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Diastereoselective Diels–Alder Reactions of a Novel Cyclopropenyl-Containing Chiral Auxiliary

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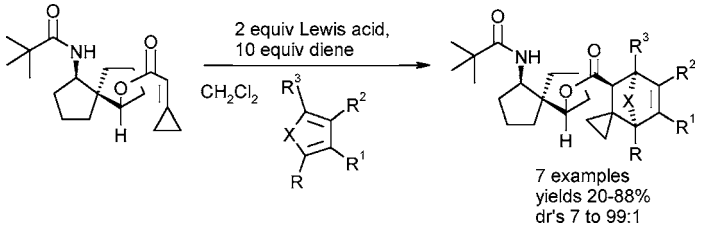
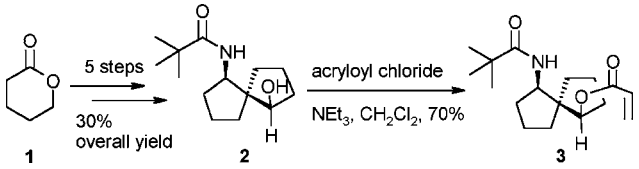
ABSTRACT



A novel cyclopropenyl-containing 1,3-spiroaminoalcohol auxiliary has been used in a variety of asymmetric Diels–Alder reactions providing endo adducts with diastereomeric ratios ranging from 2:1 up to >99:1. In addition, unexpected regiochemistry was observed for a Diels–Alder reaction between cyclopropenyl dienophile and 4-vinyl-1,2-dihydronapthalene.

The amino alcohol family of chiral auxiliaries has exhibited great success within many reactions.[1] Although 1,2-amino alcohols are most commonly used because of their ready availability, 1,3-amino alcohols are beginning to be used more widely in asymmetric transformations.[2] In 2003 we reported the synthesis and application of (1*R*,5*R*,6*R*)-6-(2,2-dimethylpropionyl-amino)spiro[4.4]non-1-yl ester (**3**) in asymmetric Diels−Alder reactions with a variety of symmetrical and unsymmetrical dienes.[3] Either enantiomer of **2** was readily available via a short, highly efficient synthesis starting from *δ*-valerolactone (**1**) (Scheme 1).[3] Dienophile **3**, made by treating **2** with acryloyl chloride, provided Diels−Alder products with very high endo selectivity (>99:1) and high diastereoselectivity (>98% de). The auxiliary was easily removed through saponification with sodium hydroxide to afford the corresponding Diels−Alder adducts with high % ee's.

Scheme 1. Synthesis of a Novel 1,3-Spiro-amino Alcohol Auxiliary



Owing to the success of auxiliary **3** in Diels−Alder reactions, it was desirable to change the dienophile component in **3** to broaden the scope and explore its limitations. *gem*-Dimethyl substituents are prevalent within natural products but are often troublesome to install.[4] One method for the introduction of *gem*-dimethyl groups involves a Diels−Alder reaction with *β*,*β*-dimethyl substituted dienophiles but this reaction generally results in poor reactivity

(1) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.
(2) Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767.
(3) Lait, S. M.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **2003**, *14*, 749.
(4) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

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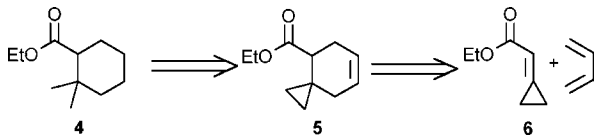
and selectivity.[5] An alternative to this strategy involves using cyclopropylidene-containing dienophile **6** (Scheme 2). A

Scheme 2

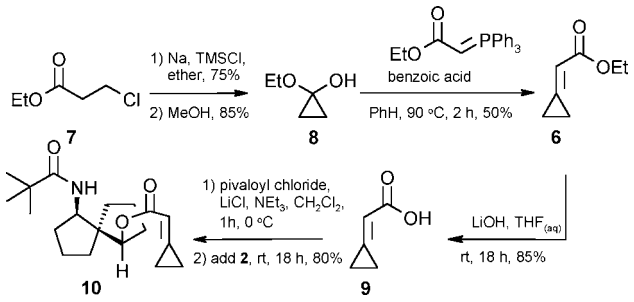


Diels−Alder reaction with **6** should provide a spiro[5.2]-octene system **5** in which the cyclopropyl ring could be hydrogenated to provide cyclohexanes **4** containing *gem*-dimethyl groups.[6]

When we started working on this project in 2004, previous reports with dienophiles such as **6** had been limited to their use in thermal Diels−Alder and 1,3-dipolar cycloaddition reactions but there were few reports in which the alcohol moiety in ester **6** had been replaced with a chiral auxiliary.[7] More recently, Kuethe et al. have reported the asymmetric Diels−Alder reaction between *β*,*β*-cyclopropyl-α,*β*-unsaturated *N*-acyloxazolidinones and cyclopentadiene.[6] Since they only reported a Diels−Alder reaction with cyclopentadiene, we decided to use spiro-amido-alcohol **2** (Scheme 1) in which the dienophile contains a cyclopropylidene unit and expand the scope of the Diels−Alder reaction by employing a range of symmetrical and unsymmetrical dienes.

Compound **10** was prepared in four steps from ethyl 2-chloropropionate (**7**, Scheme 3). Treatment of **7** with

Scheme 3

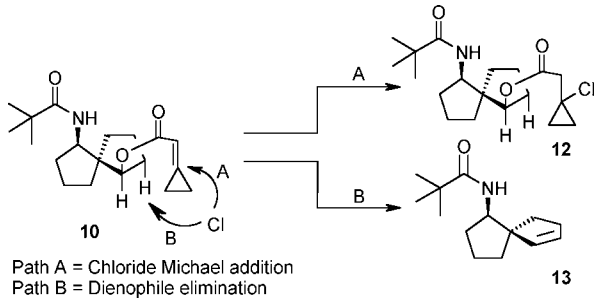


sodium metal provided hemiacetal **8**,[8,9] which was subjected to an acid-catalyzed Wittig reaction giving cyclopropylidene ester **6**. Mild saponification of **6** with lithium hydroxide in aqueous THF gave acid **9** in 85% yield.[10] Cyclopropenyl acid **9** was reacted with trimethylacetyl chloride in the presence of triethylamine to afford a mixed anhydride[7] that was reacted with spirocyclic alcohol **2** to afford **10** in 80% yield.

With **10** in hand, a variety of Lewis acids were screened by NMR spectroscopy to determine how many equiv are required to activate **10**, the compatibility of the Lewis acids with **10**, and under what reaction conditions **10** would react with cyclopentadiene. It is well-known that cyclopropenyl systems are very good Michael acceptors, and we wished to minimize potential side reactions.[11]

As with our previously reported system (Scheme 1, **3**),[3] 2 equiv of Lewis acid were necessary for complete coordination to the dienophile. The first equivalent of Lewis acid coordinated to the more basic amide moiety (determined by a noteable downfield shift of Hb and Hc in the ^{1}H NMR spectrum of **10**) while the second equivalent activated the cyclopropenyl ester (noteable downfield shift of Ha in the ^{1}H NMR spectrum of **10**). Aside from BI_3, none of the other Lewis acids gave halide-incorporated Michael addition products from **10** at −78 °C in CD_2Cl_2 (see **12** Scheme 4).

Scheme 4. Major Byproduct Pathways

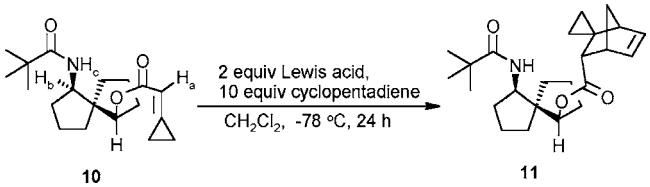


For completeness, Child's Lewis acidity measurements[12] were measured and are summarized in Table 1 with the entries organized by decreasing Lewis acid strength. Of all the Lewis acids tried, BCl_3 gave both the best conversion (87%) to adduct **11** and dr (6.7:1) for the *endo*-isomers. Although $MeAlCl_2$ gave a higher dr (7.1:1), the conversion to product (10%) was very low owing to polymerization of the cyclopentadiene.

The high conversion and promising dr with BCl_3 prompted us to further investigate its use in Diels−Alder reactions of **10** with various dienes. Lowering the reaction temperature to −100 °C for the Diels−Alder reaction with cyclopentadiene resulted in a higher dr of 7.1:1 (Table 2, entry 1). In addition, the Diels−Alder reaction occurred with a variety of other dienes. Reaction of **10** with furan proceeded at −100 °C but exhibited a 9:1 endo:exo ratio with an 11:1 dr for the endo isomers; only one exo isomer was observed by ^{1}H NMR spectroscopy. Unfortunately, this reaction only gave

(5) Muroi, H.; Kubo, I. *Biosci. Biotechnol. Biochem.* **1994**, *10*, 1925.
(6) Kuethe, J. T.; Zhao, D.; Humphrey, G. R.; Journet, M.; McKeown, A. E. *J. Org. Chem.* **2006**, *71*, 2192.
(7) Spitzner, D.; Swoboda, H. *Tetrahedron Lett.* **1986**, *27*, 1281.
(8) Ruehlmann, K.; *Synthesis* **1971**, 236.
(9) The silylhemiacetal of **8** is now commercially available from Aldrich.
(10) In our hands, attempts to make acid **9** via another synthetic route resulted in low yields and was subsequently abandoned. Limbach, M.; Dalai, S.; de Meijere, A. *Adv. Synth. Catal.* **2004**, *346*, 760.
(11) (a) Seyed-Mahdavi, F.; Teichmann, S.; Meijere, A. *Tetrahedron Lett.* **1986**, *27*, 6185. (b) Wesjohann, L.; Kress, N.; Yu, D.; Meijere, A.; *Chem. Ber.* **1992**, *125*, 867−882. (c) Belov, V. N.; Sauchenko, A. I.; Sokolov, V. V.; Straub, A.; Meijere, A. *Eur. J. Org. Chem.* **2003**, *3*, 551−561.
(12) Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801.

Table 1. Diels−Alder Reaction of **10** with Cyclopentadiene Using a Variety of Lewis Acids



10 11

Lewis acid	$\Delta\delta^a$ of H_a (ppm)	conversion (%)[c]	dr[c]
BI_3	1.5	50	6.7:1
BBr_3	1.4	100	5.3:1
BCl_3	1.2	87	6.7:1
$BF_3{\cdot}OEt_2$	0[b]		
$AlCl_3$	0.8	100	1.5:1
$MeAlCl_2$	0.78	10	7.1:1
$EtAlCl_2$	0.75	90	2.4:1
$AlMe_3$	0.60	0	
Me_2AlCl	0.55	50	5:1
Et_2AlCl	0.5	10	5.3:1

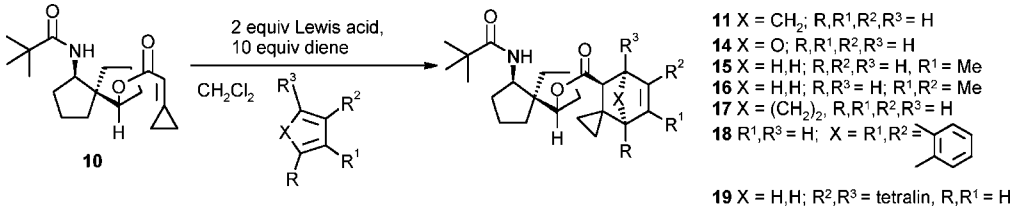
[a] $\Delta\delta$ values were obtained from 400 MHz NMR spectra at −78 °C in CD_2Cl_2. [b] $BF_3{\cdot}OEt_2$ only coordinated with the amide moiety even when used in excess. [c] Conversion and diastereomeric ratios were determined using 300 MHz NMR and GC−MS analysis.

50% conversion due to the adducts preferentially complexing to the Lewis acid.[13]

The reaction with other dienes were more problematic. No reaction was observed below −23 °C with isoprene, and at this temperature four isomers were observed (Table 2, entry 3). The reactions with 2,3-dimethyl-1,3-butadiene, 1,3-cyclohexadiene, and anthracene with BCl_3 (not shown in Table 2) were quite sluggish and lower yielding when compared with cyclopentadiene owing to the formation of **12**[14] and **13** (Scheme 4) at temperatures at or above −23 °C. These side reactions could be minimized at temperatures below −23 °C and by using newly purchased bottles of BCl_3, however the reactions took over 2 days to complete. Because of these limitations, aluminum-based Lewis acids were investigated further in this Diels−Alder reaction with **10**.

Generally, the weaker Lewis acid $EtAlCl_2$ (and Me_2AlCl) did not promote Diels−Alder reactions with dienes that were less reactive than cyclopentadiene. The reaction with isoprene at 0 °C gave a mixture of four isomers (entry 4, no reaction occurred below 0 °C), and no reaction was observed with 2,3-dimethyl-1,3-butadiene and 1,3-cyclohexadiene (entries 5 and 6) at the same temperature. Fortunately, switching to $MeAlCl_2$ provided some useful results. Although the use of $MeAlCl_2$ with **10** and cyclopentadiene led to polymerization of the diene its use with other dienes provided much higher yields of products and better diastereomeric ratios. The reaction with isoprene,[15] 2,3-dimethyl-1,4-butadiene, and 1,3-cyclohexadiene gave yields ranging from 20 to 43 after 18 h with drs ranging from 15:1 (for isoprene) to >99:1 (for 1,3-cyclohexadiene) (entries 7−10). The yield with 2,3-dimethyl-1,4-butadiene was significantly improved with longer time leading to to formation of **16** in 73% yield after

Table 2. Diels−Alder Reaction of **10** with a Variety of Dienes



entry	Lewis acid	temp (°C)	time (hours)	diene	product	% yield[a]	dr[b]
1	BCl_3	−100	8	cyclopentadiene	**11**	88 [95]	7.1:1
2	BCl_3	−100	8	furan	**14**	52 [91]	9 endo (11:1): 1 exo (1:0)
3	BCl_3	−23	9	isoprene	complex mixture[c]	54 [90]	
4	$EtAlCl_2$	0	18	isoprene	complex mixture[d]	30 [80]	
5	$EtAlCl_2$	0	18	2,3-dimethyl-1,3-butadiene	no reaction		
6	$EtAlCl_2$	0	18	1,3-cyclohexadiene	no reaction		
7	$MeAlCl_2$	−23	18	isoprene	**15**	40 [85]	15:1
8	$MeAlCl_2$	−23	18	2,3-dimethyl-1,3-butadiene	**16**	43 [81]	25:1
9	$MeAlCl_2$	−23	48	2,3-dimethyl-1,3-butadiene	**16**	73	>99:1
10	$MeAlCl_2$	−23	18	1,3-cyclohexadiene	**17**	20 [70]	>99:1
11	$MeAlCl_2$	−23	18	anthracene	no reaction		
12	$MeAlCl_2$	0	18	anthracene	**18**	80 [99]	>99:1
13	$MeAlCl_2$	−23	24	4-vinyl-1,2-dihydronapthalene[e]	**19**	59 [89]	10:1

[a] Square brackets indicate the yield based on recovered starting material. [b] Diastereomeric ratios determined by integration of 300 MHz NMR spectra and/or by GC analysis. [c] All possible isomers (stereo and regio) were observed by GC−MS in a 15:9:3.7:1 ratio. [d] All possible isomers (stereo and regio) were observed by GC−MS in a 16.7:1.3:1.3:1 ratio. [e] 4-Vinyl-1,2-dihydronapthalene was prepared from the reaction of vinylmagnesium bromide with the corresponding ketone followed by elimination of the resulting alcohol.

48 h (entry 9). Finally there was no reaction with anthracene and **10** at −23 °C but warming the mixture to 0 °C resulted in an 79% yield and 99:1 dr of adduct **18**.

The stereochemistry of the products obtained from symmetrical dienes were verified through X-ray crystallography. In all cases, (+)-**10** lead to exclusively endo adducts with a *R* configuration adjacent to the ester moiety while (−)-**10** resulted in Diels−Alder adducts with a *S* configuration at the same stereogenic center.

In addition to the reaction with isoprene, the stereo- and regioselectivity for the reaction of **10** with 4-vinyl-1,2-dihydronaphthalene was investigated (entry 13). Treatment of **10** and 4-vinyl-1,2-dihydronaphthalene (**20**) with 2 equiv $MeAlCl_2$ at −23 °C provided a 10:1 mixture of products. The major isomer crystallized and its structure was confirmed as **19** by obtaining an X-ray crystal structure (Figure 1);

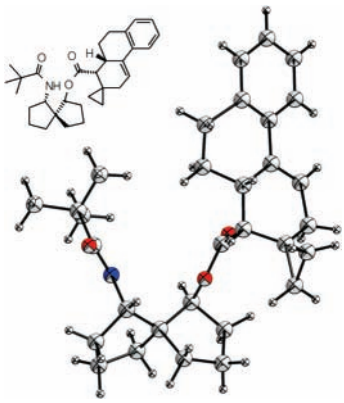
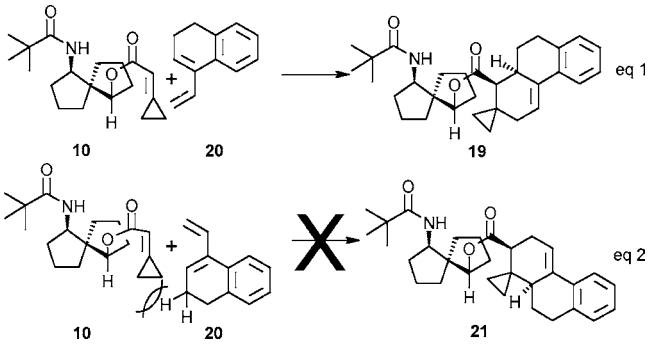


Figure 1. ORTEP of Diels−Alder adduct with 4-vinyl-1,2-dihydronapthalene.

compound **21** was not detected in the reaction mixture. Interestingly, this Diels−Alder reaction led to an unexpected reversal in the expected regiochemistry on the basis of stereoelectronic arguments. Previous work with **3** and diene **20** gave the endo product with the expected regiochemistry[3] while it appears that the introduction of the cyclopropenyl group in **10** results in a reversal of this regiochemistry (Scheme 5). Molecular modeling of this reaction indicated

Scheme 5. Unexpected Product from Diene **15**



an increased steric interaction between one of the cyclopropenyl -CH_2 groups and the allylic hydrogen atoms on the diene (eq 2, Scheme 5), which was absent in the opposite approach of the dienophile (eq 1, Scheme 5). The adducts in Table 2 could be cleaved from chiral auxiliary as previously described[3] and the auxilary **2** reused.

In summary, a novel chiral cyclopropenyl containing 1,3-spiro-amino alcohol compound **10** has been synthesized and applied to the Diels−Alder reaction with a variety of dienes. A unique reversal of regiochemistry was observed for the Diels−Alder reaction of **10** with 4-vinyl-1,2-dihydronapthalene. Studies are ongoing to enhance the scope and limitations of these reactions.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council (NSERC) and the University of Calgary for financial support. Special thanks to A. Zuccolo and C.C. Ling at the University of Calgary for use of their CB-60 cryobath.

Supporting Information Available: Experimental procedures for preparation of **10** and subsequent Diels−Alder reactions. X-ray crystal structures and data for **11**, **16**, **18**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) (a) Hunt, I. R.; Rauk, A.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 751−757. (b) Hunt, I. R.; Rogers, C.; Woo, S.; Rauk, A.; Keay, B. A. *J. Am. Chem. Soc.* **1995**, *117*, 1049−1056.

(14) For example, compound **12** was formed quickly when 1.0 M HCl in ether was added to **10** at room temperature.

(15) The regiochemistry was determined by removal of the chiral auxiliary with sodium hydroxide and acquiring a COSY NMR spectrum on the corresponding carboxylic acid of **15**.