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Cross-Metathesis between α-Methylene-γ-butyrolactone and Olefins: A Dramatic Additive Effect

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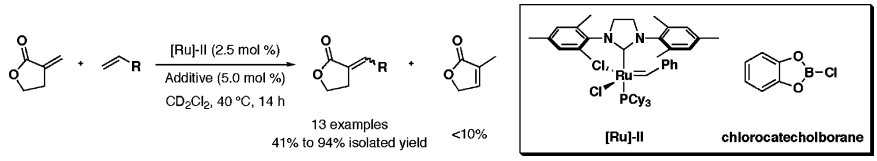
ABSTRACT



Olefin cross-metathesis between α-methylene-γ-butyrolactone and terminal olefins is described. Moderate to excellent yields of α-alkylidene-γ-butyrolactones were obtained with high *E*-stereoselectivity in the presence of low catalyst loading in refluxing CH_2Cl_2. In addition, the use of various additives was found to have a dramatic effect on the efficiency of the cross-metathesis (CM) process by circumventing the formation of the isomerized byproduct.

The α-alkylidene-γ-butyrolactone substructure has attracted particular attention not only for being present in a wide range of biologically active natural products[1] (Figure 1) but also as starting material in various synthetic transformations. They can undergo reduction,[2] oxidation,[3] aziridination,[4] 1,3-dipolar[5] and Diels−Alder[6] cycloadditions, nucleophilic conjugate additions,[6] and intramolecular Stetter reactions.[7]

Since its early days, almost half a century ago, olefin cross-metathesis (CM) has become one of the most valuable methods for the construction of carbon−carbon bonds.[8,9] Over the past decade, the commercial availability of well-defined catalysts, such as the molybdenum alkoxyimido

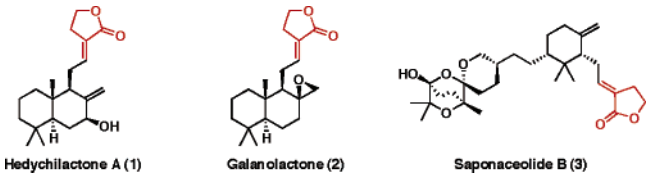


Figure 1. Natural products bearing the α-alkylidene-γ-butyrolactone substructure.

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alkylidene [Mo]-**I** (Schrock's catalyst)[10] and the ruthenium benzylidene catalysts [Ru]-**I** (Grubbs first-generation catalyst),[11] [Ru]-**II** (Grubbs second-generation catalyst),[12] and [Ru]-**III** (Hoveyda−Grubbs catalyst)[13] (Figure 2), has expanded the variety of functional groups amenable to CM and thus made olefin metathesis practical and useful in organic synthesis. As a consequence, olefin CM has been widely used in the synthesis of various drugs and other complex natural products.[14]

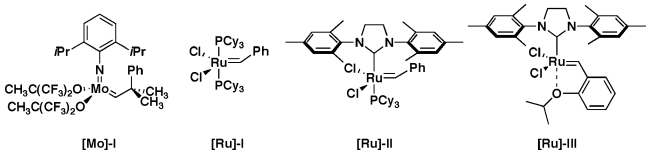
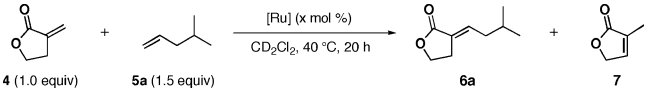


Figure 2. Commercially available ruthenium metathesis complexes.

Whereas metathesis reactions on substrates bearing various types of functionalities are fully documented in the literature, to our knowledge, only one example of a CM reaction involving an exocyclic enone has been reported so far.[15] This example concerns the CM reaction between α-methylene-β-lactones and various terminal olefins. Herein, we wish to report our endeavor focused on the development of a highly efficient CM between α-methylene-γ-butyrolactone and a large variety of olefinic partners by using additives which tend to limit the formation of the undesired isomerized byproduct.

To select the most suitable catalyst along with the best reaction conditions, preliminary experiments were carried out using a slight excess of 4-methylpentene (1.5 equiv) as the olefinic partner. Due to the volatility of both the starting material and the isomerized byproduct, the reactions were performed in refluxing CD_2Cl_2 and directly analyzed by ^1H NMR (Table 1). Interestingly, no conversion of the starting material was observed when using 10 mol % of either [Ru]-**I** or [Ru]-**III** (Table 1, entries 1 and 6). On the other hand, the use of [Ru]-**II**, under otherwise identical conditions, led to a quasi 1:1 mixture of the desired coupled product **6a** and the undesired isomerized byproduct **7**, along with the unreacted starting material **4** (**6a**/**7**/**4** = 42:48:10, Table 1, entry 2). Olefin isomerization with ruthenium catalysts is a well-known process which has been reported by several groups.[16] Unfortunately, this undesired side reaction is detrimental for the efficiency of the CM. Therefore, we decided to focus our attention on developing conditions that would eliminate, if not minimize, the formation of **7**.

Table 1. Influence of the Catalyst on the Reaction Selectivity[a]



4 (1.0 equiv) + **5a** (1.5 equiv) → **6a** + **7**

		NMR ratio[b] (%)		
entry	catalyst	**4**	**6a**	**7**
1	[Ru]-**I** (10 mol %)	100	0	0
2	[Ru]-**II** (10 mol %)	10	42	48
3	[Ru]-**II** (5.0 mol %)	9	55	36
4	[Ru]-**II** (2.5 mol %)	31	50	19
5	[Ru]-**II** (1.0 mol %)	46	44	10
6	[Ru]-**III** (10 mol %)	100	0	0

[a] All reactions were carried out on a 0.5 mmol scale using 1.5 equiv of olefin in refluxing CD_2Cl_2. [b] Ratio determined by ^1H NMR of the crude reaction mixture.

First, lowering the catalyst loading from 10 to 1 mol % decreased the amount of byproduct **7** formed. However, the level of conversion also dropped from 90% to 54% (Table 1, entries 3−5).

It is well documented that, if a chelation of the evolving carbene occurs with a functional group present in the starting material such as the lactone, the catalyst can be complexed in the form of an unreactive intermediate which will prevent the CM from taking place. Thus, to further decrease the amount of **7** formed, the influence of various additives, which would compete with the ruthenium carbene for the coordination, was studied.[17]

All the reactions were performed using 1.5 equiv of 4-methylpentene, 2.5 mol % of [Ru]-**II** catalyst, and 5.0 mol % of the selected additive in refluxing CD_2Cl_2. The results are reported in Table 2.

Interestingly, whereas complete conversion of the starting material was observed in almost all cases, the product distribution varied from one additive to another. Although the use of chlorodicyclohexylphosphine (Cy_2PCl) favored the formation of the undesired isomerized byproduct **7** (**6a**/**7**/**4** = 16:84:0, Table 2, entry 2), chlorodiphenylphos-

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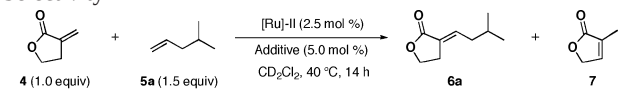
Table 2. Influence of the Additives on the Reaction Selectivity[a]



entry	additive	NMR ratio[b] (%) 4	6a	7	isolated yield (%) 6a
1	-	31	50	19	48
2	Cy_2PCl	0	16	84	14
3	Ph_3PO	0	60	40	56
4	Cy_3PO	0	67	33	64
5	Ph_3As	0	69	31	63
6	Ph_2PCl	0	88	12	71
7		14	86	0	77
8		0	91	9	87

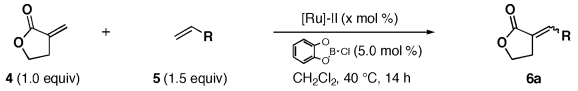
[a] All reactions were carried out on a 0.5 mmol scale using 1.5 equiv of olefin in refluxing CD_2Cl_2. [b] Ratio determined by ^1H NMR of the crude reaction mixture.

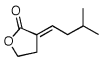
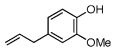
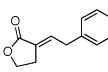
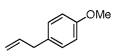
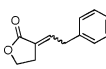
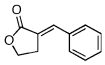
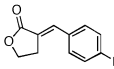
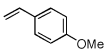
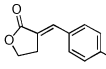
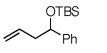
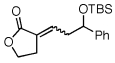
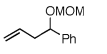
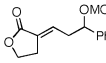
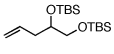
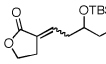
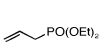
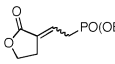
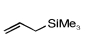
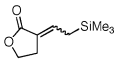
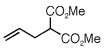
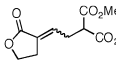
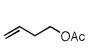
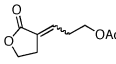
phine (Ph_2PCl) (**6a**/**7**/**4** = 88:12:0, Table 2, entry 6), 2,6-dichloro-1,4-benzoquinone (**6a**/**7**/**4** = 86:0:14, Table 2, entry 7), and chlorocatecholborane (**6a**/**7**/**4** = 91:9:0, Table 2, entry 8) led to the formation of the desired α-alkylidene-γ-butyrolactone **6a** with isolated yields ranging from 71% to 87%. Moreover, when using 2,6-dichloro-1,4-benzoquinone as the additive, complete inhibition of the isomerization process was observed as no trace of **7** was detected by ^1H NMR of the crude reaction mixture. Even though the reaction did not reach complete conversion after 14 h in refluxing CD_2Cl_2, under these conditions the coupled product could be isolated in 77% yield. Unfortunately, the effect of this specific additive appeared to be inconsistent depending on the olefinic partner used. For example, the CM reaction between α-methylene-γ-lactone **4** and eugenol **5b**, using 2,6-dichloro-1,4-benzoquinone (5.0 mol %) as the additive, led to only 15% yield of the desired CM product, along with 11% of the endocyclic enone byproduct **7** was formed. Finally, increasing the amount of 2,6-dichloro-1,4-benzoquinone from 5.0 to 10.0 mol % completely stalled the reaction as no conversion of the starting material was observed.

Taking these results into account, we ran the experiments in CH_2Cl_2 using chlorocatecholborane (5.0 mol %) as the additive under otherwise identical conditions. The results are reported in Table 3.

Hence, when α-methylene-γ-butyrolactone **4** and 1.5 equiv of olefin **5b** were heated in the presence of 2.5 mol % of [Ru]-**II** catalyst, the desired coupled product **6b** was isolated in 86% yield as a single isomer (Table 3, entry 2). The (*Z*)-isomer could not be detected by either ^1H or ^{13}C NMR, thus suggesting a selectivity superior to 95:5 in favor of the (*E*)-isomer. Interestingly, **4** reacted with **5c** to give the desired product **6c** in 54% isolated yield and a 10:1 ratio of

Table 3. Screening of a Range of Reacting Olefinic Partners[a]



entry	olefin		product		method / yield (%)	E:Z[c]
1		**5a**		**6a**	A[d] / 87[b]	>20:1
2		**5b**		**6b**	A / 86	>20:1
3		**5c**		**6c**	A / 54	10:1
4					B[e] / 70	10:1
5		**5d**		**6d**	A / 67	>20:1
6		**5e**		**6e**	A / 65	>20:1
7		**5f**		**6f**	A / 85	>20:1
8		**5g**		**6g**	A / 94	10:1
9		**5h**		**6h**	A / 51	>20:1
10					B / 88	>20:1
11		**5i**		**6i**	A / 72	8:1
12		**5j**		**6j**	A / 45	5:1
13					B / 59	5:1
14		**5k**		**6k**	A / 64	5:1
15					B / 81	5:1
16		**5l**		**6l**	A / 24	6:1
17					B / 41	6:1
18		**5m**		**6m**	A / 28	9:1
19					B / 68	9:1

[a] All reactions were carried out on a 0.5 mmol scale using 1.5 equiv of olefin in refluxing CH_2Cl_2. [b] Isolated yield. [c] *E*/*Z* ratio determined by ^1H NMR of the crude reaction mixture. [d] Method A: 2.5 mol % of [Ru]-**II** catalyst. [e] Method B: 2 × 2.5 mol % of [Ru]-**II** catalyst.

stereoisomers (Table 3, entry 3). Styrene derivatives such as styrene itself (**5d**), *para*-fluorostyrene (**5e**), and *para*-methoxystyrene (**5f**) could be coupled with **4** to form the corresponding α-alkylidene-γ-lactones in 67−78% isolated yield as the (*E*)-isomers (Table 3, entries 4−6). *tert*-Butyldimethylsilyl-protected and methoxymethyl-protected homoallylic alcohols **5g**−**i** gave the corresponding coupled products with yields ranging from 51% to 94% and stereoselectivities varying from 8:1 to >20:1 in favor of the (*E*)-isomer (Table 3, entries 7−9). Finally, olefins such as allyldiethylphosphonate (**5j**) (45%, Table 3, entry 12), allyl-

trimethylsilane (**5k**) (64%, Table 3, entry 14), allyldimethylmalonate (**5l**) (24%, Table 3, entry 16), and butenylacetate (**5m**) (28%, Table 3, entry 18) gave *E*/*Z* stereoselectivities of **6j**−**m** ranging from 5:1 to >20:1 in favor of the (*E*)-isomer.

Even though the previous conditions (2.5 mol % of [Ru]-**II** catalyst and 5.0 mol % of chlorocatecholborane in refluxing CD_2Cl_2 for 14 h) had been proven to work with a wide range of olefins, some of the conversions remained low. This was the case for olefins **5c**, **5h**, and **5k**−**m**. The conditions were therefore slightly modified to increase the yield of the desired coupled product. Thus, each reaction was performed using two subsequent additions of [Ru]-**II** (2 × 2.5 mol %) separated by a 7 h period.

Under this new set of conditions, we were able to increase the yield of the CM between α-methylene-γ-butyrolactone **4** and olefin **5c** from 54% to 70% (Table 3, entry 4). Similarly, the methoxymethyl-protected homoallylic alcohol **5h** was converted into its corresponding coupled product in 88% isolated yield, which compared favorably with the 51% yield previously obtained (Table 3, entry 10). Finally, we were also able to improve the yields of CM products with olefins such as allyldiethylphosphonate (**5j**), allyltrimethylsilane (**5k**), allyldimethylmalonate (**5l**), and butenylacetate **5m**, as the corresponding coupled products **6j**−**m** could be isolated in 59%, 81%, 59%, and 68% yield, respectively (Table 3, entries 13, 15, 17, and 19). Interestingly, the stereoselectivity of the CM remained unchanged when increasing the loading of the catalyst, thus implying that the stereoselectivity is mainly substrate-dependent rather than catalyst-dependent.[18]

In summary, an efficient and highly stereoselective access to α-alkylidene-γ-butyrolactones, which are versatile building blocks in organic synthesis, has been developed. Chlorocatecholborane appeared as the key additive to improve the efficiency of the CM by limiting the formation of the undesired isomerized byproduct. Further study on the scope of this CM reaction is currently underway. The results of these investigations will be reported in due course.

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Supporting Information Available: Experimental details and characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) No isomerization could be observed when treating the (*Z*)-isomers of each CM product (**6g**, **6i**, and **6k**−**m**) in the presence of 2.5 mol % of [Ru]-**II** catalyst and 5.0 mol % of chlorocatecholborane in refluxing CD_2Cl_2 for 14 h.