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Cross Metathesis of α-Methylene Lactones II: γ- and δ-Lactones

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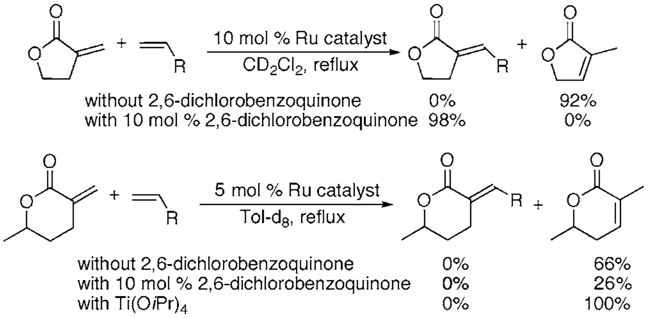
ABSTRACT



The cross metathesis reactivities of α-methylene-γ-butyrolactone and an α-methylene-δ-lactone have been investigated. α-Methylene-γ-butyrolactone undergoes rapid and efficient olefin isomerization in the presence of second-generation metathesis catalysts. However, cross metathesis can be achieved with the additive 2,6-dichlorobenzoquinone. In contrast, the α-methylene-δ-lactone neither isomerizes nor couples under similar conditions.

We recently reported[1] that α-alkylidene-β-lactones could be prepared by cross metathesis (CM) of α-methylene-β-lactones and terminal alkenes (Figure 1). The results represented the first published examples of CM with strained exocyclic enones and were remarkable for their high yields and atypical Z-selectivity. The efficiency of the coupling reactions with these strained enoates spurred us to explore the scope of CM with other classes of α-methylene lactones. It was anticipated that larger ring systems would exhibit metathesis activity similar to that of α-methylene-β-lactones. We report herein our unexpected results with the simple substrates α-methylene-γ-butyrolactone (**1**) and α-methylene-δ-lactone **2**.

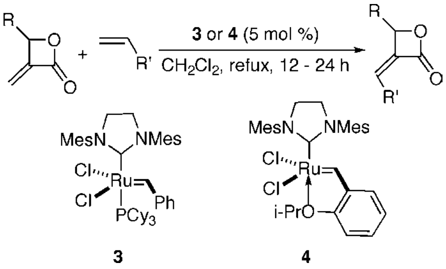


Figure 1. CM reactions of α-methylene-β-lactones.

Initial investigations began by reacting α-methylene-γ-butyrolactone with 1-acetoxy-9-decene under the conditions developed for CM of α-methylene-β-lactones (Table 1, entry 1). Interestingly, isomerization to enone **6** was the sole reaction pathway observed. Olefin isomerization with ruthenium carbene catalysts is well documented.[2] Postulating that the PCy_3 ligand might induce isomerization, reaction using phosphine-free catalyst **4** was attempted (entry 2), and the outcome was the same. As a control experiment, **1** and the acetate cross partner were heated to determine if

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(1) Raju, R.; Howell, A. R. *Org. Lett.* **2006**, *8*, 2139−2141.

(2) (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390−13391. (b) Alcaide, B.; Almendros, P. *Chem.−Eur. J.* **2003**, *9*, 1258−1262. (c) Finnegan, D.; Seigal, B. A.; Snapper, M. L. *Org. Lett.* **2006**, *8*, 2603−2606.

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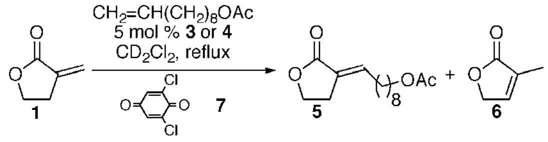
Table 1. Preliminary Investigation of CM of α-Methylene-γ-butyrolactone (**1**)[a]



entry	catalyst	**7** (equiv)	product distribution[b] **5**	**6**
1	**3**	none	0	92
2	**4**	none	0	87
3	none	none	–	0
4	**3**	none	–	98[c]
5	**4**	none	–	70[c]
6	**3**	0.10	23	25
7	**4**	0.10	67	0
8	**4**	0.10	98[d]	0

[a] A preliminary report of this data was disclosed at the ACS meeting in San Francisco, CA, September 2006. [b] Determined by ^{1}H NMR. [c] Absence of a cross partner. [d] 10 mol % of **4**, added in two portions.

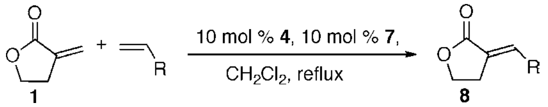
isomerization was being promoted thermally or even perhaps by trace acid (entry 3). The result was clear: heat alone did not promote isomerization.

There have been a variety of explanations for undesirable olefin isomerization in the presence of ruthenium-based olefin metathesis catalysts. We reasoned that a ruthenium hydride complex was fueling the isomerization of **1**. To address the possibility that the cross partner might be responsible for the formation of a ruthenium hydride complex, we heated **1** with either **3** or **4** in the absence of a cross partner (entries 4 and 5). Isomerization was sluggish using **4** (70% after 24 h) in comparison to **3** (98%, 20 min). These outcomes suggest that **1** is a viable hydride donor, and this can be rationalized by a π-allyl or a σ-alkyl/π-allyl mechanism.[3] Although isomerization was interesting, our goal was to achieve CM.

Electron-deficient benzoquinones have been identified[4] as efficient additives for preventing isomerization in substrates such as allylic alcohols and amines. Indeed, 2,6-dichlorobenzoquinone (**7**) (10 mol %) suppressed the isomerization of **1**. Interestingly, isomerization was not completely terminated with catalyst **3** (Table 1, entry 6) but was with phosphine-free catalyst **4**, although with incomplete conversion (entry 7). Adding 10 mol % of catalyst **4** in two portions over 24 h allowed for complete consumption of **1** (entry 8).

Lactone **1** was coupled with a variety of terminal olefins in the presence of **4** and **7** in refluxing CH_2Cl_2 (Table 2).[5] A stoichiometric or slight excess of the terminal alkene was employed for all cases except for the formation of **8b** (entry 2). Considerable conversion to **8b** was observed after 4 h

Table 2. CM Reactions of α-Methylene-γ-butyrolactone (**1**)



entry	R[a]	yield (%)[b]	*E*/*Z*
1	$(CH_2)_2CH_3$	**8a**, 83	20:1
2	CH_3[c]	**8b**, 93	6:1
3	$(CH_2)_8OAc$	**8c**, 80	15:1
4	$(CH_2)_2OAc$	**8d**, 75	10:1
5	$(CH_2)_2Br$	**8e**, 43	20:1
6	CH_2Cl	**8f**, 44	20:1

[a] For experimental conditions, see footnote 5. [b] All yields are isolated yields for the combined *E*/*Z* isomers. [c] 2-Methyl-2-butene (10 equiv) is the cross partner.

(83%) using 10 equiv of 2-methyl-2-butene and 5 mol % of **4**. In other cases, increasing the equivalents of the cross partner decreased the rate of formation of **8**. For entries 1, 3, and 4, a maximum of 69% conversion was observed spectroscopically using 5 mol % of **4**; to obtain complete conversion, an additional 5 mol % was required. The low yields obtained for **8e** and **f** were a consequence of incomplete conversion, even using 10 mol % of **4**. Moreover, increasing catalyst loading (up to 25 mol %) did not improve the yields.

On the basis of the CM results with **1**, our initial expectation was that **2** would behave in a similar fashion. However, **2** failed to undergo either isomerization or significant CM in the presence of catalysts **3** and **4** (Table 3, entries 1 and 2). Heating for a lengthy period (4 days) or increasing catalyst loading did not alter the outcome. Running the reaction at higher temperature (entry 3) gave no cross product but did result in isomerization. Although the addition of **7** suppressed isomerization somewhat (from 66% to 26%, entry 4), it did not promote CM. Puzzled by the lack of reactivity of **2**, we postulated that the catalyst might be forming a complex with the substrate.[6] To address this possibility, a Lewis acid, $Ti(O^{i}Pr)_4$ (**11**), was added. In toluene, but not dichloromethane, complete isomerization occurred within 8 h (entries 5 and 6). No CM was observed, even in the presence of **7** (entry 7), although this may be a reflection of incompatability of **11** and **7**. These results do not mean that CM cannot be achieved with α-methylene-δ-lactones. For example, HOAc[4b] promoted CM and sup-

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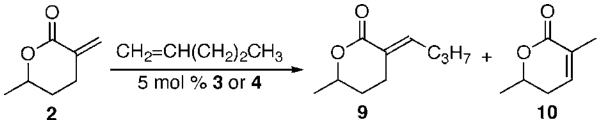
(3) Schmidt, B. *Eur. J. Org. Chem.* **2004**, *2004*, 1865–1880 and references therein.

(4) (a) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415. (b) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–1716.

(5) **General Cross Metathesis Protocol.** The olefin cross partner (1–1.5 equiv, except for entry 2) was added to a solution of lactone **1** (1 equiv) in CH_2Cl_2 (0.3–0.4 M in lactone). Additive **7** (0.10 equiv) was added followed by the addition of catalyst **4** (0.05 equiv) to the solution, which was heated under N_2 at reflux for 12 h. After 12 h, 0.05 equiv of more catalyst was added to the reaction mixture. The reaction was monitored by ^{1}H NMR. Upon consumption of **1**, the solution was cooled and concentrated in vacuo, and the brown residue was purified by flash chromatography on silica gel.

(6) (a) Furstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136. (b) Wipf, P.; Weiner, W. S. *J. Org. Chem.* **1999**, *64*, 5321–5324. (c) Bai, C.-X.; Lu, X.-B.; He, R.; Zhang, W.-Z.; Feng, X.-J. *Org. Biomol. Chem.* **2005**, *3*, 4139–4142. (d) Yang, Q.; Xiao, W. J.; Yu, Z. *Org. Lett.* **2005**, *7*, 871–874.

Table 3. Preliminary Investigation of CM of α-Methylene-δ-lactone (**2**)



				product distribution[c]	
entry	catalyst	additive[a]	solvent[b]	**9**	**10**
1	**3**	none	CD_2Cl_2	19	0
2	**4**	none	CD_2Cl_2	11	0
3	**3**	none	Tol-d_8	0	66
4	**3**	**7**	Tol-d_8	0	26
5	**3**	**11**	CD_2Cl_2	0	0
6	**3**	**11**	Tol-d_8	0	100
7	**3**	**7** and **11**	Tol-d_8	0	100
8[d]	**3**	HOAc	CD_2Cl_2	54	trace

[a] 10 mol % of **7**, 20 mol % of **11**, and/or 150 mol % of HOAc employed in appropriate entries. [b] Reactions using CD_2Cl_2 and Tol-d_8 were heated at reflux. [c] Determined by ^{1}H NMR. Entries 1−5 reflect conversion after 48 h. Entries 6 and 7 reflect conversion after 8 h. [d] 10 mol % of **3** added in two portions; conversion after 36 h.

pressed isomerization (entry 8). However, given the catalyst loading (10 mol %) and inefficient conversion (maximum, 54% at 36 h), HOAc does not appear to be an optimal additive. From these results, it is apparent that under standard conditions, even with typical additives, CM does not proceed efficiently. Nevertheless, it is germane that complete isomerization occurs with **11**, and CM proceeds to some extent with HOAc. This suggests that there may be some combination of additives or a superior additive that would permit productive CM.

In conclusion, the CM reactivities of α-methylene-γ-lactone **1** and α-methylene-δ-lactone **2** have been compared to our previously described results with β-lactones. In contrast to the ease of CM of β-lactones, the CM of these larger cyclic enoates is sluggish and hampered by competitive isomerization. We have circumvented isomerization of **1** using **7** and have effectively promoted CM with reasonable yields. We are not unmindful of the high catalyst loading for **1** to undergo CM, but this may also reflect substrate−catalyst complexation. In sharp contrast, δ-lactone **2** neither isomerizes nor couples to any significant extent under conditions used with β-lactones and **1**. It is reasonable to postulate that as the ring size increases a stable chelate may form, thus sequestering the active catalyst and inhibiting metathesis. This chelation was reduced at higher temperatures, but then only unwanted isomerization was observed. Lewis acid **11** efficiently displaced the bound catalyst, but, once again, isomerization was the only reaction observed. HOAc suppressed isomerization and modestly promoted CM. A survey of additives might reveal one compatible with **2**. We feel that the CM reactivity of these four-, five-, and six-membered α-methylene lactones reveals distinct behaviors that were not predictable a priori. These results provide a foundation for further exploration of these systems.

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Supporting Information Available: Experimental procedures and characterization data, as well as copies of high-resolution ^{1}H and ^{13}C NMR spectra for those new compounds for which elemental analyses are not reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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