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Absence of the Thorpe–Ingold effect by *gem*-diphenyl groups in ring-closing enyne metathesis

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Abstract—In tandem ring-closing metathesis of alkynyl silaketals containing two different tethered olefins, the *gem*-dimethyl group showed the expected Thorpe–Ingold effect, thereby giving good level of group selectivity. Unexpectedly, however, the corresponding *gem*-diphenyl group did not show any Thorpe–Ingold effect for the ring-closure reaction.

The Thorpe–Ingold effect is a well-appreciated parameter that profoundly affects ring-closure rates and efficiency.[1,2] In our approach to develop group-selective enyne ring-closing metathesis (RCM) methods,[3,4] we envisioned that the ring-closure rate difference of two equilibrating alkylidene intermediates can be tuned by the Thorpe–Ingold effect to provide a product with selectivity among several possible ones.[4] To examine this concept, we turned our attention to dialkenylsilaketal **1** as an appropriate substrate platform (Scheme 1).[5,6] Should the Thorpe–Ingold effect play a significant role during RCM of **1**, the initial ring closure of **2a** containing the *gem*-dialkyl substituents should occur faster than that of **2b** ($k_1 > k_2$). Given that the pre-ring-closure steps are reversible and occur at higher rates than that of the first ring-closure event ($k_{ex} \gg k_1$ or k_2), irrespective of the selectivity in the initiation event to generate alkylidene species **2a** or **2b**, the tandem RCM of a dienyne[5] such as **1** is expected to yield preferentially **4a** via **3a** over **4b** via **3b**. Although the rate difference (k_3 vs k_4) in the second ring-closure step (conversion of **3** to **4**) could affect the overall selectivity, we surmised that the first ring closure would be the primary selectivity-determining step because the process between **2** and **3** is virtually irreversible. Here we report a very unexpected absence of the Thorpe–Ingold effect by *gem*-diphenyl groups while the corresponding *gem*-dimethyl group manifested this effect to give group selectivity in RCM reactions in concentration-dependent manners.

The current study was triggered by the unusual selectivity for the RCM of **6a** with Grubbs carbene complex **5**,[7] generating **8a** exclusively while **9a** provided a mixture of **10a** and **11a** in a 1:1.5 ratio (Scheme 2).[8] Considering the faster ring closure to form smaller rings first,[9] **7a** and **10a** should have been the major products from **6a** and **9a**. The deviation of the observed selectivity for RCM of substrate **6a** might be justified by the steric hindrance of the *gem*-diphenyl group near the alkene, prohibiting the initiation from that alkene moiety. This hypothesis, indeed, was supported by the observed selectivity change along with a change from the *gem*-diphenyl in **6a** to the *gem*-dimethyl group in **6b**, where probably the reduced steric hindrance of the *gem*-dimethyl group increased the formation of **7b** to give the observed product ratio of 1:4 at 0.003 M. Increase in concentration further decreased the ratio of **7b**:**8b** as expected. To negate any ambiguous assignment of the RCM products due to the potential difficulty in differentiating the two very similar structures, first, a homonuclear decoupling experiment was conducted on the fully protodesilylated product derived from **8a** (Scheme 3).[5] Upon irradiation of the vinyl proton with triplet splitting, loss of the doublet splitting pattern for the methylene protons was observed, which implicates structure **8a′**, where

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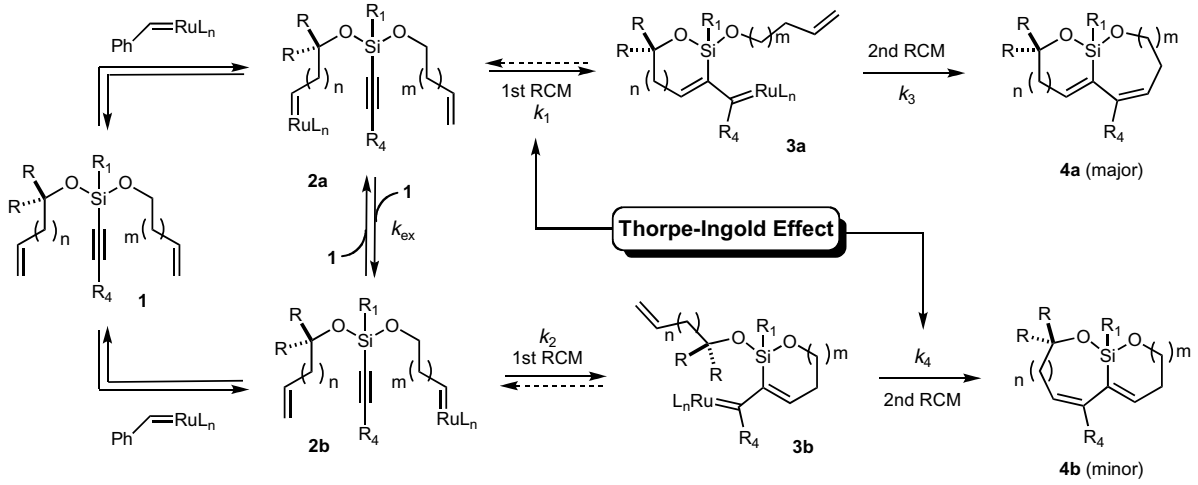
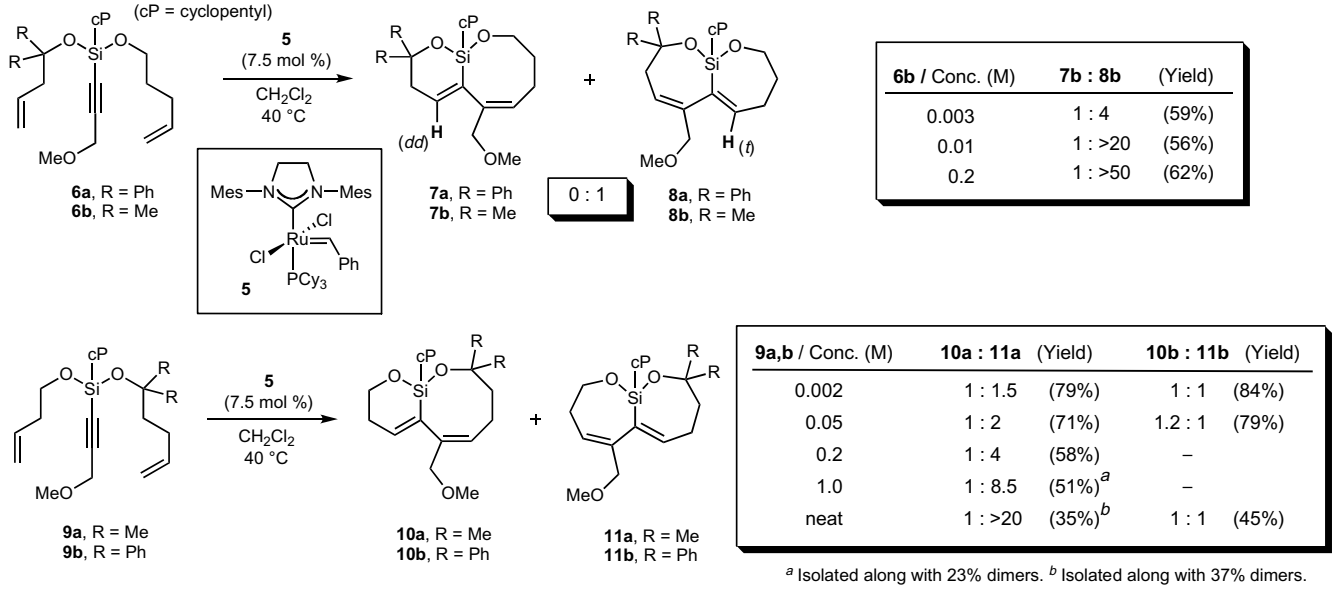


Scheme 1.

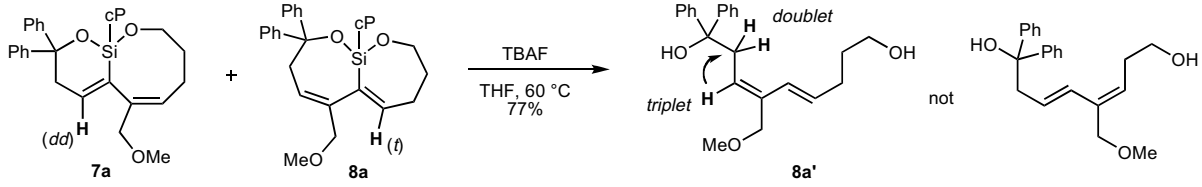


6b / Conc. (M)	7b : 8b	(Yield)
0.003	1 : 4	(59%)
0.01	1 : >20	(56%)
0.2	1 : >50	(62%)

9a,b / Conc. (M)	10a : 11a	(Yield)	10b : 11b	(Yield)
0.002	1 : 1.5	(79%)	1 : 1	(84%)
0.05	1 : 2	(71%)	1.2 : 1	(79%)
0.2	1 : 4	(58%)	–	
1.0	1 : 8.5	(51%)[a]	–	
neat	1 : >20	(35%)[b]	1 : 1	(45%)

[a] Isolated along with 23% dimers. [b] Isolated along with 37% dimers.

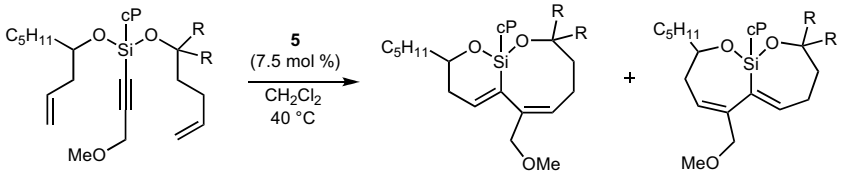
Scheme 2.



Scheme 3.

the methylene protons adjacent to the tertiary hydroxyl group can couple only to the adjacent vinyl proton.[10]

The 1:1.5 selectivity between **10a** and **11a** in the RCM of **9a** deviates from the prediction that favors the formation of **10a** over **11a**, but does not seem to have a steric origin as in the case of **6a** and **6b**. In this example, it is likely that the Thorpe–Ingold effect is operating such that the initial ring closure of the alkene tether containing the *gem*-dimethyl group (following path **1**–**2a**–**3a**–**4a**, Scheme 1) to form the seven-membered ring is more favored over the six-membered ring (following path **1**–**2b**–**3b**–**4b**). On the basis of the hypothesis that the two competing alkylidene species formed from the two different tethered alkenes will likely undergo faster exchange reaction at higher concentration, the selectivity between the two products will depend solely on the ring-closure rate difference between the alkylidenes regardless



12a, R = Me
12b, R = Ph

13a, R = Me
13b, R = Ph

14a, R = Me
14b, R = Ph

12a,b / Conc. (M)	**13a : 14a** (Yield)		**13b : 14b** (Yield)	
0.003	2 : 1	(99%)	1 : 1	(85%)
0.2	4 : 1	(66%)	1 : 1	(73%)

Scheme 4.

of the initiation event.[11] Indeed, the selectivity between **10a** and **11a** was increased significantly with the increase in reaction concentration. On the other hand, the diphenyl counterpart **9b** showed competitive formation of the two possible bicycles **10b** and **11b** in a 1:1 ratio at all concentrations examined. The mechanistic hypothesis based on the Thorpe–Ingold effect shown in Scheme 1 nicely explains the RCM selectivity trend of **9a**; the ring-closure rate of the longer alkene with *gem*-dimethyl substituents outruns that of the shorter, which is revealed only when the alkylidene exchange rate (k_{ex}) becomes higher than that of the first ring closure (k_1 and k_2) at higher concentrations.[11] However, the unexpected 1:1 ratio of the two products from RCM of **10b** and **11b** from **9b** even under neat conditions is perplexing, as it suggests that *gem*-diphenyl substituents in this case do not have the expected capacity to induce the Thorpe–Ingold effect.[12]

Given the contradicting Thorpe–Ingold effect induced by the *gem*-dimethyl and *gem*-diphenyl substituents, we further examined silaketals **12a** and **12b** that contain *gem*-dialkyl substituents on the longer alkene tether and a monoalkyl substituent on the shorter alkene tether (Scheme 4). However, the RCM selectivity profile of these substrates is very similar to that of **9a** and **9b**, implicating that the monoalkyl substitution does not significantly affect the initial ring-closure event.

In summary, we have observed a highly unusual discrepancy between the *gem*-dimethyl group and the *gem*-diphenyl group in their capacity to manifest the Thorpe–Ingold effect. The *gem*-dimethyl substituent played an evident role to promote ring closure at higher concentrations, selectively generating one of the unsymmetrical bicyclic silaketals. Very unexpectedly, however, the corresponding substrates with *gem*-diphenyl groups under identical reaction conditions did not show any observable Thorpe–Ingold effect. Further exploration of this discrepancy is in progress.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.063.

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8. *Representative RCM in dilute solution:* Silaketal **9a** (70 mg, 0.200 mmol) was dissolved in dry CH_2Cl_2 (100 mL, 0.002 M) in a round-bottom flask equipped with a reflux condenser. Nitrogen was bubbled through the solution for 30 min before adding catalyst **5** (13 mg, 0.015 mmol) in CH_2Cl_2 (5 mL). The reaction was then stirred under reflux until its completion (approx. 2 h). The solvent was removed in vacuo to yield a brown residue that was purified by flash chromatography on silica gel (95:5 hex–ether) to afford 51 mg (79%) of **10a** and **11a** as a 3:2 mixture (diastereomers not separable by column chroma-

tography). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.69 (t, $J = 5.2$ Hz, 0.6H), 6.66 (dd, $J = 5.8$, 3.0 Hz, 0.4H), 5.69–5.61 (m, 0.4H), 5.53 (t, $J = 4.9$ Hz, 0.6H), 4.20–3.79 (m, 4H), 3.35 (s, 1.8H), 3.3.4 (s, 1.2H), 2.25–2.10 (m, 4H), 2.04–1.38 (m, 10H), 1.36 (s, 1.2H), 1.33 (s, 1.8H), 1.24 (s, 1.8H), 1.21 (s, 1.2H), 1.04–0.85 (m, 1H); ^{13}C NMR (75.4 MHz) δ 147.2, 143.6, 138.4, 136.9, 136.4, 135.7, 128.1, 124.2, 77.7, 77.5, 74.7, 73.5, 62.1, 61.5, 58.2, 58.0, 43.1, 41.3, 33.7, 31.4, 31.3, 30.9, 30.4, 30.3, 27.8, 27.5, 27.4, 27.2, 27.1, 27.0, 26.9, 26.8, 25.7, 25.1, 23.0; HRMS (ESI) calcd for $C_{18}H_{30}O_3Si$ $[M+Na]^+$ 345.1863, found 345.1862. *Representative RCM in neat conditions:* Silaketal **9a** (140 mg, 0.400 mmol) was added to a small vial containing catalyst **5** (26 mg, 0.030 mmol) under nitrogen. The reaction was stirred at approx. 50 °C for 1.5 h. The reaction mixture was directly loaded onto a silica gel column (eluted with 95:5–85:15 hex–ether) to afford 45 mg (35%) of product **10a** (>20:1 **10a**:**11a**) along with 50 mg of a major byproduct (monocycle dimer). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.69 (t, $J = 5.2$ Hz, 1H), 5.53 (t, $J = 4.9$ Hz, 1H), 4.14 (m, 1H) 3.97–3.81 (m, 3H), 3.35 (s, 3H), 2.45–2.40 (m, 4H), 1.95–1.39 (m, 10H), 1.33 (s, 3H), 1.24 (s, 3H), 0.96 (m, 1H); ^{13}C NMR (75.4 MHz) δ 147.2, 136.9, 136.4, 124.2, 77.7, 73.5, 61.5, 58.2, 43.1, 33.7, 30.9, 30.3, 27.8, 27.4, 27.1, 26.9, 26.8, 25.7; HRMS (ESI) calcd for $C_{18}H_{30}O_3Si$ $[M+Na]^+$ 345.1863, found 345.1862.

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10. Deducing from the decoupling experiment, we conclude that the single siloxane product resulting from the RCM of **6a** must be **8a**, which results from the initial enyne RCM of the longer, unsubstituted alkene tether of **6a**. Furthermore, in order to systematically interpret the ratio of the mixture of two bicycles obtained from the concentration-dependent studies, we were able to utilize the chemical shift and splitting patterns observed for the vinyl protons β to the silicon that were distinct between that in a six-membered ring and that in a seven-membered ring (i.e., **7a** vs **8a**). Notably, the splitting patterns for this downshifted vinyl proton signals were consistent among the different products and therefore allowed a simple and reliable assignment of the ratios of the chromatographically inseparable mixture of the two bicycles.
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