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Olefin Metathesis Involving Ruthenium Enoic Carbene Complexes

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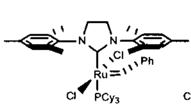
Olefin metathesis has become a valuable reaction in organic synthesis, as has been demonstrated by its frequent use as the key bond constructions for total syntheses of many natural products.[1] With the recent discovery of highly active catalyst **1**, trisubstituted and functionalized alkenes have been synthesized efficiently by cross-metathesis (CM), further expanding the substrate scope for this reaction.[2] With these successes in hand, unprecedented metathesis reactions were explored. There have been no previous reports of the dimerization of α,*β*-unsaturated carbonyl compounds by a metathesis mechanism. Molybdenum- and tungsten-based catalysts form metallocyclobutane with acrylates, but they are inactive due to carbonyl oxygen chelation.[3] Our group reported the synthesis of ester carbene **4** by a nonmetathesis route and showed that **4** was extremely reactive. In fact, ester carbene **4** was the first carbene to ring-open cyclohexene but did not react in a catalytic fashion.[4] The nontrivial synthesis, lack of stability, and the ineffective catalytic activity of ester carbene **4** has limited its uses in organic synthesis.



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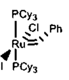

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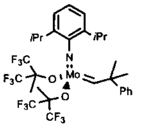

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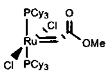


4

Previous reports on the mechanism of cross-metathesis reactions between terminal olefins and α,*β*-unsaturated carbonyl compounds, state that catalyst **1** reacts preferentially with terminal olefins to form an alkylidene which crosses onto α,*β*-unsaturated carbonyl compounds to form methylidene and CM product.[2c] At that time, the formation of the unstable enoic carbene **5** was believed to be less likely. However, it was recently discovered that the electron-rich catalyst **1** was, in fact, able to react with α,*β*-unsaturated carbonyl compounds directly to form enoic carbene **5** effectively under certain conditions. Herein, we report the first efficient generation of enoic carbenes **5** in situ with catalyst **1** (Scheme 1), and successful catalytic CM and ring-opening reactions of previously inactive metathesis substrates.

Scheme 1. Direct Generation of Enoic Carbene

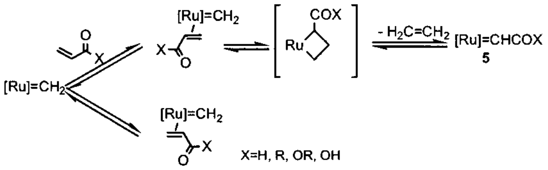
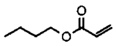
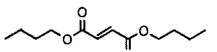
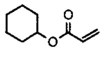
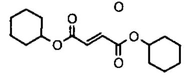
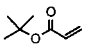
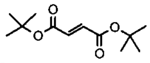
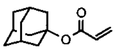
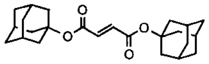
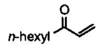
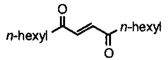
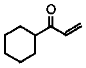
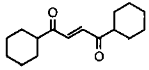
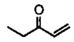
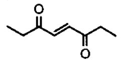


Table 1. Dimerization of α,*β*-Unsaturated Carbonyl Compounds[a]

entry	substrate	product[b]	conc.	Isolated yield
1			0.4 M	**6**: 87%
2			0.4 M	**7**: 75%
3			0.4 M	**8**: 94%
4			0.4 M	**9**: 80%
5			0.05 M	**10**: 77%
6			0.05 M	**11**: 95%
7			0.05 M	**12**: 94%[c]

[a] 5 mol % catalyst **1** in refluxing CH_2Cl_2 for 3 h. [b] Only the *E* isomer was obtained. [c] Yield was determined by ^1H NMR.

The formation of enoic carbene **5** was initially discovered in the dimerization of acrylates to form fumarates. Initial attempts to dimerize of *n*-butyl acrylate at 0.2 M in refluxing CH_2Cl_2 only gave 44% of the desired product of *E* isomer, and the balance as starting material. GC analysis showed the reaction was completed in less than 2 h, and no carbenes were observed by ^1H NMR. This suggests enoic carbene **5** is still unstable, with a much shorter lifetime than other alkylidene or benzylidene carbenes. To our delight, an attempt to increase the rate by doubling the concentration to 0.4 M resulted in 87% yield of dimer (Table 1, entry 1). Other solvents such as $CHCl_3$, CCl_4, C_6H_6, and THF were tried, but they all produced much poorer results than CH_2Cl_2.[5] Various acrylates were effectively dimerized by this procedure (Table 1, entries 1−4).

Interestingly, vinyl ketones behaved quite differently from acrylates. Dimerization of hexyl vinyl ketone at 0.4 M gave only 29%, and increasing concentration further decreased the yield (less than 5% at 0.6 M by ^1H NMR). However, decreasing the concentration increased the yield where optimized yield was obtained at 0.05 M (Table 1, entries 5−7).

Following the reactions by ^1H NMR revealed that at 0.05 M, the rate of formation of keto-carbene was at least 5 times faster than that of acrylates.[6] Therefore, a high concentration is required for acrylates to speed up the reactions, whereas at that condition, a much higher concentration of unstable keto-carbene leads to bimolecular decomposition.[4]

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(1) For recent reviews on organic applications, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2067. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (e) Blechert, S. *Pure Appl. Chem.* **1999**, *71*, 1393. (f) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013.

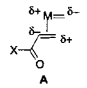
(2) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751. (c) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (d) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem.* **2001**, *113*, 1317; *Angew. Chem. Int. Ed.* **2001**, *40*, 1277. (e) Chatterjee, A. K.; Choi, T.-L.; Grubbs, R. H. *Synlett* **2001**, 1034.

(3) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Oranometallics* **1989**, *8*, 2260.

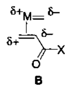
(4) Ulman, M.; Belderrain, T. R.; Grubbs, R. H. *Tetrahedron Lett.* **2000**, *41*, 4689.

(5) An opposite solvent effect was observed previously. See Furstnet, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

(6) The faster formation of keto-carbene can be explained by the following arguments. To form **5**, the complex has to adopt **A** conformation, not **B**, and ab initio calculation (HF6-31G**) suggests that olefins of vinyl ketones are more polarized than those of acrylates, favoring state **A**. Also acrylates have more electron-rich carbonyls, and the chelation effect **C** may slow down the formation. See ref 2d.



A



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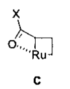
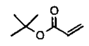
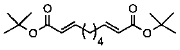
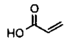
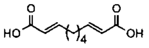
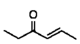
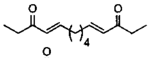
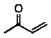
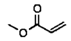
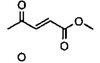
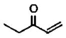
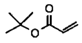
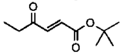
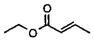
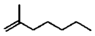
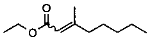
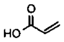
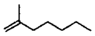
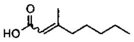
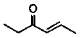
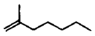
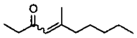
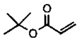
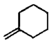
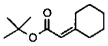
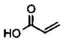
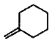
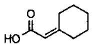
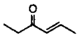
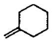
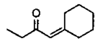


C

10.1021/ja016386a CCC: $20.00

Table 2. Ring-Opening or Cross Metathesis Reactions of Enoic Carbenes[a]

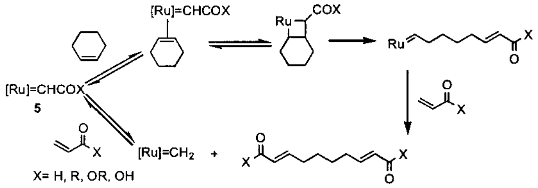
entry	carbene precusor	cross-partner	product[b]	Isolated yield
1				**13**: 88%[c]
2				**14**: 94%[c]
3				**15**: 72%[c]
4				**16**: 41%[d]
5				**17**: 41%[d]
6				**18**: 83%[e,f]
7				**19**: 83%[e,f]
8				**20**: 68%[e,f]
9				**21**: 75%[g]
10				**22**: 83%[g]
11				**23**: 99%[g]

[a] 5 mol % catalyst **1** at 0.1−0.3 M in refluxing CH_2Cl_2 for 3 h. [b] Only the *E* isomer was observed by ^1H NMR. [c] 3 equiv of cyclohexene was used. [d] 2 equiv of acrylates was used. [e] 4 equiv of α-methyl disubstituted olefin was used. [f] $E/Z = 2.0$. [g] 2 equiv of methylenecyclohexene was used.

GC analysis showed dimethyl maleate (*Z* isomer) isomerized to dimethyl fumarate (*E* isomer) very slowly when compared to unfunctionalized internal *cis* olefins.[7] Also, only the *E* isomer was obtained even at early conversion in dimerization reactions, suggesting that the *E* isomer is the kinetic as well as thermodynamic product in theses CM reactions.

Applications of the enoic carbene to various metathesis reactions beyond simple enone dimerization are shown in Table 2. Although cyclohexene is unique compared to other cycloalkenes because it is not polymerized by ROMP,[8] our group previously reported that catalyst **4**, unlike catalysts **1**−**3**, could ring-open thermodynamically stable cyclohexene.[4] However, this reaction required a stoichiometric amount of catalyst **4** because the product of one turnover is an alkylidene which was unreactive toward cyclohexene or acrylates. However, now that enoic carbene **5** could be generated in situ by catalyst **1**, ring-opening of cyclohexene could be achieved catalytically (Scheme 2) yielding linear C-10 chains of α,*β*-unsaturated carbonyl compounds being doubly crossed (Table 2, entries 1−3). An excess of cyclohexene (3 equiv) was used to minimize the dimerization of α,*β*-unsaturated carbonyl compounds since the ring-opening reaction competes with dimerization to products that slowly undergo secondary metathesis reactions.

Scheme 2. Ring Opening of Cyclohexene with **5**



To access more synthetically useful hetero-coupled products, we attempted the CM between different α,*β*-unsaturated carbonyl compounds. Cross couplings of methyl acrylates and methyl vinyl ketones were attempted, and only a statistical mixture of 41% of the cross-coupled products was obtained (Table 2, entries 4, and 5). Cross-metathesis reactions between α,*β*-unsaturated carbonyl compounds and α-methyl disubstituted olefin were also studied. Unlike CM between terminal olefins and acrylates, analogous conditions gave the acrylate dimer as a major product and only a trace amount of desired cross product, suggesting the catalyst **1** reacted with acrylates preferentially to form enoic carbene **5**. Although the formation of **5** is thermodynamically less favorable, it is kinetically preferred over reaction with bulky disubstituted alkenes.[2b] However, increasing the stoichiometry of the disubstituted olefins produced CM products with good yields. For example, with 2 equiv of α-methyldisubstituted olefin, a 5:4 mixture of acrylate dimer and the cross product yield was obtained, whereas up to 83% yield of the cross product was achieved by using 4 equiv of α-methyldisubstituted olefin with an *E*-to-Z ratio of 2:1 (entries 6−8). Not surprisingly, less sterically hindered methylenecyclohexane proved to be a better cross partner, producing up to 99% of the CM products with 2 equiv of the *gem*-disubstituted olefin. Compared to terminal α,*β*-unsaturated carbonyl compounds, *β*-methyl-disubstituted α,*β*-unsaturated carbonyl compounds improved the CM yields by 2−40% because the rate of dimerization was suppressed by the methyl group, thereby increasing the relative rate of CM reaction. This observation is particularly useful in the reactions where dimer was a substantial side-product (Table 2, entries 3, 6, 8, and 11).[9]

In conclusion, we have demonstrated that the highly active catalyst **1** reacts with α,*β*-unsaturated carbonyl compounds directly to form enoic carbene **5**. It illustrates that the more electron-donating ligand stabilizes the electron-deficient enoic carbene **5**. With the in situ generation of enoic carbenes, enone dimerization, cross-coupling with *gem*-disubstituted olefins, and catalytic ring-opening of cyclohexene are now attainable.

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Supporting Information Available: Experimental procedures and characterization data (^1H and ^{13}C NMR, HRMS) (PDF). This material is available free of charge via the Internet at http://pub.acs.org.

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(8) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, 2nd ed.; Academic: San Diego, 1997.

(9) Acrolein and acrylamide also worked but with less efficiency. Unfortunately attempted ring-closing metathesis of bis-acrylates failed, only resulting in mixtures of linear dimer, trimer, and oligoners. However, macrocyclization of bis-acrylate was achieved in modest yield: Lee, C. W.; Grubbs, R. H. Unpublished result.