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Ruthenium-Catalyzed Alkylative Lactonization and Carbocyclization

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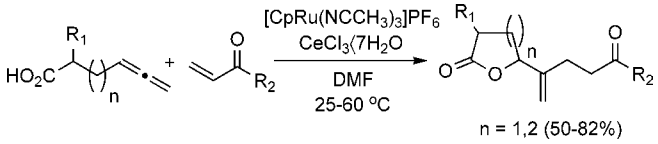
ABSTRACT



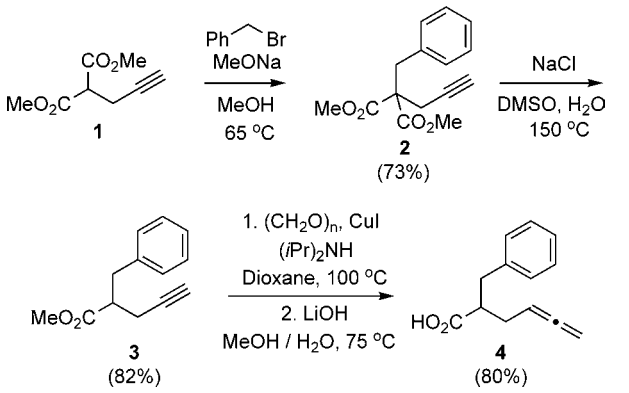
The cationic ruthenium complex $[CpRu(NCCH_3)_3]PF_6$ promotes the coupling of monosubstituted allene carboxylic acids and simple α,β-unsaturated olefins to form five- and six-membered lactones. The mild reaction conditions allow for the presence of various functional groups.

The development of atom-economical reactions is one of the most important challenges to be met in contemporary organic synthesis.[1] To the extent that we can increase the number of addition reactions in a synthetic sequence, we improve the efficiency with which we use our raw materials. Thus, our group has engaged in a program of developing ruthenium-catalyzed addition reactions in which all of the reactant atoms are expressed in the product.[2] The development of one such reaction, ruthenium-catalyzed alkylative lactonization, was envisioned. However, because allyl esters are known substrates for ruthenium-catalyzed allylic alkylation,[3] the potential instability of such products under the reaction conditions could be detrimental to such a process.

Some years ago, our group demonstrated that certain ruthenium complexes can mediate C−C bond formation between the central carbon of a terminal allene and the β-carbon of an α,β-unsaturated olefin.[4] Upon consideration of possible mechanistic rationales, we reasoned that the putative ruthenacycle would be intercepted by appropriately situated nucleophiles, thus bypassing β-hydride elimination. Indeed, tethered alcohols and amines lead to formation of the corresponding heterocyclic products.[5] Herein, we describe the use of carboxylic acids as nucleophiles in this process.

The preparation of substrates was straightforward, with most being accessed through a traditional malonic ester-type synthesis (Scheme 1). For example, dimethyl propargyl malonate was alkylated with benzyl bromide. Hydrolysis and decarbalkoxylation to the monoester,[6] followed by homolo-

Scheme 1. Representative Substrate Synthesis



(1) (a) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.

(2) (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695−705. (b) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096.

(3) Trost, B. M.; Fraisse, P.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059−1061.

(4) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 4068−4069.

(5) (a) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 10842−10843. (b) Trost, B. M.; Pinkerton, A. B.; Kremzow, D. *J. Am. Chem. Soc.* **2000**, *122*, 12007−12008.

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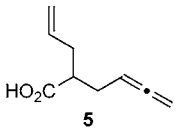
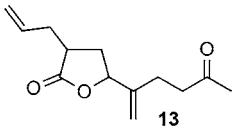
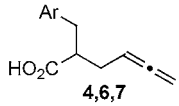
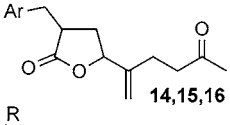
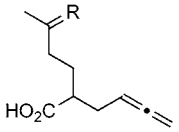
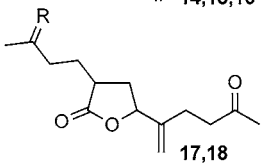
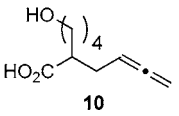
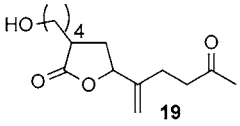
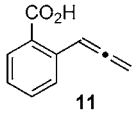
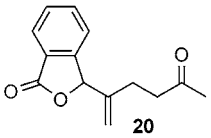
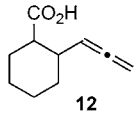
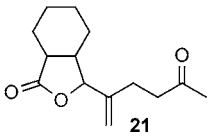
gation of the alkyne to the allene[7] and saponification, gave the allene carboxylic acid substrate in good overall yield.

The substrates were then subjected to the reaction conditions. As seen in Table 1, the reaction was highly efficient in forming the five-membered lactone products.

Table 1. Scope of Allene Carboxylic Acids

substrate	product	yield (%)
 **5**	 **13**	77[b,c]
 **4,6,7**	 **14,15,16**	Ar = Ph 79[a,c] Ar = 4-OMe-Ph 78[a,c] Ar = 4-NO_2-Ph 81[a,c]
 **8,9**	 **17,18**	R=O 76[a,c] R=$(OCH_2)_2$ 78[a,c]
 **10**	 **19**	82[a,c]
 **11**	 **20**	67[a]
 **12**	 **21**	76[a,d]

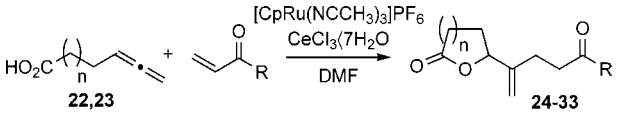
[a] 1.25 equiv of MVK, 5% $[CpRu(NCCH_3)_3]PF_6$, 5% $CeCl_3 \cdot 7H_2O$, DMF, 25 °C, 30 min. [b] 1.50 equiv of MVK, 10% $[CpRu(NCCH_3)_3]PF_6$, 10% $CeCl_3 \cdot 7H_2O$, DMF, 60 °C, 2 h. [c] Product was obtained as a 1:1 mixture of diastereomers. [d] Product was obtained as a mixture of four diastereomers.

The catalyst loading, temperature, and reaction time were all lower than in the corresponding cyclizations of alcohols and amines. The compatibility of an olefin, which could potentially form a ruthenacycle with the proximal allene and the catalyst, is noteworthy. Both electron-rich and electron-poor aromatic rings were tolerated in the reaction. Functional groups that could coordinate to the catalyst, such as ketone, ketal, and alcohol, did not interfere with the reaction.

The formation of lactones with simple α,β-unsaturated olefins is seen in Table 2. In general, five-membered lactones formed in higher yields than six-membered lactones.

(6) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957−960.

Table 2. Scope of α,β-Unsaturated Olefins



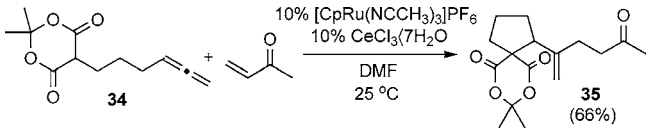
electrophile (R)	conditions[a]	yield (%)
H	A	**24**, $n = 1$, 63
	B	**25**, $n = 2$, 55
Me	A	**26**, $n = 1$, 78
	B	**27**, $n = 2$, 65
Et	A	**28**, $n = 1$, 75
	B	**29**, $n = 2$, 58
Ph	B	**30**, $n = 1$, 79
	B	**31**, $n = 2$, 71
*t*Bu	B	**32**, $n = 1$, 58
	B	**33**, $n = 2$, 50

[a] A: 1.25 equiv of electrophile, 5% $[CpRu(NCCH_3)_3]PF_6$, 5% $CeCl_3 \cdot 7H_2O$, DMF, 25 °C, 30 min. B: 1.50 equiv of electrophile, 10% $[CpRu(NCCH_3)_3]PF_6$, 10% $CeCl_3 \cdot 7H_2O$, DMF, 60 °C, 2 h.

In terms of carbonyl groups, aldehydes, methyl ketones, and ethyl ketones functioned quite well at room temperature for five-membered ring formation, whereas the more sterically demanding phenyl and *tert*-butyl ketones required longer reaction times, higher temperatures, and increased catalyst loadings. Introduction of substituents on the olefin led to a recovered allene carboxylic acid substrate, as did changing the electron-withdrawing group to a nitrile, ester, or sulfone.

Interestingly, carbon nucleophiles of an acidity comparable to carboxylic acids can be used in this reaction. Thus, a Meldrum's acid derivative can be used as a substrate to give the corresponding carbocyclic product in which two carbon−carbon bonds are created, one of them being quaternary (Scheme 2).

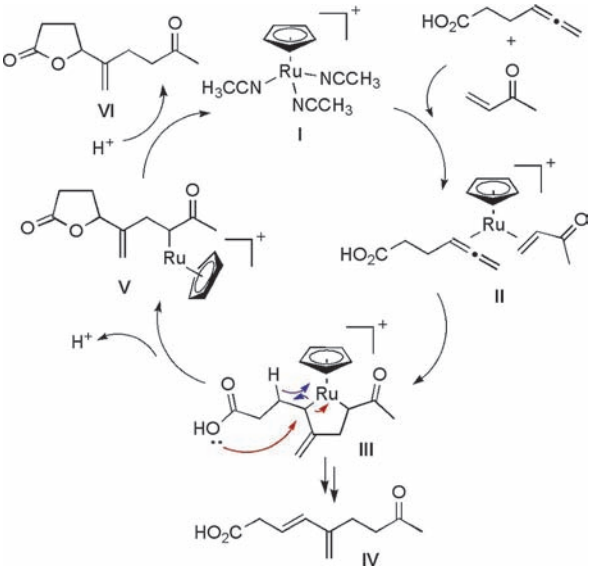
Scheme 2. Carbon Nucleophile: Carbocycle Formation



A plausible mechanism for this reaction is depicted in Scheme 3. Coordination of the allene and the α,β-unsaturated olefin to the ruthenium catalyst **I** provides complex **II**. Oxidative coupling then leads to ruthenacycle **III**, which is the key intermediate. The coordination of the carbonyl with the cocatalyst $CeCl_3$ may promote this step. Although **III** is depicted as a σ-allyl complex, we do not rule out its existence as a π-allyl structure. From this complex, β-hydride elimination or E_2 elimination could

(7) Crabbe, P.; Fillion, H.; Andre, D.; Luche, J.-L. *Chem. Commun.* **1979**, 859−860.

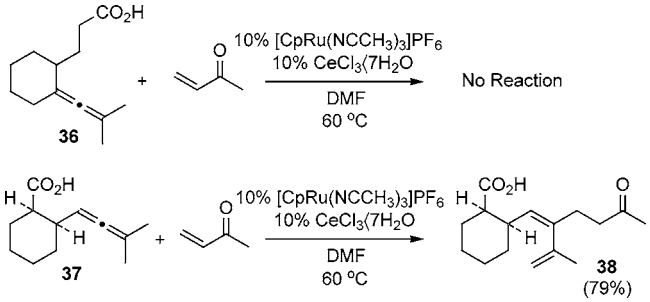
Scheme 3. Mechanism of Ruthenium-Catalyzed Alkylative Lactonization



eventually lead to the 1,3-diene product **IV**. Alternatively, nucleophilic trapping by the tethered carboxylic acid may give **V** which, following protonation of the metal and reductive elimination, gives lactone product **VI** and regenerates the catalyst.

The tetrasubstituted allene carboxylic acid **36** did not participate in the reaction (Scheme 4). Oxidative coupling of this substrate to form the ruthenacycle corresponding to **III** likely does not occur due to steric constraints. In the case of the trisubstituted allene carboxylic acid **37**, the ruthenacycle corresponding to **III** does not undergo nucleophilic capture. Elimination to the 1,3-diene product corresponding to **IV** is not observed either, as such a process would involve loss of a hindered proton and formation of a relatively unstable methylene cyclohexane. Instead, a facile E_2' elimination leads to the 1,3-diene product **38**.

Scheme 4. Limitations of Allene Substitution



In summary, an important extension of the ruthenium-mediated formation of heterocycles from allenes and α,β-unsaturated olefins has been reported. Substrates for the reaction could be synthesized in high yield. The use of mild reaction conditions and lower catalyst loadings and the tolerance of several functional groups constitute important features of this addition reaction. The extension to carbocycle formation further suggests the likelihood of this process having a broad scope in terms of the nature of the nucleophile in the cyclization event.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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