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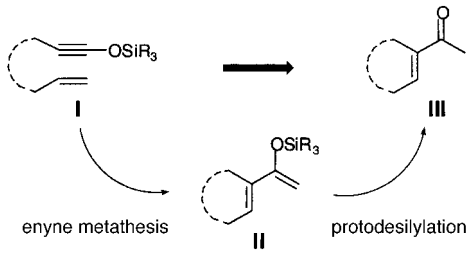
Siloxyalkyne – Alkene Metathesis: Rapid Access to Highly Functionalized Enones**

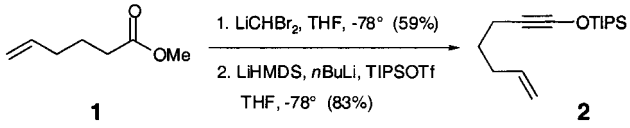
Michael P. Schramm, D. Srinivasa Reddy, and Sergey A. Kozmin*

The advent of structurally defined metal alkylidenes capable of promoting π-bond metathesis under mild conditions, with high efficiency and functional group compatibility, has had a profound effect on modern organic synthesis.[1] Among a range of synthetically useful transformations, the enyne metathesis is particularly noteworthy for the ability to assemble two carbon – carbon bonds in a single step starting from appropriate alkyne and alkene components.[2] However, elaboration of the full synthetic potential of this process has been limited largely to the use of simple, unactivated enyne precursors.[3] We report here a mechanistically intriguing example of the participation of siloxyalkynes in the intramolecular Ru-catalyzed metathesis with terminal alkenes, which resulted in the development of a new method for the synthesis of highly functionalized enones **III** starting from readily accessible acyclic precursors **I** (Scheme 1).[4] Furthermore, this approach represents a novel method for the construction of silyldienol ethers **II** starting directly from enyne **I**, conceptually different from the conventional enol silylation of carbonyl compounds.



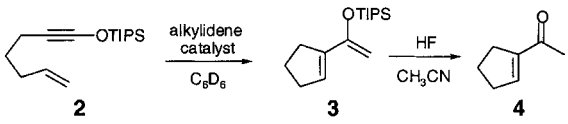
Scheme 1. Projected outcome of the siloxyalkyne – alkene metathesis.

Our studies began with the preparation of a model cyclization substrate **2** (Scheme 2). Construction of siloxyalkyne **2** was accomplished according to a modified Kowalski protocol[5] entailing the initial conversion of ester **1** to the corresponding dibromoketone, followed by generation of the ynolate anion (LHMDS, *n*BuLi) and silylation with TIPSOTf to afford enyne **2**.



Scheme 2. Preparation of siloxyalkyne **2**. LiHMDS = lithium bis(trimethylsilyl)amide, TIPSOTf = triisopropyl trifluoromethanesulfonate.

We next systematically examined several olefin metathesis catalysts in order to achieve the desired conversion of siloxyalkyne **2** to the corresponding diene **3** [Eq. (1)]. Following the unsuccessful attempts to employ either the



original Grubbs Ru-complex **5**[6] or the Schrock Mo-catalyst **6**[7] (Table 1, entries 1 and 2), we turned our attention to the recently developed Ru-complexes bearing highly nucleophilic imidazolylidene ligands.[8] To our delight, both **7**[9] and **8**[10] were found to promote the desired transformation, nevertheless they displayed a noticeable difference in reactivity.[11] The reaction proceeded to completion in the presence of **8** (5 mol%) over a period of 13 h at 20 °C, and within minutes at 60 °C (entries 4, 5). The cyclization employing complex **7** was

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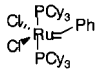
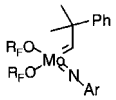
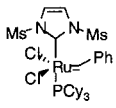
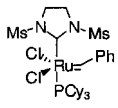
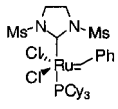
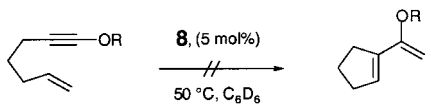
Table 1. Siloxyalkyne – alkene metathesis: initial catalyst evaluation.

Entry	Catalyst[a]	mol %	Conditions	Conv. [%]
1	 **5**	10	60 °C, 6 h	< 5
2	 **6**	10	60 °C, 12 h	< 5
3	 **7**	5	60 °C, 12 h	85
4	 **8**	5	20 °C, 13 h	95
5	 **8**	5	60 °C, 15 min	98

[a] Cy = cyclohexyl, Ar = 2,6-diisoprophylphenyl, $OR_F = OCMe(CF_3)_2$, Ms = methanesulfonyl.

considerably slower requiring 12 h at 60 °C to reach 85 % conversion (entry 3); no reaction was observed at 20 °C. Treatment of the crude reaction mixture (entry 5) with a dilute solution of HF gave acetylcyclopentene **4** as a sole reaction product.

Interestingly, subjection of either ethoxyalkyne **9**[12] or alkynyl phosphate **10**[13] to catalyst **8** did not lead to any detectable amounts of the corresponding diene even under forcing conditions (Scheme 3). This result is particularly intriguing since Clark and co-workers demonstrated that alkynyl ethers with an internal oxygen tether were found to undergo Ru-catalyzed enyne metathesis with good efficiency.[4b]

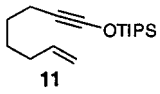
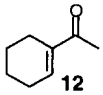
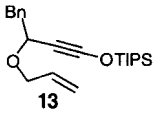
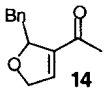
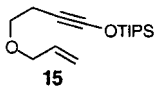
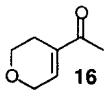
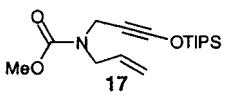
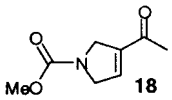
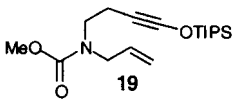
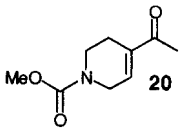
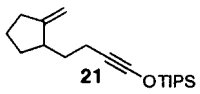
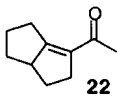
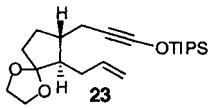
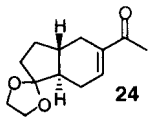
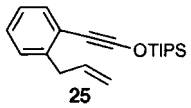
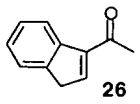
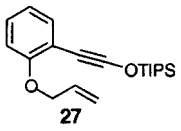
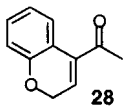
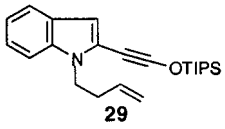
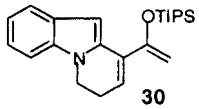


9: R = Et
10: R = P(O)(OEt)$_2$

Scheme 3. Unsuccessful enyne metatheses of alkynyl ether **9** and alkynyl phosphate **10**.

Having established a functional protocol, we next examined the scope of this process (Table 2). All of the siloxyalkynes used in this study were prepared according to the Kowalski protocol,[5] which illustrates the generality of this method. Formation of acetyl cyclohexene **12** proceeded with comparable efficiency (81 % yield, entry 1). Ether and carbamate functional groups were found compatible and afforded the corresponding five- and six-membered heterocycles (entries 2 – 5). The alkyl substitution at the position directly adjacent to the alkyne was well tolerated (86 % yield, entry 2).

Table 2. Siloxyalkyne – alkene metathesis: substrate scope.[a]

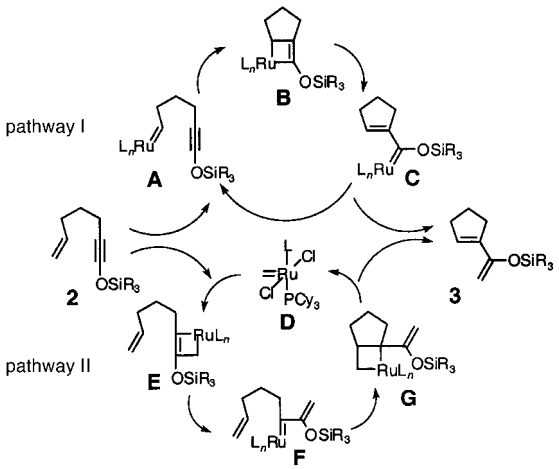
Entry	Siloxyalkyne	Product	Yield [%]
1	 **11**	 **12**	81
2	 **13**	 **14**	86
3	 **15**	 **16**	88
4	 **17**	 **18**	91
5	 **19**	 **20**	95
6	 **21**	 **22**	50[b]
7	 **23**	 **24**	68[c]
8	 **25**	 **26**	88
9	 **27**	 **28**	80
10	 **29**	 **30**	92

[a] General procedure: A solution of the respective siloxyalkyne in benzene (0.1 M) was treated with catalyst **8** (3 – 10 mol %), and warmed to 50 – 60 °C. Upon disappearance of the starting material (15 – 60 min), the reaction mixture was concentrated, treated with 1.0 M solution of HF in MeCN (1.5 – 2 equiv) for 30 min, and purified by chromatography on silica gel. [b] The catalyst loading was 20 mol %. [c] Protodesilylation was conducted by using tetrabutylammonium fluoride to prevent the acetal hydrolysis.

Notably, the siloxyalkyne – alkene metathesis provides a powerful alternative to the existing methods for the preparation of cyclic enones, as this approach avoids the potential β-elimination or regioselectivity problems associated with intramolecular aldol condensation or with Friedel – Crafts acylation. Furthermore, this process offered rapid access to a variety of bicyclic ring systems, that is, diquinane **22**[14] and hydrindane **24**. Arene-conjugated siloxyalkynes **25** and **27** successfully underwent enyne reorganization to yield indene **26** and benzopyran **28**, respectively. In addition, cyclization of the indole-containing siloxyalkyne **29** afforded the tricyclic

diene **30** in 92% yield. Interestingly, multiple attempts to protodesilylate diene **30** proved unsuccessful, presumably because of the instability of the corresponding enone, which suggests the difficulty in the preparation of this siloxydiene by conventional enol silylation approach. The above data collectively illustrate that the siloxyalkyne–alkene metathesis offers a mild and efficient method for the assembly of a wide range of highly functionalized enones representing valuable synthetic intermediates.

Apart from the preparative utility of siloxyalkyne–alkene metathesis, this process raises several mechanistically relevant issues. Whereas bond reorganization of enyne **2** (see Scheme 4) exhibits strong thermodynamic preference for the



Scheme 4. Proposed mechanism of siloxyalkyne–alkene metathesis.

conversion to silyldienol ether **3**,[15] the formation of the observed product is less apparent from a mechanistic standpoint, as two alternative catalytic cycles can be postulated.[16] Among the two pathways, we strongly favor pathway I that involves initial formation of Ru-alkylidene **A**, [2+2] annulation to give metallacyclobutene **B**, and structural reorganization to afford vinyl carbene **C**. Transfer of the methylene unit from substrate **2** results in the formation of diene **3** and regeneration of alkylidene **A**. Although pathway II can not be ruled out entirely at this point, the dominance of pathway I was strongly supported by several NMR experiments. These involved the competition between siloxyalkyne **31** and terminal alkene **32** in the presence of a stoichiometric amount of Ru-benzylidene **8** ($\delta = 19.61$, Figure 1A). Addition of **8** to a solution of alkyne **31** resulted in no reaction after 30 min at 57 °C (Figure 1B). On the other hand, treatment of benzylidene **8** with alkene **32** at 57 °C immediately afforded a new signal corresponding to the Ru-alkylidene ($\delta = 18.35$, Figure 1C).[17] Finally, mixing of the three components **8**, **32**, and **31** (Figure 1D) led to the disappearance of the benzylidene resonance with a concomitant formation of the alkylidene signal; the siloxyalkyne remained unchanged. While this experiment clearly indicated a more facile reaction of benzylidene **8** with terminal alkene component of the enyne **2**, a starting point in pathway I, the intermediacy of a stabilized siloxycarbene **C** (Scheme 4) is less apparent, as this carbene would be expected to display a decreased metathesis reactivity due to the electron-donating nature of the siloxy substituent. We believe, however, that the activating nature of the perhydroimidazolylidene ligand combined with the overall thermodynamically favored release of diene **4**[15] overrides the unfavorable electronic effect of the siloxy group and results in productive catalytic turnover.

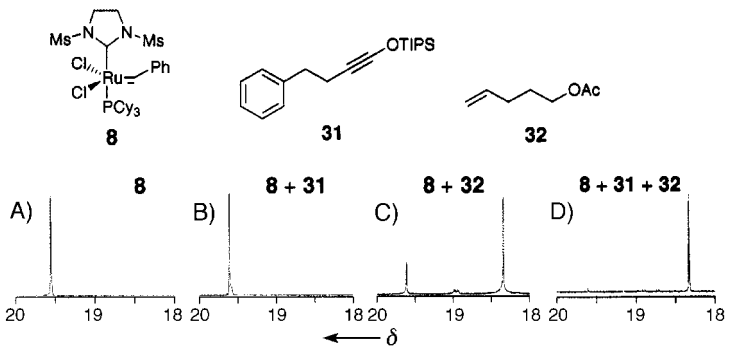


Figure 1. ^{1}H NMR (400 MHz) competition experiments carried out in [D_6]benzene with stoichiometric quantities of reaction partners.

In closing, we have demonstrated the first example of an efficient participation of siloxyalkynes in the intramolecular metathesis with terminal alkenes. This process resulted in the development of a simple and efficient approach to highly functionalized enones starting from readily accessible acyclic precursors. It further expands the synthetic potential of the enyne metathesis. Additional studies on the mechanism and utility of this technology for the construction of highly diverse chemical libraries are in progress and will be reported in due course.

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A Novel Electrophilic Diamination Reaction of Alkenes**

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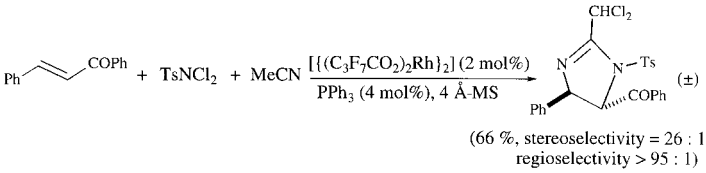
Electrophilic addition reactions of olefins have been of fundamental importance in organic chemistry[1] because these reactions can convert inexpensive petroleum alkenes into chemically and biologically useful compounds. At present, olefinic additions involving three or more components in a single operation are rare,[2, 3] which is probably because of the fact that only a few electrophilic addition intermediates enable multistep transformations.[4, 5] Recently, we developed several new eletrophilic addition reactions, aminohalogenation, and α,β-differentiated diamination reactions by using *N*-halogenosulfonamides as the electrophiles.[6, 7] The regio- and stereochemical features of the resulting haloamine and diamine products have unambiguously proven the formation of *N*-(*p*-tosyl),*N*-haloaziridinium or *N*-(*o*-nosyl),*N*-haloaziridinium species during the reaction processes. In our continuing research on this topic we have now discovered a novel three-component reaction (Scheme 1) which provides access to imidazolines[8] and α,β-diamino derivatives.[9, 10]



Scheme 1. Chalcone-based electrophilic diamination reaction.

The current study was initiated by attempts to render the parent version of the aminohalogenation reaction asymmetric and catalytic.[6] Unfortunately, the success of this effort has been seriously limited thus far. For most of the cases we examined the reaction was either significantly deactivated or poor enantiomeric excesses resulted when chiral amine ligands were employed together with copper or zinc ions. Therefore, the search for other metal alternatives or metal – ligand complexes became necessary. When rhodium compounds were examined[11] (for example, rhodium(II) acetate dimer, rhodium(II) trifluoroacetate dimer, and rhodium(II) heptafluorobutyrate dimer) the reaction of methyl cinnamate with $TsNCl_2$ (Ts = tosyl = toluene-4-sulfonyl) led to the formation of complexes and a major side product. This side product was isolated in a yield varying between 18 – 25 % when the above catalysts were employed, although the haloamine product was generated predominantly. The subsequent X-ray structural analysis revealed that this new side product is essentially a multifuctionalized imidazoline derivative (Figure 1).

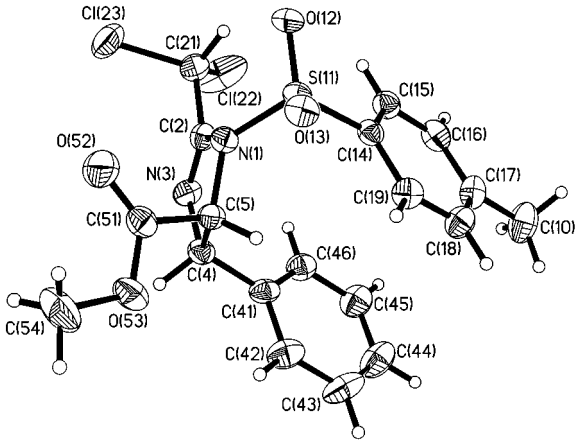


Figure 1. X-ray structure of 1-*p*-toluenesulfonyl-2-dichloromethyl-4-phenyl-5-methyloxycarbonylimidazoline.

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