OL | Organic Letters

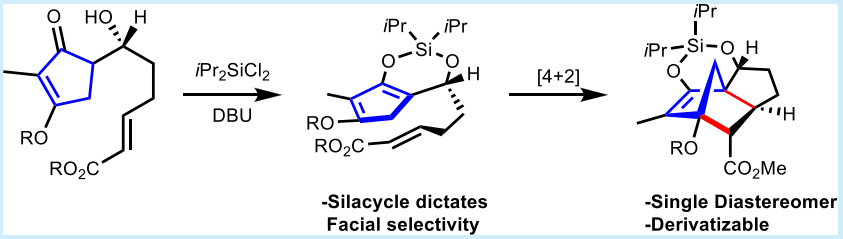
pubs.acs.org/OrgLett Letter

Silacycle-Templated Intramolecular Diels–Alder Cyclizations for the Diastereoselective Construction of Complex Carbon Skeletons

Paul R. Carlson, Alexander S. Burns, Emily A. Shimizu, Shilin Wang, and Scott D. Rychnovsky*

Cite This: *Org. Lett.* 2021, 23, 2183–2188 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: The utility of the dioxasiline ring as a π-facial directing group in the intramolecular Diels–Alder cyclization is explored. An initial investigation of substrate scope demonstrates that the rigidity of this directing group delivers robust stereocontrol across a number of substrates, affording single diastereomers in moderate to good yields. A mechanistic investigation reveals that the reactive diene is formed through γ deprotonation followed by [1,5] hydride shifts.

The intramolecular Diels–Alder (IMDA) cyclization has proven to be one of the most powerful tools in the synthetic chemist's arsenal for the rapid construction of molecular complexity. Its high degrees of diastereoselectivity and regioselectivity have made it a key disconnection in a number of notable total syntheses.[1,2] While the primary strength of the IMDA reaction lies in its easily predictable stereocontrol over multiple centers, there are certain aspects of IMDA stereocontrol that remain challenging. For example, the typical endo selectivity that can be predicted for an intermolecular Diels–Alder cyclization based on electronic factors is less certain in the intramolecular domain, especially for complex intermediates in total synthesis, as more steric and torsional factors come into play.[3−6] The most prominent selectivity challenge for structurally complex IMDA cyclizations is that of π-facial selectivity, i.e., the face of the diene over which the dienophile approaches. In the construction of complex carbon skeletons, π-facial selectivity is crucial in attaining the desired diastereomer, and as such, a number of investigations have been dedicated to understanding the π-facial selectivity of the Diels–Alder reaction in a variety of specialized systems.[7−11]

A common strategy for approaching the problem of π-facial selectivity in the IMDA reaction is to install a directing group to bias the approach of the dienophile to the desired face. For example, Boeckman and co-workers have used an alkyl trimethylsilane as a directing group for the construction of hydrindene and octalin scaffolds through an IMDA reaction.[12] This strategy makes use of $A_{1,3}$ strain with the bulky silane to bias one facial approach over the other (Scheme 1a). In an alternate strategy, Roush and Halvorsen have performed an IMDA reaction in which the dienophile is bound as part of a siloxacyclopentene. As a result, the two faces of the dienophile are sterically differentiated, leading to the observed π-facial selectivity (Scheme 1b).[13]

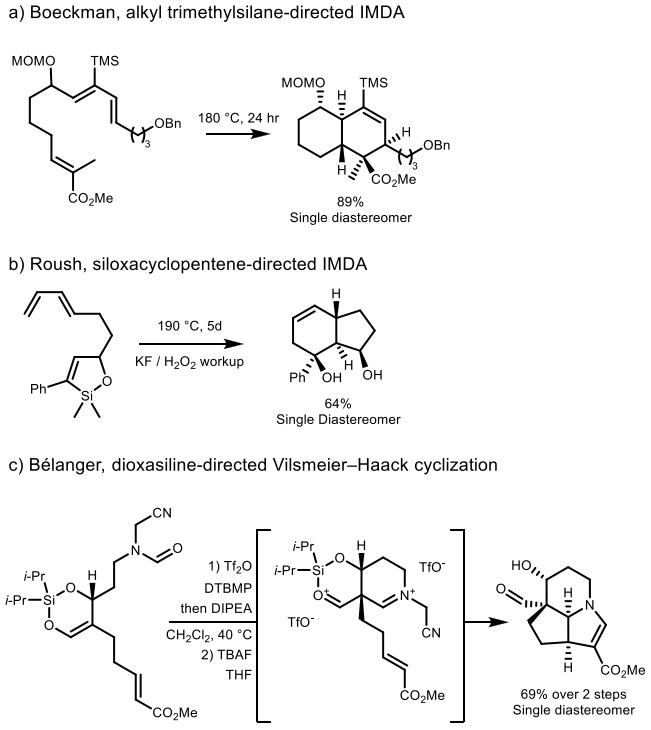
The inspiration for the strategy presented herein originated from the work of Bélanger in which, similar to Roush's siloxacyclopentene work, the rigidity of a dioxasiline ring was used to direct the facial selectivity of an intramolecular Vilsmeier–Haack cyclization (Scheme 1c).[14] Following this initial silacycle-directed cyclization, a subsequent azomethine ylide 1,3 dipolar cycloaddition followed by cleavage of the silyl group afforded the desired tricyclic core as a single diastereomer.

Through a similar strategy, our group has recently found success in directing π-facial selectivity in the IMDA reaction of **A** to construct complex tricycle **D** en route to illisimonin A (Scheme 2).[15] Similar to the work of Bélanger, π-facial selectivity was achieved using a dioxasiline ring as a directing group. The *in situ* formation of the dioxasiline served the secondary purpose of forming the reactive Danishefsky-like diene found in **B** for the IMDA addition.[16] The rigidity of the silacycle enforced the desired π-facial selectivity, affording **D** as a single diastereomer after an HF workup.

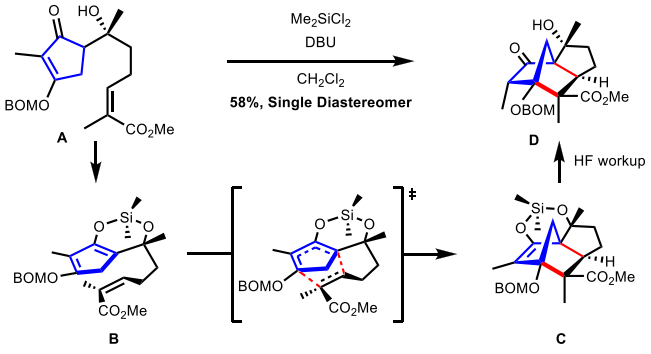
Received: January 28, 2021
Published: February 26, 2021

https://dx.doi.org/10.1021/acs.orglett.1c00340
Org. Lett. 2021, 23, 2183–2188

Scheme 1. Relevant Directing Group Strategies



Scheme 2. Strategy for π-Facial Control in the Synthesis of Illisimonin A

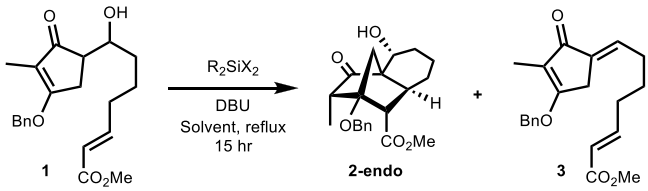


While individual cases of silacycles directing[13] and initiating[17] an IMDA cyclization have been reported, there is no precedent, to the best of our knowledge, for taking advantage of both features simultaneously beyond our own work on illisimonin A. Furthermore, given the skeletal complexity and number of stereocenters that this directing group delivered in **D**, it is evident that the full potential of the dioxasiline in IMDA cyclizations remains underdeveloped. As such, we sought to develop our IMDA silacycle directing strategy into a general method for accessing complex carbon skeletons.

Some of the promising advantages of this method are as follows. It allows for complete control of up to six stereocenters, as highlighted by the formation of **D**. Furthermore, the starting materials bear a β-hydroxy carbonyl oxidation pattern, allowing for their straightforward preparation through a strategic aldol disconnection. Such an aldol addition does not need to be *syn*/*anti* selective, as the configuration at the α-carbon is typically ablated in the course of the reaction, allowing for *syn*/*anti* mixtures to be employed without separation. The silacycle directing group is installed *in situ* and can be removed with a simple HF workup, adding no steps to the synthetic sequence. Finally, should a milder workup be chosen to preserve the silacycle and yield a product analogous to **C**, the resulting silyl enol ether is a highly versatile synthon that allows for further derivatization of the Diels–Alder adducts.[18−22]

We began developing our initial success with illisimonin A into a broader method with an optimization study. The model substrate chosen for optimization was **1** (Table 1), mainly for its greater synthetic accessibility compared to that of the original illisimonin substrate **A**. The major differences in this new substrate are in the olefin geometry of the dienophile, the substitution at the alcohol center, and the identity of the vinylogous ester protecting group.

Table 1. Reaction Optimization



entry	R	X	solvent	temp (°C)	yield of **2**[a]	yield of **3**[a]
1	Me	Cl	CH_2Cl_2	40	40	–
2	*t*Bu	Cl	CH_2Cl_2	40	–	–
3	*t*Bu	OTf	CH_2Cl_2	40	30	9
4	Ph	Cl	CH_2Cl_2	40	65	9
5	Ph	Cl	$ClCH_2CH_2Cl$	80	60	–
6	***i*Pr**	**Cl**	**CH_2Cl_2**	**40**	**92**	–
7	*i*Pr	Cl	$ClCH_2CH_2Cl$	80	78	–
8	*i*Pr	OTf	CH_2Cl_2	40	82	–
9	*i*Pr	OTf	$ClCH_2CH_2Cl$	80	76	10

[a]As determined by ^{1}H NMR using 0.5 equiv of 5,6-dibromobenzo-(1,3)dioxole as an internal standard.

In previous studies as part of our synthesis of illisimonin A, the identity of the base was found to be crucial for this reaction to proceed; thus, optimization focused on the identity of the bis-electrophilic silane and the reaction solvent and temperature. Seeing as the original conditions employing the sterically unencumbered dimethyldichlorosilane gave a poor yield with our model substrate (Table 1, entry 1), we next employed a much bulkier silane (entries 2 and 3). However, neither of these *tert*-butylsilanes showed improvement over entry 1, with the first returning starting material and the second giving an unimpressive NMR yield along with competing elimination to form **3**. Next, we turned to a silane of a more intermediate steric bulk (entries 4 and 5). This diphenyldichlorosilane showed a promising increase in yield, which an increased reaction temperature failed to improve further. Finally, we discovered that diisopropyl dichlorosilane gave a much improved 92% NMR yield (entry 6). Neither an increased reaction temperature (entry 7) nor the corresponding silyl ditriflate (entries 8 and 9) further improved the results of entry 6.

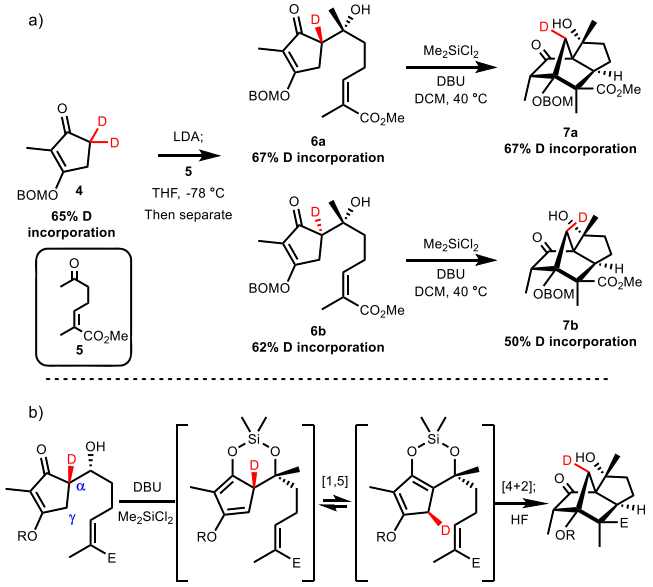
Next, we sought to elucidate the mechanism of this reaction. Although **B** (Scheme 2), which ultimately engages in the observed cycloaddition, would be the direct result of deprotonation at the α-position of **A**, it could also result

https://dx.doi.org/10.1021/acs.orglett.1c00340
Org. Lett. 2021, 23, 2183−2188

from an alternative mechanism involving deprotonation at the γ-carbon of **A** followed by facile [1,5] hydride shifts.[23,24]

To elucidate which of these two plausible pathways was operative in the case of the formation of **D**, we sought to access **6a** and **6b**, deuterated versions of our original system **A** (Scheme 3a). If α-deprotonation were the operative mechanism for the formation of the reactive diene, then when **6a** or **6b** was subjected to the standard IMDA conditions, the deuterium atom would be removed, yielding fully protiated product **D**. Alternatively, if γ-deprotonation were the operative mechanism, then when **6a** or **6b** was subjected to the standard IMDA conditions, the deuterium atom would be retained after initial deprotonation, after which it would engage in a [1,5] sigmatropic shift to generate the reactive diene, leaving it at the γ-position in the final Diels–Alder product (Scheme 3b). Finally, should both α- and γ-deprotonation compete in some ratio, we reasoned that the approximate ratio could be deduced from the extent of deuterium enrichment lost.

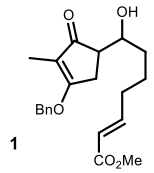
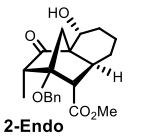
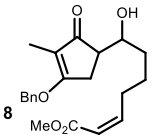
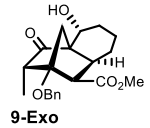
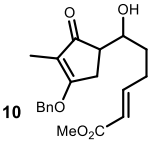
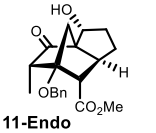
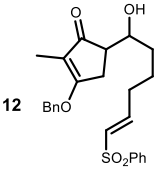
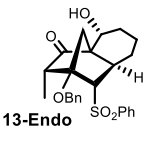
Scheme 3. Deuterium Labeling Study



The synthesis of **6a** and **6b** began with **4**, which was synthesized from the protiated analogue through two rounds of LDA deprotonation followed by an ethanol-d_6 quench, giving moderate deuterium incorporation (65%) at the α-carbon. Vinylogous ester **4** underwent an aldol addition with aldehyde **5** to afford diastereomers **6a** and **6b** with good deuterium retention (67% and 62%, respectively).

Subjecting **6a** and **6b** to our original IMDA conditions gave **7a** and **7b**, respectively, with near-quantitative deuterium migration to the γ-position (67% and 50% incorporation, respectively). Furthermore, deuterium migration was diastereospecific, with each aldol diastereomer yielding a unique epimer at the deuterated carbon.

The high degree of deuterium retention in this experiment provides compelling evidence that the mechanism of formation for the reactive diene proceeds primarily through γ-deprotonation. On the basis of the small deuterium loss from **6b** to **7b**, we can reason that <20% of this material undergoes an α-deprotonation mechanism. For conversion of

entry	substrate	product	yield	$\Delta\Delta G^{\ddagger}$ (Kcal/mol)
1			70%	9.70
2			77%	-6.98
3			56%	6.39
4			54%	10.17

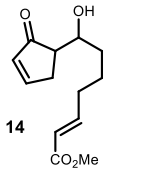
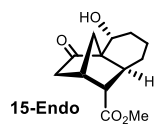
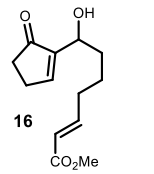
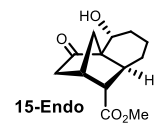
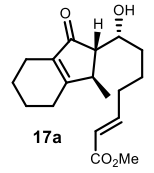
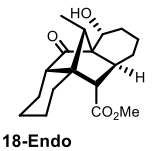
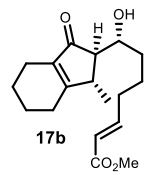
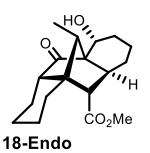
entry	substrate	product	yield	$\Delta\Delta G^{\ddagger}$ (Kcal/mol)
5			46%	9.02
6			38%	9.02
7			65%	6.32
8			45%	6.32

Figure 1. Substrate scope of the silacycle-templated IMDA reaction. Standard conditions include $i\mathrm{Pr_2SiCl_2}$ (2 equiv), DBU (6 equiv), dry $\mathrm{CH_2Cl_2}$, 0–40 °C, and 16 h. Calculated values of $\Delta G^{\ddagger}_{exo} - \Delta G^{\ddagger}_{endo}$ using ωB97xd/6-311G(d,p)//ωB97xd/6-31G(d) for each substrate are presented. Entries 5–8 were run in dry $\mathrm{Cl_2CH_2CH_2Cl_2}$ from 0 to 80 °C.

https://dx.doi.org/10.1021/acs.orglett.1c00340
Org. Lett. 2021, 23, 2183–2188

6a to **7a**, quantitative deuterium retention suggests that γ-deprotonation is the sole mechanism involved. Furthermore, the diastereospecific nature of the deuterium migration between the two diastereomers strongly suggests that the migration occurs via a suprafacial [1,5] sigmatropic shift, leaving the γ-deprotonation route (Scheme 3b) as the most plausible mechanism.

Our investigation of the substrate scope of our silacycle-templated IMDA strategy began with some simple modifications to the original system. First, we report our model substrate **1** from the optimization study (Figure 1, entry 1). The desired IMDA proceeded in good recovered yield, albeit less than our measured NMR yield from Table 1. Nonetheless, this entry demonstrates that an extension of the dienophile-bearing chain by one methylene unit can efficiently deliver a cyclohexyl-fused norbornane skeleton. Exclusive exo selectivity was achieved from **8**, which bears a *Z* olefin geometry at the dienophile (entry 2). Entry 3 catalogues an endo selective IMDA to afford a cyclopentene-fused norbornane scaffold. Finally, in entry 4, a vinyl sulfone proves to be a competent dienophile for this reaction, furnishing the corresponding norbornane in moderate yield. Attempts to expand this methodology to six-membered vinylogous esters have thus far proven unsuccessful, as elimination of the β-alcohol outcompetes the desired Diels–Alder reaction for these substrates. A detailed table of failed substrates can be found in the Supporting Information.

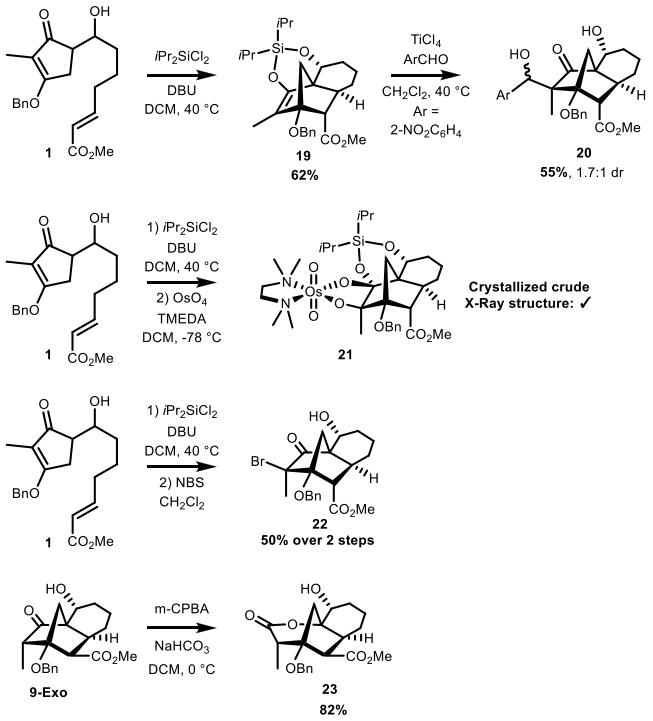
Next, we probed more challenging changes to our system using substrates that no longer benefit from being highly activated, Danishefsky-like dienes. It is worth noting that these substrates required increased temperatures (80 °C in $ClCH_2CH_2Cl$) to reach full conversion, likely as a result of the lower HOMO energy of the diene. Replacing the cyclic vinylogous ester of previous substrates with the simple cyclopentenone in **14** (entry 5) afforded simple norbornane **15-endo** in moderate yield. The decrease in yield as compared to those of the more activated substrates is attributed to a competing elimination of the alcohol to afford a product analogous to **3**. Interestingly, **16**, the constitutional isomer of **14** (entry 6), also afforded **15-endo**, albeit in low yield. Presumably, this convergence is possible as the result of [1,5] hydride shifts allowing the silacycle intermediate of **16** to sample all possible reactive dienes for the IMDA. It is worth noting that substrates such as **16** can be derived from a strategic Baylis–Hillman disconnection. This outcome highlights a practical use of the conclusions drawn from our mechanistic study.

Finally, entries 7 and 8 present an intriguing mechanistic case. We initially probed these two substrates anticipating that their respective Diels–Alder adducts would be epimeric at the methylene bridge. However, we were surprised to find that both **17a** and **17b** afforded **19** in moderate yield.[25] One possible explanation for this outcome arises from regioselective deprotonations of the different diastereomers. If ketone **17a** were to exclusively undergo an α-deprotonation pathway and ketone **17b** were to exclusively go through γ-deprotonation, then, after [1,5] hydride shifts, the same diene would be produced in both cases, which would lead to the observed product **19**. Such a result would not necessarily be at odds with our mechanistic study given that the additional substitution at the γ-position may lead to a deprotonation preference different from that observed in Scheme 3.

The IMDA reactions presented herein were modeled using DFT calculations. For each substrate, the transition state was identified for the endo and exo product, and the geometries and energies for starting materials and products were determined. (The Bn group was replaced by Me in entries 1–4.) For compound **1**, the activation energy for the endo transition state was 17.05 kcal/mol, and the preference for the endo transition state was 9.70 kcal/mol with respect to the exo TS. The activation energies for the transition states ranged from 17 to 21 kcal/mol. The preference for the observed transition state (endo or exo) is included in Table 1 for each entry, and full details of the calculations are reported in the Supporting Information.

Finally, we sought to explore synthetically useful derivatizations of the products of our silacycle-templated IMDA cyclizations. To this end, it was desirable to isolate the silyl enol ether intermediate analogous to **C**, as this functional group is a synthon for a number of useful transformations. Gratifyingly, upon replacement of the typical HF workup with a mild aqueous workup, silacycle-containing Diels–Alder adduct **19** was isolated in 62% yield (Scheme 4). This silyl

Scheme 4. Product Derivatizations



enol ether was subsequently employed in a Mukaiyama aldol reaction that successfully forged an all-carbon quaternary center and afforded **20** in moderate yield as a mixture of diastereomers. Less sensitive reactions allowed **19** to be taken forward without purification, avoiding any hydrolysis of this sensitive functional group that may occur in the course of silica gel chromatography. For example, crude **19** was successfully derivatized as osmate ester **21**, allowing for X-ray crystallographic analysis to confirm our assigned relative configuration (Figure 2).[26−28] Additionally, crude **19** was brominated to afford tertiary bromide **22** in 50% yield over two steps. Finally, to target carbon skeletons beyond the cyclopentyl- and cyclohexyl-fused norbornanes explored thus far, a Baeyer–

https://dx.doi.org/10.1021/acs.orglett.1c00340
Org. Lett. 2021, 23, 2183−2188

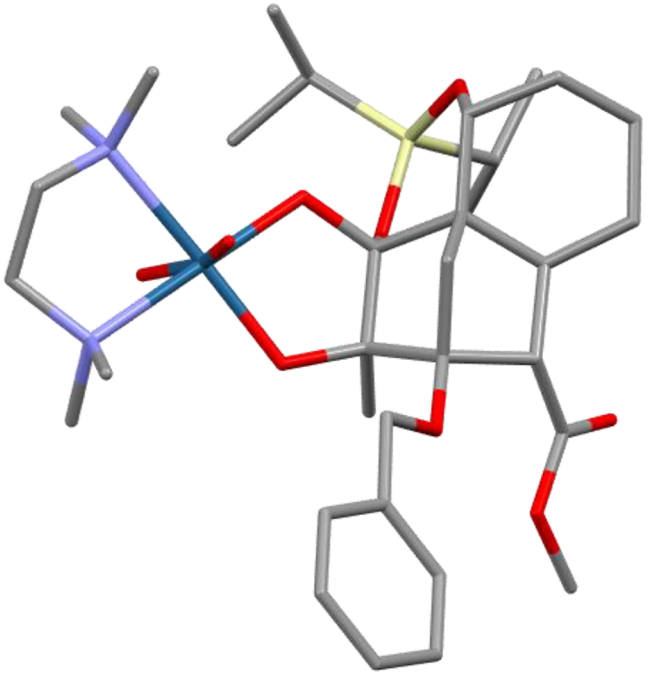


Figure 2. X-ray structure of osmate ester **21**.

Villiger oxidation was performed on **9-exo** to afford lactone **23** in good yield.[29]

We have demonstrated that a dioxasiline ring serves as an effective directing group for the control of π-facial selectivity in IMDA cyclizations while serving the dual function of forming the reactive diene. Using this highly diastereoselective strategy, we have successfully set up to seven stereocenters in a single reaction. This directing group is easily installed *in situ* and may be removed with an HF workup or otherwise preserved as a silyl enol ether. This silyl enol ether serves as a useful functional handle for further manipulations. Finally, we have elucidated an interesting mechanism involving γ-deprotonation followed by a [1,5] hydride shift to form the reactive diene.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00340.

Experimental procedures, characterization data, X-ray crystallographic data for **21**, computational details, and related NMR spectra for new compounds (PDF)

Accession Codes

CCDC 2059469 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Scott D. Rychnovsky − *Department of Chemistry, University of California at Irvine, Irvine, California 92697, United States;* orcid.org/0000-0002-7223-4389; Email: srychnov@uci.edu

Authors

Paul R. Carlson − *Department of Chemistry, University of California at Irvine, Irvine, California 92697, United States*

Alexander S. Burns − *Department of Chemistry, University of California at Irvine, Irvine, California 92697, United States*

Emily A. Shimizu − *Department of Chemistry, University of California at Irvine, Irvine, California 92697, United States*

Shilin Wang − *Department of Chemistry, University of California at Irvine, Irvine, California 92697, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00340

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Erdwin Orellana [University of California at Irvine (UCI)] for an initial investigation into the substrate scope of this transformation. The authors thank Dr. Joe Ziller (UCI) for determining the X-ray structure of osmate **21**. The National Science Foundation (CHE 1764380) provided support.

■ REFERENCES

(1) Takao, K. I.; Munakata, R.; Tadano, K. I. Recent Advances in Natural Product Synthesis by Using Intramolecular Diels−Alder Reactions. *Chem. Rev.* **2005**, *105*, 4779−4807.

(2) Juhl, M.; Tanner, D. Recent Applications of Intramolecular Diels−Alder Reactions to Natural Product Synthesis. *Chem. Soc. Rev.* **2009**, *38*, 2983−2992.

(3) Roush, W. R.; Gillis, H. R.; Ko, A. I. Stereochemical Aspects of the Intramolecular Diels−Alder Reactions of Deca-2,7,9-Trienoate Esters. 3. Thermal, Lewis Acid Catalyzed, and Asymmetric Cyclizations. *J. Am. Chem. Soc.* **1982**, *104*, 2269−2283.

(4) Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. Total Synthesis of Norzoanthamine. *Science* **2004**, *305*, 495−499.

(5) Snider, B. B.; Che, Q. Synthesis of (±)-Deoxysymbioimine Using an Intramolecular Diels−Alder Reaction with an *N*-Alkoxycarbonyl 2,3-Dihydropyridinium Cation as the Dienophile. *Angew. Chem., Int. Ed.* **2006**, *45*, 932−935.

(6) Jones, G. A.; Paddon-Row, M. N.; Sherburn, M. S.; Turner, C. I. On the Endo/Exo Stereoselectivity of Intramolecular Diels−Alder Reactions of Hexadienylacrylates: An Interesting Failure of Density Functional Theory. *Org. Lett.* **2002**, *4*, 3789−3792.

(7) Yadav, V. K.; Senthil, G.; Babu, K. G.; Parvez, M.; Reid, J. L. Heteroatom Influence on the π-Facial Selectivity of Diels−Alder Cycloadditions to 1-Oxa-4-Thia-6-Vinylspiro[4.5]Dec-6-Ene, 3-Methoxy-3-Methyl-2-Vinylcyclohexene, and 3-Methoxy-2-Vinylcyclohexene. *J. Org. Chem.* **2002**, *67*, 1109−1117.

(8) Letourneau, J. E.; Wellman, M. A.; Burnell, D. J. Diels−Alder Reactions of 5-Alkyl-1,3-Cyclopentadienes. *J. Org. Chem.* **1997**, *62*, 7272−7277.

(9) Wellman, M. A.; Burry, L. C.; Letourneau, J. E.; Bridson, J. N.; Miller, D. O.; Burnell, D. J. Facial Selectivity in the Diels−Alder Reactions of 5-Chloro-, 5-Bromo-, and 5-Iodo-1,3-Cyclopentadiene and Derivatives. *J. Org. Chem.* **1997**, *62*, 939−946.

(10) Crisp, G. T.; Gebauer, M. G. Diels−Alder Reactions of Chiral 1,3-Dienes. *J. Org. Chem.* **1996**, *61*, 8425−8431.

(11) Kahn, S. D.; Fisher, M. J.; Hehre, W. J.; Overman, L. E. Face Selectivity in Diels−Alder Reactions of Chiral Dienes Containing Allylic Substituents. *J. Am. Chem. Soc.* **1988**, *110*, 4625−4633.

(12) Boeckman, R. K.; Barta, T. E. Stereocontrol in the Intramolecular Diels−Alder Reaction. 7. Use of the Trimethylsilyl Group as a Removable Stereocontrol Element To Provide Greatly Enhanced Levels of Diastereoselection. *J. Org. Chem.* **1985**, *50*, 3421−3423.

(13) Halvorsen, G. T.; Roush, W. R. Siloxacyclopentenes as Dienophile-Linked Directing Groups in Intramolecular Diels−Alder Reactions. *Org. Lett.* **2008**, *10*, 5313−5316.
(14) Boissarie, P.; Bélanger, G. Short Approach toward the Nonracemic A,B,E Tricyclic Core of Calyciphylline B-Type Alkaloids. *Org. Lett.* **2017**, *19*, 3739−3742.
(15) Burns, A. S.; Rychnovsky, S. D. Total Synthesis and Structure Revision of (−)-Illisimonin A, a Neuroprotective Sesquiterpenoid from the Fruits of *Illicium simonsii*. *J. Am. Chem. Soc.* **2019**, *141*, 13295−13300.
(16) Danishefsky, S.; Kitahara, T. A Useful Diene for the Diels−Alder Reaction. *J. Am. Chem. Soc.* **1974**, *96*, 7807−7808.
(17) Akai, S.; Tsujino, T.; Fukuda, N.; Iio, K.; Takeda, Y.; Kawaguchi, K. I.; Naka, T.; Higuchi, K.; Akiyama, E.; Fujioka, H.; Kita, Y. Asymmetric Total Synthesis of Fredericamycin A: An Intramolecular Cycloaddition Pathway. *Chem. - Eur. J.* **2005**, *11*, 6286−6297.
(18) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. Peracid Oxidation of Trimethylsilyl Enol Ethers: A Facile α-Hydroxylation Procedure. *Tetrahedron Lett.* **1974**, *15*, 4319−4322.
(19) Mukaiyama, T.; Banno, K.; Narasaka, K. New Cross-Aldol Reactions. Reactions of Silyl Enol Ethers with Carbonyl Compounds Activated by Titanium Tetrachloride. *J. Am. Chem. Soc.* **1974**, *96*, 7503−7509.
(20) Ito, Y.; Hirao, T.; Saegusa, T. Synthesis of α, β-Unsaturated Carbonyl Compounds by Palladium(II)-Catalyzed Dehydrosilylation of Silyl Enol Ethers. *J. Org. Chem.* **1978**, *43*, 1011−1013.
(21) Reuss, R. H.; Hassner, A. Halogenation of Carbonyl Compounds via Silyl Enol Ethers. *J. Org. Chem.* **1974**, *39*, 1785−1787.
(22) Hillers, S.; Niklaus, A.; Reiser, O. Ozonolysis of Cyclic Enol Ethers: An Efficient Strategy to Aldol and Homoaldol Compounds. *J. Org. Chem.* **1993**, *58*, 3169−3171.
(23) Hess, B. A.; Baldwin, J. E. [1,5] Sigmatropic Hydrogen Shifts in Cyclic 1,3-Dienes. *J. Org. Chem.* **2002**, *67*, 6025−6033.
(24) Stille, J. R.; Grubbs, R. H. Intramolecular Diels−Alder Reaction of α,β-Unsaturated Ester Dienophiles With Cyclopentadiene and the Dependence on Tether Length. *J. Org. Chem.* **1989**, *54*, 434−444.
(25) A reviewer has brought to our attention that an alternative γ-deprotonation at the cyclohexane moeity is possible for **17a** and **17b**, which would lead to a nonreactive diene and possibly decrease the reaction efficiency.
(26) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. Directed Dihydroxylation of Cyclic Allylic Alcohols and Trichloroacetamides Using OsO_4/TMEDA. *J. Org. Chem.* **2002**, *67*, 7946−7956.
(27) Burns, A. S.; Dooley, C.; Carlson, P. R.; Ziller, J. W.; Rychnovsky, S. D. Relative and Absolute Structure Assignments of Alkenes Using Crystalline Osmate Derivatives for X-Ray Analysis. *Org. Lett.* **2019**, *21*, 10125−10129.
(28) CCDC deposition number for osmate **21**: 2059469.
(29) Another derivitization technique that we explored was the epimerization of our products at the α-position to allow for further stereocontrol. However, we found that subjecting **11-endo** to K_2CO_3/MeOH resulted only in a retro-Michael addition.

https://dx.doi.org/10.1021/acs.orglett.1c00340
Org. Lett. 2021, 23, 2183−2188