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Ruthenium-Catalyzed Tandem Cross-Metathesis/Wittig Olefination: Generation of Conjugated Dienoic Esters from Terminal Olefins

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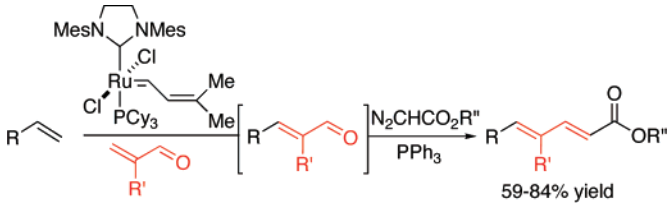
ABSTRACT



In the presence of ruthenium-based olefin metathesis catalysts and triphenylphosphine, α,β-unsaturated aldehydes can be olefinated with diazoacetates. This ruthenium-catalyzed transformation has been employed in tandem with olefin cross-metathesis to convert terminal olefins into 1,3-dienoic esters in a single operation.

Over the past decade, olefin metathesis has emerged as a powerful and widely used transformation.[1] Among the structurally defined olefin metathesis catalysts, ruthenium alkylidenes **I**−**IV** (Figure 1) are particularly attractive because of their robust activity and functional group tolerance.[2,3] Despite their recognized importance in effecting olefin metatheses, these catalysts have also been implicated in other modes of reactivity.[4] Some of the alternative transformations have been attributed to catalyst impurities and decomposition pathways, thus extensive studies have gone into the characterization of these ruthenium species;[5]

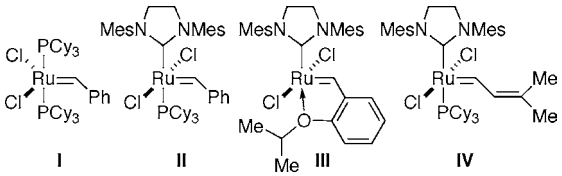


Figure 1. Commercially available ruthenium-based olefin metathesis catalysts.

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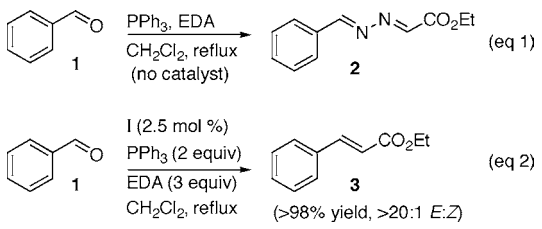
however, often the responsible complex is not clear. Nevertheless, these discoveries have opened the door to the development of several novel ruthenium-catalyzed tandem processes, in which the metal promotes two or more mechanistically distinct transformations in the same reaction vessel.[6]

Given the costs associated with reagents, solvents, and waste for each unique transformation, as well as the time required for material handling and purification, significant economic advantages are possible for running multiple transformations in a single reaction vessel. Accordingly, we have developed several tandem processes where olefin metathesis is used in conjunction with olefin isomerizations,[7] Kharasch additions,[8] cyclopropanations,[9] or olefin oxidations.[10] Herein, we demonstrate the use of ruthenium catalysts **I**−**IV** in a tandem olefin metathesis/Wittig olefination sequence.

Over the past decade, metal-catalyzed or "salt-free" Wittig olefinations have gained interest as an alternative to classic base-mediated Wittig olefinations.[11] To the best of our knowledge, the first example of a ruthenium-catalyzed version of this transformation was published in 1998 by Fujimura and Honma, who demonstrated that ethyl diazoacetate (EDA) and Ph_3P in the presence of substoichiometric amounts of $RuCl_2(PPh_3)_3$ couple to give a phosphonium ylide capable of aldehyde olefination.[12a] In the absence of catalyst, the ethyl diazoacetate reacted with the aldehyde (**1**) to give azine **2** (eq 1).[13] Since then, several alternative ruthenium



catalysts have been developed to carry out this transformation.[14] Although the olefin metathesis catalysts **I**−**IV** have not been used in Wittig olefinations, recent work indicates that a phosphonium ylide is likely generated during catalyst decomposition.[5a] In light of these findings, we anticipated that a metal-catalyzed olefination could be carried out using one of these popular ruthenium metathesis catalysts.

Preliminary studies on the olefination of benzaldehyde using ruthenium complexes **I**−**IV** were encouraging. Although the reaction did not go to completion using conditions developed for $RuCl_2(PPh_3)_3$,[12] the desired ethyl cinnamate **3** was observed. In addition, considerable amounts of diethyl maleate and fumarate were also formed in this reaction. This was not surprising given a report by Hodgson and Angrish on the ability of complex **II** to dimerize EDA.[4b] To circumvent this undesired side reaction, slow addition of the diazoester to the reaction mixture was explored. Gratifyingly, under these conditions, the desired olefinated product **3** is obtained with high yield and selectivity (eq 2).

Given the prevalence and synthetic utility of $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl-containing compounds,[15] we decided to explore their preparation through a ruthenium-catalyzed cross-metathesis (CM) of terminal olefins with acrolein and methacrolein, followed by a ruthenium-catalyzed Wittig olefination of the resulting aldehyde with diazoacetates. Direct CM to generate these electron-deficient dienes is possible;[16] however, the selectivity of the transformation can be compromised in the absence of steric and/or electronic bias. For example, Grubbs and co-workers reported access to such structures from terminal olefins by carrying out a

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(6) For examples of tandem reaction sequences with ruthenium metathesis catalysts developed outside of our laboratory, see: (a) Schmidt, B.; Pohler, M. *J. Organomet. Chem.* **2005**, *690*, 5552. (b) Whelan, A. N.; Elaridi, J.; Harte, M.; Smith, S. V.; Jackson, W. R.; Robinson, A. J. *Tetrahedron Lett.* **2004**, *45*, 5252. (c) Beligny, S.; Eibauer, S.; Maechling, S.; Blechert, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 1900. (d) Schmidt, B.; Pohler, M. *Org. Biomol. Chem.* **2003**, *1*, 2512. (e) Johnson, L. K.; Mecking, S.; Brookhart, M. *Polym. Mater. Sci. Eng.* **1997**, *76*, 246. (f) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312. For a recent review, see: (g) Dragutan, V.; Dragutan, I. *J. Organomet. Chem.* **2006**, *691*, 5129. Also, see: (h) Burling, S.; Paine, B. M.; Nama, D.; Brown, V. S.; Mahon, M. F.; Prior, T. J.; Pregosin, P. S.; Whittlesey, M. K.; Williams, J. M. J. *J. Am. Chem. Soc.* **2007**, *129*, 1987. (i) Otterlo, W. A. L.; Coyanis, E. M.; Panayides, J.-L.; de Koning, C. B.; Fernandes, M. A. *Synlett* **2005**, 501.

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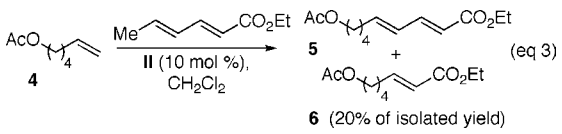
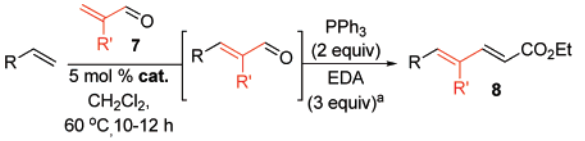
CM with electron-deficient dienes (eq 3).[17] The methodology



was limited due to the CM reactivity of both the α,β- and γ,δ-double bonds of the diene. Fortunately, this drawback could be overcome with unsaturated amides or unsaturated esters with internal olefins in the *Z*-configuration or with additional substitution. In light of this shortcoming, a ruthenium-catalyzed tandem cross-metathesis/Wittig olefination may offer a complementary strategy toward these polyunsaturated systems. Along these lines, a related Horner−Wadsworth−Emmons olefination has been shown to tolerate complex **II** and can be used in a "one-pot" operation.[18]

Table 1. One-Pot Synthesis of Dienoic Esters.



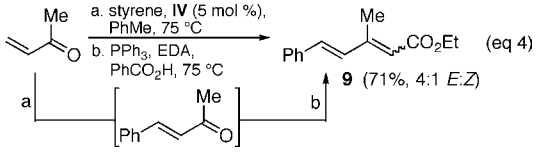
entry	olefin	enone (7)	catalyst	product	yield[b]
(1)	*n*-Hex	Me (0.5 equiv)	IV	*n*-Hex, CO$_2$Et, Me **8a**	(81%)
(2)	*n*-Hex	Me (0.5 equiv)	IV	*n*-Hex, CO$_2$*t*-Bu, Me **8b**	(84%)[c]
(3)	TBSO$_{(8)}$	Me (0.5 equiv)	IV	TBSO$_{(8)}$, CO$_2$Et, Me **8c**	(75%)
(4)	BnO$_{(5)}$	Me (0.5 equiv)	IV	BnO$_{(5)}$, CO$_2$Et, Me **8d**	(72%)
(5)	AcO$_{(4)}$	Me (5.0 equiv)	IV	AcO$_{(4)}$, CO$_2$Et, Me **8e**	(86%)
(6)	*n*-Hex	(10.0 equiv)	III	*n*-Hex, CO$_2$*t*-Bu **8f**	(59%)[c]
(7)		(10.0 equiv)	III	CO$_2$Et **8g**	(65%)

[a] EDA (ethyl diazoacetate) added over 4 h at 40 °C. Reaction sealed and heated to 60 °C for an additional 4−8 h. [b]Isolated yield. [c]*t*-Butyl diazoacetate used in place of EDA.

As summarized in Table 1, vinylidene complex **IV** is an effective and selective catalyst for the CM of methacrolein with terminal olefins (entries 1−5).[19] Furthermore, this same ruthenium complex (**IV**) can serve as a Wittig olefination catalyst when the resulting unsaturated aldehydes are treated in situ with PPh_3 and diazoesters. The results from this tandem, ruthenium-catalyzed metathesis/olefination sequence are dienoic esters formed in 59−86% yields with >20:1 *E*,*E*-selectivity. Entries 6 and 7 indicate that acrolein can also be used in this tandem sequence. In this case, ruthenium alkylidene **III** was employed given its proven ability to cross-metathesize acrolein.[20] Entries 2 and 6 show that *t*-butyl diazoacetate can be substituted for ethyl diazoacetate with similar efficiency in the Wittig olefination step.[21] In entries 1−4, the unsaturated aldehyde is used as the limiting reagent; however, as demonstrated in entries 5−7, a slightly modified protocol allows the terminal olefin to be used as the limiting reagent. In these cases, the excess electron-deficient olefin needs to be evaporated before the olefination step, reducing the overall operational simplicity of the tandem sequence. Entry 7 demonstrates the chemoselectivity of the process. In this case, the resulting aldehyde generated in the CM is olefinated selectively in the presence of a ketone to provide diene **8g**.

A successful ruthenium-catalyzed Wittig olefination of a ketone is also possible if the tandem process is run in toluene at higher temperatures with the addition of benzoic acid as an additive (Scheme 1). The conditions are modeled after

Scheme 1



those developed by Kühn and co-workers during additive studies for salt-free ketone olefinations.[22] Higher amounts of the phosphine and diazoacetate are also needed for complete conversion, and the *E*/*Z* selectivity is not as high as the aldehyde olefinations. Nonetheless, this newly designed tandem process does provide access to these β-substituted dienoic esters (**9**).

In summary, we have demonstrated that a variety of popular ruthenium metathesis catalysts are capable of

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catalyzing a salt-free Wittig olefination with diazoacetates and triphenylphosphine. When employed in conjunction with olefin cross-metathesis, rapid entries into dienoic esters are achieved.

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Supporting Information Available: Experimental procedures and data on new compounds are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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