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Regio- and Stereoselective Enyne Cross Metathesis of Silylated Internal Alkynes

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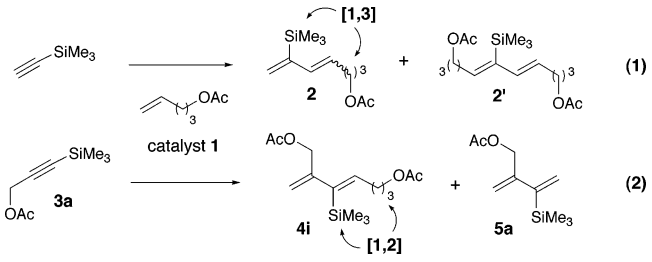
Olefin metathesis has emerged as one of the most powerful contemporary synthetic tools in organic chemistry.[1] Contrary to the widespread application of ring-closing metathesis (RCM), that of cross metathesis (CM)[2] has been limited partly because of low chemoselectivity (homo- vs heterocoupling) and stereoselectivity (*E* vs *Z*). The ***e****n****y****ne* ***CM*** (EYCM) reaction, in which the CM occurs between an alkene and an alkyne, renders regioselectivity as another dimension of complexity.[3] To circumvent the selectivity problem of forming an inseparable mixture of isomers,[4] the EYCM reaction has been confined to the pairings of internal alkyne-ethylene[5] and terminal alkyne-terminal alkene.[6] To the best of our knowledge, the stereoselective EYCM reaction between unsymmetrical internal alkynes and unsymmetrical alkenes has not been realized.[7] We envisioned that silyl functionality, known for its steric and stereoelectronic biasing effect in a variety of reactions,[8] could be instrumental in influencing the regio- and stereoselectivity of the EYCM reaction of silylated alkynes.[9] We report herein the first example of a highly regio- and stereoselective EYCM reaction of silylated internal alkynes with functionalized alkenes.

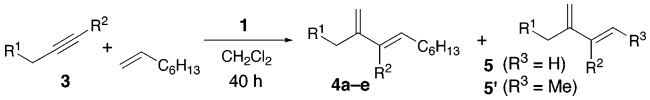
The EYCM reaction of silylated internal and terminal alkynes catalyzed by $(H_2Imes)(PCy_3)(Cl)_2Ru{=}CHPh$ (**1**) resulted in quite different regio- and stereoselectivity.[10] Terminal alkynes such as trimethylsilylacetylene gave 1,3-diene **2** (58%) having a 1,3-relationship between the alkenyl substituent and $SiMe_3$ with low stereoselectivity (3:1) and double-CM product **2′** (7%, single isomer) (eq 1). On the other hand, internal alkyne **3a** afforded diene **4i** (71%), possessing a 1,2-relationship of these substituents, as a single regio- and stereoisomer[11] along with a small amount of ethylene-crossed product **5a** (<5%) (eq 2).[12]



To gain more insight regarding the regio- and stereoselectivity of this process, we examined what effect propargylic substituents[13] in alkynes **3a**−**e** would exert during an EYCM reaction with 1-octene. The EYCM products **4a**−**c** and **4e** were isolated as single regio- and stereoisomers with varying amounts of **5** and **5′** (Table 1). Silylated alkyne **3d** having a simple alkyl chain gave low conversion, indicating the importance of the heteroatom substituent at the propargylic site (entry 4). The EYCM reaction of **3c** afforded not only **4c** but also **5c′** (15%), which is derived from a double bond-migrated internal alkene (entry 3).[14]

Next, the scope of this EYCM reaction was further examined by employing various functionalized 1-alkenes and alkynes **3a**, **3c**, and **3e**, which provided 1,3-diene products **4f**−**p** as single stereoisomers except for **4q** (*Z*/*E*, >95:5) (Table 2). In general, alkenes with a longer distance between the double bond and the heteroatom substituent gave better efficiency in the CM reaction (entries 1, 2,

Table 1. CM between Silylated Alkynes and 1-Octene[a]



entry	alkyne	R^1	R^2	yield of **4** (%)[b]	ratio (**4**:**5′**)
1	**3a**	OAc	$SiMe_3$	76[c]	**4** only
2	**3b**	OMe	$SiMe_3$	30[d]	**4** only
3	**3c**	Ts(Me)N	$SiMe_3$	71	2:1 (**4**:**5′**)
4	**3d**	C_5H_{11}	$SiMe_3$	—[e]	**4** only
5	**3e**	OMe	$SiPh_2(OHex)$	81[f]	10:1 (**4**:**5**)

[a] **1** (7−15 mol %) and 1-octene (4−8 equiv) in CH_2Cl_2 (0.03 M) at 40 °C. [b] Isolated yields. [c] Reaction with the first-generation Grubbs catalyst, $(PCy_3)_2(Cl)_2Ru{=}CHPh$, gave only **5a**. [d] Low yield because of desilylation. [e] Low yield from low conversion and volatility of **4d**. [f] 96:4 of *Z*/*E* isomer.

Table 2. CM of Silylated Alkynes with Functionalized Alkenes[a]

Entry	alkyne	alkene	1,3-diene	yield (%)[b]
1	**3a**	n = 1	**4f**	53
2		n = 2	**4g**	79
3		n = 1	**4h**	63
4		n = 3	**4i**	71
5		n = 4	**4j**	80
6			**4k**	30
7			**4l**	43
8	**3c**		**4m**	65[c]
9			**4n**	79[d]
10	**3e**		**4o**	54
11			**4p**	61
12			**4q**	56[e,f]

[a] **1** (7−15 mol %) and 1-alkene (4−8 equiv) in CH_2Cl_2 (0.03 M) at 40 °C. [b] Isolated yields. [c] Mixture of **4m** and **5c′** (5.6:1). [d] Mixture of **4n** and **5c′** (2.2:1). [e] Isolated as a mixture of **4q** and **5e**. [f] 95:5 mixture of *Z*/*E*.

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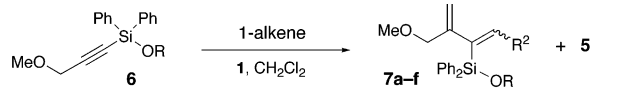
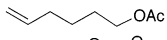
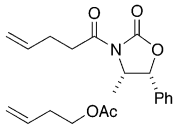
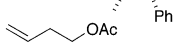
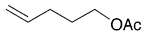
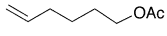
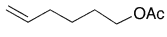
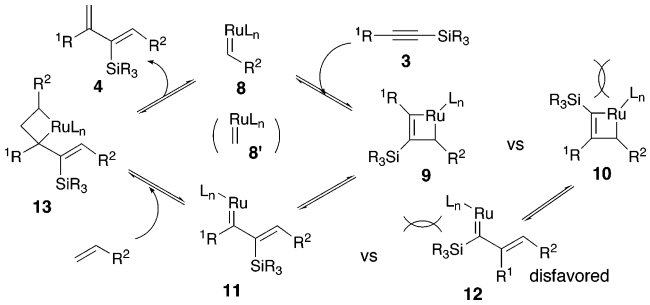
Table 3. CM of Silylated Alkynes Possessing a Tethered Alkene[a]



Entry	R	1-alkene	yield of **7**(%)[b,c]	ratio (*Z*/*E*)[d]
1	**6a**		83	97 : 3
2			44	single isomer
3	**6b**		64	93 : 7
4			65	96 : 4
5			60	96 : 4
6	**6c**		84	95 : 5

[a] **1** (7−15 mol %) and 1-alkene (2 equiv) in CH_2Cl_2 (0.03 M) at 40 °C. [b] Isolated yields. [c] **5** constitutes the remaining mass balance. [d] Ratio was determined by ^{1}H NMR.

Scheme 1

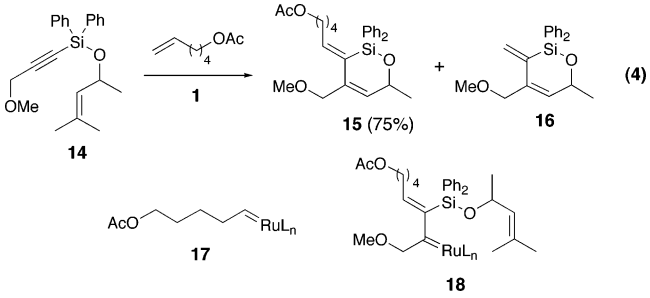


and 3−5). Bromide, ester, imide, ether, and ketone functionalities are tolerant toward the metathesis reaction, whereas alcohols and aldehydes are less effective, exhibiting either low conversion or partial decomposition of products, respectively.

Silylated alkynes **6a**−**c** having a tethered alkene showed somewhat different behavior, requiring much shorter reaction time for completion compared to that of **3a**−**e** (4 h vs 40 h) (Table 3). Moreover, an increased amount of the second stereoisomer of **7** formed, albeit in a very minor amount (<7%). The origin of this increased reactivity and reduced selectivity of **6a**−**c** is not obvious but one speculation is the coordination of the alkene functionality to the Ru-metal center, thereby stabilizing the initially formed alkylidene intermediates.[15]

The regio- and stereoselectivity of the current EYCM reaction can be explained by a mechanism shown in Scheme 1. We believe that alkylidene **8** plays a major role as the key propagating species as opposed to methylidene **8′** proposed by Blechert.[6] The observed regiochemistry originates from the preferential formation of **9** and **11** over that of **10** and **12** because of the latter's more severe steric interaction between the bulky SiR_3 and the ligands on the metal. The geometry of the double bond in **11** is best explained by a stereospecific [2 + 2] cycloreversion of metallacyclobutene **9**, whereby the preferred outward rotation of R^2 would place the alkylidene moiety and R^2 trans to avoid unfavorable steric interactions.[16] Subsequent formation of **13** from **11** followed by its cycloreversion would complete the catalytic cycle, generating the final 1,3-diene **4** and the propagating alkylidene **8**.

The proposed mechanism is further supported by the EYCM reaction of enyne **14**, affording **15** in 75% yield accompanied by a small amount of **16** (7%) (eq 4).[17] The formation of **15** is possible only if both alkylidene intermediates **17** and **18** are involved and their sequence of individual steps follows the path shown in Scheme 1.



In summary, we have developed a highly regio- and stereoselective CM reaction between silylated alkynes and functionalized alkenes. The selectivity is assumed to be the result of the steric and stereoelectronic biasing effect of the silyl group. The reaction mechanism regarding the propagating alkylidene species and its regiochemistry of addition to an alkyne was unambiguously demonstrated by employing a tandem CM-RCM reaction. Further investigation regarding the origin of the observed selectivity is in progress.

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Supporting Information Available: General experimental procedures and characterization of **4a**−**c** and **4e**−**q**. This material is available free of charge via the Internet at http://pubs.acs.org.

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