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# Intramolecular Diels–Alder reactions using chiral ruthenium Lewis acids and application in the total synthesis of *ent*-ledol<sup>†</sup>

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One-point binding chiral ruthenium Lewis acids incorporating the  $C_2$ -symmetric electron-poor bidentate phosphinite ligand BIPHOP-F and a Cp or an indenyl 'roof' can efficiently catalyze asymmetric intramolecular Diels–Alder reactions of trienes to form bicyclic adducts with good to excellent asymmetric induction. This reaction forms the key step in a total synthesis of *ent*-ledol in 96% ee. The synthesis also helps to clarify the stereochemical assignment of ledol and inconsistencies in the measured optical rotation.

### Introduction

The Diels–Alder reaction is arguably the most powerful method to access six-membered rings compounds. The reaction generates up to four stereogenic centers in a single step. 6-Membered rings are ubiquitous in biologically active natural products. Over recent years, asymmetric catalytic Diels–Alder methodologies have experienced an enormous advancement,<sup>1</sup> but less reactive dienes or dienophiles are still inherently difficult to engage in this reaction.

We have developed single-point binding chiral Ru Lewis acid catalysts based on cationic half-sandwich complexes incorporating a pentafluorophenyldiphosphinite ligand (Fig. 1). This ligand creates the chiral environment around the coordination site of the catalyst. The electron poor ligand also offsets the donor properties of the electron rich arene roof and thus enhances the Lewis acidity of the metal center. These catalysts were first employed successfully in intermolecular Diels-Alder (DA) cycloaddition reactions of enals with various dienes.<sup>2</sup> Applications in asymmetric 1,3dipolar cycloadditions of nitrones<sup>3</sup> and nitrile oxides<sup>3c,4</sup> followed. Furthermore, catalyst 1a was successfully applied in Michael addition reactions of enones with diverse thiophenols.<sup>5</sup> In all these reactions the enals coordinated to the transition metal center and the ground state anti-s-trans conformation of the coordinated enal was also the one undergoing reaction as indicated by the product's absolute configuration. Slow addition of the dipolarophile helped in cases of competitive coordination.

 $\alpha$ , $\beta$ -Unsaturated ketones are far more difficult substrates since they lack the high lone pair differentiation of aldehydes. Coordination is in the *anti*-s-*trans* conformation and that conformation



Fig. 1 Chiral Ru Lewis acid catalysts.

mode leads to opposite asymmetric inductions. One-point binding chiral Lewis acid catalysts for this reaction are therefore scarce.

Successful solutions were reported by Corey and by Hawkins using chiral boron Lewis acids.<sup>6</sup> Another approach was chosen by MacMillan and Northrup *via* formation of a chiral iminium salt using a chiral imidazolidinone as catalyst.<sup>7</sup> In an earlier publication we have shown that the chiral catalysts 1 are also able to give high asymmetric induction in intermolecular [4 + 2] cycloaddition reactions.<sup>8</sup> We found that while the ground state structure of [Ru(BIPHOP-F)(Cp)(methyl vinyl ketone) shows a preferential *anti-s-trans* conformation in the X-ray structure, the reacting conformation apparently is the one having a *syn-strans* arrangement. This study also included a first example of an intramolecular Diels–Alder (IMDA) reaction as depicted in Scheme 1.



Scheme 1 A first IMDA reaction catalyzed by 1a.

We here report on a follow-up of asymmetric IMDA reaction of triene **2** and its application in the total synthesis of *ent*-ledol. This first synthesis is performed in order to clarify the conflicting data for ledol and related diastereomers (globulol and viridiflorol).

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Although there have been many reports on the isolation of ledol from various natural sources, several inconsistencies remain in the reported structures and spectral assignments. As shown below, our data confirm those of Goh,<sup>9a</sup> Gottlieb<sup>9b</sup> and Szafranek<sup>9c</sup> Moreover, we also detail the use of CpRu **1a** and IndRu **1b** in IMDA reactions with trienes **4–15** (Fig. 2).



Fig. 2 Trienes probed in the chiral [Ru] catalyzed IMDA reactions.

#### Synthesis of ent-ledol

Ledol is a sesquiterpene that belongs to the class of aromadendrenes. Its structural characteristics include a gemdimethylcyclopropane ring fused to a hydroazulene skeleton (Fig. 3). It exhibits antitussive<sup>10a,b</sup> and antifungal<sup>10c</sup> (Coriolus renatus) properties. Ledol was first isolated from Ledum palustre (Rhododendron tomentosum, also commonly known as Labrador tea or wild rosemary), a plant common to sphagnum meadows.<sup>11a</sup> Its relative stereochemistry was elucidated by X-ray diffraction.12 An asymmetric synthesis of ledol was previously reported starting from (+)-aromadendrene.<sup>13</sup> A racemic synthesis via IMDA reaction was reported by Shea.<sup>14</sup> A literature survey of ledol shows many conflicting stereochemical assignments and due to different solvents used there is confusion about the sign of optical rotation. We therefore decided to prepare ent-ledol to compare spectroscopic data and optical rotation. The present synthesis will help to solve several structure misassignments<sup>15</sup> and be useful for the study of biological activity.



Fig. 3 Ledol and its diastereoisomers globulol and viridiflorol.

Asymmetric type 2 IMDA reactions were previously documented by Shea with dual function Ru catalysts<sup>16</sup> (modest induction) and by MacMillan with organocatalysis<sup>17</sup> (high induction), and by ourselves using the chiral Ru Lewis acid 1a (Scheme 2). We have now scaled up this reaction in order to provide sufficient material for the synthesis of *ent*-ledol by using (S,S)-1a with triene 2 to provide the crucial intermediate (S)-3 in good yield with excellent ee.



The X-ray structure of the CpRu Lewis acid complex helps to rationalize the observed enantioselectivity in the IMDA reaction as shown in Fig. 4. The *syn-s-trans* conformation of the enone (orange) is arranged such as to avoid adverse steric interactions between the three methylene groups of the side chain and the Cp ligand of the catalyst. The diene (blue) approaches the *Si*-face of the dienophile in *endo* fashion because the *Re*-face is shielded by a pentafluorophenyl group of the ligand.



**Fig. 4** Modelled approach of trienone **2** coordinated to Ru in (S,S)-**1a** in a *syn*-s-*trans* orientation (catalyst part taken from the X-ray structure of [Ru(acetone)(Cp)((S,S)-BIPHOP-F)][SbF<sub>6</sub>]).<sup>2a</sup>

With (S)-3 in hand, we proceeded with the synthesis of *ent*ledol by following to a large extent Shea's route.<sup>14</sup> Treatment of **3** with MeLi and alcohol protection with TBSOTf afforded the *endo* product **16** as a single diastereomer with an ee of 92%. Ozonolysis of **16** furnished diketone **17** in 76% yield. Aldol condensation provided the expected enone which was directly used in a highly diastereoselective hydrogenation leading to the [7,5]fused ring compound **18** in 90% yield in 2 steps. Isolation at this step also showed the material to have higher enantiomeric purity (Scheme 3).

Generation of bicyclic alkene **19** involved formation of the enol phosphate and hydrogenolysis (Scheme 4).

Next the dimethylcyclopropane moiety needed to be installed. Seyferth's reagent<sup>18</sup> was previously employed to furnish the dibromocyclopropane precursor.<sup>14</sup> To avoid the use of a mercury reagent and benzene as solvent, we investigated more environmentally benign conditions. The haloform cyclopropanation procedure fulfils these requirements.<sup>19</sup> This procedure was first optimized on the model alkene **21**, obtained from bicyclic ketone **20**. The



reaction yielded dibromocyclopropane **22** in high yield with excellent diastereoselectivity. Treatment of **22** with *in situ* generated lithium dimethylcuprate, and then with MeI,<sup>20</sup> yielded the corresponding *gem*-dimethyl compound **23** (Scheme 5). The relative stereochemistry in **23** was established by Nuclear Overhauser Effect Spectroscopy (NOESY). The observed NOE's are shown in Scheme 5 and they show that, as expected, the product obtained was the one issued from cyclopropanation on the convex face of **21**.



This cyclopropanation procedure was applied to the *cis*-fused ring compound **19** to furnish dibromocyclopropane **24**, followed by *gem*-dimethylation with methyl cyano cuprate providing dimethylated compound **25** in excellent diastereoselectivity and thus retaining the high enantiomeric excess (Scheme 6). Cleavage of the TBS group of **25** by refluxing with TBAF in THF then yielded *ent*-ledol in excellent enantioselectivity. Its spectroscopic data matched literature data.<sup>9,14a</sup>



The <sup>1</sup>H-NMR resonances C(1a)–H and C(7b)–H are the principal distinguishing spectroscopic characteristics for ledol and its diastereomers. These are found at  $\delta = 0.33$  and 0.72 ppm for ledol, at 0.51 and 0.59 ppm for globulol, and at 0.11 and 0.61 ppm for viridiflorol. Another characteristic is the melting point: 103–105 °C for ledol, 86–88 °C for globulol, and 72–74 °C for viridiflorol.<sup>9,13</sup>

To confirm the absolute configuration of the synthesized *ent*-ledol, the specific optical rotation  $([\alpha]_D^{25})$  was measured and compared to literature data of ledol (Table 1). In an early, brief report on the isolation of ledol, Naves reported the  $[\alpha]_D^{20}$  to have a negative sign in chloroform but a positive one in ethanol.<sup>21b</sup> This note was overlooked and a negative sign measured in chloroform led to confusion and what must have been ledol was erroneously assigned to *ent*-ledol.<sup>15a</sup>

Moreover, a negative Cotton effect in the CD spectrum of *ent*ledol in EtOH is indicated (Fig. 5) but not in CHCl<sub>3</sub> and toluene because of the overlapping between solvent and ledol peaks.



Fig. 5 CD Spectrum of *ent*-ledol in EtOH showing a negative Cotton effect.

#### Asymmetric IMDA reactions

We next probed type 1 IMDA reactions.<sup>22</sup> Triene 4<sup>23</sup> was unreactive, and coordination to 1a does not appear to occur as evidenced

Table 1 Optical rotations of ledol (lit. data) and of ent-ledol

Entry	Solvent	$[\alpha]^{25}_{D}$ of Ledol	Cond."	$[\alpha]^{25}_{D}$ of <i>ent</i> -Ledol <sup>b</sup>
1	EtOH	+1.9 <sup>21a</sup> +2.6 <sup>21b</sup>	25 °C (0.98) 20 °C (0.05)	-2.3
2	MeOH	+2.0 <sup>9b</sup>	$nr^{c}$ (1.40)	
3	CHCl <sub>3</sub>	-4.3 <sup>9a</sup>	nr <sup>c</sup> (0.42)	+4.6
		-5.6 <sup>21b</sup>	20 °C (0.05)	
		-5.8 <sup>13d</sup>	$nr^{c}$ (1.50)	
4	Toluene	c		-9.8
5	CH <sub>3</sub> CN	c		+0.5
6	THF	<i>c</i>		+0.4

<sup>*a*</sup> Temperature (concentration) for measurement of  $[\alpha]_{D}$ . <sup>*b*</sup> This study, average value of three determinations at 25 °C ( $c = 0.10 \text{ g L}^{-1}$ ) with cuvette cell. <sup>*c*</sup> Temperature not specified.

by the lack of change in the <sup>1</sup>H-NMR spectrum when mixing trienone **4** with an equimolar quantity of complex **1a**. Ketone **4** may be too bulky to fit into the Lewis acidic site. The same holds for triene **5**. Moreover, this compound presented an additional difficulty in that it underwent IMDA reaction spontaneously on generation *via* oxidation of trienol **26** (Scheme 7).<sup>24</sup>



Trienone **6** afforded low product yield with low ee (CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 7 d and rt, 10 d). <sup>1</sup>H NMR data indicates enone **6** to coordinate to the catalyst. On mixing **6** with **1a** (ratio 10:1, CH<sub>2</sub>Cl<sub>2</sub>, 15 min) resulted in important <sup>1</sup>H NMR shifts (7.51 (COCH= CH), 2.60 (CH<sub>3</sub>) and 2.51 (COCH=CHCH<sub>2</sub>) compared to the values of 6.82, 2.24 and 2.27 respectively, for **6** alone. Also in the IR spectrum, the  $v_{co}$  band shifted from 1672 to 1640 cm<sup>-1</sup>.

We conclude that either the activation provided by 1a is insufficient to promote IMDA reaction or that the substrate cannot adopt a folding leading to IMDA reaction. Based on the results discussed below we favor the first explanation. At this stage it is important to remind the reader that these catalysts are weak Lewis acids best compared to ZnCl<sub>2</sub>.<sup>25</sup>

We then turned to aldehyde substrates. Without catalyst, trienal 7 did not undergo cycloaddition (Table 2, entry 1). The catalytic reaction, while very slow, afforded products in good yield and in high diastereoselectivity and enantioselectivity, albeit that the yields did not reach the values previously reported by Yamamoto and coworkers.<sup>26a,b</sup> 2,6-Lutidine was added to scavenge traces of acid in order to suppress the acid catalyzed reaction leading to the racemic product. The data shows that both the yield and the ee are higher when catalyst 1b is used rather than 1a. The first is likely to be linked to a looser ion pair in complex 1b enabling more efficient turnover.<sup>2d</sup> The higher enantioselectivity may result from a more restricted space in the reaction site in the indenyl catalyst when compared to the Cp catalyst.<sup>2b,22</sup> As detailed in the preliminary communication of this paper, the absolute configuration of 27 was ascertained by an X-ray structure determination after derivatization.22

Table 2Optimized IMDA reactions conditions of triene  $7^{a}$ 

онс		5 mol % ( <i>S</i> , <i>S</i> )- <b>1</b> ;	OHC H	
7		2 mol% 2,6-lutidine CH <sub>2</sub> Cl <sub>2</sub> , cond.		H 27
				<i>endo:exo</i> = 99:1
Entry	Cat.	Cond."	Conv. <sup>b</sup>	% yield <sup>c</sup> (ee) <sup>d</sup>
1		rt, 7 d	2	(0)
2	1a	rt, 9 d	100	82 (72)
3	1a	40 °C, 4 d	96	70 (69)
4	1b	rt, 7 d	100	92 (84)
5	1b	40 °C, 4 d	100	82 (82)

<sup>*a*</sup> All reactions were carried out at least 3 times in 0.2–0.3 M concentration and were followed by TLC (10% Et<sub>2</sub>O in pentanes). <sup>*b*</sup> % Conversion was determined by <sup>1</sup>H NMR. <sup>*c*</sup> Isolated yield. <sup>*d*</sup> ee of the *endo*-isomer was determined by chiral GC (Hydrodex- $\beta$ , H<sub>2</sub>, 100 °C hold 30 min then heating at 0.5 °C min<sup>-1</sup> to 120 °C: *t*<sub>R</sub> of *endo* product (min) = 33.69 (minor), 35.30 (major)).

Triene **9**, previously investigated in the asymmetric IMDA reaction with a chiral acyloxy borane catalyst,<sup>26c</sup> was prepared and used in IMDA reactions with chiral Ru catalysts **1a** and **1b** (Table 3). As expected cycloadduct **28**, incorporating a quaternary carbon center, was formed with high enantioselectivities, although diastereoselectivities were modest and reaction times long.

More efficient catalytic IMDA reactions resulted with trienals **10** and **11**. This can be attributed largely to the Thorpe–Ingold effect of the dimethyl malonate moiety. It also made the synthesis of this triene more efficient. The reaction of triene **10** was followed by *in situ* IR analysis recording the decay of the aldehyde  $v_{co}$  band associated with **10**. TLC was unsuitable because of an overlap of starting material and product spots. Reactions were considerably faster with cycloadducts being formed in hours rather than days.

Trienal **10** undergoes spontaneous, uncatalyzed cycloaddition (Table 4, entry 1). While the catalysts accelerate the reaction and impart asymmetric induction, the background reaction prevents

 Table 3
 IMDA reactions of triene 9<sup>a</sup> <sup>22</sup>

He OHC 9		5 mol % ( <i>S</i> , <i>S</i> )- <b>1a</b> or ( <i>S</i> , <i>S</i> )- <b>1b</b> 2 mol % 2,6-lutidine CH <sub>2</sub> Cl <sub>2</sub> , cond.		CHO Merry H +
			→ <u>:</u> → H endo- <b>28</b>	H exo- <b>28</b>
Entry	Cat.	Cond."	endo: exo <sup>b</sup>	% yield <sup><math>c</math></sup> (ee) <sup><math>d</math></sup>
1 2 3 4 5	— 1a 1b 1b	rt, 6 d rt, 7 d 40 °C, 4 d rt, 6 d 40 °C, 4 d	84 : 16 82 : 18 81 : 19 79 : 21	$1^{e}(-)$ 82 (92, 91) 66 (88, 90) 85 (84, 90) 60 (78, 87)

<sup>*a*</sup> All reactions were carried out in 0.2–0.3 M concentration. The progress of the reaction was followed by TLC (10% Et<sub>2</sub>O in pentanes). <sup>*b*</sup> Determined by <sup>1</sup>H NMR. <sup>*c*</sup> Isolated yield. <sup>*d*</sup> ee of *endo*- and *exo*-isomers, respectively were determined by chiral GC (Hydrodex- $\beta$ , H<sub>2</sub>, 100 °C hold 30 min then heating 0.5 °C min<sup>-1</sup> to 120 °C): t<sub>R</sub> of *exo* product (min) = 34.82 (major), 38.03 (minor) and t<sub>R</sub> of *endo* product (min) = 40.85 (minor), 41.52 (major)). <sup>*e*</sup> % Conversion was determined by <sup>1</sup>H NMR.

 Table 4
 IMDA reactions of trienals 10 and 11<sup>a22</sup>



<sup>*a*</sup> All reactions were carried out in 0.2–0.3 M concentration and monitored by IR spectroscopy. <sup>*b*</sup> 2–5 mol% of 2,6-lutidine was added to scavenge acid impurities. <sup>*c*</sup> Isolated yield. <sup>*d*</sup> % Conversion was determined by <sup>1</sup>H NMR. <sup>*e*</sup> ee of *endo*-isomer was determined by chiral GC. <sup>*f*</sup> ee of *endo*-isomer, determined by <sup>1</sup>H NMR of its chiral imine derivative.<sup>22</sup>

the obtention of the product with high enantiomeric enrichment (systematic optimization was performed as shown in Table 4). Chiral Ru Lewis acid-catalysed IMDA reactions of trienes 10 and 11 furnished the *endo*-isomer as a major product in a 99:1 ratio. The ee of 29 could not be increased to more than 56% (entries 3 and 4) due to the competitive background reaction. The uncatalyzed reaction was much less important with the less electron rich diene of triene 11 (entry 5) and, with catalyst 1b, high yields and asymmetric induction were achieved (entry 7).

Extension to more challenging systems such as trienes **8**, **12** and **13** would provide [6,6]- and [6,7]-fused bicyclic systems, respectively. The optimal conditions of entries 2 and 4 in Table 2 were used for IMDA of triene **8** but low conversion and ee were observed with both catalysts (with **1a**, rt, 7d: 7% conv., 99:1 of *endo*:*exo*, 0% ee and with **1b**, rt, 7d: 18% conv., 99:1 *endo*:*exo*, 19% ee). Unfortunately, poor diastereo- and enantioselectivities were observed for triene **12** (with **1a**, rt, 7d: 100% conv., 66:34 *endo*:*exo*, 9% ee for *endo*-isomer and 18% ee for *exo*-isomer and with **1b**, rt, 7d: 74% conv., 54:46 *endo*:*exo*, 33% ee for both isomers). Triene **13** did not yield a Diels–Alder product under Lewis acid catalysed conditions.<sup>27</sup> Unfavorable energetics to form the transition state leading to the [6,7]-fused bicyclic systems might be the reason.

Our results suggest only [6,5]-*trans* fused ring adducts can be readily formed by IMDA reactions with the chiral Ru Lewis acids 1. This encouraged us to explore IMDA reactions of trienones 14 and 15. Unfortunately, the IMDA background reactions were high for both trienones, resulting in products of less than 10% ee.

X-ray structures of chiral Ru Lewis acid/substrate complexes have been very helpful for the interpretation of observed selectivities in cycloaddition reactions.<sup>2-4,5,8</sup> For the IMDA reaction involving triene 7 the diene approach leading to the observed *endo* product **27** was modelled using the X-ray structure of (S,S)-**1a**. We propose that the enal dienophile (orange) coordinates to the Ru in an *anti*-s-*trans* conformation and the diene (blue) approaches the *Re*-face of the enal moiety in an *endo* mode. The C<sub> $\alpha$ </sub>-S*i*face is shielded by the pentafluorophenyl moiety of the (S,S)- BIPHOP-F ligand (Fig. 6). This results in the observed product stereochemistry of **27**.



**Fig. 6** Modelled approach of trienal 7 coordinated to Ru in (S,S)-1b in an *anti-s-trans* orientation (catalyst part taken from the X-ray structure of [Ru(Cl)((S,S)-BIPHOP-F)(Indenyl)][SbF<sub>6</sub>]).<sup>2b</sup>

The absolute configurations of 28-30 were assigned based on direct comparison of their CD spectra with that of the hydrazone derivative of adduct 27 after transforming to their corresponding hydrazone compounds.<sup>22</sup>

#### Conclusions

The first catalytic IMDA reaction with chiral one-point binding transition metal Lewis acids have been probed. The bridgehead adduct (*S*)-**3** was used in the first synthesis of *ent*-ledol. The overall yield of *ent*-ledol is 13% in 6 steps with 96% ee. The investigation of IMDA reaction was extended. Modest to excellent enantioselectivities and diastereoselectivities of adducts were obtained, especially with the 3 carbon tethers of trienals. With trienones only the type 2 IMDA reaction leading to product **3** proved efficient. The observed stereochemistry of the Diels–Alder products is in agreement with a model based on the X-ray structure of catalysts.

#### **Experimental section**

#### Synthesis of ent-ledol

Triene 2 was prepared as detailed by Shea and coworkers.<sup>14a</sup>

Spectral data (<sup>1</sup>H, <sup>13</sup>C, IR and MS) of **3**, **16–19** and **25** are in agreement with those already reported.<sup>14a</sup> <sup>1</sup>H and <sup>13</sup>C NMR of *ent*-ledol are represented in the electronic experimental section.

(S)-7-Methylbicyclo[4.3.1]dec-6-en-2-one (3). In a 50 mL Schlenk tube equipped with a magnetic stirring bar and activated powder molecular sieve 4 Å (50 mg), at r.t. and under N<sub>2</sub>, [Ru(acetone)((*S*,*S*)-BIPHOP-F)(Cp)][SbF<sub>6</sub>] (1a) (140 mg, 0.10 mmol, 0.05 eq) was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3.00 mL). To the stirring mixture, 2,6-lutidine (2.8  $\mu$ L, 0.012 mmol, 0.006 eq) and a solution of triene 2 (328 mg, 2 mmol, 1 eq) in CH<sub>2</sub>Cl<sub>2</sub> (2.00 mL) were carefully added, and the yellow–orange solution stirred at room temperature (r.t.) and under N<sub>2</sub> for 5 days. The reaction was then monitored by GC by injecting 2  $\mu$ L aliquots. At the end of the reaction, CH<sub>2</sub>Cl<sub>2</sub> was removed under vacuum and hexane (30 mL) was added, and the mixture was filtered through a Celite 545 plug. Volatiles were removed *in vacuo* and the residue was purified by flash column chromatography (f.c.) using a silica

gel column (1–5% Et<sub>2</sub>O in pentanes) to give a pale yellow oil of adduct **3** (230 mg, 1.40 mmol, 70% yield). Chiral GC (Hydrodex- $\beta$ , H<sub>2</sub>, 100 °C hold 30 min then heating 0.5 °C min<sup>-1</sup> to 120 °C):  $t_{\rm R}$  of product (min) = 53.9 (major)/55.0 (minor), 92% ee.  $[\alpha]_{\rm D}^{25} =$ +24.1 (c = 0.25, CH<sub>2</sub>Cl<sub>2</sub>)

tert-Butyl(((2S)-2,7-dimethylbicyclo[4.3.1]dec-6-en-2-yl)oxy) dimethylsilane (16). To a stirred solution of the ketone (200 mg, 1.2 mmol, 1 eq) in THF (8.75 mL) at -78 °C was added MeLi (1.6 M in Et<sub>2</sub>O, 0.78 mL, 2.4 mmol, 2 eq). After 30 min, the reaction was warmed to r.t. and was quenched with sat. NH<sub>4</sub>Cl. The mixture was extracted with  $CH_2Cl_2$  (2×10 mL). The combined organics were dried and concentrated in vacuo. To a stirred solution of the crude alcohol in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) and pyridine (0.3 mL, 3.6 mmol, 3 eq) at 0 °C was added TBSOTf (0.42 mL, 1.8 mmol, 1.5 eq). The reaction was allowed to warm to r.t. When the reaction was complete monitoring by TLC, the mixture was diluted with hexanes and poured into sat. NaHCO<sub>3</sub>. The organics were separated and further washed once with brine. The organics were dried (anh. MgSO<sub>4</sub>) and concentrated in vacuo. The residue was chromatographed on silica gel (100% pentanes) to give the protected alcohol 16 as a colorless oil (315 mg, 1.07 mmol, 89% yield). Chiral GC (CP-Chirasil-Dex CB, H<sub>2</sub>, 100 °C hold 5 min then heating 1 °C min<sup>-1</sup> to 170 °C hold 20 min):  $t_{\rm R}$  of product (min) = 54.2 (major)/54.8 (minor)1, 92% ee.  $[\alpha]_{D}^{25}$  = +42.1 (c = 1.00, CH<sub>2</sub>Cl<sub>2</sub>).

(3*R*,4*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-3-(3-oxobutyl)cycloheptanone (17). Ozone gas was bubbled through a solution of the TBS ether 16 (220 mg, 0.75 mmol, 1 eq) in MeOH (14 mL) at -78 °C until the characteristic light blue color appeared. The reaction was then purged of ozone with oxygen and trimethyl phosphite (0.162 mL, 1.37 mmol, 1.8 eq) was added. The reaction was allowed to warm to r.t. and stirred for 1.5 h. The mixture was poured into sat. NH<sub>4</sub>Cl and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organics were dried (anh. MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was chromatographed on silica gel (10–20% EtOAc in pentanes) to give the diketone 17 as a colorless oil (185 mg, 0.57 mmol, 76% yield). GC conditions could not be found to determine ee.  $[\alpha]_D^{25} - 23.6$  (*c* 1.00, CH<sub>2</sub>Cl<sub>2</sub>).

(3S,3aS,8S,8aR)-8-((tert-Butyldimethylsilyl)oxy)-3,8-dimethyloctahydroazulen-4(1H)-one (18). To a stirred solution of the diketone 17 (145 mg, 0.44 mmol, 1 eq) in MeOH (45 mL) was added KOH (1.36 g, 24.2 mmol, 55 eq). The reaction was heated to 60 °C for 3 h when TLC analysis showed the reaction was complete. The mixture was cooled and poured into sat. NH<sub>4</sub>Cl and was extracted with  $CH_2Cl_2$  (3 × 7 mL). The combined organics were dried (anh. MgSO<sub>4</sub>) and concentrated in vacuo to give the bicyclic enone as pale yellow oil ( $R_f 0.16$ , 10% Et<sub>2</sub>O in pentanes). This enone and Pd-C (10%, 76 mg, 0.075, 0.17 eq) in EtOH (17 mL) were hydrogenated under H<sub>2</sub> pressure (25 psi) and shaken in a Parr apparatus. After 4.5 h, the reaction mixture was filtered through a Celite plug and concentrated in vacuo. The residue was chromatographed on silica gel (10% Et<sub>2</sub>O in pentanes) to give ketone 18 as a colorless oil (122 mg, 0.39 mmol, 90% yield). Chiral GC (CP-Chirasil-Dex CB, H<sub>2</sub>, 100 °C hold 5 min, then heating 1 °C min<sup>-1</sup> to 170 °C hold 20 min):  $t_{\rm R}$  of product (min) = 70.0 (major)/71.4 (minor), 95% ee.  $[\alpha]_{D}^{25} = +42.4$  (c = 0.50, CH<sub>2</sub>Cl<sub>2</sub>).

tert-Butyl(((1S, 3aR, 4S, 8aR)-1, 4-dimethyl-1, 2, 3, 3a, 4, 5, 6, 8aoctahydroazulen-4-yl)oxy)dimethylsilane (19). To a stirred solution of diisopropylamine (0.19 mL, 1.3 mmol, 5 eq) in THF (1.7 mL) at -78 °C was added n-BuLi (1.6 M in hexanes, 0.50 mL, 0.78 mmol, 3 eq). After 45 min, to this LDA was added the ketone 18 (80 mg, 0.26 mmol, 1 eq) as a solution in dry TMEDA (0.43 mL). The reaction mixture was warmed up to -30 °C. After being stirred at -30 °C for 10 min, the diethyl chlorophosphonate (0.19 mL, 1.3 mmol, 5 eq) was added and cooling bath was removed. After 1 h, the reaction mixture was poured into ice-water and extracted with  $CH_2Cl_2$  (3 × 10 mL). The combined organics were washed with brine, dried (anh. MgSO<sub>4</sub>) and concentrated in vacuo. The obtained yellow oil was dissolved in t-BuOH (0.08 mL) and THF (5.7 mL) and was added to a solution of lithium (excess) in liquid ammonia at -78 °C. After 1 h, the reaction was carefully quenched with sat. NH<sub>4</sub>Cl and was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$ 10 mL). The combined organics were dried (anh. MgSO<sub>4</sub>) and concentrated in vacuo. F.c. on silica gel (100% pentanes) gave the alkene 19 as a colorless oil (40 mg, 0.136 mmol, 52% yield). Chiral GC (CP-Chirasil-Dex CB, H<sub>2</sub>, 100 °C hold 5 min then heating 1 °C min<sup>-1</sup> to 170 °C hold 20 min):  $t_{\rm R}$  of product (min) = 54.6 (major)/55.3 (minor), 95% ee.  $[\alpha]_{D}^{25}$  -47.8 (c 0.50, CH<sub>2</sub>Cl<sub>2</sub>).

tert-Butyldimethyl(((1aS,4S,4aR,7S,7aR,7bR)-1,1,4,7-tetramethyldecahydro-1*H*-cyclopropa[*e*]azulen-4-yl)oxy) silane (25). Bicyclic alcohol 19 (30 mg, 0.1 mmol, 1 eq) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (0.2 mL) followed by addition of CHBr<sub>3</sub> (0.36 mL, 4 mmol, 40 eq) and powdered NaOH (68 mg, 1.70 mmol, 17 eq). The reaction mixture was stirred at 50-60 °C for 48 h. This mixture was diluted with water (1 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub>  $(3 \times 2 \text{ mL})$ . The combined organic phases were dried (anh. MgSO<sub>4</sub>) and were filtered. Solvents were removed in vacuo. The residue was directly used in the next step. Tricyclic 24 was added as a solution in THF (1.3 mL) to a mixture of CuCN (33 mg, 0.36 mmol, 3 eq) and MeLi (1.6 M in Et<sub>2</sub>O, 0.38 mL, 0.60 mmol, 5 eq) in THF (1.3 mL) at -78 °C. The reaction was slowly warmed to -20 °C for 3-4 h. After that, MeI (0.15 mL, 2.4 mmol, 20 eq) was added at -63 °C and this mixture was stirred for 1 h and poured into sat. NaHCO<sub>3</sub>. This was extracted with CH<sub>2</sub>Cl<sub>2</sub>  $(3 \times 5 \text{ mL})$ . The combined organics were dried (anh. MgSO<sub>4</sub>) and concentrated in vacuo. FC on silica gel (100% pentanes) gave a colorless solid of gem-dimethylcyclopropane 25 (30 mg, 0.089 mmol, 74% yield). Chiral GC (CP-Chirasil-Dex CB, H<sub>2</sub>, 100 °C hold 5 min then heating 1 °C min<sup>-1</sup> to 170 °C hold 20 min):  $t_{\rm R}$  of product (min) = 66.9 (major)/55.2 (minor), 95% ee.  $[\alpha]_{\rm D}^{25}$  –9.5 (*c* 0.50, CH<sub>2</sub>Cl<sub>2</sub>).

*ent*-Ledol. The silyl ether 25 (15 mg, 0.045 mmol) was treated with TBAF (1 M in THF 1.5 mL, 50 eq). The reaction was heated to reflux. After 24 h, the mixture was added with water (1 mL) and extracted with ether (3 × 5 mL). The combined organics were dried (anh. MgSO<sub>4</sub>) and concentrated *in vacuo*. FC on silica gel (20% Et<sub>2</sub>O in hexanes) gave *ent*-ledol (7 mg, 0.032 mmol, 70% yield) with mp 104–105 °C. Chiral GC (CP-Chirasil-Dex CB, H<sub>2</sub>, 100 °C hold 5 min then heating 1 °C min<sup>-1</sup> to 170 °C hold 20 min):  $t_{\rm R}$  of product (min) = 48.2 (minor)/50.0 (major), 96% ee.  $[\alpha]_{\rm D}^{25}$  –2.3 (*c* 0.10, EtOH), +4.6 (*c* = 0.10, CHCl<sub>3</sub>), –9.8 (*c* = 0.10, toluene), +0.5 (*c* = 0.25, CH<sub>3</sub>CN), +0.4 (*c* = 0.10, THF).

## **General experimental procedure for IMDA of trienal 7, 9, 10 and** 6388; (c)

In a 50 mL oven-dried Schlenk tube equipped with a magnetic stirring bar at r.t. and under  $N_2$ , Ru catalyst (70 mg, 0.05 mmol, 0.05 eq) was dissolved in dry  $CH_2Cl_2$  (1.80 mL). To the stirred mixture, 2,6-lutidine (2.3  $\mu$ L, 0.02 mmol, 0.02 eq) and a solution of triene (1.00 mmol, 1 eq) in dry  $CH_2Cl_2$  (1.50 mL) was carefully added, and the resulting solution was stirred at r.t. under  $N_2$ . The progress of the reaction was monitored by TLC or IR. At the end of the reaction,  $CH_2Cl_2$  was removed under vacuum and hexane (20 mL) was added. The suspension was filtered through a Celite 545 plug. The Ru catalyst could be recovered. Volatiles were removed *in vacuo* and the residue was purified by f.c. using a silica gel column to give the Diels–Alder product.

#### Synthesis of trienes and their cycloaddition products

Experimentals and characterization of 6, 7, 9–11 were already detailed.<sup>22</sup> The syntheses and spectroscopic data of 4, 5, 8, and 12–15 and their adducts are described in the supporting information.†

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