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

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**Keywords**

asymmetric Diels–Alder reaction; cycloaddition; cyclization; hydrazinodienes; sigmatropic rearrangement

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 $CD_3OD$, 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

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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 $C_\alpha$-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]

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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 by 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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5. Fleming and Carter noted in ref. [2a] that “the ability to move the double bond of a Diels–Alder adduct in this way has wide implications in the design of organic syntheses.”

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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]).

10. This study is based on: Xie H. PhD Thesis. Princeton UniversityUSA2009

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13. Methacrolein, a $C_{\alpha}$-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.

15. Thus, the configurations of the nitrogen- and carbonyl-bearing stereocenters in **19a** are both assigned as *S*.

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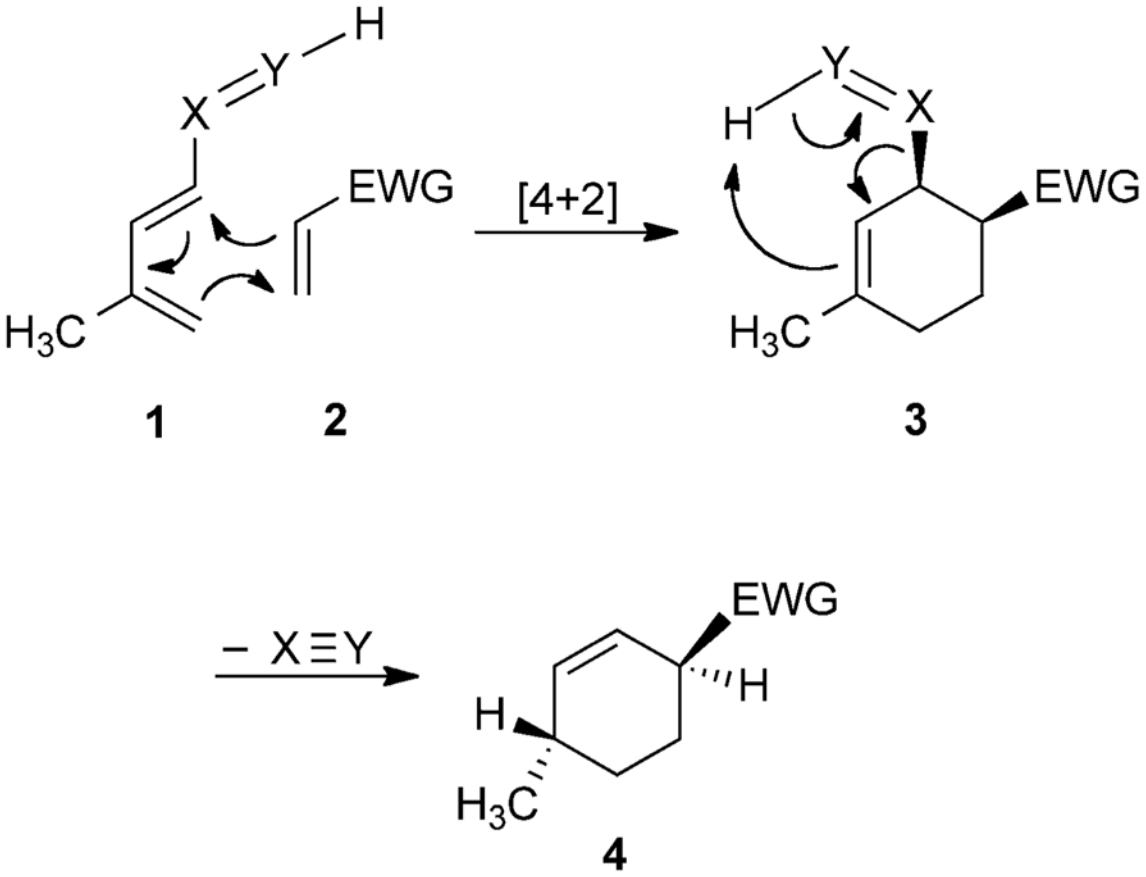


**Scheme 1.**
A cyclohexene synthesis featuring a post-cycloaddition reductive transposition.

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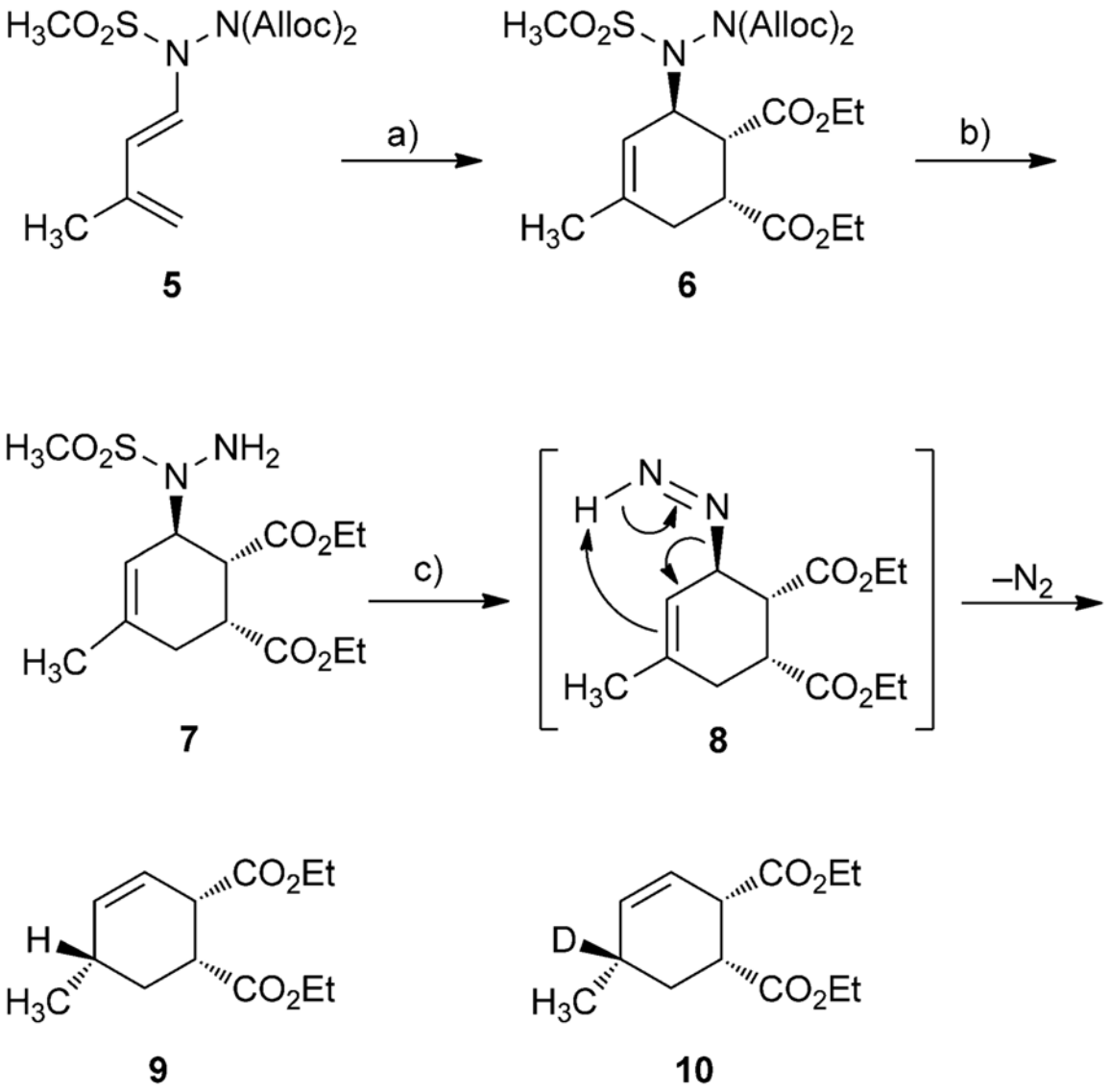


**Scheme 2.**

The Diels–Alder and reductive transposition chemistry of a 1-hydrazinodiene. Reaction conditions: a) diethylmaleate, $Et_2AlCl$, 23 °C, 75%; b) $Pd_2(dba)_3$, $Et_2NH$, THF, 23 °C; c) NaOAc, MeOH, 49% over two steps; Alloc: allyloxycarbonyl.

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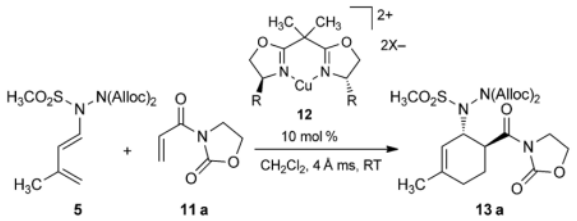
**Table 1**

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*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** | **t*Bu*** | **$SbF_6$** | **100** | **>20:1** | **49:1** |
| 5 | *t*Bu | OTf | 100 | >20:1 | 28:1 |
| 6 | *t*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 $CH_2Cl_2$ (250 μL) at room temperature for 3 h.

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

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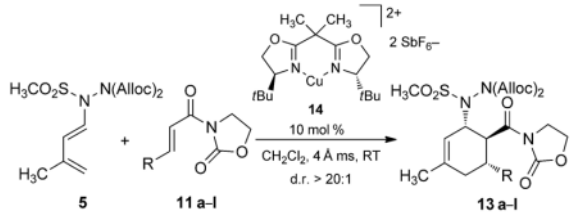
## Table 2

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** | $CH_2CH_3$ | 74 | 6 | 24:1 |
| **13d** | $CH_2CH_2CH_3$ | 75 | 12 | 99:1 |
| **13e** | $CH(CH_3)_2$ | 65 | 24 | 99:1 |
| **13 f** | Ph | 66 | 6 | 49:1 |
| **13g** | *p*$CH_3$Ph | 65 | 12 | 32:1 |
| **13h** | *p*ClPh | 64 | 12 | 21:1 |
| **13i** | *p*BrPh | 54 | 12 | 21:1 |
| **13j** | *p*$CF_3$Ph | 60 | 12 | 21:1 |
| **13k** | $CH=CHCH_3$ | 54 | 18 | 21:1 |
| **13l** | $CO_2CH_2CH_3$ | 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 $CH_2Cl_2$ (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.

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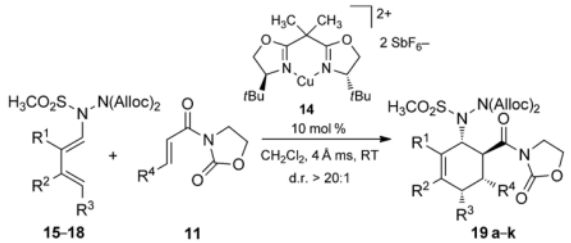
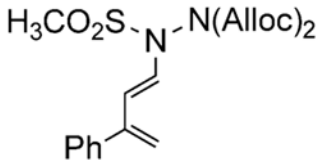
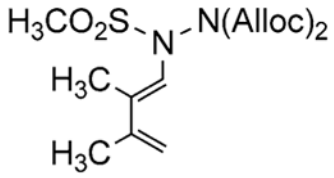
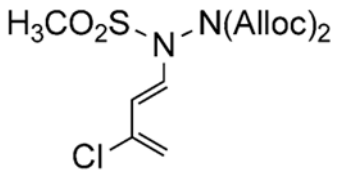
**Table 3**

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




| Diene | Dienophile | Product | Reaction time [h] | Yield[b] [%] | e.r.[c] |
|---|---|---|---|---|---|
|  **15** | **11a** $R^4$=H | **19a** | 3 | 72 | 49:1 |
| | **11b** $R^4$=$CH_3$ | **19b** | 3 | 76 | 32:1 |
| | **11 f** $R^4$=Ph | **19c** | 6 | 78 | 32:1 |
| | **11l** $R^4$=$CO_2Et$ | **19d** | 3 | 66 | 199:1 |
|  **16** | **11a** $R^4$=H | **19e** | 12 | 70 | 32:1 |
| | **11l** $R^4$=$CO_2Et$ | **19 f** | 12 | 91 | 99:1 |
|  **17** | **11a** $R^4$=H | **19g** | 4 | 76 | 66:1 |
| | **11l** $R^4$=$CO_2Et$ | **19h** | 4 | 80 | 199:1 |

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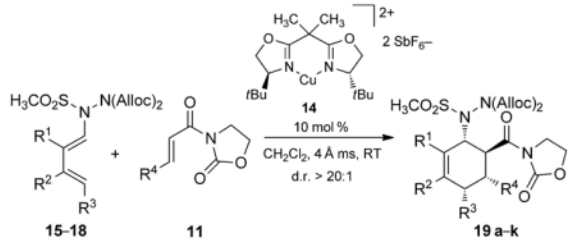
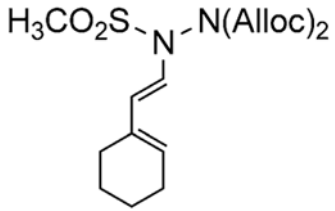



| Diene | Dienophile | Product | Reaction time [h] | Yield[b] [%] | e.r.[c] |
|---|---|---|---|---|---|
|  | **11a** $R^4$=H | **19i** | 6 | 94 | 49:1 |
| | **11b** | **19j** | 18 | 57 | 66:1 |
| | $R^4$=$CH_3$ | | | | |
| | **11l** | **19k** | 6 | 84 | 199:1 |
| | $R^4$=$CO_2Et$ | | | | |
| **18** | | | | | |

[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.



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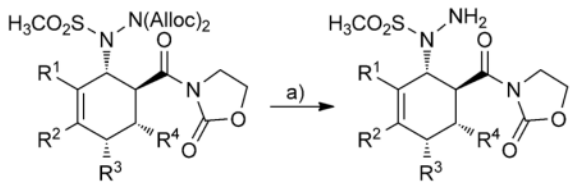
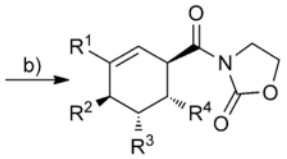
**Table 4**

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




**13 or 19** **20 a–h**




**21 a–h**

| Substrate | Product | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield [%][b] |
|---|---|---|---|---|---|---|
| **13a** | **21a** | H | $CH_3$ | H | H | 80 |
| **13b** | **21b** | H | $CH_3$ | H | $CH_3$ | 87 |
| **13 f** | **21c** | H | $CH_3$ | H | Ph | 81 |
| **13l** | **21d** | H | $CH_3$ | H | $CO_2Et$ | 77 |
| **19a** | **21e** | H | Ph | H | H | 85 |
| **19e** | **21 f** | $CH_3$ | $CH_3$ | H | H | 73 |
| **19g** | **21g** | H | Cl | H | H | 56 |
| **19i** | **21h** | H | $CH_2CH_2$ | $CH_2CH_2$ | H | 76 |

[a]Reagents and conditions: a) cycloadducts **13** or **19** (0.20 mmol), $Pd_2$-(dba)$_3$·$CHCl_3$ (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) $CH_3OH$, 50 °C.

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

Alloc: allyloxy carbonyl; dba: dibenzylideneacetone.