Photochemistry

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# Regioselective Chromatic Orthogonality with Light-Activated Metathesis Catalysts**

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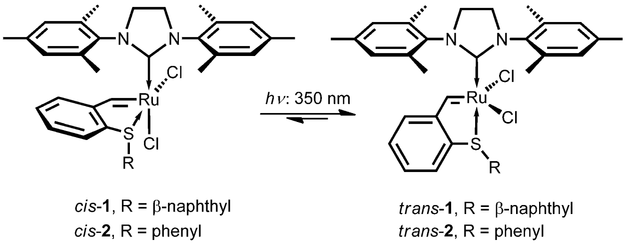
**Abstract:** *The ability to selectively guide consecutive chemical processes towards a preferred pathway by using light of different frequencies is an appealing concept. Herein we describe the coupling of two photochemical reactions, one the photoisomerization and consequent activation of a sulfur-chelated latent olefin-metathesis catalyst at 350 nm, and the other the photocleavage of a silyl protecting group at 254 nm. Depending on the steric stress exerted by a photoremovable neighboring chemical substituent, we demonstrate the selective formation of either five- or six-membered-ring frameworks by light-triggered ring-closing metathesis. The orthogonality of these light-induced reactions allows the initiation of these processes independently and in interchangeable order, according to the wavelength of light used to promote them.*

Arguably one of the most impressive examples of efficient use of energy is the way nature has exploited photons to advance living systems. The wavelength of light determines the exact energy delivered by a photon, and chemists, like nature, have harnessed this energy in processes called photochemical reactions.[1] A novel concept developed by Bochet and co-workers[2] is the use of chromatically orthogonal procedures as sequential chemical reactions that are carried out selectively in the presence of light of different energies.[3] These processes have been developed mostly by the use of complex functional-group-deprotection schemes, in which the photoinduced removal of a specific protecting group is necessary in the presence of another protecting group that remains intact.[4]

Photocatalytic processes that enable efficient chemical reactions to occur have been widely used and studied.[5] At times, light promotes these catalytic processes by activation of a dormant catalyst.[6] For example, the lower activity of *cis*-dichloro ruthenium olefin-metathesis catalysts with respect to the corresponding *trans*-dichloro isomers[7] has been exploited for the activation of sulfur-chelated ruthenium benzylidenes by a photoisomerization process.[8] Whereas the photoactivation of ruthenium olefin-metathesis initiators has clear uses in polymer synthesis,[9] the development of a photocatalytic orthogonal process could expand the utility of these catalysts for other synthetic applications. Herein, we show how the order of light irradiation of a latent catalyst and a protected substrate influences the selectivity for the generation of either a five- or six-membered cycloalkene isomer as the preferred final product.

The activation of latent precatalysts **1** and **2** (Scheme 1) by light encouraged us to search for applications of this process in novel light-guided synthetic pathways. Thus, **1** and **2** were irradiated at two different wavelengths in the presence of the benchmark ring-closing-metathesis (RCM) substrate diethyl diallylmalonate (DEDAM). As previously reported, photoisomerization of the precatalysts by irradiation at 350 nm afforded the active *trans* isomers and led to concurrent ring closing of DEDAM.[8a,10] However, when solutions of **1** and **2** in dichloromethane were irradiated with ultraviolet light at 254 nm, the *cis* isomer remained intact, and, as expected, no RCM reaction occurred (see the Supporting Information). Having shown that olefin metathesis could be induced with UV chromatic selectivity, we decided to combine the photoactivation of RCM with an orthogonal photodeprotection reaction. We chose to pursue this approach by using the tris(trimethylsilyl)silyl protecting group (supersilyl),[11,12] a photochemically removable protecting group that may be photocleaved at the selected wavelength, 254 nm, and is not deprotected at 350 nm.



**Scheme 1.** Photoisomerization of sulfur-chelated ruthenium benzylidene complexes.

To study the orthogonality of the system, we prepared 4-[tris(trimethylsilyl)silyloxy]hepta-1,6-diene (**4**) from 1,6-heptadien-4-ol (**3**; Scheme 2a). First, the supersilyl protecting group in **4** was fully cleaved after irradiation for 20 min at 254 nm in $CH_2Cl_2$ with methanol to regenerate **3** (Scheme 2b). Moreover, irradiation of **4** at 350 nm for 1 h did not cleave the protecting group: an essential requisite for the orthogonal system. In a parallel experiment, the olefin-

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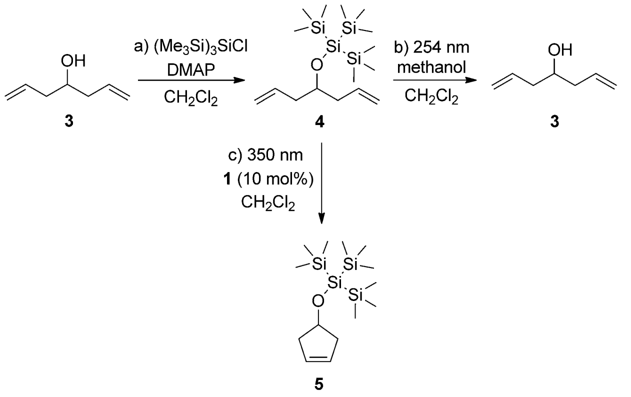
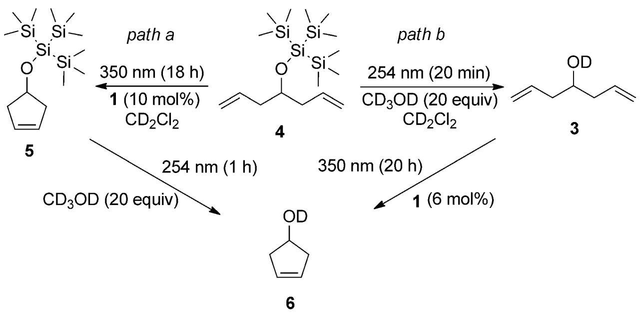


***Scheme 2.*** Orthogonal deprotection–RCM sequence. a) Synthesis of the supersilyl-protected compound **4** from alcohol **3** (69 % yield). b) Irradiation of **4** at 254 nm for 20 min in the presence of methanol (10 equiv) in $CH_2Cl_2$ (quantitative conversion). c) Ring-closing metathesis of **4** provided cyclopentene **5** with 88 % conversion after irradiation for 18 h at 350 nm in $CH_2Cl_2$. DMAP = 4-dimethylaminopyridine.

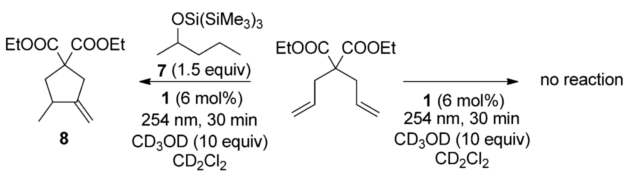
metathesis reactivity of compound **4** in the presence of precatalyst **1** was tested. As expected, UV irradiation of a solution of **4** and **1** in $CH_2Cl_2$ at 350 nm afforded the RCM product **5** (88 % yield; Scheme 2 c).

Once the individual orthogonal processes were secured, a commutative chromatic orthogonal experiment was set up on the basis of two converging pathways (Scheme 3). Path a involved the addition of the precatalyst **1** to a solution of **4**, followed by irradiation at 350 nm to produce cyclopentene **5**. Methanol (20 equiv) was then added, and irradiation at 254 nm afforded compound **6**. Path b required the irradiation of a solution of **4** at 254 nm for 20 min, which led to removal of the silyl protecting group; then **1** was added to the mixture, and irradiation at 350 nm afforded RCM product **6** (see the Supporting Information for full experimental details).



***Scheme 3.*** Commutative chromatically orthogonal sequences.

The photochemical reactions presented in Scheme 3, although one-pot processes, require the external addition of reagents after the first step. A more challenging endeavor would be to perform the reactions just by changing the order of light irradiation without any additional interference throughout the entire process, that is, in a closed system. Thus, a solution of diene **4**, precatalyst **1**, and methanol in $CH_2Cl_2$ was prepared. Irradiation of this solution with UV light, first at 350 nm and later at 254 nm, produced the expected compound **6** with good overall conversion. In contrast, the alternative path, starting with irradiation at 254 nm, provided disappointing results. Even though the complex did not undergo isomerization at 254 nm, it strongly absorbs light in this region, thus leading to a sunscreen effect.[8a,13] Longer irradiation times were required for the photoinduced deprotection owing to short-wave UV absorption by the ruthenium complex, which eventually led to the decomposition of the precatalyst. Furthermore, undesired cycloisomerization[14] was observed. To further investigate potential causes for the occurrence of these side reactions, we irradiated a solution of DEDAM and **1** at 254 nm in the presence of a simple protected alcohol, 2-[tris(trimethylsilyl)silyloxy]pentane (**7**; Scheme 4). Whereas irradiation for 30 min without the protected 2-pentanol did not affect the starting materials, the cycloisomerized product **8** was obtained when **7** was added. Thus, cycloisomerization occurred only when the silyl group was present in the reaction vial. This result falls in line with previous reports of cycloisomerization promoted by ruthenium–benzylidene-type catalysts in the presence of trimethylsilyl vinyl ether[15] and suggests that decomposition products of supersilyl photocleavage affect the latent form of sulfur-chelated ruthenium benzylidene complexes as well. Ruthenium hydride formation in the presence of alcohols or vinyl ethers has been reported previously;[16] however, we could not discern any cycloisomerization process without the addition of the silyl group and UV irradiation at 254 nm, even after adding methanol.



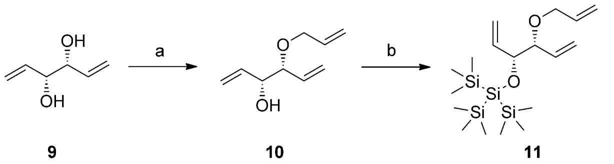
***Scheme 4.*** Influence of the silyl ether **7** on the irradiation of DEDAM with precatalyst **1** at 254 nm in $CH_2Cl_2$.

Further research with other solvents revealed that reduced irradiation times were possible for the photoinduced deprotection when 1,1,2,2-tetrachloroethane (TCE) was used.[17] This finding permitted the photocleavage of the supersilyl group in the presence of the ruthenium complex just by changing the solvent. The adjusted procedure involved mixing diene **4** with methanol (100 equiv) and catalyst **1** (11 mol %) in TCE. First, irradiation at 254 nm provided the alcohol in 30 min; next, irradiation at 350 nm for 21 h ($CH_2Cl_2$ was added at this stage to enhance the photoisomerization of precatalyst **1**) gave the RCM product in over 90 % yield (see the Supporting Information for full experimental details). Cleavage of the protecting group in the presence of the catalyst in this way without triggering metathesis (or other unwanted side reactions) thus provided the foundation for a chromatic orthogonal catalytic process.

The examples described above are commutative; that is, the order of irradiation does not influence the final result.

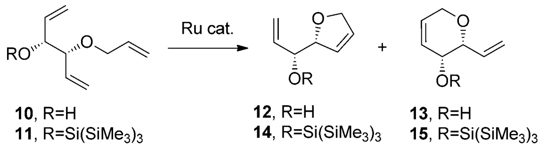
Inspired by the documented property of a supersilyl functional group to influence the stereochemical outcome of reactions,[18] and also by the pioneering studies on triene substrates by Schmidt and Nave,[19] we set out to develop a noncommutative olefin-metathesis catalytic cycle in which the order of irradiation with light of different wavelengths could be used to guide the selectivity of a reaction.

For this purpose, compound **11** containing three carbon–carbon double bonds and a supersilyl ether group was prepared. Diol **9** was selectively allylated to afford triene **10**, which was protected with a tris(trimethylsilyl)silyl group to provide substrate **11** (Scheme 5).



***Scheme 5.*** Synthesis of the triene supersilyl compound **11**. a) Allyl bromide, NaH, THF (58%); b) $(Me_3Si)_3SiCl$, DMAP, $CH_2Cl_2$ (49%).

The regioselectivity of the ring-closing metathesis reaction was studied both in the presence and absence of the supersilyl protecting group with different ruthenium catalysts. Compounds **10** and **11** may independently produce two different RCM products,[20] namely, five- and six-membered heterocycles (Scheme 6), depending on which double bonds participate in the reaction (the formation of a cyclobutene would be disfavored owing to its high steric strain).



***Scheme 6.*** Possible RCM products derived from **10** and **11**.

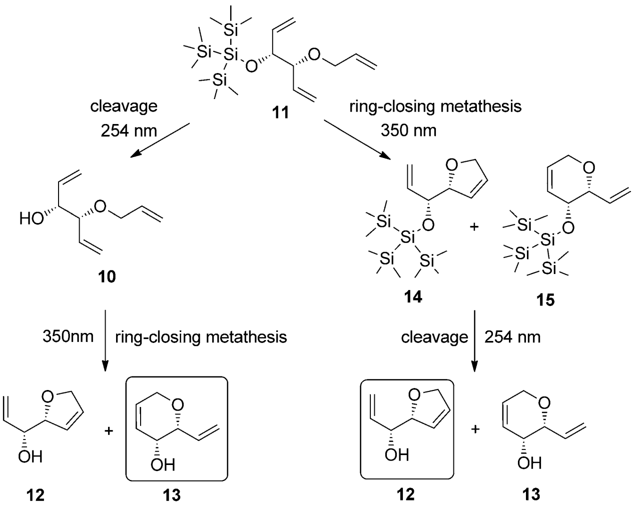
In line with the findings of Schmidt,[19] when substrate **10** was used, the first-generation ruthenium olefin-metathesis catalysts produced five- and six-membered rings as approximately 1:1 mixtures (Table 1). However, the second-generation catalysts provided compound **13** with a six-membered ring as the major product. Notably, the observed regioselectivity with **2** for the formation of a dihydropyran structure is surprisingly high.[19a]

When the bulky substrate **11** was used, a reversal of selectivity was expected with a preference for the five-membered-ring product. Indeed, all ruthenium catalysts tested showed good selectivity for the formation of **14**. Notably, the use of the supersilyl protecting group also enhanced the selectivity for the five-membered-ring product with the second-generation catalysts, in contrast with previous results by Schmidt and Nave when using bulky esters.[19b]

***Table 1:*** RCM of triene **10** or **11** with benzylidene ruthenium precatalysts.[a]

| Catalyst | Conversion [%][b] | | | |
|---|---|---|---|---|
| | **10→12** | **10→13** | **11→14** | **11→15** |
| Grubbs I | 42 | 36 | 99 | 1 |
| Hoveyda–Grubbs I | 51 | 49 | 99 | 1 |
| Grubbs II | 18 | 82 | 87 | 13 |
| Hoveyda–Grubbs II | 26 | 74 | 90 | 10 |
| catalyst **1** | 18[c] | 82[c] | 54[d] | 3[d] |
| catalyst **2** | 12[c] | 88[c] | 87[d] | 12[d] |

[a] Reactions were carried out at room temperature in $CH_2Cl_2$ with methanol (10 equiv) and a catalyst loading of 6 mol% unless otherwise indicated. [b] Conversion was measured by $^1H$ NMR spectroscopy and GC–MS. [c] The reaction was carried out with a catalyst loading of 10 mol% and irradiation at 350 nm for 18 h. [d] The reaction was carried out with a catalyst loading of 15 mol% and irradiation at 350 nm for 60 h.



***Scheme 7.*** Chromatically orthogonal system.

Finally, the orthogonal sequence was examined with triene **11** (Scheme 7). Thus, triene **11** was dissolved with catalyst **1** in $CD_2Cl_2$, and the solution was irradiated at 350 nm for 68 h. The total conversion observed was approximately 80%, with the five-membered-ring compound **14** obtained as the major product (**14**: 62%, **15**: 15%). Next, methanol was added, and irradiation at 254 nm for 2.4 h promoted the desired photocleavage to give the dihydrofuran product **12** with 6:1 selectivity over **13** (**10**: 20%, **12**: 69%, **13**: 11%; Table 2, entry 1). The orthogonal pathway began with the irradiation of **11** at 254 nm for 40 min to afford alcohol **10**. Catalyst **1** was then added, and irradiation at 350 nm for 2 h delivered RCM products **13** and **12** in a 9:1 ratio with full conversion (Table 2, entry 4).

Following the successful development of this noncommutative sequence, closed-system experiments were carried out in which all the reactive components were within the reaction vessel from the start. Once again, upon irradiation first at 350 nm and then at 254 nm, good conversion was observed, and **12** was synthesized selectively (Table 2, entries 2 and 3). With the more active precatalyst **2**, a high conversion of 88% was observed with high selectivity of around 30:1. For the alternative pathway (Table 2, entries 6 and 7), substrate **11**

***Table 2:*** Chromatic synthesis of dihydrofuran **12** and dihydropyran **13**.[a]

| Entry | Catalyst | MeOD [equiv] | System | Irradiation order | Conv. [%][b] **(12/13)** |
|---|---|---|---|---|---|
| 1[c] | **1** | 20 | sequential | 350 nm→254 nm | 80 (6:1) |
| 2[c] | **1** | 5 | closed | 350 nm→254 nm | 46 (10:1) |
| 3[c] | **2** | 10 | closed | 350 nm→254 nm | 88 (28:1) |
| 4[d] | **1** | 5 | sequential | 254 nm→350 nm | 100 (1:9) |
| 5[d] | **2** | 5 | sequential | 254 nm→350 nm | 100 (1:5) |
| 6[e] | **1** | 100 | closed | 254 nm→350 nm | 54 (1:6) |
| 7[e] | **2** | 80 | closed | 254 nm→350 nm | 32 (1:4) |

[a] Reactions were carried out at room temperature in CD$_2$Cl$_2$ with a catalyst loading of 10 mol% unless otherwise indicated. [b] Conversion was measured by $^1$H NMR spectroscopy. [c] Irradiation time: 50–68 h at 350 nm, 40–160 min at 254 nm. [d] Irradiation time: 40 min at 254 nm, 2–16 h at 350 nm. [e] The reaction was carried out in [D$_2$]TCE with a catalyst loading of 11 mol%; CD$_2$Cl$_2$ (0.4 mL) was also added, and the mixture was irradiated at 350 nm overnight.

was mixed with methanol and a catalyst in [D$_2$]TCE, and irradiation at 254 nm provided alcohol **10** after 30 min. The addition of CD$_2$Cl$_2$ and irradiation at 350 nm overnight gave the desired metathesis product **13** with 6:1 selectivity over the five-membered-ring product **12** when precatalyst **1** was used. Notably, in this pathway, the use of the less active precatalyst **1** gave better results, probably as a result of lessened decomposition during the short-wave irradiation period.

In conclusion, we designed, developed, and demonstrated a proof of concept for a novel catalytic chromatically orthogonal system based on a light-sensitive protecting group and a light-triggered latent olefin-metathesis catalyst. Different synthetic pathways were followed by taking advantage of the chromatic selectivity of the latent sulfur-chelated olefin-metathesis precatalyst. Photoisomerization of a *cis*-dichloro ruthenium benzylidene complex and photocleavage of a silyl ether protecting group at different wavelengths enabled the selective production of either dihydrofuran or dihydropyran scaffolds, depending on the order in which the processes were activated. Further development of this concept may lead to the use of chemical systems in which light of different wavelengths can be used to produce desired compounds for smart applications or in environments in which actual physical intervention is precluded.

**Keywords:** chromatic orthogonality · cyclization · heterocycles · olefin metathesis · photochemistry

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[17] Diene **4** was mixed with methanol (10 equiv) in CD$_2$Cl$_2$ or [D$_2$]TCE. After irradiation for 10 min at 254 nm, only 10% protecting-group removal was observed in CD$_2$Cl$_2$ as opposed to about 50% in [D$_2$]TCE; further irradiation for 10 min enabled 70% deprotection in CD$_2$Cl$_2$ versus 96% photocleavage in [D$_2$]TCE. For experimental details, see the Supporting Information.

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