JOC The Journal of Organic Chemistry

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A Highly Stereospecific Claisen−Sakurai Approach to Densely Functionalized Cyclopentenols

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Cite This: J. Org. Chem. 2022, 87, 12250−12256 Read Online

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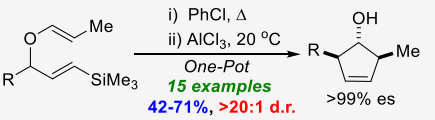
ABSTRACT: The formation of highly substituted cyclopentenols was developed using a Claisen−Sakurai reaction. Both elements of the reaction can be performed in a one-pot sequence that provides the corresponding cyclized products in high stereoselectivity. The stereochemical outcome is defined by a combination of Claisen stereospecificity and stereoelectronic effects in the Sakurai cyclization that promotes reactivity via an *anti*-S_E' antiperiplanar transition state. This was determined by examination of the product stereochemistry and through detailed DFT analysis.



INTRODUCTION

Densely functionalized five-membered ring systems are prevalent in many natural products and have become increasingly sought after by the pharmaceutical industry (Figure 1).[1] These types of compounds are ideal scaffolds for drug discovery due their rigid nature while retaining a high sp^3:sp^2 atom ratio which can provide enhanced pharmacokinetic properties.[2] This motif is especially prevalent in virology with compounds with carbocyclic nucleoside analogue reverse transcriptase inhibitors, such as abacavir, licensed to combat HIV and HBV.[3] The neuraminidase inhibitor peramivir also contains a stereochemically dense cyclopentane core.[4] Complex cyclopentanes are found in numerous natural products, including terpenes,[5] polyketides,[6] and alkaloids,[7] such as palau'amine.[8] Therefore, new stereoselective methods and strategies for their syntheses are needed.

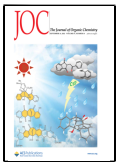
The stereoselective synthesis of five-membered ring systems can be problematic due to their dynamic conformational nature leading to both thermodynamic and kinetic selectivity issues.[9] Indeed, the pioneering prostaglandin research from the 1970s onward highlighted the inherent challenges producing these systems in a stereodefined manner.[10] Currently available methods for the synthesis of cyclopentanes suffer from a lack of flexibility in both the substitution tolerated and stereochemistry of the product possible.[11] These include ring opening of bicyclic structures,[12] multistep conversion of carbohydrates,[13] functionalization of cyclopentenones,[14] allylic functionalization of cyclopentenes,[15] Nazarov cyclizations,[16] [2,3]-dipolar cycloadditions,[17] and ring-closing metathesis strategies.[18]

We envisaged that a method for the synthesis of functionalized cyclopentenols could be developed through the union of the Claisen and Sakurai reactions which would harness the stereoelectronics of these reactions to provide high levels of stereocontrol. Isolated reports of the Claisen and Sakurai reactions being combined in a single synthetic sequence have been previously described. Based on Nakai's pioneering work,[19] Paquette demonstrated that a Sakurai ring closure could be achieved following a thermal Claisen (Figure 1, eq 1), alongside a single report of a Lewis acid mediated cascade Claisen−Sakurai reaction (Figure 1, eq 2).[20] Panek reported the use of an intramolecular Sakurai allylation to form more substituted cyclopentenols with up to three contiguous stereocenters with high levels of stereocontrol.[21] Although effective, this method was generally limited to simple alkyl substituents and required long synthetic schemes to form the allylsilane aldehyde prior to cyclization (Figure 1, eq 3). Our approach was to utilize readily synthesized silylated allyl vinyl ethers (**1**)[22] and perform a Claisen−Sakurai sequence in either a one-pot stepwise or a cascade fashion (Figure 1, eq 4). The result is a very modular synthesis of 1,2,5-trisubstituted cyclopent-3-en-1-ols (**2**) that can utilize the stereospecificity of both Claisen and intramolecular Sakurai reactions. Herein, we describe the realization of the Claisen−Sakurai reaction pathway to produce highly substituted cyclopentenols.

RESULTS AND DISCUSSION

Our optimization studies examined the conversion of benzyl-substituted allyl vinyl ether **1a** to the corresponding cyclopentenol **2a**. A thermal Claisen rearrangement was performed on **1a** in chlorobenzene at 110 °C, followed by cooling to ambient temperature, and the addition of a Lewis acid to affect the Sakurai−cyclization. A range of Lewis acids were tested; however, aluminum reagents were the most effective (Table 1). No cyclized product was observed with $AlMe_3$, with significant amounts of aldehyde alkylation detected (entry 1). The more

Received: June 13, 2022
Published: September 6, 2022



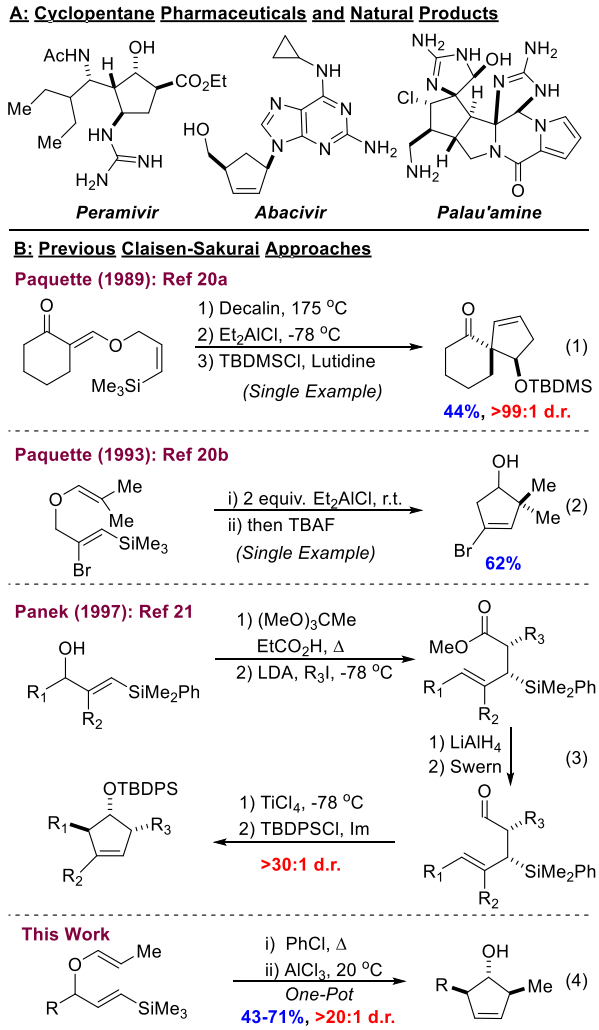
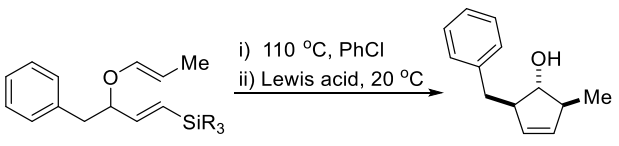


Figure 1. Importance of cyclopentanes and Claisen−Sakurai approaches.

Table 1. Optimization Studies



1a **2a**

Entry	R_3Si	Lewis Acid	Yield[a] (%)	dr[b]
1	$SiMe_3$	1.5 equiv of $AlMe_3$	0	na
2	$SiMe_3$	1.5 equiv of Et_2AlCl	59	>20:1
3	$SiMe_3$	1.5 equiv of $EtAlCl_2$	45	>20:1
4	**$SiMe_3$**	**1.5 equiv of $AlCl_3$**	**65**	>20:1
5[c]	$SiMe_3$	1.5 equiv of $AlCl_3$[c]	59	>20:1
6	$SiMe_3$	1 equiv of $AlCl_3$	34	>20:1
7	$SiMe_3$	2 equiv of $AlCl_3$	47	>20:1
8	$SiEt_3$	1.5 equiv of $AlCl_3$	47	>20:1
9	$SiMe_2Ph$	1.5 equiv of $AlCl_3$	37[d]	8:1

[a]Determined by ^1H NMR against an internal standard (1,3,5-triisopropylbenzene); [b]Determined by ^1H NMR analysis; [c]Lewis acid reaction performed at 0 °C. [d]Product formed as a mixture of *O*-silylated and free OH.

Lewis acidic reagents (Et_2AlCl, $EtAlCl_2$, $AlCl_3$) provided the cyclized product **2a** in good yields and excellent diastereoselectivity (entries 2−4). $AlCl_3$ provided the cleanest reactions due to the absence of any alkylation reaction, with 1.5 equiv of Lewis acid proving optimal (entries 4−7).

The reactions are clean, as judged by the crude reaction mixtures; therefore, the mass balance can be accounted for by competing decomposition. Alternative silanes, other than $SiMe_3$, were also tested; however, $SiEt_3$ and $SiMe_2Ph$ groups had a deleterious effect on the reactivity and stereochemical outcome (entries 8 and 9). High levels of stereocontrol with >20:1 dr were observed in all cases except with the less nucleophilic and more sterically encumbered $SiMe_2Ph$ variant (entry 9). The stereochemical outcome was assigned as the *anti,anti*-isomer shown by NMR and computational methods (*vide infra*).

With the optimized conditions in hand, we examined the scope of this reaction (Scheme 1). The optimized conditions described above (Table 1, entry 4) were applied to other alkyl-substituted allyl vinyl ethers (**1a−c**). Cyclohexyl- (**1b**) and benzyloxyethyl-substituted (**1c**) variants provided **2b** and **2c** in good to moderate yields and excellent stereoselectivity >20:1 dr. Aryl-substituted allyl vinyl ethers (**1d−1o**) were also examined. These substrates exhibited an accelerated Claisen rearrangement, compared to **1a−c**, allowing the initial reaction to occur at 90 °C or below.[23] This transformation was very general and relatively insensitive to functionality and substitution pattern. Good yields of the cyclopentenol products (**2d−2o**) and high levels of stereocontrol (>20:1) were obtained in all cases. Although σ-withdrawing groups do not significantly influence the reaction efficiency, mesomeric electron-donating groups provide slightly higher overall yields and faster reaction times. This is exemplified by examining 4-substitution on the benzene ring where OMe (**2e**), CF_3 (**2f**), OCF_3 (**2g**), and F (**2h**) all provide similar reactivity with **2e** being formed more efficiently. We also examined the effect of the substitution position by comparing the formation of 4-F (**2h**), 3-F (**2i**), and 2-F (**2j**) cyclopentenols. There were minimal differences in reaction efficiency between these regioisomers (**1h−j**), demonstrating no clear electronic sensitivity. More complex arene substitution was also examined. 2-Naphthyl cyclopentenol (**2k**) was produced in excellent yield, and 2,4-disubstituted groups were well tolerated. Specifically, 2-fluoro-4-methoxy (**2l**), 2,4-difluoro (**2m**), and 2-fluoro-4-chloro (**2n**) products could be isolated in good yields. Finally, we demonstrated the use of hetero-aromatic groups in this reaction with the *N*-tosyl indole derivative (**2o**) being isolated with high efficiency. To further demonstrate the synthetic utility of this reaction, we performed the rearrangement of **1d** on a 1 mmol scale with comparable results. Formation of the allyl vinyl ethers (**1**) containing groups other than methyl groups was more challenging using the Ir(I) isomerization approach (see SI for details).

This transformation converts allyl vinyl ethers (**1**), which contain a single stereogenic center, into cyclopentenols (**2**) that contain three contiguous stereocenters. We therefore examined whether the absolute stereochemistry of enantioenriched allyl vinyl ethers could be transferred to the products (**2**) to provide a new enantioselective route to these structures. Enantiospecificity would render this reaction even more impactful due to the abundance of methods of enantiocontrolled allylic and propargylic alcohol synthesis.[24] To test this hypothesis, we prepared a sample of allyl vinyl ether ***S*-1d** in 86% ee from the corresponding allylic alcohol[25] with no erosion of stereochemistry. When ***S*-1d** was subjected to

https://doi.org/10.1021/acs.joc.2c01397
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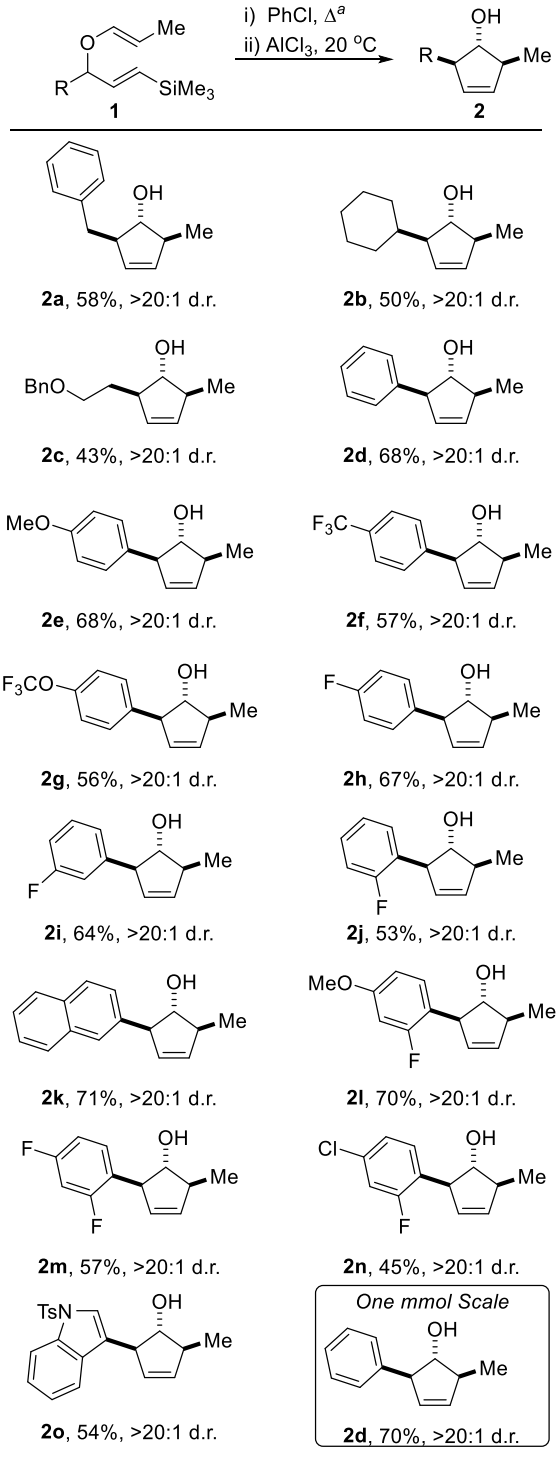
Scheme 1. Substrate Scope[a−c]

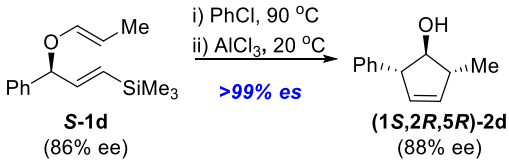


[a]Conditions: **1a−1c** (110 °C), **1d−1n** (90 °C), **1o** (70 °C); [b]Isolated yields. [c]Determined by ^{1}H NMR analysis.

reaction conditions identical to those described in Scheme 1, the corresponding cyclopentenol (**2d**) was produced with no loss of enantioenrichment (Scheme 2). This stereospecificity is evidence of the concerted nature of the Claisen rearrangement and that Sakurai cyclization is significantly faster than any epimerization mechanism.

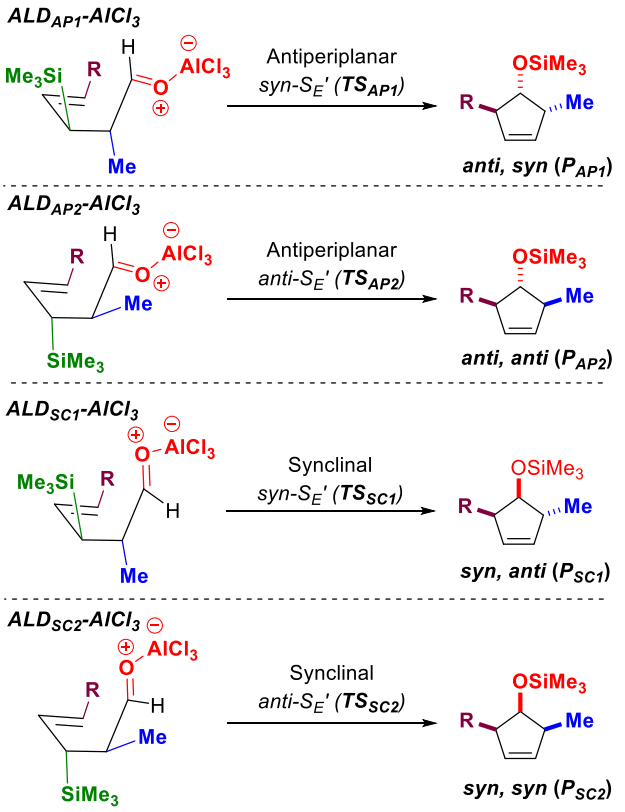
To investigate the origin of this stereocontrol, especially the origin of the Sakurai selectivity, we conducted DFT

Scheme 2. Enantiospecificity of Rearrangements



calculations. The stereochemical outcome of the reaction is determined by two factors: the internal diastereoselection and relative asymmetric induction (Scheme 3). The former

Scheme 3. Origin of Sakurai Stereoselectivity



describes the relative disposition between the aldehyde group and *trans*-alkene and can be defined as antiperiplanar (*AP*) and synclinal (*SC*), which determines the relative stereochemistry between the R and OH groups. The latter refers to the direction of electrophilic attack of the $AlCl_3$-bound carbonyl (**3a−d**), which can approach the alkene from the same side as silicon electrofuge (*syn*-S_E') or from the opposite side (*anti*-S_E') dictating the diastereomer between the OH and Me groups.[26] Therefore, the possible transition states (and consequently, reaction pathways) can be limited to four combinations: *AP syn*-S_E' ($\mathbf{TS_{AP1}}$); *AP anti*-S_E' ($\mathbf{TS_{AP2}}$); *SC syn*-S_E' ($\mathbf{TS_{SC1}}$); and *SC anti*-S_E' ($\mathbf{TS_{SC2}}$) (Scheme 3).

Calculations were conducted for the formation of four diastereomeric silylated alcohols ($\mathbf{P_{AP1}}$, $\mathbf{P_{AP2}}$, $\mathbf{P_{SC1}}$, and $\mathbf{P_{SC2}}$) (Scheme 4), with all four of the transition-state structures described above considered. These computations showed that the ground-state energies of all four $AlCl_3$-bound aldehyde reactive conformations (**ALD-AlCl$_3$**) are within 1.0 kcal/mol; therefore, these conformers are easily interconvertible. In contrast, the corresponding TS energies for the Sakurai cyclization are in the range of 10.1−16.9 kcal/mol (Scheme

https://doi.org/10.1021/acs.joc.2c01397
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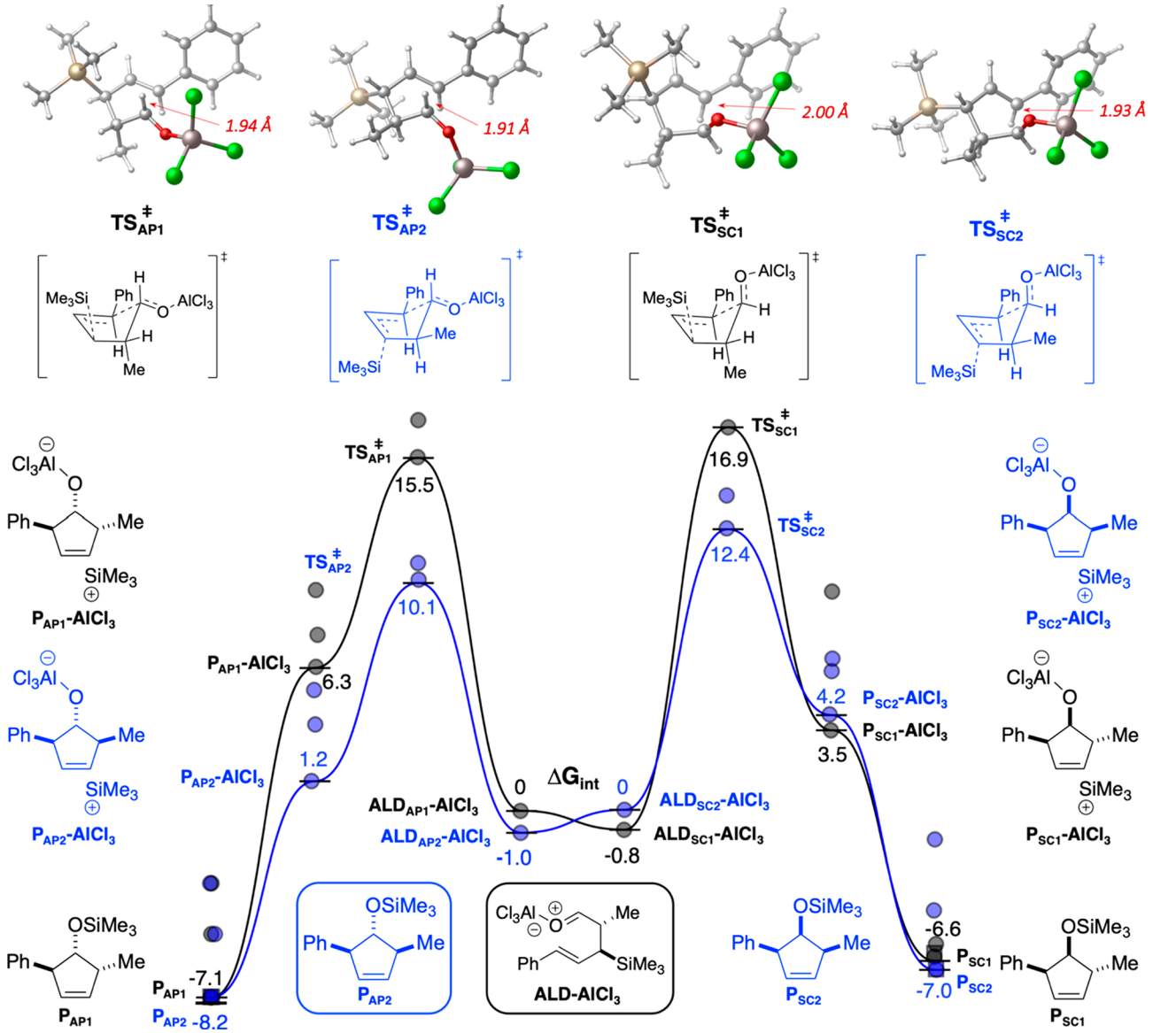
Scheme 4. Potential Energy Surface of Intramolecular $AlCl_3$-Mediated Sakurai Allylation[a]



[a]Calculations were performed at C-PCM (chlorobenzene)-M11L/6-311++G(2d,2p)//C-PCM (chlorobenzene)-B3LYP/6-31+G(d). The quasi-harmonic Gibbs Free energies are reported at 293.15 K and 1 mol/L standard state. The energies were corrected using accessible conformations based on the Boltzmann-weighted energies of the conformers. Individual conformers are shown as dots. Structures of the lowest energy TS conformer are shown.

4). This Curtin−Hammett scenario proceeds via the lowest overall transition state ($\mathbf{TS_{AP2}}$), with the antiperiplanar *anti*-S_E' pathway providing the *anti, anti*-isomer $\mathbf{P_{AP2}}$. The $\Delta\Delta G^{\ddagger}$ between the two lowest transition states ($\mathbf{TS_{AP2}}$ and $\mathbf{TS_{SC2}}$) is 2.3 kcal/mol, corresponding to >50:1 relative rates and is in agreement with experimentally derived data. Alternative conformations of $AlCl_3$-carbonyl binding were also considered; values quoted represent the energies corrected using accessible conformations based on the Boltzmann-weighted energies of the conformers. Importantly, our computations are in agreement with stereochemical outcomes stated in other Sakurai-cyclization methods by Paquette[20a] and Panek[21] (Figure 1). Both reports show structures of products from antiperiplanar-*anti* S_E' cyclization, which provides further credence to our computational models. Although products were experimentally isolated as the corresponding alcohols (**2**), we observed the *O*-silylated products with alternative workup procedures. We therefore believe the aqueous NaOH cleaves the TMS during workup.

The stereochemical outcome appears to be dictated by two deleterious steric interactions (Figure 2). First, the relative asymmetric induction is controlled through conformational effects resulting from a destabilizing *syn*-pentane interaction. Steric interference between the pseudoaxial substituents increases torsional strain in the *syn*-S_E' variants ($\mathbf{TS_{AP1}}$ and $\mathbf{TS_{CS1}}$) which results in a significant twisting of the structure during the C−C bond-forming step. Second, the internal diastereoselection is determined by Gauche interactions as the new bond is produced. The synclinal transition states ($\mathbf{TS_{SC1}}$ and $\mathbf{TS_{SC2}}$) proceed through orientations where the Lewis acid bound carbonyl experiences two Gauche interactions, whereas the antiperiplanar ($\mathbf{TS_{AP1}}$ and $\mathbf{TS_{AP2}}$) variants only experience

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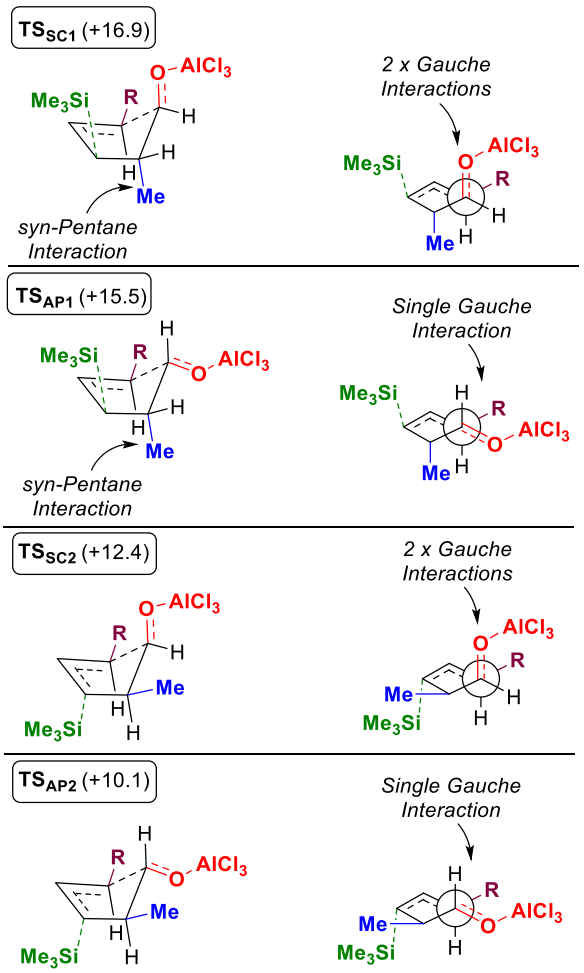
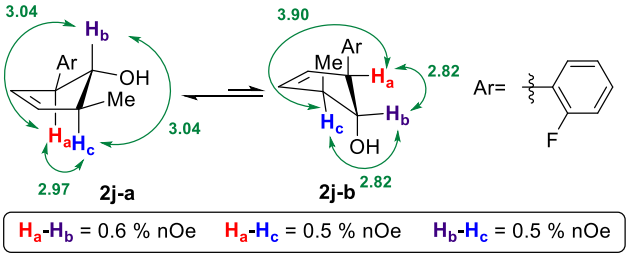


Figure 2. Steric considerations for stereocontrol.

one such interaction. The molecular orbitals were also examined; however, there were no significant stereoelectronic effects observed, such as the increased orbital mixing reported by Denmark; therefore, we believe that steric arguments alone rationalize the stereochemical outcome.[26] The *syn*-pentane interaction is destabilizing by 4.5−5.4 kcal/mol, whereas the effects of the Gauche interacts are more moderate (1.4−2.3 kcal/mol). As a result, the antiperiplanar *anti*-S_E' conformation (**TS$_{AP2}$**) is the preferred transition state structure, as can be observed in the *anti,anti*-stereochemistry of the cyclopentenol products **2** (Scheme 1).[27]

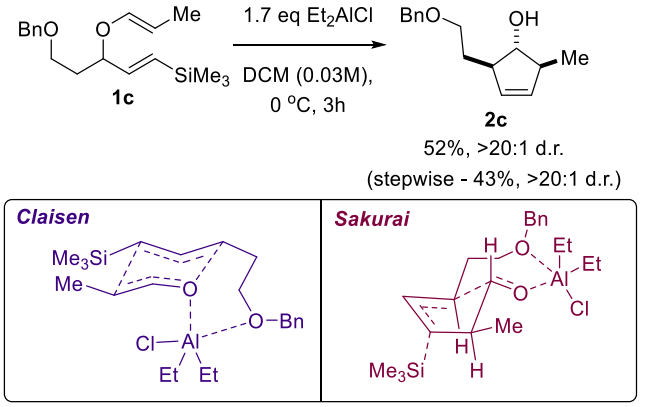
To elucidate the relative stereochemistry of the cyclopentenol products (**2**) experimentally, we conducted NMR studies. Compound **2j** was chosen because of optimal peak resolution. 1D-NOESY experiments showed weak correlations (0.5−0.6%) between all three of the sp^3-bound hydrogen atoms (H_a, H_b, and H_c, Scheme 5).[28] The magnitude and similarity of these through-space spin−spin polarizations suggest relatively distant, yet similar, spatial positioning from each other, implying all pseudoaxial (**2j−a**) or pseudoequatorial (**2j−b**) orientations. These represent the two ring-flipped conformations of *anti,anti*-product **2j** (Scheme 5). DFT calculations predict a conformational mixture of 7.8:1 at equilibrium between **2j-a** and **2j-b** ($\Delta\Delta G^0$ = 1.2 kcal/mol), which interconvert much faster than the NMR time scale. We are therefore observing an average correlation based on this conformational makeup. When one examines the average H−H distances of **2j**, we find that all three hydrogen atoms (H_a−H_c) are close to equidistant from each other with 3.01 Å (H_a−H_b), 3.07 Å (H_a−H_c), and 3.01 Å (H_b−H_c). Importantly, this is the only stereoisomer that provides such similar average H−H distances and is consistent with both the magnitude and similarity of the correlations measured (see the SI for details of other stereoisomers). By combining the NMR and DFT data, we have a high degree of confidence in our stereochemical assignment of the *anti,anti*-isomer.

Scheme 5. Stereochemical Assignment by 1D-NOESY NMR Spectroscopy



As was alluded to earlier, this Claisen−Sakurai reaction could, in theory, be mediated by a single Lewis acid analogous to Paquette's single example.[20] This cascade process has been investigated; however, the silylated allyl vinyl ethers (**1**) proved unstable under Lewis acidic conditions resulting in numerous degradation products. These decomposition pathways were problematic for both alkyl and aryl substituents providing only trace amounts of cyclized products (**2**) and intractable mixtures of side products. Nevertheless, when OBn-substituted allyl vinyl ether (**1c**) was treated with Et_2AlCl at 0 °C, a cascade Claisen−Sakurai reaction was observed, providing the product **2c** in 52% yield (Scheme 6). Furthermore, this reaction resulted in both the same stereochemical ratio and major diastereoisomer. Indeed, this reaction was more efficient than the stepwise procedure described in Scheme 1, with minimal degradation observed. The dichotomy between **1c** and other vinyl ethers can be rationalized via an internal Lewis acid−base interaction between the aluminum and the benzyl ether. This interaction provides a two-point binding that both lowers the Lewis acidity and, thus, prevents ionization and preorganizes the substrate closer to the reactive conformation. A similar two-point binding motif can also be invoked for the

Scheme 6. Cascade Claisen−Sakurai Reaction of Benzyl Ether (1c)



https://doi.org/10.1021/acs.joc.2c01397
J. Org. Chem. 2022, 87, 12250−12256

Sakurai ring-closure, providing the same (*anti,anti*) stereoisomer of **2c**.

CONCLUSIONS

In conclusion, we have developed a highly stereoselective and general method for the synthesis of substituted cyclopentenols. This reaction can tolerate a wide range of electronic and steric environments, producing the cyclized products in >20:1 dr. Alongside the scope and synthetic utility, we also investigated the mechanism of this reaction, with the origin of the stereoselectivity of particular interest. Our findings highlight a complex dynamic equilibrium which is under Curtin−Hammett control. Computations and experimental findings suggest the major stereoisomer is the *anti,anti*-isomer which results from an antiperiplanar *anti*-S_E' mechanism. We also demonstrated the first example of a Claisen−Sakurai cascade reaction where multiple stereocenters are formed with excellent levels of stereocontrol. This example is mediated by an internal Lewis acid−base interaction that provides high reactivity and selectivity. The potential applications of these methods are numerous in both synthetic and medicinal chemistry.[29]

ASSOCIATED CONTENT

Supporting Information

Supporting Information (experimental procedures, compound characterization $^1H/^{13}C$ NMR spectra, computational methods/coordinates) are available free of charge via the Internet. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01397.

Cartesian coordinates (XYZ)

Experimental procedures, compound characterization, $^1H/^{13}C$ NMR spectra, and computational methods/coordinates (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Professor Sharon Neufeldt for useful discussions on the DFT studies. Calculations were performed on the Hyalite High Performance Computing System at MSU. Support from the NSF (DBI-1532078/CHE-2018388) and Murdock Charitable Trust Foundation (2015066:MNL) provided funds for the 400 and 500 MHz NMR spectrometers used in this research.

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