Rhodium Catalysis

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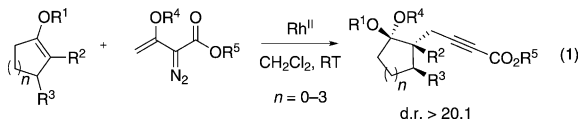
Alkynoate Synthesis through the Vinylogous Reactivity of Rhodium(II) Carbenoids**

*Damien Valette, Yajing Lian, John P. Haydek, Kenneth I. Hardcastle, and Huw M. L. Davies**

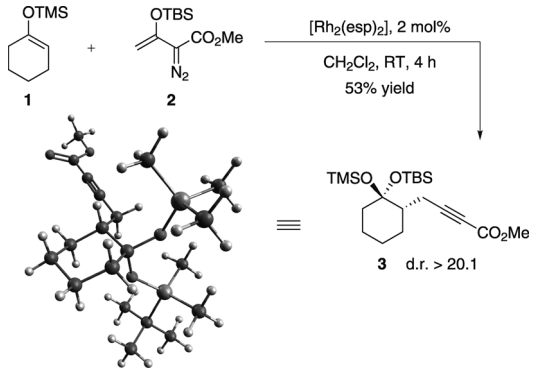
2-Alkynoates represent a versatile class of synthetic intermediates in the field of organic synthesis[1] and are useful precursors to numerous biologically active compounds.[2] Despite significant interest from the synthetic community, facile incorporation of an alkynecarboxylate moiety remains a challenge. The difficulty associated with the direct alkylation of 2-alkynoates is due to their tendency to isomerize under basic conditions into the corresponding allenes, which are then prone to undergo conjugate addition.[3] In practice, commonly reported procedures require a multistep reaction sequence.[4] A reasonably direct alternative approach to introduce the alkynecarboxylate group is the Nicholas reaction,[5] which allows the functionalization of propargylic sites with a variety of nucleophiles.[6] This approach requires the use of stoichiometric dicobalt reagents as well as the need to perform an oxidative decomplexation to regenerate the alkyne moiety following substitution. Herein, we describe a new stereoselective approach that allows a straightforward access to highly functionalized alkyl 2-alkynoates by means of a rhodium-catalyzed transformation between silyl enol ethers and 3-siloxy 2-diazobutenoates [Eq. (1)].



(1)

The successful development of the aforementioned alkylation protocol is based on the discovery of an unusual transformation of rhodium-stabilized vinylcarbenoids. Transient vinylcarbenoids undergo a wide variety of synthetically useful reactions,[7] and their chemistry is particularly rich because they display electrophilic character at both the carbenoid site and the vinylogous position.[8] Especially versatile vinylcarbenoids are those derived from 3-siloxy 2-diazobutenoates. Reactions initiated at its carbenoid site have been used for stereoselective cyclopropanation[9] and the tandem cyclopropanation/Cope rearrangement,[10] leading to the synthesis of three-, five-, or seven-membered carbocycles. The combination of siloxy α-diazoacetates with cinnamaldehydes offers access to complementary motifs.[11] More recently, the addition of nitrones to the vinylogous position of this carbenoid as well as a number of unusual transformations have been reported.[12] The key transformation behind the 2-alkynoate alkylation protocol also involves reaction at the vinylogous position of a vinylcarbenoid, but this is then followed by an unprecedented siloxy group migration.

We extensively investigated the scope of substrates that undergo selective vinylogous addition over carbenoid-type transformations.[8] During these studies, we discovered that the $[Rh_2(esp)_2]$[13]-catalyzed reaction of 1-(trimethylsiloxy)-cyclohexene (**1**) with 3-siloxy 2-diazobutenoate (**2**) unexpectedly led to the formation of alkyne **3** as a single diastereomer in 53% yield (Scheme 1). The structure of compound **3** was unambiguously confirmed by single-crystal X-ray diffraction.[14]



Scheme 1. X-ray crystal structure of product **3** formed from 3-siloxy 2-diazobutenoate (**2**) and 1-(trimethylsiloxy)cyclohexene (**1**). esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

This reaction was intriguing, not only because the formation of **3** occurred by vinylogous addition, but also because the disiloxy ketal functional group arose from the migration of the OTBS group from the vinylcarbenoid to the cyclohexyl moiety. To the best of our knowledge, such migration is unprecedented in the literature about carbenoids. In order to evaluate the stereospecificity of the transformation, the reaction between the siloxy cyclohexene and β-siloxy vinyldiazoacetate was repeated with the TBS and TMS substituents interconverted (Table 1, entry 1). The diastereomer to **3** was obtained in a highly stereoselective manner.

[*] Dr. D. Valette, Dr. Y. Lian, J. P. Haydek, Dr. K. I. Hardcastle, Prof. Dr. H. M. L. Davies
Department of Chemistry, Emory University
1515 Dickey Drive, Atlanta, GA 30322 (USA)
E-mail: hmdavie@emory.edu
Homepage: http://www.chemistry.emory.edu/

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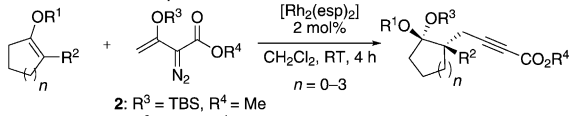
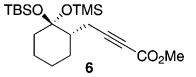
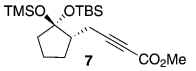
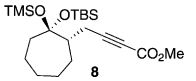
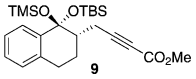
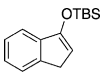
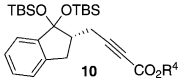
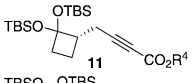
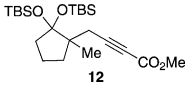
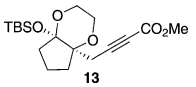
Table 1: Substrate scope.



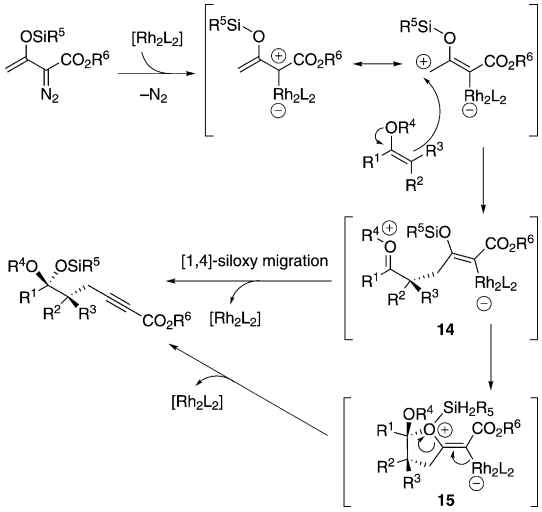
2: R^3 = TBS, R^4 = Me
4: R^3 = TMS, R^4 = Me
5: R^3 = TBS, R^4 = *t*Bu

Entry	Enol	Diazo compd	Product	Yield[a] [%]
1		**4**	 **6**	49[b]
2		**2**	 **7**	79[b]
3		**2**	 **8**	61[b]
4		**2**	 **9**	69[b]
5		**2**	 **10**	33[c]
6		**5**		84[d]
7		**2**	 **11**	51[c,e]
8		**5**		98[d]
9[f]		**2**	 **12**	56
10[f]		**2**	 **13**	53[b]

[a] Yields of isolated products. [b] d.r. > 20:1. [c] R^4 = Me. [d] R^4 = *t*Bu. [e] Yield refers to the isolated alkynoate product, which was separated from the cyclopropanated by-product by column chromatography. [f] Reaction was run at reflux.

The scope of this transformation was then explored with a range of cyclic enol ethers. The reaction proceeded in moderate to excellent yields, and in all cases only a single diastereomer of the product was generated. With certain substrates, such as siloxy indene and siloxy cyclobutene, the potentially competing products derived from carbenoid reactivity became apparent and resulted in lower isolated yields of the alkynoate products (Table 1, entries 5 and 7). We have demonstrated that increasing the size of the ester group in the vinylcarbenoid enhances the vinylogous reactivity.[8c,e] Indeed, when the reactions on these substrates were repeated using *tert*-butyl 3-siloxy 2-diazobutenoate **5**, alkynoates **10** and **11** were isolated as the sole products in 84 and 98% yield, respectively (entries 6 and 8). The vinylogous reactions to the carbenoid derived from 3-butenediazoacetate **2** are also applicable to tetrasubstituted vinyl ethers and led to the formation of alkynoates containing two adjacent quaternary centers (entries 9 and 10). The relative configuration of products **6–13** was assigned by analogy to alkynoate **3**, because an equivalent migration is presumed to be involved in the formation of those compounds.

It is well established that donor/acceptor carbenoids are more selective than their acceptor-only homologs.[15] We have previously demonstrated that the reaction between donor/acceptor carbenoids and silyl enol ethers favors C–H insertion[16] or the combined C–H functionalization/Cope rearrangement[17] over cyclopropanation. In this particular alkynoate transformation, we rationalize that the open/unsubstituted vinylogous position of the vinylcarbenoid is responsible for the vinylogous addition by the silyl enol ether. In addition, the use of sterically demanding nucleophiles, essentially tri- and tetrasubstituted olefins, is certainly accountable for the enhancement of vinylogous reactivity.[8e,g] A plausible mechanism for the alkynoate formation is detailed in Scheme 2. Addition of the silyl enol ether to the

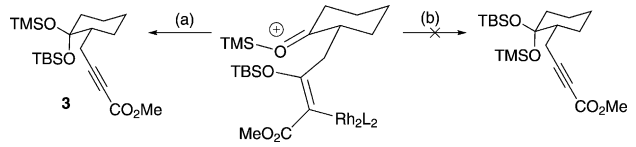


Scheme 2. Proposed mechanism.

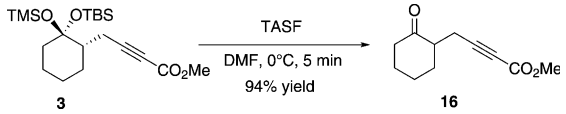
unsubstituted γ-position of the activated β-siloxy vinylcarbenoid would result in the formation of the zwitterionic intermediate **14**. Subsequent direct [1,4]-siloxy group transfer or stepwise addition to the oxocarbenium ion via intermediate **15** followed by β-elimination would lead to the alkynoate product. Previous studies have shown that rhodium-stabilized β-siloxy vinylcarbenoids have a strong preference for the *s-cis* conformation, in which the siloxy group points away from the "wall" of the catalyst.[17,18] We postulate that this conformational preference would be consistent with the rhodium carboxylate and the siloxy group adopting an anti-periplanar conformation, which would then facilitate the β-elimination to afford the alkynoate product.

The X-ray structure of alkynoate **3** unambiguously shows that both the alkynyl side chain and the siloxy migrating group are on the same face of the cyclohexane. This led us to propose that the siloxy migration could be considered as an intramolecular transfer process that would preferentially occur in a suprafacial manner (path a vs. b in Scheme 3).

Having established the basic propargylation method, studies were then conducted to determine the synthetic potential of the transformation. One obvious application would be to use the disiloxy ketal as a carbonyl protecting group. Indeed the alkynoate products generated are readily converted into the corresponding ketones in high yield by simple treatment with tris(dimethylamino)sulfonium difluo-



Scheme 3. Rationale for the diastereoselectivity.

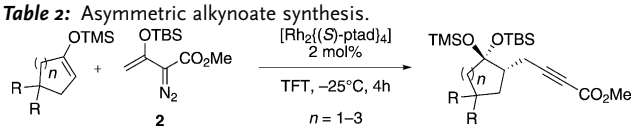


Scheme 4. Access to 1,6-dicarbonyl compound **16**. DMF = *N*,*N*-dimethylformamide.

rotrimethylsilicate (TASF); ketone **16** was isolated in 94% yield (Scheme 4).

An exploratory study was then conducted to determine whether an enantioselective version of this transformation was feasible. Extensive experimentation showed that the use of $[Rh_2(S\text{-PTAD})_4]$ at −25 °C in TFT were the optimal conditions (see the Supporting Information for further discussion on the optimized conditions). Representative examples are summarized in Table 2. Moderate levels of

Table 2: Asymmetric alkynoate synthesis.

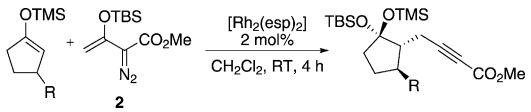


Entry	R	n	Yield[a] [%]	d.r.[b]	*ee*[c] [%]
1	H	1	87	>20:1	50
2	H	2	53	>20:1	60
3	$O(CH_2)_2O$	2	49	>20:1	46
4	H	3	69	>20:1	70

[a] Yields of isolated products. [b] Determined from ^{1}H NMR spectra of the crude reaction mixture. [c] Determined by HPLC analysis on a chiral stationary phase after hydrolysis of the disiloxy ketal. (*S*)-ptad = (*S*)-(+)-(1-adamantyl)-(*N*-phthalimido)aceto, TFT = trifluorotoluene.

enantioinduction were observed, which demonstrated that the chiral catalyst was capable of limited facial selectivity. Interestingly, the enantiomeric excess of the products increased proportionally with the size and flexibility of the ring (Table 2, entries 1, 2, and 4).

The study was then extended to 3-substituted silyl enol ethers (Scheme 5). The $[Rh_2(esp)_2]$-catalyzed reactions of siloxy vinyldiazoacetate **2** with compounds **17**–**19** generated



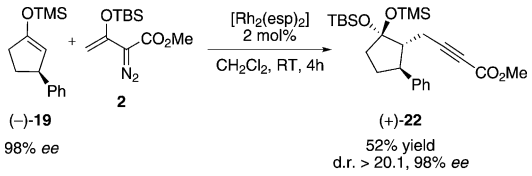
17: R = Me
18: R = *n*Bu
19: R = Ph

20 57%, d.r. > 20.1
21 50%, d.r. > 20.1
22 58%, d.r. > 20.1

Scheme 5. Scope of α-substituted silyl enol ethers.

products **20**–**22** as single diastereomers that bear three contiguous stereogenic centers. The relative configuration of **20** was determined by 1D-NOE NMR studies and extended by analogy to compounds **21** to **22**. This result is consistent with a nucleophilic addition of the silyl enol ether *anti* to the 3-substituent, followed by intramolecular siloxy group migration *syn* with respect to the alkyne moiety.

To demonstrate the practicality of this reaction, the above transformation was repeated with the enantioenriched silyl enol ether (−)-**19** (Scheme 6, 98% *ee*). As anticipated,



Scheme 6. Alkynoate formation with conservation of enantioenrichment.

product (+)-**22** was isolated as a single diastereomer with complete transfer of stereochemical information. As chiral 3-substituted silyl enol ethers, such as (−)-**19**, are readily obtained by asymmetric conjugate addition to unsaturated carbonyl compounds,[19] this allows the propargylation procedure to be effectively used for the synthesis of highly enantioenriched products that contain three contiguous stereogenic centers.

In summary, we have developed a highly diastereoselective method for the rapid access to highly functionalized 2-alkynoates in a single step using cyclic silyl enol ethers and siloxy vinylcarbenoids under rhodium(II) catalysis. Further studies are in progress to extend this reaction to acyclic enol ethers and to find systems that will give higher levels of asymmetric induction. These studies underscore the rich chemistry of rhodium-stabilized vinylcarbenoids, which has led to their broad application in a number of novel synthetic transformations.

Experimental Section

General procedure: A solution of siloxy vinyldiazoacetate (1.0 mmol, 2.0 equiv) in dried, degassed CH_2Cl_2 (6 mL) was added by syringe pump over three hours to a flame-dried 25 mL flask containing $[Rh_2(esp)_2]$ (7.7 mg, 0.02 equiv) and enol ether (0.5 mmol, 1.0 equiv) in dried, degassed CH_2Cl_2 (6 mL) at room temperature under an argon atmosphere. The solution was stirred at room temperature for an additional hour. The mixture was concentrated under reduced pressure and purified by flash chromatography (see the Supporting Information for eluents) on silica gel to give the product.

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[14] CCDC 882822 (**3**)contains 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.

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