; 1:387. [PubMed: 21572919] (b) Antoline JE, Krenske EH, Lohse AG, Houk KN, Hsung RP. J Am Chem Soc. 2011; 133:14443. [PubMed: 21851070]
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.

Figure 1.
X-Ray Structures of **22a**, **27b**, and **29a**.

Figure 2.
Different Facial Preference of Chiral Amides.

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

Scheme 2.
Effect of the Chiral Auxiliary on Selectivity.

Scheme 3.
Assignment of Possible *exo*-Cycloadducts.

Table 1

Identification of a Suitable Lewis Acid.

entry	LA	additive	solvent	temp [°C]	time [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	InCl 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; and in all cases 1.0 equiv of Lewis acid was used with exceptions of entries 7 and 8.

^b Ratios determined using ¹H and/or ¹³C NMR.

^c A complex mixture likely resulting from decomposition of 6 was obtained with no observable desired cycloadduct.

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^d 0.50 equiv of SnCl₄ was used.

^e 0.25 equiv of SnCl₄ was used.

^f N.D. = Not Determined.

^g Complete recovery of starting diene **6**.

Table 2

Some Limitations on Dienophiles.^{a,b}

cyclic diene	dienophiles	yield [%] and <i>dr</i>	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]	

^aFor each reaction, conditions would follow those described for entry 6 in Table 1. All are isolated yields.^bRatios denote *endo-I* to *endo-II* and are determined using ¹H and/or ¹³C NMR.^cFor 3-butyne-2-one: ZnCl₂ in CH₂Cl₂ at 0 °C to rt was also examined.^dFor 2-cyclohexenone: AlCl₃ in toluene as well as TfOH in CH₂Cl₂ at 0 °C to rt was also examined.

Table 3

A Highly Stereoselective [4 + 2] Cycloaddition.^{a,b}

cyclic dienes	dieneophiles	yield [%] and <i>dr</i>	dieneophiles	yield [%] and <i>dr</i>
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

^aReactions conditions followed those described for entry 6 in Table 1. All are isolated Yields.^bRatios denote *endo-I* to *endo-II* and are determined using ¹H and/or ¹³C NMR.

^cThe two minor isomers appear to be *exo-I* and *exo-II* (see Reference 20).