Heterocycles

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Cycloadditions of Oxacyclic Allenes and a Catalytic Asymmetric Entryway to Enantioenriched Cyclic Allenes

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Abstract: *The chemistry of strained cyclic alkynes has undergone a renaissance over the past two decades. However, a related species, strained cyclic allenes, especially heterocyclic derivatives, have only recently resurfaced and represent another class of valuable intermediates. We report a mild and facile means to generate the parent 3,4-oxacyclic allene from a readily accessible silyl triflate precursor, and then trap it in (4+2), (3+2), and (2+2) reactions to provide a variety of cycloadducts. In addition, we describe a catalytic, decarboxylative asymmetric allylic alkylation performed on an α-silylated substrate, to ultimately permit access to an enantioenriched allene. Generation and trapping of the enantioenriched cyclic allene occurs with complete transfer of stereochemical information in a Diels–Alder cycloaddition through a point-chirality, axial-chirality, point-chirality transfer process.*

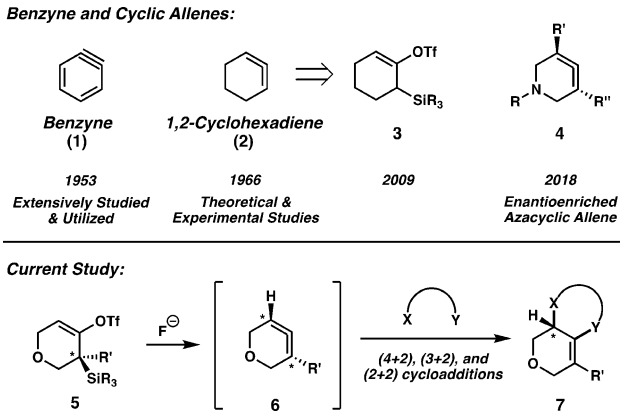

Figure 1. Highlights of benzyne and cyclic allene chemistry and cycloadditions of oxacyclic allenes described in this study. OTf = trifluoromethanesulfonate.

Despite once being mere scientific curiosities, strained cyclic intermediates have become a popular arena for chemical discoveries. A notable breakthrough in the field was the discovery of benzyne (**1**), initially proposed by Wittig in 1942 and validated by Roberts and co-workers in 1953 (Figure 1).[1] In the modern era, benzyne (**1**) and other cyclic alkynes are readily used to make natural products,[2] medicinal agents,[3] agrochemicals,[4] materials,[5] tools for chemical biology,[6] and ligands for catalysis.[7,8] The related intermediate 1,2-cyclohexadiene (**2**) has generally received less attention despite being validated not long after benzyne (**1**) in 1966.[9] Historically, theoretical studies of **2** and its derivatives have been popular.[10] However, only recently has **2** seen synthetic use in cycloadditions.[11] This is largely due to the fact that it can be accessed under mild fluoride-mediated conditions from silyl triflate **3**.[12,13]

One exciting opportunity in the field of strained cyclic intermediates is the ability to access heterocyclic allenes. Early efforts in this field relied on harsh reaction conditions;[14,15] however, we recently demonstrated that azacyclic allenes **4** (Figure 1) can be accessed using mild reaction conditions. Moreover, by using chiral separation technology, enantioenriched **4** was intercepted (R = Cbz, R′ = H, R″ = Me), and its stereospecific trapping allowed for a unique approach to access enantioenriched cycloadducts.[16]

Given the potential for heterocyclic allenes to provide a facile means to rapidly assemble stereochemically rich scaffolds,[16] we wondered whether oxacyclic allenes **6** could be employed efficiently in cycloadditions to access oxygen-containing heterocycles.[17] Oxygenated heterocycles are often seen in natural products and drugs[18–21] and are known bioisosteres for their nitrogen- and sulfur-containing counterparts.[22] A single report by Christl and Schreck demonstrated that **6** (R′ = H) could be generated using the Doering–Moore–Skattebøl rearrangement, however, this required harsh organolithium-based conditions.[14] If **6** could be generated under mild conditions from silyl triflates **5**, the synthetic utility of this species could be unlocked. Additionally, we sought to access **6** in enantioenriched form, ideally by preparing an enantioenriched precursor to the desired allene **6** using asymmetric catalysis. By accessing enantioenriched **5**, we could explore the possibility of transferring stereochemical information from allene precursor **5** to cycloadduct **7** through a point-chirality, axial-chirality, point-chirality transfer process. The results presented herein not only demon-

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strate the scope and utility of oxacyclic allene cycloadditions, but also showcase an exciting strategy that merges asymmetric catalysis with cyclic allene chemistry as a means to access enantioenriched scaffolds.

Density functional theory (DFT) calculations on the structure of heterocyclic allene **8** were performed using ωB97XD/6-31G(d) (Figure 2).[10a,c,d,23] The C=C bond length of the allene is 1.32 Å, which is only slightly longer than the

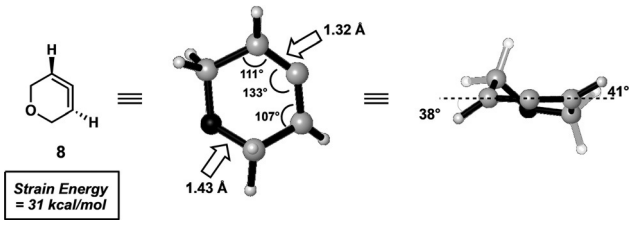
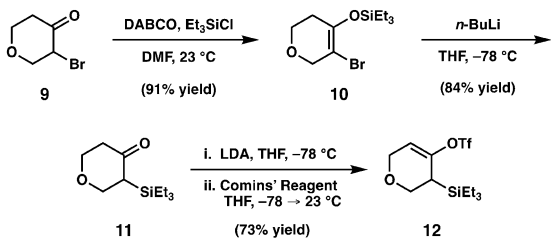


Figure 2. Ground-state structure of oxacyclic allene **8**. The structure was computed using ωB97XD/6-31G(d).

C=C bond length in a linear allene.[16] Furthermore, the internal angle at the central allene carbon is 133°, which is a significant deviation from the typical internal angle of 180° seen in linear allenes. The allene π orbitals in **8** are not perfectly orthogonal, resulting in the C–H bonds being twisted out of plane (i.e., 38° and 41°). Thus, **8** is inherently chiral, in a manner analogous to linear allenes. The ground state geometry deviates from C2 symmetry because the molecule adopts an envelope shape; inversion of the envelope requires only 0.8 kcal mol^{-1}. Interestingly, oxacyclic allene **8** is calculated to possess 31.0 kcal mol^{-1} of strain energy, which is nearly 4 kcal mol^{-1} more than the azacyclic variant we previously reported.[16] This difference can be attributed to the smaller atomic radius of oxygen and the shorter C–O bond length relative to the C–N bond length in the azacyclic variant. The significant strain associated with oxacyclic allene **8** is expected to promote rapid cycloadditions.

With the aim of accessing oxacyclic allene **8**, we first targeted silyl triflate **12** (Scheme 1), given the wide synthetic utility of silyl triflates as precursors to strained alkyne and allene intermediates.[12,24] Bromoketone **9** (commercially available or readily synthesized from tetrahydro-4-pyranone) was converted into triethylsilyl enol ether **10** upon treatment



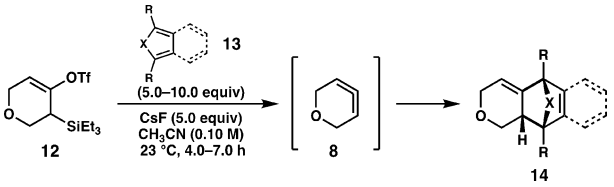
Scheme 1. Synthesis of silyl triflate **12**. DABCO = 1,4-diazabicyclo-[2.2.2]octane, DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofuran, LDA = lithium diisopropylamide, Comins' Reagent = *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide), OTf = trifluoromethanesulfonate.

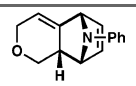
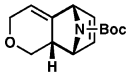
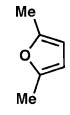
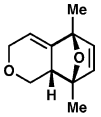
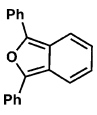
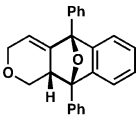
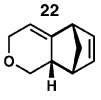
with DABCO and TESCl.[25] Subsequent retro-Brook rearrangement furnished the desired α-silyl ketone **11**. Finally, triflation afforded silyl triflate **12**.[16] Our three-step scalable[26] synthesis of **12** provides a new strategy to synthesize α-silyl ketones en route to cyclic allene precursors. Currently, α-silyl ketones are most commonly prepared by 1,4-reduction of the corresponding α,β-unsaturated ketones.[11a,12,16,27]

With silyl triflate **12** in hand, we generated and trapped **8** in Diels–Alder, (3+2), and (2+2) cycloadditions. By simply employing a variety of dienes, a number of cycloadducts were prepared in good to excellent yields (Table 1, entries 1–5).[28] In almost all cases, the reactions were performed at 23 °C, thus highlighting the mildness of the reaction conditions. Although the diastereoselectivity was variable, in all examples, the major diastereomer observed is the *endo* product. The observed diastereoselectivity is supported by computations.[26] It should be noted that in each case, the products formed are considerably complex from a structural perspective, with each bearing three stereocenters, a bridged [2.2.1]-bicyclic framework, and one or two heteroatoms.

The results of the (3+2) and (2+2) cycloadditions are shown in Figure 3 and Table 2. The use of simple nitrones gave high yields of isoxazolidine products **27**–**29**, whereas

Table 1: Mild generation of oxacyclic allene **8** and its trapping in Diels–Alder cycloadditions.



Entry	Diene	Cycloadduct[a]	Yield[b] Diastereoselectivity[c]
1	 15	 16	91% 3.8:1 dr
2	 17	 18	74% 6.2:1 dr
3	 19	 20	86% 9.2:1 dr
4	 21	 22	97%[d] 2.0:1 dr
5	 23	 24	83% 1.6:1 dr

[a] The major diastereomer is shown. [b] Yields reflect an average of two isolation experiments. [c] Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. [d] The reaction was performed at 60 °C for 2.5 h using 2.0 equiv of diene **21**. Boc = *tert*-butyloxycarbonyl, OTf = trifluoromethanesulfonate.

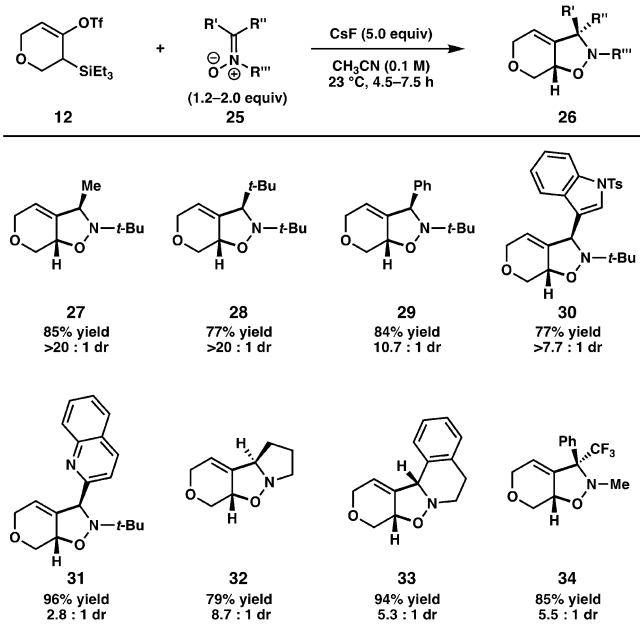
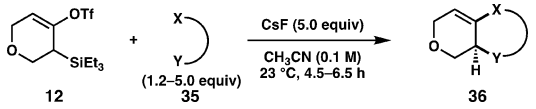
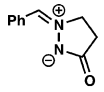
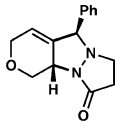
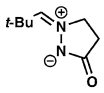
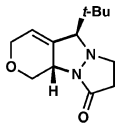
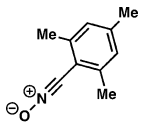
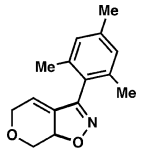
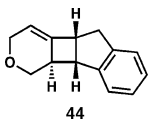


Figure 3. (3+2) Cycloadditions with nitrones. The major diastereomeric product is shown. Yields reflect an average of two isolation experiments. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. OTf = trifluoromethanesulfonate, Ts = para-toluenesulfonyl.

Table 2: Additional (3+2) and (2+2) cycloadditions.



Entry	Trapping Agent	Cycloadduct[a]	Yield[b] Diastereoselectivity[c]
1	 37	 38	76% 7.6:1 dr
2	 39	 40	83% >20:1 dr
3	 41	 42	91% N/A
4	 43	 44	96% 5.2:1 dr

[a] The major diastereomer is shown. [b] Yields reflect an average of two isolation experiments. [c] Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture, OTf = trifluoromethanesulfonate.

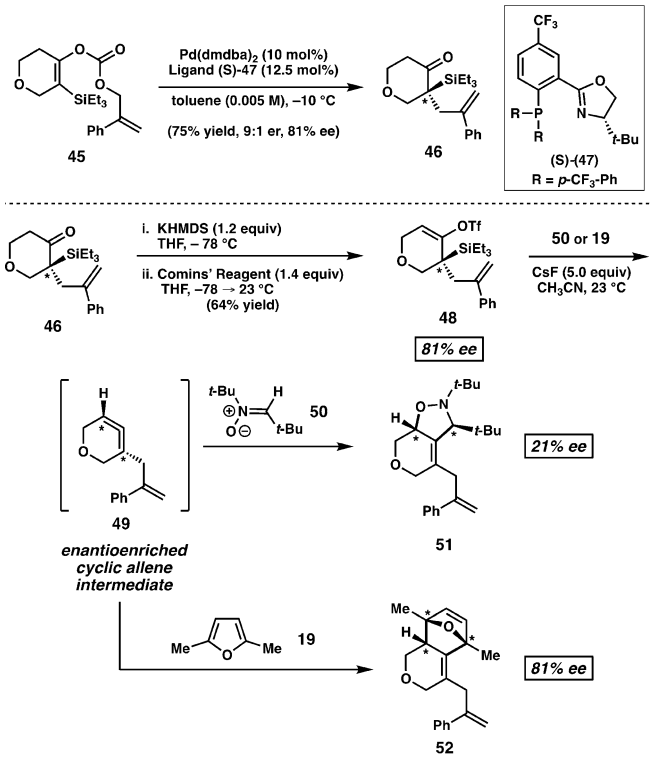
nitrones bearing either an indole or quinoline unit delivered cycloadducts **30** and **31**. We also evaluated two cyclic nitrones where R″ and R‴ of **25** were tethered, which furnished tri- and tetracyclic products **32** and **33**. Additionally, a ketone-derived nitrone was utilized, ultimately giving rise to the heteroatom-rich trifluoromethylated product **34**. Azomethine imines **37** and **39** were tested, giving rise to the corresponding pyrazolidines, **38** and **40**, with good to excellent diastereoselectivity (Table 2, entries 1 and 2). The use of nitrile oxide **41** led to the formation of isoxazoline **42** in 91% yield (entry 3). With regard to a (2+2) cycloaddition, the use of indene gave cyclobutane **44** in excellent yield and with high regioselectivity (entry 4).

Overall, silyl triflate **12** was elaborated to 17 different sp^3-rich heterocyclic cycloadducts. Several of these bear a multitude of rings, stereocenters, and heteroatoms, thus showcasing the value of oxacyclic allenes for the rapid generation of complex scaffolds. Accordingly, this method should be especially valuable in drug discovery.[17]

As noted earlier, one of the most exciting opportunities regarding cyclic allene chemistry is the possibility of intercepting enantioenriched allenes for the synthesis of enantioenriched cycloadducts. In a seminal study, Christl and coworkers generated 1-phenyl-1,2-cyclohexadiene in enantioenriched form, as judged by the formation of an enantioenriched cycloadduct, albeit in low yield, likely owing to the necessary use of organolithium reagents.[29] Our laboratory recently disclosed a mild, alternative strategy whereby silyl triflate precursors to the desired cyclic allenes could be employed in enantioenriched form.[16] However, in both cases, the key substrates were only accessible through chiral separation technologies. A catalytic asymmetric strategy to access enantioenriched cyclic allene precursors has not been reported.

Our efforts in this area are highlighted in Scheme 2. Enol carbonate **45** was formed by intercepting the enolate intermediate generated during the retro-Brook rearrangement of **10** (see Scheme 1). This set the stage for a Pd-catalyzed decarboxylative asymmetric allylic alkylation. Allylation was attractive, given that allyl groups serve as versatile handles for further manipulation.[30] After extensive experimentation,[26] it was found that treatment of **45** with $Pd(dmdba)_2$ and (*S*)-$(CF_3)_3$-*t*Bu-PHOX ligand **47** in toluene at −10 °C gave the desired ketone **46** in 9:1 er (81% *ee*) and 75% yield. This is the first example of a decarboxylative asymmetric allylic alkylation reaction being performed on an α-silyl-substituted enol carbonate. In fact, decarboxylative asymmetric allylic alkylations on substrates bearing α-heteroatoms are significantly underdeveloped.[30,31] **46** was converted into silyl triflate **48** in one-step, thus establishing the first catalytic asymmetric strategy for the synthesis of enantioenriched cyclic allene precursors.

48 was treated with trapping agent **50** or **19** in the presence of CsF in acetonitrile at 23 °C. Interestingly, the nitrone cycloadduct, isoxazolidine **51**, was obtained in 21% *ee*. On the other hand, the Diels–Alder cycloadduct, oxabicycle **52** was obtained in 81% *ee* (>20:1 dr), which reflects complete transfer of stereochemical information. Given this latter result, we surmise that enantioenriched **49** is formed under



Scheme 2. Catalytic asymmetric approach and cycloaddition results. dmdba = 3,5,3′,5′-dimethoxydibenzylideneacetone, KHMDS = potassium bis(trimethylsilyl)amide. Comins' Reagent = *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide), THF = tetrahydrofuran, OTf = trifluoromethanesulfonate.

the mild reaction conditions with complete transfer of stereochemical information. In the case of the nitrone trapping, previous computational studies have demonstrated that trapping may occur through either a stepwise or concerted pathway,[11a] which accounts for the partial loss of stereochemical information.[32] However, in the case of the Diels–Alder reaction, it is likely that a concerted pathway is operative, based on our recent computational investigation of azacyclic allenes,[16] thus leading to complete transfer of stereochemical information.

The overall conversion of **48** to **49** to **52** deserves special attention. This is a scenario wherein the silyl-bearing stereocenter in **48** was ultimately accessed by asymmetric catalysis. The point chirality in **48** is then transferred to the axially chiral transient intermediate **49**, which is then relayed to product **52**, which possesses point chirality. Enantioenriched cycloadduct **52** contains three stereocenters, none of which were present in the starting material, which bears only one stereocenter. The transformation occurs preferentially at the olefin more distal to the 2-phenyl allyl group undergoing cycloaddition. This is presumably because of favorable electronic interactions in the transition state based on our prior studies,[16] however, we cannot rule out the steric impact of the 2-Ph allyl chain as a contributor to the observed regioselectivity.

We have discovered an efficient synthetic route to prepare a silyl triflate precursor to 3,4-oxacyclohexadiene, the first generation of an oxacyclic allene under mild conditions, and the in situ trapping of the oxacyclic allene in diastereo- and regioselective cycloadditions. These efforts collectively establish the synthetic utility of oxacyclic allenes for the rapid generation of complex heterocyclic scaffolds. In addition, we have uncovered the first catalytic, asymmetric approach to access an enantioenriched cyclic allene precursor. This relies on a Pd-catalyzed allylic allylation, performed for the first time on an α-silyl-substituted substrate, which ultimately permitted access to the necessary enantioenriched silyl triflate precursor. We show that trapping of the enantioenriched oxacyclic allene in a Diels–Alder reaction occurs with complete transfer of stereochemical information through a point-chirality, axial-chirality, point-chirality transfer process. These results showcase an exciting strategy that merges asymmetric catalysis with cyclic allene chemistry as a means to access densely functionalized, enantioenriched scaffolds.

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Conflict of interest

The authors declare no conflict of interest.

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