Endo selectivity in the (4+3) cycloaddition of oxidopyridinium ions

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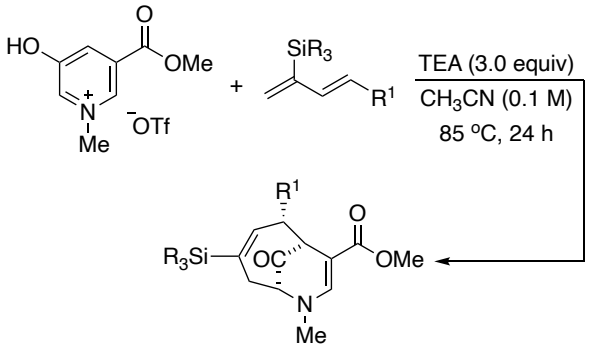
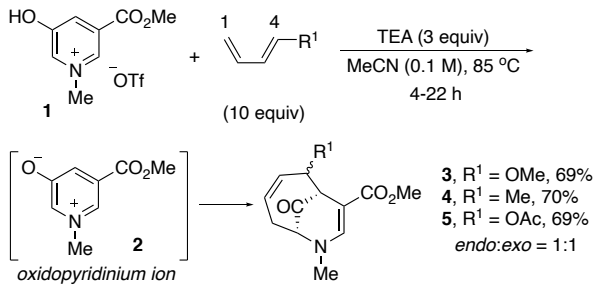


ABSTRACT: The (4+3) cycloaddition of 2-trialkylsilyl-4-alkylbutadienes with an *N*-methyloxidopyridinium ion affords cycloadducts with high regioselectivity and excellent *endo* selectivity.

We recently reported a highly regioselective (4+3) cycloaddition of *N*-methyloxidopyridinium ions with dienes (Scheme 1).[1] A related reaction of *N*-aryloxidopyridinium ions was introduced by Katritzky,[2] while Cha[3] studied its potential application in natural product synthesis. Although these studies suggested great promise for this type of process, one of the difficulties not yet overcome has been to achieve high levels of *endo*/*exo* diastereoselectivity. Thus, while 4-substituted 1,3-butadienes reacted with oxidopyridinium ion **2** to afford (4+3) cycloadducts as single regioisomers in very good yields (Scheme 1), *endo*/*exo* selectivity was absent, the products being formed as ca. 1:1 mixtures of diastereoisomers.

SCHEME 1. Regioselective but not Diastereoselective (4+3) Cycloadditions of an *N*-Methyloxidopyridium Ion (2) with 4-Substituted 1,3-Butadienes



We report here the development of a diastereoselective variant of this cycloaddition that achieves a high level of *endo* selectivity by strategically tuning the substituents on the diene.

In exploring the stereodirecting influences of the diene substituents, we were particularly interested in substituents that could be easily removed or modified, for example through a coupling reaction. We drew inspiration from substituent-directed stereoselectivities observed in the Diels–Alder reaction. For example, Su, Song, and coworkers recently reported high *exo* selectivity in the Diels–Alder reaction of butadienes substituted at C2 with a very bulky bis(silyl)methyl group.[4] The selectivity was rationalized on the basis of steric effects, a computational analysis showing that the *endo* transition state (TS) was destabilized by steric clashing between the $CH(SiR_3)_2$ group and the dienophile.[4] We reasoned that similar interactions might result in high *endo* selectivity in the (4+3) cycloaddition reaction of **2** or its congeners (Figure 1).

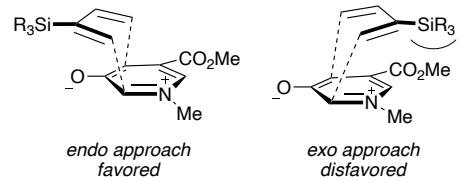
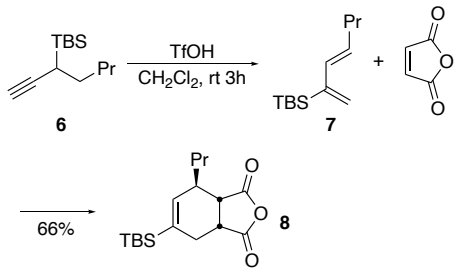


FIGURE 1. *Endo* and *exo* approaches of a 2-trialkylsilyl-1,3-butadiene to oxidopyridinium ion **2**.

However, we sought to further simplify the "steric steering" group and were inspired by the work of Turks, who showed that a 2-SiR_3 group was also an effective stereodirecting group for the Diels–Alder reaction to give a cycloadduct

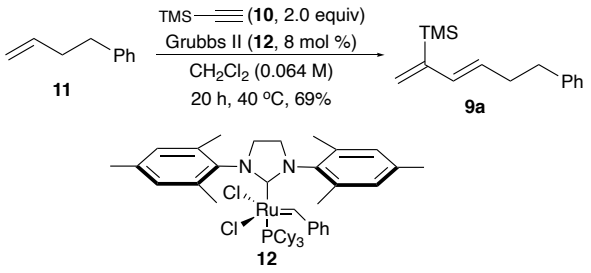
with complete *exo* selectivity (Scheme 2),[5] though *endo* selectivity has been observed more commonly with such dienes.[6] Moreover, the expected (4+3) cycloadducts obtained from 2-silyl dienes would contain a synthetically versatile vinylsilane functional group.[6a-b,7]

SCHEME 2. Highly *Exo*-Selective Diels–Alder Reaction



Thus, we prepared 2-silyldienes **9** (Table 1) using the methodology introduced by Welker and others (Scheme 3).[8] As a representative example, the reaction of excess trimethylsilylacetylene (**10**, 2 equiv) with 4-phenyl-1-butene (**11**) in the presence of 8 mol % of Grubbs II catalyst (**12**) at 40 °C for 20 h afforded diene **9a** in 69% yield after chromatographic purification. Other 2-silyldienes were prepared in the same general fashion, except for **9k** and **9l**, which were not accessible using the standard procedure. We solved this synthesis issue by employing ethylene gas instead of an argon atmosphere to obtain the desired dienes, as also demonstrated by Welker.[8b]

SCHEME 3. Silylated Diene Synthesis



The (4+3) cycloadditions of the silyl-substituted dienes **9** with oxidopyridinium ion **2** are summarized in Table 1. Heating the oxidopyridinium precursor **1** with triethylamine (TEA, 3 equiv) and diene **9a** (3 equiv) in a sealed tube for 24 h afforded an 81:13:6 mixture of cycloadducts **13a**-**c**, as established by ^{1}H NMR analysis of the crude reaction mixture. No **13d** could be detected. This result equates to an overall *endo*/*exo* selectivity [(**13a**+**13c**)/**13b**] of 87:13. The major isomer **13a** was *endo*, as we had expected. Its structure was established by X-ray crystallography of its ketone reduction product (see SI). In this case and in general, separation of the cycloadduct isomers proved to be very challenging when using traditional liquid chromatography approaches (normal and reversed-phase). Instead, semipreparative supercritical fluid chromatography (SFC) using a chiral stationary phase column enabled separation,[9,10] after which NMR analyses of the individual diastereomers (**13a**-**c**) could be performed.

We assigned the structure of the minor isomer **13b** by NMR. Attempts to obtain crystals of the ketone reduction product of **13b** were not successful. Instead, NOESY spectra of the reduction product were used to establish the regiochemistry. In the alcohol derived from **13b**, the C-6 proton appeared at 3.26 ppm, a signal that correlated with the N-methyl group at 2.93 ppm and correlated (COSY and NOESY) with a 1H doublet of doublets at 2.45 ppm, which we assigned as one of the diastereotopic hydrogens at C-5. The latter proton was coupled to the signal of its geminal partner at 2.77 ppm and the protons of the TMS group at 0.02 ppm. This established the regiochemistry of **13b** as being the same as **13a**, confirming **13b** as the *exo* diastereomer of the two. For **13c**, the stereochemistry was established in full after we fortunately grew a crystal of **13c** for X-ray analysis.

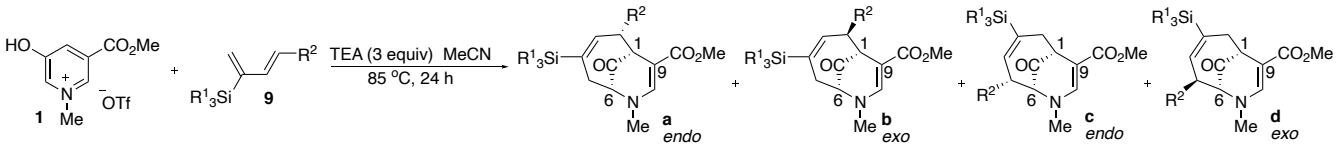
The (4+3) cycloadditions of a range of other silylated dienes gave results similar to **9a**. The major product in each case was the expected *endo* isomer (**14a**-**19a**) and the kinetic *endo*/*exo* selectivities ranged from 82:18 to 91:9. Yields ranged from 67–93%. The structures of these cycloadducts were assigned by comparison to the NMR data for **13a**-**c**, and by crystallography in the cases of **15a** and **19a**.

In order to quantify the influence of the silyl group on the selectivity, we explored the reaction of diene **9h** lacking a silyl group. This diene gave two cycloadduct isomers, **20a**+**b**, in approximately equal amounts (46:54). As expected from our previous studies,[1] the products had identical regiochemistry. Their relative stereochemistry was assigned based on their NMR spectra.[1] The lack of diastereoselectivity observed with **9h** confirms that the silyl group was indeed responsible for the highly diastereoselective cycloadditions of **9a**-**g**.

In these reactions, the silyl group leads to a slight erosion of the regioselectivity, producing small amounts (0–6%) of the minor *endo* regioisomers **13c**-**19c**. In our earlier work, other 2-substituted dienes like isoprene and 2-methoxybutadiene reacted well with **1**, but gave low regioselectivity.[1] Therefore, any regiochemical preference observed with 2-silyl dienes was of interest, even if it worked against the regiochemical preference of the terminal substituent on the diene. To explore this further, reactions were performed with dienes **9i** and **9j**, containing the 2-silyl group but lacking a substituent at C-4. As expected, in each case two regioisomeric cycloadducts were formed (**21a**+**c** or **22a**+**c**), in a ca. 46:54 ratio (Table 1, entries 9 and 10) in very good to near quantitative yield. This suggests that the 2-silyl group exerts a modest regiodirecting influence, favoring the **"c"** isomer. The regiodirecting influence is countered by a 4-alkyl group, to favor "***a***". Finally, entry 13 illustrates the selectivity with a TIPS group on the diene.[5] The *endo*/*exo* selectivity increases to 94:6, as might be expected from the increased size of the TIPS group.

We performed DFT computations to understand why 2-silyl-4-alkyl dienes give high levels of diastereoselectivity. The transition states calculated with M06-2X in SMD acetonitrile for the *endo* and *exo* (4+3) cycloadditions of **2** with two model dienes, **9o** and **9p**, in the favored regiochemistry are shown in Figure 2. The computations show that the silyl group in **9o** raises the $\Delta G^{\ddagger}$ of the *exo* transition state (**TS-B**) by 1.3 kcal/mol relative to the *endo* transition state (**TS-A**). This value corresponds to a theoretical diastereomer ratio of 86:14 at 85 °C, close to experiment (e.g., 81:13 for **9a**). The *endo*

Table 1. ***Endo*** **Selective (4+3) Cycloaddition Reactions of an** ***N*****-Methyloxidopyridinium Ion**



entry	diene	SiR^1_3	R^2	product	**a**:**b**:**c**[a]	*endo*/*exo* selectivity[b]	yield (%)[c]
1	**9a**	TMS	$-(CH_2)_2Ph$	**13**	81:13:6	87:13	93
2	**9b**	TES	$-(CH_2)_2Ph$	**14**	81:15:4	85:15	88
3	**9c**	TMS	$-(CH_2)_7Me$	**15**	82:14:4	86:14	71
4	**9d**	TES	$-(CH_2)_7Me$	**16**	89:9:2	91:9	77
5	**9e**	TMS	$-(CH_2)_2CO_2Et$	**17**	80:16:4	84:16	87
6	**9f**	TES	$-(CH_2)_2CO_2Et$	**18**	83:16:1	84:16	74
7	**9g**	TMS	cyclohexyl	**19**	86:14:0	86:14	67
8	**9h**	H	$-(CH_2)_2Ph$	**20**	46:54:0	46:54	86
9	**9i**	TES	H	**21**	41:0:59	—	99
10	**9j**	TIPS	H	**22**	46:0:54	—	68
11	**9k**	TMS	Ph	**23**	47:0:53	100:0	74
12	**9l**	TES	Ph	**24**	46:0:54	100:0	70
13	**9m**	TIPS	$-(CH_2)_2Me$	**25**	92:6:2	94:6	85
14	**9n**	$-SiMe_2Ph$	$-(CH_2)_2Ph$	**26**	87:13:0	87:13	89

[a]Ratios were determined by integration of ^1H NMR spectra of crude reaction mixtures. Isomer **d** was not detected. [b]Entry = (sum of all *endo* isomers)/(sum of all *exo* isomers). [c]Yields are the average of two runs after column chromatographic purification.

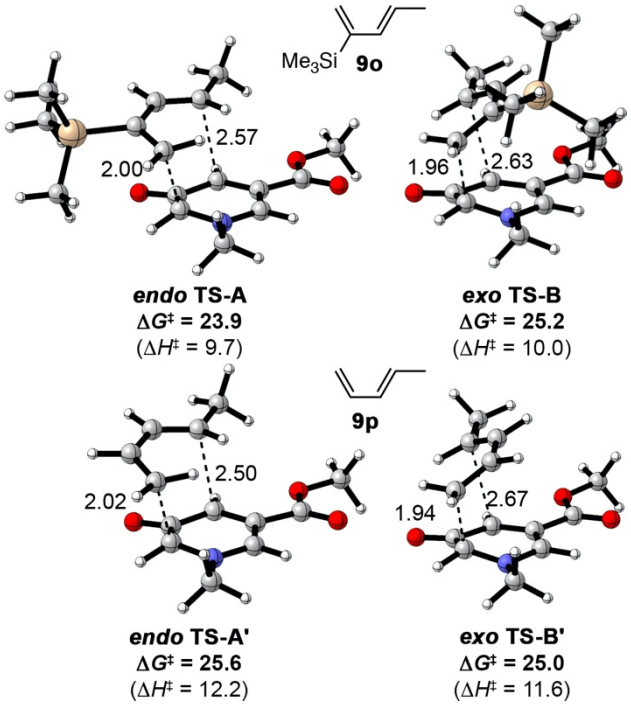


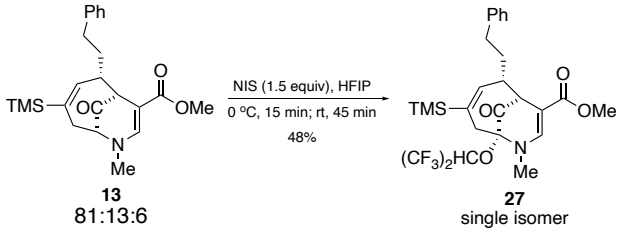
FIGURE 2. Transition states for (4+3) cycloadditions of dienes **9o** and **9p** with oxidopyridinium ion **2**, calculated with M06-2X/6-311+G(d,p) in SMD acetonitrile. Distances in Å, $\Delta G^‡$ and $\Delta H^‡$ in kcal/mol.

selectivity originates from two effects: an enthalpic effect and an entropic effect. The enthalpic effect arises because *endo* **TS-A** can accommodate the silyl group without introducing major steric interactions, but the *exo* **TS-B** must distort to avoid the clash between the silyl group and the *N*-methyl group. Thus, compared to the silyl-free *exo* TS (**TS-B'**), the diene and dienophile in **TS-B** are tilted away from each other by 0.1 Å. This distortion destabilizes **TS-B**. **TS-B** is also more compact than the *endo* **TS-A**, especially in the region of the silyl group, making **TS-B** entropically disfavored. Interestingly, theory predicts enhanced reactivity for silylated dienes.[12] While no quantitative experimental studies have yet been undertaken, the reaction of **9a** with **1** was able to be performed at a lower temperature than is usually required for these reactions; the cycloaddition at 60 °C produced **13a-c** in an 88:10:2 ratio in 71% yield after 24 h.

In general, a 2–3 equiv excess of diene was used in the reactions shown in Table 1. This represents a considerable decrease from the 10 equiv we used at the outset of our work on oxidopyridinium cycloadditions.[1a] On a small scale, the reactions were conducted in resealable pressure tubes. However, we also performed a one-gram scale reaction in a more conventional way. Based on studies that had shown that the use of 2 equiv diene gave a better yield than 1 equiv, we reacted 1 gram of **1** with 2 equiv of **9a** in acetonitrile in the presence of TEA at reflux for 24 h. Cycloadducts **13a-c** were obtained in a respectable 84% yield in a ratio of 78:16:6. This result suggests that the process is scalable more generally than previously established without having to use pressure tubes.[1b]

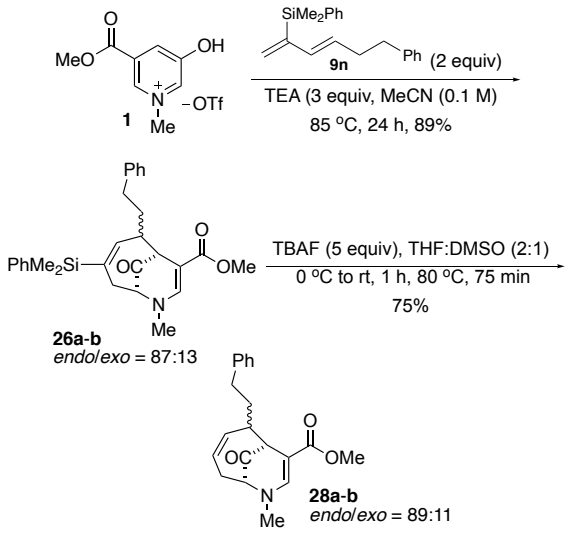
In our original work,[1a] we established a clear example of reversibility in the cycloaddition of **2** with 1-phenyl-1,3-butadiene. The cycloadditions of the two related phenyl-substituted 2-silyl dienes, **9k** and **9l**, were performed (Table 1, entries 11 and 12) and were anticipated to afford products of thermodynamic control. Indeed, the fact that two *endo* cycloadducts were formed, as we had observed with 1-phenyl-1,3-butadiene, indicated that these two reactions likewise proceeded reversibly. Both reactions gave complete *endo* selectivity but gave low regioselectivity, affording ca. 1:1 mixture of **23a+c** or **24a+c**, respectively. These **a**:**c** ratios can be understood in terms of a situation intermediate between purely kinetic and purely thermodynamic control.[11]

SCHEME 4. Reaction of 13 with NIS



To begin to establish some cycloadduct chemistry, we explored the desilylation of cycloadduct **13**. Treatment of the mixture of **13a**-**c** with TBAF in THF at 55 °C for 22 h resulted in recovery of starting material.[13] With acids, retrocycloaddition was observed: the diene could be recovered in yields ranging from 0% (excess HCl) to 99% (camphorsulfonic acid). Treatment with KOTMS in DMSO at

SCHEME 5. Synthesis and desilylation of a phenyldimethylsilyl-substituted (4+3) cycloadduct



100 °C afforded the desilylated cycloadduct (**20**) in 38% yield.[14] Attempts to brominate or iodinate the alkene with NBS or NIS, respectively, failed.[15,16] However, the reaction with NIS did produce a product in which functionalization had occurred at the bridgehead to afford **27** (Scheme 4). This process is currently being investigated as a method of cycloadduct functionalization and results will be reported at a later date.

In contrast to the difficulty encountered in removing the TMS substituent from **13**, successful desilylation was achieved with the $SiPhMe_2$-substituted cycloadduct mixture **26**, which was obtained as an 87:13 mixture of *endo*/*exo* isomers (single regioisomer, Scheme 5 and Table 1, entry 14). The ^{13}C chemical shifts of **26a**-**b** for C-9 are 93.3 and 90.9 ppm, respectively. Those of **13a**-**b** are 93.7 and 91.4 ppm. These shifts lead to the stereochemical/regiochemical assignments shown, based on our previous work.[1] Reaction of this cycloadduct with TBAF afforded a 75% yield of the desilylated cycloadducts **28a**+**b** as an 89:11 mixture of isomers (Scheme 5).

In summary, we have developed a (4+3) cycloaddition of an oxidopyridinium ion that is both highly diastereoselective and regioselective, by using a 2-silyl substituent on the diene as a directing group. Efforts to explore related dienes, explore the chemistry of the cycloadducts, design *exo*-selective processes, and broaden the scope of the dienophiles used in the cycloaddition are being undertaken. Progress will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental Procedures, copies of NMR data, computational results, methods, data, and references and X-ray data (PDF)

X-ray data compound **13c** (cif)
X-ray data reduction product of **13a** (cif)
X-ray data compound **15** (cif)
X-ray data compound **19** (cif)

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Author Contributions

The manuscript was written through contributions of all authors.

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(9) Conditions as follows: Injection volume: 1.7 mL sample in CH_3OH, column: Chiralpak IC (21 x 250 mm, 5 µm), mobile phase: isocratic 15% MeOH/85% CO_2, flow rate: 70 mL/min, detection: UV at 205 nm, backpressure regulator (BPR): 100 bar.

(10) In this process, we also separated the enantiomers of each individual diastereomer, but this is not relevant to the present study.

(11) Consistent with this idea, the isomeric TS energies for the (4+3) cycloaddition of **2** with **9k** follow a similar order to those with **9a** (i.e., **23a** is kinetically favored), but the product energies predict that **23c** is the most stable product. Details are provided in the Supporting Information.

(12) See supporting information for a discussion of this point

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