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Construction of Cyclopentanol Derivatives via Three-Component Coupling of Silyl Glyoxylates, Acetylides, and Nitroalkenes

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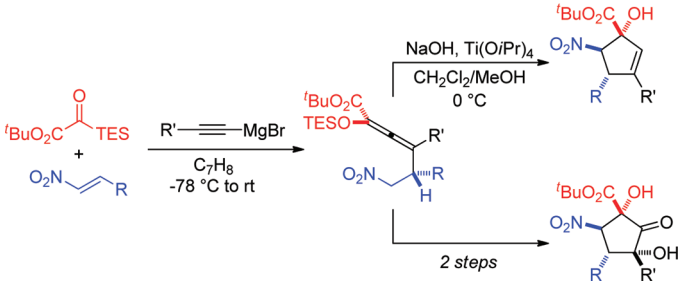
ABSTRACT



The three-component coupling of Mg acetylides, silyl glyoxylates, and nitroalkenes results in a highly diastereoselective Kuwajima–Reich/vinylogous Michael cascade that provides tetrasubstituted silyloxyallene products. The regio- and diastereoselectivity were studied using DFT calculations. These silyloxyallenes were converted to cyclopentenols and cyclopentitols via a unique Lewis acid assisted Henry cyclization. The alkene functionality present in the cyclopentanol products can be elaborated using diastereoselective ketohydroxylation reactions.

The efficient synthesis of densely functionalized cyclopentane derivatives remains an important task due to the ubiquity of this structure in Nature. Cyclopentitols, polyhydroxylated cyclopentanes,[1] are of particular significance because of their presence in a variety of medicinally relevant natural products such as trehazolin,[2] pactamycin,[3] and ryanodine.[4] Additionally, cyclopentenols are important because of their presence in numerous biologically active targets such as pentenomycin,[5] monotropein,[6] and a variety of carbanucleosides such as (−)-neplanocin A and related analogues.[1] Although there are known processes for synthesizing various cyclopentanol derivatives, efficient methodologies that deliver functional group rich cyclopentanols from simple starting materials would be welcome additions to the synthetic toolbox.[1c] Herein are reported details for the diastereoselective synthesis of densely functionalized cyclopentanol derivatives utilizing tetrasubstituted silyloxyallene intermediates. The latter are prepared via a diastereoselective three-component coupling of silyl glyoxylates, magnesium acetylides, and nitroalkenes via an alkynylation-initiated Kuwajima–Reich rearrangement[7]/vinylogous Michael cascade.

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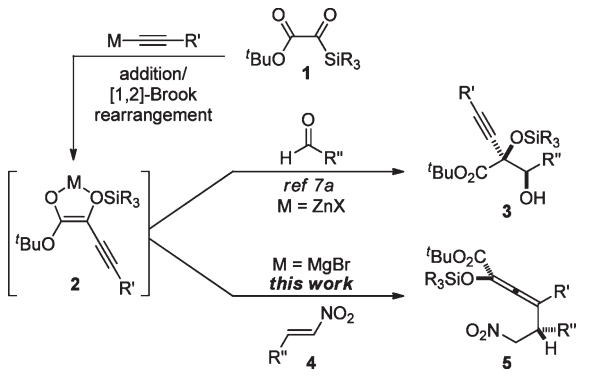
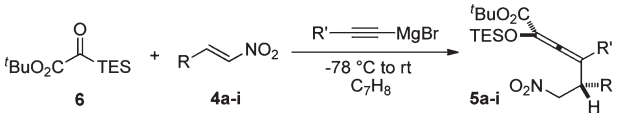
Scheme 1. Acetylide-Initiated Cascade of Silyl Glyoxylates



Silyl glyoxylates have emerged as a reliable class of conjunctive reagents for the union of nucleophilic and electrophilic partners.[8] The three-component coupling of silyl glyoxylates, acetylide nucleophiles, and aldehyde secondary electrophiles provides the α-adduct **3** (Scheme 1).[8b] More recently, the chemistry of silyl glyoxylates has been expanded to include vinylogous Michael addition as a viable pathway.[8e] This manifold emerged from the reaction of vinyl Grignard and a silyl glyoxylate, leading to in situ metallodienolate generation and subsequent trapping by a nitroalkene as the terminal vinylogous Michael acceptor. In contemplating other reagent combinations that could trigger γ-reactivity to complement extant α-trapping, a proposal for a new reaction emerged. Addition of an acetylide nucleophile to **1** would provide an α-alkoxypropargyl silane, triggering a Kuwajima–Reich rearrangement driven in part by the presence of the electron-withdrawing ester functionality; the (*Z*)-glycolate enolate[8d] **2** would result. An electrophilic alkene like **4** could engage the presumed transient secondary nucleophile **2** through the π-system in a vinylogous Michael fashion to provide 5-nitrosilyloxyallenes **5**. These heretofore unknown nitrosilyloxyallene substances appear poised for interesting subsequent transformations.

Allenes are a versatile and unique class of compounds with a reactivity profile distinct from simple alkenes.[9] Silyloxyallenes are a subset class that have found utility in α-functionalization reactions[7,10] and as a precursor for numerous cycloadditions including [3 + 2],[11a] [4 + 2],[10b,11b] and [5 + 3][11c] cyclizations. Other methods for the synthesis of silyloxyallenes exist,[12] but the Kuwajima–Reich rearrangement is especially convenient and flexible. The latter occurs when α-hydroxypropargyl silanes undergo a [1,2]-Brook rearrangement[13] in the presence of base and engage a secondary electrophile in a vinylogous fashion; excellent γ-selectivity has been demonstrated for a variety of electrophiles such as alkyl halides, disulfides, H^+, and DMF.[7] Most relevant to the present work is the precedent that 1-silyloxyallen-3-ylcopper reagents generated by lithiation and transmetalation of silyloxyallenes undergo conjugate additions with enones.[14]

Table 1. Substrate Scope for Three-Component Coupling



product	R	R′	yield (%)	dr
5a	Ph	Me	83	>20:1
5b	2-thienyl	Me	77	>20:1
5c	2-furyl	Me	67	>20:1
5d	C_5H_{11}	Me	42	>20:1
5e	*i*-Pr	Me	56	>20:1
5f	Ph	Ph	77	>20:1
5g	Ph	C_5H_{11}	71	>20:1
5h	Ph	*i*-propenyl	76	>20:1
5i	Ph	TMS	39	>20:1

Initial experiments with triethylsilyl glyoxylate **6**, β-nitrostyrene, and commercially available 1-propynylmagnesium bromide at −78 °C provided the three-component coupling product **5a** in 83% yield. Consistent with other silyl glyoxylate chemistry, a 50% excess of triethylsilyl glyoxylate and alkynyl nucleophile were required to compensate for the competing silyl glyoxylate oligomerization pathway.[7e] The silyloxyallene product was formed with greater than 20:1 diastereoselection. The identity of the predominant diastereomer was determined by an X-ray diffraction study on the triisopropylsilyloxyallene homologue.[15]

An examination of various alkyl, aryl, and heteroaryl nitroalkenes was conducted with the results compiled in

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(13) Brook, A. G. *Acc. Chem. Res*. **1974**, *7*, 77–84.

(14) Matsuoka, R.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett*. **1987**, *28*, 1299–1302.

(15) CCDC 827440 (**5a-TIPS**) and CCDC 830724 (**8a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 1. The yields ranged from 42 to 83% with aryl and heteroaryl nitroalkenes outperforming the alkyl substrates when 1-propynylmagnesium bromide was used as the nucleophilic partner (**5a**–**e**). The identity of the alkynyl Grignard was also investigated with the yields ranging from 39 to 77% for substituted alkynes when β-nitrostyrene was employed as the secondary electrophile (**5f**–**i**). The alkyl, alkenyl, and aryl examples all provided very good yields (> 70%), while the trimethylsilyl acetylide provided a significantly lower yield (39%) This diminished yield is likely a function of the added steric bulk from the TMS group. The permutations tested all provided greater than 20:1 diastereoselection.

Given the excellent diastereo- and regioselectivity observed in this three-component coupling, the reaction was further investigated through a quantum mechanical evaluation of the intermediates and transition states using the density functional theory (DFT) approach at the level of B3LYP/6-311G(d).[16] We felt this could be a fruitful endeavor since the vinylogous Michael reaction has rarely been studied computationally.[17]

A (*Z*)-glycolate enolate (e.g., **2**) is the kinetic product in the 1,2-Brook rearrangement of silyl glyoxylates due to FMO constraints,[8d] however, since the geometric isomerization is possible in certain cases,[8c] an assessment of the thermodynamic stabilities of the other candidate intermediates appeared warranted. The calculations confirmed that the (*Z*)-glycolate enolate is the thermodynamic product relative to the (*E*)-glycolate enolate or the allenyl anion,[18] indicating that the (*Z*)-glycolate enolate should still predominate even if a mechanism for equilibration existed. Proceeding on the presumed intermediacy of the (*Z*)-glycolate enolate **2**, the transition states for the formation of both potential diastereomers were optimized. The barrier height between the two optimized transition states corresponds to a 3.0 kcal/mol difference in favor of **TS1**, a finding that is consistent with the experimental results and the identity of the major isomer. The key distinction between the two transition states is the nature of the interaction between the nitro group and the (*Z*)-glycolate enolate. In **TS1**, the nitro functionality acts as a chelating group[19] with the MgBr cation, while **TS2** exhibits monodentate nitro/MgBr binding as illustrated in Figure 1.

Based on this theoretical analysis, the regioselectivity hinges on bidentate coordination of the nitro group that provides favorable overlap of the electrophilic center of the nitroalkene with the γ-position of the nucleophile. No productive overlap is possible at the α-center. **TS1** accounts

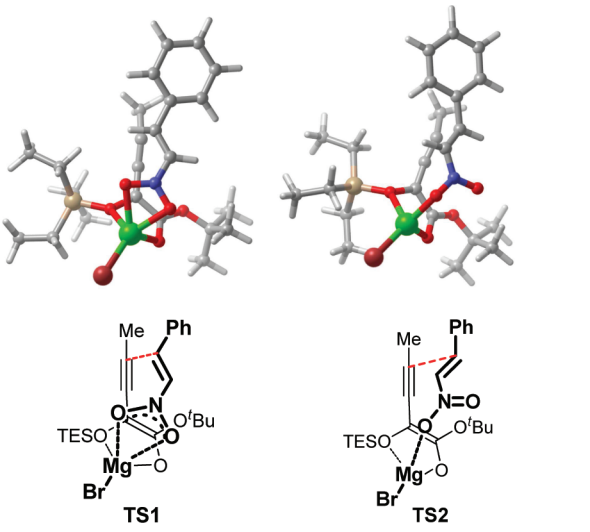
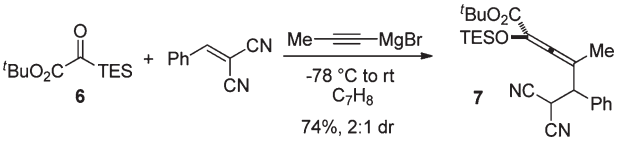


Figure 1. DFT-optimized transition states.

for the high diastereoselectivity via the fixed approach of the nitroalkene with respect to the (*Z*)-glycolate enolate. The C–N bond rotamers of the nitroalkene (180°) would have negligible overlap with the α- or γ-centers of the nucleophile, resulting in no reactivity for these conformations.

To experimentally interrogate the validity of **TS1**, a suitable electrophilic species was sought that would enter into the same reaction manifold, but be incapable of chelation. Benzylidenemalononitrile emerged as a reasonable candidate under these criteria. Exposing the α, α-dicyanoolefin to the reaction conditions provided the desired vinylogous adduct **7** in a 74% yield and a 2:1 diastereoselectivity as illustrated in Scheme 3. The poor diastereoselection is congruent with the importance of the chelating nitro group as well as the qualitative applicability of the theoretical studies. The success of the benzylidenemalononitrile electrophile moreover argues against an alternative mechanism for the formation of **5** involving α-addition of **2** to $\pi^*_{N=O}$ followed by [3,3]-sigmatropic rearrangement.[20]

Scheme 3. α,α-Dicyanoolefin-Terminated Three-Component Coupling



In addition to the many known transformations of allenes, we hypothesized that these 5-nitrosilyloxyallenes would be poised to undergo Henry cyclization[21] by

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(18) See the Supporting Information for a computational analysis of the three possible isomers of the secondary nucleophile.

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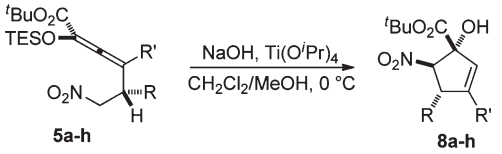
(21) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915–945.

utilizing these substrates as latent tethered nitroketones. Subjecting the silyloxyallene **5a** to the deprotection/Henry cyclization conditions of sodium hydroxide in a mixture of dichloromethane and methanol provided no desired product.[8e] Gratifyingly, the addition of a substoichiometric amount of titanium(IV) isopropoxide to the reaction enabled the formation of **8a** in 75% yield and greater than 20:1 diastereoselection. The identity of the predominant diastereomer was determined by NOESY analysis and confirmed through an X-ray diffraction study of **8a**.[15] The precise role of the titanium(IV) isopropoxide remains unidentified, but the Lewis acid assisted Henry cyclization provides an excellent synthetic handle for further elaboration at C4 and C5 due to the preservation of the olefin.

Table 2. Substrate Scope for Lewis Acid Assisted Henry Cyclization



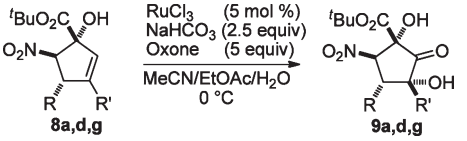
product	R	R′	yield (%)	dr
8a	Ph	Me	75	>20:1
8b	2-thienyl	Me	86	>20:1
8c	2-furyl	Me	60	>20:1
8d	C_5H_{11}	Me	57	>20:1
8e	*i*-Pr	Me	39	>20:1
8f	Ph	Ph	61	>20:1
8g	Ph	C_5H_{11}	69	>20:1
8h	Ph	*i*-propenyl	66	>20:1

The cyclization of various silyloxyallenes was conducted with the results summarized in Table 2. The yields ranged from 39 to 86% with those substrates possessing an aryl substituent outperforming the dialkyl examples. All cyclopentenol products were prepared with greater than 20:1 diastereoselection.

Lastly, we sought to advance these cyclopentenols to cyclopentitols via a ketohydroxylation of the olefin. Exposing cyclopentenol **8a** to modified ketohydroxylation conditions[22] provided cyclopentanone **9a** in 67% yield and a 3:1 mixture of diastereomers. Cyclopentenes are reported to be problematic substrates for ketohydroxylation, but increasing the catalyst loading to 5 mol % and extending the reaction time at 0 °C remedies the sluggish reactivity of these substrates. NOESY analysis established the diol stereochemistry as *syn* for the major diastereomer. While not documented for this exact reaction, the diastereoselectivity may conceivably arise from polar group participation.[23]

A summary of the results of the ketohydroxylation of selected cyclopentenols is illustrated in Table 3. The yields ranged from 58 to 67% with both alkyl and aryl substituents being amenable to the reaction parameters. The diastereoselectivity appeared to be highly substrate dependent with **9d** and **9g** providing excellent diastereoselection, while **9a** provided only a modest diastereomeric ratio of 3:1. The diverse functionality of these cyclopentitols should also allow for substantial derivatization.

Table 3. Substrate Scope for the Ketohydroxylation



product	R	R′	yield (%)	dr
9a	Ph	Me	67	3:1
9d	2-thienyl	Me	59	>20:1
9g	2-furyl	Me	58	>10:1

A new reactivity pattern for silyl glyoxylates, acetylides, and nitroalkenes has been disclosed. The resulting highly diastereoselective Kuwajima–Reich rearrangement/vinylogous Michael cascade affords silyloxyallenes that are primed to undergo a Henry cyclization cascade to provide cyclopentenols with superb diastereoselection. Alkene ketohydroxylation has been documented and a myraid of other useful alkene functionalizations can be envisioned. The diastereoselectivity observed in the three-component coupling was analyzed through a quantum mechanical study using density fucntional theory (DFT) to provide an understanding of the mechanism. This study also provided further support or the (*Z*)-geometry of the in situ generated glycolate enolate accessed through silyl glyoxylate chemistry as well as a theoretical investigation of the transition state of a vinylogous Michael reaction.

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Supporting Information Available. Experimental details and characterization data for new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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