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Stereoselective Synthesis of Substituted Tetrahydropyrans via Domino Olefin Cross-Metathesis/Intramolecular Oxa-Conjugate Cyclization

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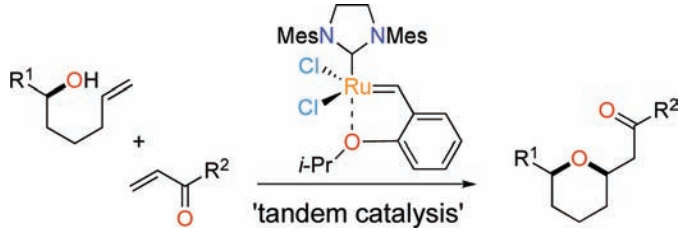
ABSTRACT



A novel strategy for the stereoselective synthesis of substituted tetrahydropyrans has been developed on the basis of a domino olefin cross-metathesis/intramolecular oxa-conjugate cyclization catalyzed by the Hoveyda−Grubbs second-generation catalyst.

Domino reactions are able to build up complex molecules by forming and/or cleaving multiple bonds in a single reaction vessel.[1] Due to their atom- and step-economical aspects, the development of domino reactions becomes increasingly important nowadays toward realization of sustainable chemistry. The ruthenium alkylidene complexes, commonly known as the Grubbs catalysts, have emerged as an indispensable tool for olefin metathesis reactions due to their high reactivity, ease of handling, and commercial availability.[2] The Grubbs catalysts are also known to tolerate a wide range of functionalities, as their numerous applications can be seen in the total synthesis of complex natural products.[3] Meanwhile, recent reports have described domino reactions that involve nonmetathetic applications of the Grubbs catalysts.[4–10] The exceptionally high chemoselectivity coupled with potential utility in nonmetathetic reactions render the Grubbs catalysts as an attractive source for inspiring domino reactions. Nevertheless, there have been only a few reports that describe domino reactions catalyzed solely by a Grubbs catalyst;[5,6,7e,10] the use of an additive is necessary for some of the reported domino reactions.[7a−d,8,9]

Substituted tetrahydropyrans are a common structural motif that can be found in a diverse array of biologically significant natural products, such as marine macrolides and polycyclic

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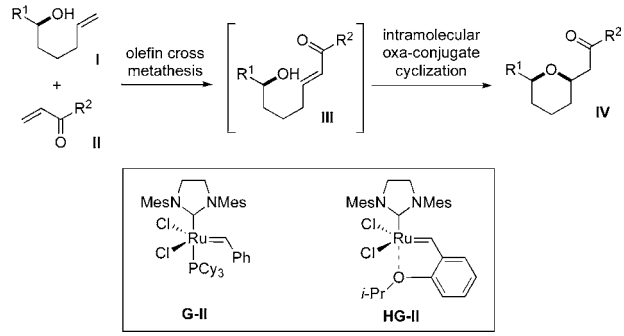
ethers.[11] There is a continuous demand for atom- and step-economical methods for the synthesis of substituted tetrahydropyrans. Herein, we report the development of a domino olefin cross-metathesis/intramolecular oxa-conjugate cyclization[12] by using the Hoveyda−Grubbs second-generation catalyst (**HG-II**),[13] which enables a rapid, efficient, and stereoselective synthesis of substituted tetrahydropyrans from readily available acyclic materials in a single flask.

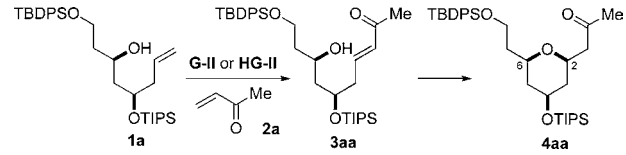
We envisioned that olefin cross-metathesis of a hydroxy alkene **I** and an enone **II** catalyzed by the Grubbs second-generation catalyst (**G-II**) or **HG-II** should generate a hydroxy enone **III**, which would undergo intramolecular oxa-conjugate cyclization to furnish a tetrahydropyran **IV** under suitable conditions (Scheme 1). It is well accepted that oxa-conjugate addition reaction of an alcohol to an enone can be accomplished either by deprotonation with a strong base to activate a weakly nucleophilic hydroxy group or by activation of a carbonyl group with a Lewis or Brønsted acid. We thought a domino olefin cross-metathesis/intramolecular oxa-conjugate cyclization would be achievable by in situ activation of intermediate **III** with an appropriate Lewis or Brønsted acid. Importantly, the product tetrahydropyran **IV** is synthetically useful in subsequent transformations, such as aldol reaction or acetalization, by exploiting the carbonyl functionality.[14]

Scheme 1. Concept of the Present Work



We initially used δ-hydroxy olefin **1a**[15] as a model compound to probe its reactivity toward olefin cross-metathesis with methyl vinyl ketone **2a** (Table 1). Treatment of a mixture of **1a** and **2a** with **HG-II** (10 mol %) in CH_2Cl_2 at 35 °C for 12 h gave hydroxy enone **3aa** in 88% yield as the sole isolable product (entry 1). In contrast, when the reaction was performed in 1,2-dichloroethane at 80 °C for 15 h, tetrahydropyran **4aa** was directly obtained in 80% yield (2,6-*cis*/2,6-*trans* = 9:1, entry 2). **G-II** was less effective than **HG-II** for the present purpose, as the reaction using **G-II** resulted in incomplete conversion even after 15 h at 80 °C, giving **4aa** in 31% yield with poor diastereoselectivity (entry 3). Upon microwave (MW) irradiation[16] of a mixture of **1a**, **2a**, and **HG-II** in CH_2Cl_2 at 100 °C for 30 min, **4aa** was isolated in 94% yield (2,6-*cis*/2,6-*trans* = 7:1, entry 4).

Table 1. Screening of the Reaction Conditions



			product(s)	
			3aa	**4aa** (%)
entry	catalyst	conditions	(%)	(*cis*/*trans*)[a]
1	**HG-II**	CH_2Cl_2, 35 °C, 12 h	88	
2	**HG-II**	$ClCH_2CH_2Cl$, 80 °C, 15 h		80 (9:1)
3	**G-II**	$ClCH_2CH_2Cl$, 80 °C, 15 h	19	31 (2:3)[b]
4	**HG-II**	CH_2Cl_2, 100 °C (MW), 30 min		94 (7:1)

[a] Ratio of 2,6-*cis* and 2,6-*trans* diastereomers was estimated by ^{1}H NMR analysis (500 or 600 MHz, $CDCl_3$). [b] **1a** was recovered in 43% yield.

Encouraged by these preliminary results, we examined the use of several olefin coupling partners in the domino process (Table 2). Coupling of **1a** with enones **2b**−**e** (1.5 equiv) under the MW conditions (10 mol % **HG-II**, CH_2Cl_2, 100 °C, 20−30 min) provided the respective tetrahydropyrans **4ab**−**ae** in good yields with synthetically useful levels of diastereoselectivity (entries 1−4).[17]

The scope of the domino reaction was further explored using δ-hydroxy olefins **1b** and **1c** (Table 3). In all cases, the product tetrahydropyrans **4ba**−**bc**,**ca**,**cb** were exclusively isolated as 2,6-*cis* isomers in good to excellent yields.

At this stage, we tried to figure out an actual active species for the intramolecular oxa-conjugate cyclization process by several control experiments (Scheme 2). When a solution of **3aa** with or without **HG-II** (10 mol %) in CH_2Cl_2 was heated at 100 °C (MW) for 30 min, **3aa** was recovered almost quantitatively with no sign of cyclization by ^{1}H NMR analysis. In contrast, MW heating of a mixture of **3aa**, styrene (1 equiv),

(5) (a) Seigal, B. A.; Fajardo, C.; Snapper, M. L. *J. Am. Chem. Soc.* **2005**, *127*, 16329–16332. (b) Faulkner, J.; Edlin, C. D.; Fengas, D.; Preece, I.; Quayle, P.; Richards, S. N. *Tetrahedron Lett.* **2005**, *46*, 2381–2385.

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(8) Kim, B. G.; Snapper, M. L. *J. Am. Chem. Soc.* **2006**, *128*, 52–53.

(9) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700–6701.

(10) Chen, J.-R.; Li, C.-F.; An, X.-L.; Zhang, J.-J.; Zhu, X.-Y.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489–2492.

(11) For recent reviews, see: (a) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053. (b) Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683–2723.

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(13) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

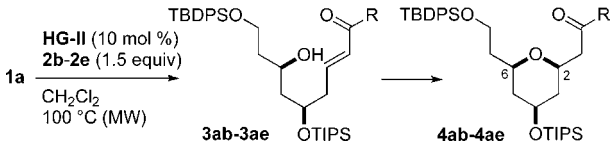
(14) For recent examples, see: (a) O'Neil, G. W.; Ceccon, J.; Benson, S.; Collin, M.-P.; Fasching, B.; Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9940–9945. (b) Fürstner, A.; Fenster, M. D. B.; Fasching, B.; Godbout, C.; Radkowski, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 5506–5510.

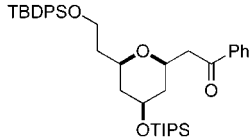
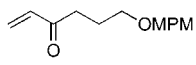
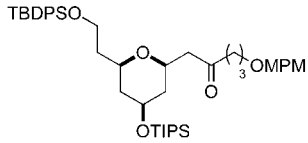
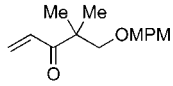
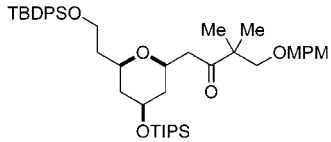
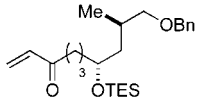
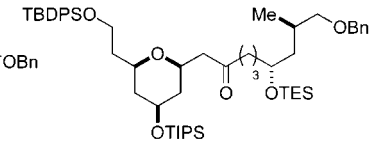
(15) Fuwa, H.; Sasaki, M. *Org. Lett.* **2010**, *12*, 584–587.

(16) For a recent review on microwave-assisted olefin metathesis, see: Coquerel, Y.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 1125–1132.

(17) The reaction of **1a** with crotonaldehyde in the presence of **HG-II** under the MW conditions gave a mixture of the corresponding hydroxy enal (60%) and tetrahydropyran (19%, *cis*/*trans* = 5:1), while that with methyl acrylate gave the corresponding hydroxy enoate in 98% yield.

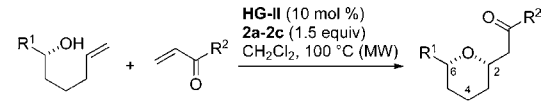
Table 2. Reaction of **1a** with a Variety of Coupling Partners

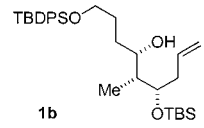
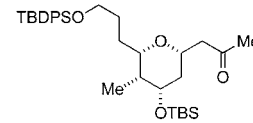
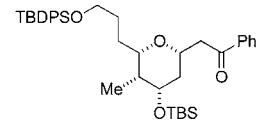
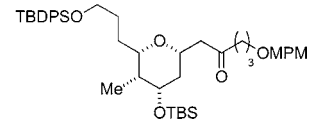
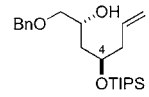
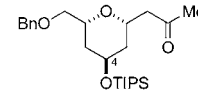
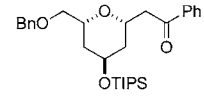


entry	enone	product (yield, *cis*/*trans*)[a]
1	 **2b**	 **4ab** (79%, 14:1)
2	 **2c**	 **4ac** (84%, 10:1)
3	 **2d**	 **4ad** (70%, 10:1)
4	 **2e**	 **4ae** (94%, 8:1)

[a] All reactions were carried out using **HG-II** (10 mol %) and **2b**−**e** (1.5 equiv) in CH_2Cl_2 at 100 °C (MW) for 20−30 min. Ratio of 2,6-*cis* and 2,6-*trans* diastereomers was estimated by ^{1}H NMR analysis (500 MHz).

Table 3. Synthesis of a Variety of 2,6-*cis*-Tetrahydropyrans[a]



entry	olefin	enone	product (yield, *cis*/*trans*)
1	 **1b**	**2a**	 **4ba** (97%, >20:1)
2	**1b**	**2b**	 **4bb** (77%, >20:1)
3	**1b**	**2c**	 **4bc** (94%, >20:1)
4	 **1c**[b]	**2a**	 **4ca** (95%, >20:1)[b]
5	**1c**[b]	**2b**	 **4cb** (79%, >20:1)

[a] All reactions were performed using **HG-II** (10 mol %) and **2a**−**c** (1.5−5 equiv) in CH_2Cl_2 at 100 °C (MW) for 20−30 min. The ratio of 2,6-*cis* and 2,6-*trans* diastereomers was estimated by ^{1}H NMR analysis (500 MHz). [b] Approximately 10:1 mixture of diastereomers at the C4 stereogenic center.

methyl acrylate (1.5 equiv), and **HG-II** (10 mol %) in CH_2Cl_2 at 100 °C for 30 min effected complete consumption of **3aa** as judged by TLC and ^{1}H NMR analysis. After purification by flash chromatography on silica gel, **4aa** was isolated in 66% yield (2,6-*cis*/2,6-*trans* = 9:1) along with methyl *trans*-cinnamate (90% yield based on styrene). From these experiments, we assumed an active ruthenium species responsible for the cyclization step must be generated in situ after initiation of the cross-metathesis step. Previous related reports[8,9] described ruthenium methylidene complex [$(H_2IMes)(Cl)_2Ru{=}CH_2$] (H_2IMes = 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene) generated in the propagation step of olefin metathesis to be the Lewis acidic species. However, the possibility that ruthenium species resulting from decomposition of the ruthenium methylidene complex under high temperature conditions (e.g., ruthenium hydride species)[18] may act as a Lewis acid led us to perform the domino reaction in the presence of 2,6-dichloro-1,4-benzoquinone.[19] In the event, reaction of **1a** and **2a** in the presence of 10 mol % of **HG-II** and 0.2 equiv of 2,6-dichloro-1,4-benzoquinone in CH_2Cl_2 at 100 °C (MW) for 30 min gave **4aa** in 17% yield along with δ-hydroxy enone **3aa** in 73% yield. Thus, the cyclization step of the domino reaction obviously slowed down in the presence of 2,6-dichloro-1,4-benzoquinone (cf. Table 1, entry 4). This result suggested that the cyclization of the intermediary δ-hydroxy enone would be mainly promoted by the ruthenium hydride species derived from degradation of the thermally unstable ruthenium methylidene complex.

To probe the origin of the observed diastereoselectivity of the cyclization process, control experiments were next performed (Scheme 3). Treatment of **3aa** with NaH in THF at room temperature gave **4aa** in 89% yield with a moderate preference for the 2,6-*trans* product (2,6-*cis*/2,6-*trans* = 1:2). This product was heated in CH_2Cl_2 at 100 °C (MW) for 30 min together with styrene (1 equiv), methyl acrylate (1.5 equiv), and **HG-II** (10 mol %). ^{1}H NMR analysis of the crude reaction mixture showed that the diastereomer ratio of **4aa** was not

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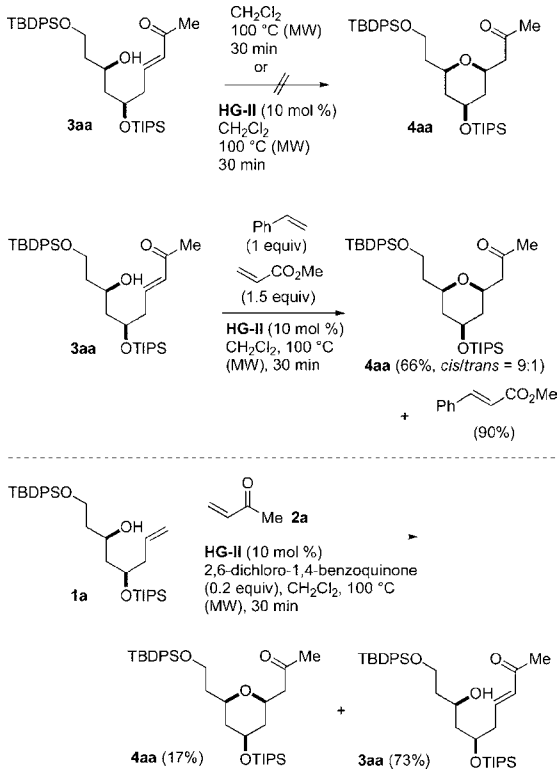
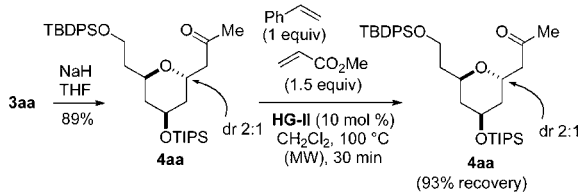
(19) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

Scheme 2. Control Experiments To Elucidate the Actual Active Species Responsible for the Cyclization Step



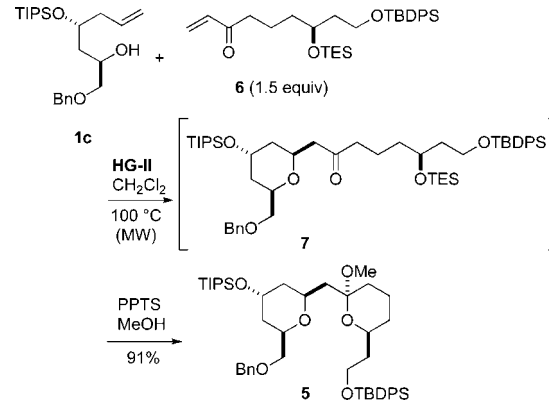
changed at all. This result suggested that the 2,6-*cis* and 2,6-*trans* products would not equilibrate under the reaction conditions and that the 2,6-*cis* products should arise from kinetic control.[20]

Scheme 3. Control Experiments To Elucidate the Origin of the Stereoselectivity of the Cyclization Step



A concise synthesis of methylene bis-tetrahydropyran **5**, a common structural motif found in several marine macrolide natural products,[21] showcases the synthetic feasibility of our domino reaction (Scheme 4). Coupling of **1c** and **6** (1.5 equiv) under the MW conditions (10 mol % **HG-II**, CH_2Cl_2, 100 °C) cleanly provided ketone **7**.[22] Addition of PPTS and MeOH to the reaction flask at room temperature smoothly effected methyl acetalization with concomitant loss of the TES group, giving methyl acetal **5** in 91% yield as a single stereoisomer after purification by flash chromatography on silica gel. Significantly, four bonds and two stereogenic centers were newly formed with complete stereoselection in a single reaction vessel.

Scheme 4. Stereoselective Synthesis of Methylene Bis-tetrahydropyran **5**



In conclusion, we developed a novel domino olefin cross-metathesis/intramolecular oxa-conjugate cyclization, which provides a variety of substituted tetrahydropyrans in good to excellent yields in a stereoselective manner from readily available acyclic precursors. Importantly, the present domino reaction is catalyzed by **HG-II** alone at elevated temperatures, which represents a new nonmetathetic application of the Grubbs catalysts and demonstrates the power and efficiency of "tandem catalysis" for the synthesis of complex molecules.[23] Application of the present domino reaction to the total synthesis of natural products is currently under investigation.

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Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) In a separate experiment, ketone **7** was isolated in 90% yield as a single stereoisomer after purification by flash chromatography on silica gel. Treatment of **7** with PPTS in MeOH/CH_2Cl_2 at room temperature gave methyl acetal **5** in 99% yield. See the Supporting Information for details.

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