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The Catalytic Asymmetric Diels–Alder Reactions and Post-cycloaddition Reductive Transpositions of 1-Hydrazinodienes

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Dienes that enable structural rearrangements in the wake of a Diels–Alder event can afford structurally unique and complex cyclohexenes that can be inaccessible by the direct cycloaddition route.^[1–4] A particular problem in natural product synthesis required a substituted cyclohexene of the type **4**, and we were drawn to the idea that an initial pairing of a hypothetical diene of type **1** with an activated dienophile of type **2** might be followed by a suprafacial, reductive transposition of **3** to the desired cyclohexene **4** (Scheme 1).

In principle, the Diels–Alder chemistry of Fleming’s 1-trimethylsilyl-1,3-butadiene in conjunction with a post-cycloaddition protodesilylation step offers an attractive path to a type **4** structure.^[2,5] While this strategy is feasible, 1-trimethylsilyl-1,3-butadiene displays low levels of regioselectivity in cycloadditions with unsymmetrical dienophiles, and the subsequent protodesilylation step can afford mixtures of epimers when a new stereocenter is produced. Given these circumstances, we designed a 1-hydrazinodiene that allows a stepwise realization of the concept outlined in Scheme 1.^[6] For example, *exo* cycloadduct **6** is produced by a stereospecific union of 1-hydrazinodiene **5** with diethyl maleate and subsequently converted to the isolable hydrazine derivative **7** by a palladium-catalyzed cleavage of the two allyloxy carbonyl groups in **6** (Scheme 2). By the action of a weak base (e.g., sodium acetate), compound **7** is then transformed to the desired cyclohexene **9** via the putative allylic diazene **8**; the spontaneous process that transforms **8** to **9** is formulated as a retroene rearrangement with loss of molecular nitrogen.^[7–9] Interestingly, if the base-induced elimination of methanesulfinic acid from **7** is conducted in CD₃OD, H–D exchange occurs and the ensuing reductive transposition stereospecifically affords the deuterated cyclohexene **10**.

A growing number of examples demonstrate that 1-hydrazinodienes undergo a range of Lewis acid-catalyzed Diels–Alder reactions that are both regio- and diastereoselective as a setup for subsequent, stereospecific reductive transpositions to rearranged cyclohexenes. In this report, we describe our more recent discovery that 1-hydrazinodienes are amenable to

chiral catalyst-controlled, enantioface-selective Diels–Alder cycloadditions, as well as the cycloaddition behavior of new 1-hydrazinodienes for use in chemical synthesis.^[10]

In our effort to merge electron-deficient dienophiles with 1-hydrazinodiene **5** with high margins of stereoselectivity, we discovered that the chiral copper(II) bis(oxazoline) catalysts of Evans and co-workers^[11] mediate efficient, regioselective, and highly stereoselective Diels–Alder reactions of *N*-acryloyl oxazolidinones with diene **5**. Unions of 1-hydrazinodiene **5** with *N*-acryloyl oxazolidinone **11a** were best achieved in methylene chloride at room temperature in the presence of 4 Å molecular sieves and 10 mol% of the freshly prepared copper(II) bis(oxazoline) catalyst. In all cases, *exo* cycloadduct **13a** was produced as the major diastereo-isomer with varying levels of enantioselectivity. The results summarized in Table 1, reveal the impact of the identity of the group R on the chiral bis(oxazoline) ligand and the counterion on Diels–Alder diastereo- and enantioselectivity. The *tert*-butyl bis(oxazoline) ligand afforded excellent levels of diastereo- and enantioselectivities. While the chloride salt of the copper(II) bis(oxazoline) catalyst was unreactive, the hexafluoroantimonate and triflate salts displayed excellent reactivities. The good-to-excellent *exo* diastereoselectivities exhibited in these reactions are consistent with our prior observations on the stereochemical outcomes of 1-hydrazinodiene cycloadditions to C_α-unsubstituted dienophiles.^[6,12] Our hypothesis is that dienophiles lacking α-substitution should undergo *exo* selective Diels–Alder reactions to minimize nonbonded interactions between the Lewis acid-activated carbonyl and the substituents attached to the hydrazine moiety of the diene.^[13]

Having identified the (*S,S*)-(-)-2,2'-isopropylidene-bis(4-*tert*-butyl-2-oxazoline) chiral ligand and the hexafluoroantimonate counter ion as key components of an effective chiral catalyst, we examined a variety of β-substituted *N*-acryloyl oxazolidinones in asymmetric Diels–Alder reactions with 1-hydrazinodiene **5** (Table 2).

Although there was some variation in reaction times, all of the unions leading to *exo* cycloadducts **13a–l** displayed diastereomer ratios of greater than 20:1 and enantiomer ratios ranging from 21–99:1. Evans's copper(II) catalyst **14** is clearly capable of mediating cycloadditions of diverse, β-substituted *N*-acryloyl oxazolidinones to diene **5** with high margins of stereoselectivity.

To further increase the scope of this chemistry, we leveraged our previously described method^[6] to achieve syntheses of an expanded set of hydrazinodienes with diverse substitution patterns. Thus, from simple α,β-unsaturated aldehydes and monoallyloxycarbonyl (Alloc) hydrazine, 1-hydrazinodienes **15–18** (Table 3) were synthesized in three steps^[14] and employed in asymmetric Diels–Alder reactions with α,β-unsaturated imides **11a**, **11b**, **11 f**, and **11l**.

Qualitatively, these new hydrazinodienes were judged to be comparable with respect to reactivity, although dienes **16** and **18** reacted more slowly in relation to the others. All of these chiral catalyst-directed cycloadditions were regioselective and afforded *exo* cycloadducts **19a–k** in good to excellent yields and with diastereomer ratios greater than 20:1. The major, *exo* diastereomers were also produced with high levels of enantioselectivity. X-ray crystallographic analysis confirmed the relative and absolute stereochemical configurations of cycloadduct **19a**; this analysis was fully consistent with the prior observations of Evans and co-workers^[11] on how the architecture of the dienophile-copper(II) BOX complex imparts high levels of stereoface selectivity in Diels–Alder reactions.^[15]

In the wake of the asymmetric Diels–Alder events, it was straightforward to execute the desired reductive transpositions to rearranged cyclohexenes (Table 4). Thus, the Diels–Alder adducts arising from diene **5** and the four dienes shown in Table 3, were smoothly transformed to the isolable hydrazine derivatives **20a–h** by mild, palladium(0)-catalyzed cleavages of the Alloc protecting groups. The reductive transpositions to cyclohexenes **21a–h** were subsequently achieved by warming solutions of compounds **20a–h** in methanol to 50°C. Through a retroene-like rearrangement^[7] of a putative allylic diazene intermediate, molecular nitrogen is expelled, the alkene is shifted to a new position within the six-membered ring, and a new stereochemical relationship is established in this pivotal step.

In the presence of Lewis acids, 1-hydrazinodienes undergo efficient [4+2] cycloadditions with fumarate and maleate esters, as well as α,β -unsaturated aldehydes, ketones, and imides. To gain some insight into the relative reactivity of 1-hydrazinodienes, the HOMO Eigenvalues for 1-dimethylamino-3-*tert*-butyldimethylsilyloxy-1,3-butadiene,^[16] 1-methoxy-3-trimethylsilyloxy-1,3-butadiene,^[17] 1-hydrazinodiene **5**,^[6] and isoprene were calculated as –0.172, –0.190, –0.207, and –0.226, respectively, by the method of Gaussian 03 B3LYP at the 6-31G(d) level of theory.^[18] By this analysis, the HOMO energy of 1-hydrazinodiene **5** was judged to be less than the HOMO energies of the synergistic dienes of Rawal and Kozmin^[16] and Danishefsky and Kitahara,^[17] but greater than that of isoprene.

As a class, the 1-hydrazinodienes have value in synthesis because they are easily constructed, amenable to efficient and highly stereoselective Diels–Alder reactions with a variety of dienophiles, and enable mild, post-cycloaddition rearrangements to new cyclohexenes that would likely be challenging to produce by alternative methods of synthesis. Our efforts to further extend the utility of 1-hydrazinodienes in organic synthesis are continuing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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9. Addition of the mild base tetra-*n*-butylammonium acetate to the reaction mixture for the palladium-catalyzed Alloc deprotections enables a one-flask conversion of compound **6** to cyclohexene **9** (see ref. [6]).
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13. Methacrolein, a C_α-substituted dienophile, reacts with 1-hydrazinodiene **5** in the presence of diethylaluminum chloride (20 mol%) through a transition state that presumably minimizes steric interactions between the branched methyl group and the groups on the diene, and affords a 92:8 mixture of diastereoisomers favoring the *endo* cycloadduct (see ref. [6]).
14. 1-Hydrazinodienes **15–18** were obtained as stable solids. The syntheses of these compounds, including characterization data, are provided in the Supporting Information.
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Scheme 1.

A cyclohexene synthesis featuring a post-cycloaddition reductive transposition.

Scheme 2.

The Diels–Alder and reductive transposition chemistry of a 1-hydrazinodiene. Reaction conditions: a) diethylmaleate, Et₂AlCl, 23 °C, 75%; b) Pd₂(dba)₃, Et₂NH, THF, 23 °C; c) NaOAc, MeOH, 49% over two steps; Alloc: allyloxycarbonyl.

Table 1

Chiral copper(II) bis(oxazoline)-catalyzed Diels–Alder cycloadditions of diene **5** with *N*-acryloyl oxazolidinone **11a**.^[a]

Entry	R	X	Conversion [%] ^[b]	d.r. ^[b]	e.r. ^[c]
1	<i>i</i> Pr	SbF ₆	100	10.2:1	6:1
2	Ph	SbF ₆	100	7.7:1	4:1
3	Bn	SbF ₆	100	8.5:1	6:1
4	<i>t</i> Bu	SbF ₆	100	>20:1	49:1
5	<i>i</i> Bu	OTf	100	>20:1	28:1
6	<i>i</i> Bu	Cl	0	n.d.	n.d.

^[a]Reactions were carried out with diene **5** (0.125 mmol), dienophile **11a** (0.188 mmol), copper(II) bis(oxazoline) catalyst **12** (0.0125 mmol), powdered 4 Å molecular sieves (ms; 19 mg), and CH₂Cl₂ (250 μL) at room temperature for 3 h.

^[b]Conversion and d.r. were determined by analyses of the crude reaction mixtures by ¹H NMR spectroscopy.

^[c]Enantiomer ratios are reported for the major *exo* diastereoisomer and were determined by chiral high-performance liquid chromatography on a Chiralcel OD column.

Alloc: allyloxy carbonyl; d.r.: diastereomer ratio; e.r.: enantiomer ratio; n.d.: not determined.

Table 2

Chiral catalyst-controlled, asymmetric Diels–Alder cycloadditions of diene **5** to β -substituted *N*-acryloyl oxazolidinones **11a–l**.^[a]

Product	R	Yield [%] ^[b]	Reaction time [h]	e.r. ^[c]
13a	H	84	3	49:1
13b	CH ₃	79	4	99:1
13c	CH ₂ CH ₃	74	6	24:1
13d	CH ₂ CH ₂ CH ₃	75	12	99:1
13e	CH(CH ₃) ₂	65	24	99:1
13 f	Ph	66	6	49:1
13g	<i>p</i> CH ₃ Ph	65	12	32:1
13h	<i>p</i> ClPh	64	12	21:1
13i	<i>p</i> BrPh	54	12	21:1
13j	<i>p</i> CF ₃ Ph	60	12	21:1
13k	CH=CHCH ₃	54	18	21:1
13l	CO ₂ CH ₂ CH ₃	83	3	49:1

^[a]Reactions were carried out with diene **5** (0.25 mmol), dienophile **11** (0.375 mmol), copper(II) bis(oxazoline) catalyst **14** (0.025 mmol), powdered 4 Å molecular sieves (ms; 37.5 mg), and CH₂Cl₂ (521 μ L) at room temperature.

^[b]Isolated yield after purification by silica gel column chromatography.

^[c]Enantiomer ratios are reported for the major *exo* diastereoisomer and were determined by chiral high-performance liquid chromatography or supercritical fluid chromatography.

Alloc: allyloxy carbonyl; d.r.: diastereomer ratio; e.r.: enantiomer ratio.

Table 3

Chiral catalyst-controlled, asymmetric Diels–Alder cycloadditions of additional 1-hydrazinodienes.^[a]

Diene	Dienophile	Product	Reaction time [h]	Yield[b] [%]	e.r.[c]
$\text{H}_3\text{CO}_2\text{S}-\text{N}-\text{N}(\text{Alloc})_2$ 15	11a $\text{R}^4=\text{H}$	19a	3	72	49:1
	11b $\text{R}^4=\text{CH}_3$	19b	3	76	32:1
	11f $\text{R}^4=\text{Ph}$	19c	6	78	32:1
	11i $\text{R}^4=\text{CO}_2\text{Et}$	19d	3	66	199:1
$\text{H}_3\text{CO}_2\text{S}-\text{N}-\text{N}(\text{Alloc})_2$ 16	11a $\text{R}^4=\text{H}$	19e	12	70	32:1
	11i $\text{R}^4=\text{CO}_2\text{Et}$	19f	12	91	99:1
$\text{H}_3\text{CO}_2\text{S}-\text{N}-\text{N}(\text{Alloc})_2$ 17	11a $\text{R}^4=\text{H}$	19g	4	76	66:1
	11i $\text{R}^4=\text{CO}_2\text{Et}$	19h	4	80	199:1

^[a] Reactions were carried out with diene (0.25 mmol), dienophile (0.375 mmol), copper(II) bis(oxazoline) catalyst **14** (0.025 mmol), powdered 4 Å molecular sieves (ms; 37.5 mg), and CH_2Cl_2 (521 μL) at room temperature.

^[b] Isolated yield after purification by silica gel column chromatography.

^[c] Enantiomer ratios are reported for the major *exo* diastereoisomer and were determined by chiral high-performance liquid chromatography or supercritical fluid chromatography.

Alloc: allyloxy carbonyl; d.r.: diastereomer ratio; e.r.: enantiomer ratio.

Table 4

Deprotections and reductive transpositions of selected Diels–Alder products.^[a]

^[a] Reagents and conditions: a) cycloadducts **13** or **19** (0.20 mmol), Pd₂(dba)₃·CHCl₃ (0.01 mmol), 1,2-bis(diphenylphosphino)ethane (0.02 mmol), morpholine (1.6 mmol) in THF (1.0 mL), room temperature, 0.25 h; b) CH₃OH, 50 °C.

^[b] Isolated product yield after purification by silica gel column chromatography for two steps.

Alloc: allyloxy carbonyl; dba: dibenzylideneacetone.