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Ruthenium-Catalyzed Decarboxylative Allylation of Nonstabilized Ketone Enolates

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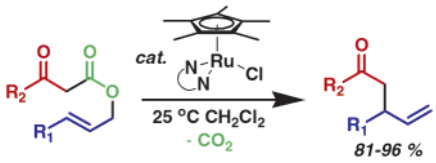
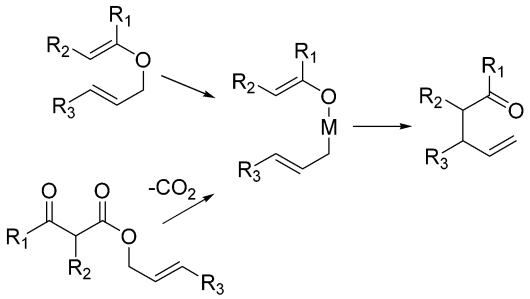
ABSTRACT



Bipyridyl(pentamethylcyclopentadienyl)ruthenium chloride is an efficient catalyst for the formal [3,3] rearrangement of allyl β-ketoesters. The mechanism of the transformation involves formation of π-allyl ruthenium intermediates, which are selectively attacked at the more substituted allyl terminus by freely diffusing enolates. Decarboxylation of β-ketocarboxylates allows generation of enolates under extremely mild conditions.

Efficient catalysis of sigmatropic rearrangements is a long-standing goal in chemical synthesis. Despite the recognized synthetic utility of Claisen-type rearrangements, only recently have successful approaches to catalysis been realized.[1] Although both anionic[2] and cationic[3] acceleration of Claisen rearrangements are well-known, the majority of attempts at catalysis have focused on Lewis acid activation. A conceptually different approach toward catalysis is the oxidative addition of an allyl vinyl ether to a transition metal, producing an enolato-metal-allyl that could couple these fragments to form the desired unsaturated ketone (Scheme 1).

Scheme 1



Given the difficulty of metal insertion into ether C−O bonds, we have directed our initial efforts toward catalysis of the Carroll (decarboxylative Claisen) rearrangement,[4] which utilizes the more reactive and more easily synthesized allyl-β-ketoesters. Herein we report that bipyridyl(pentamethylcyclopentadienyl)ruthenium chloride [Cp*Ru(bpy)Cl] is an efficient and selective catalyst for the rearrangement of allyl-β-ketoesters.

Saegusa reported the first catalytic rearrangement of allyl-β-ketoesters using palladium; however, the primary products were those of [1,3] rearrangement.[5] This result was explained by the intermediacy of palladium π-allyl complexes that are

(1) (a) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9276−9277. (b) Abraham, L.; Czerwonka, R.; Hiersmann, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4700−4703. (c) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412−12413. (d) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43−50.

(2) (a) Denmark, S. E.; Marlin, J. E. *J. Org. Chem.* **1987**, *52*, 5742−5743. (b) Denmark, S. E.; Harmata, M. A. *J. Org. Chem.* **1983**, *48*, 3369−3370. (c) Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572−5573.

(3) (a) Boeckman, R. K.; Flann, C. J.; Poss, K. M. *J. Am. Chem. Soc.* **1985**, *107*, 4359−4362. (b) Dhanalekshmi, S.; Venkatachalam, C. S.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1994**, 511−512.

(4) (a) Carroll, M. F. *J. Chem. Soc.* **1940**, 704−706. (b) Kimel, W.; Cope, A. C. *J. Am. Chem. Soc.* **1943**, *65*, 1992−1998.

(5) (a) Tsuda, T.; Chujo, Y.; Nishi, S.-I.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381−6384. (b) Tsuji, J. *Pure Appl. Chem.* **1982**, *54*, 197−206. (c) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M. Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988−2995.

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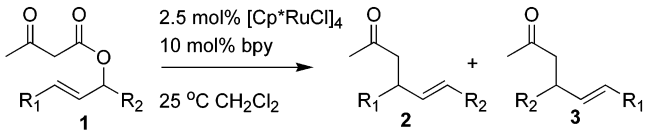
known to undergo nucleophilic attack at the least substituted allyl terminus.[6]

In the interest of discovering catalysts that would provide primarily the products of [3,3] rearrangement, we chose to investigate various ruthenium catalysts. Ruthenium carboxylates are known to readily decarboxylate[7] much like the carboxylates of palladium, and the chemistry of ruthenium allyls is well-studied.[8] For example, Trost has shown that $Cp^*Ru(NCCH_3)_3PF_6$ catalyzes the allylation of stabilized nucleophiles with high regioselectivity for addition at the more substituted allyl terminus.[8b]

The rearrangement of cinnamyl β-ketoester (R = Ph, **1a**) was used to investigate the activity of various ruthenium catalysts and conditions (Scheme 2). Initially, it was found

Scheme 2



that 2.5 mol % $[Cp^*RuCl]_4$ in CH_2Cl_2 led to complete rearrangement, but the reaction was quite slow and the branched ([3,3]) to linear ([1,3]) ratio was not that high (Table 1). Addition of 10 mol % bipyridine accelerated the

Table 1. Activity and Selectivity of Carroll Rearrangement Catalysts toward Reaction with **1a** (R_1 = Ph, R_2 = H)[a]

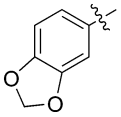
catalyst	ligand	time (h)	solvent (temp)	conversion (**2**:**3**)[a]
$[Cp^*RuCl]_4$		1.5	CH_2Cl_2	9 (6.2)
$[Cp^*RuCl]_4$	2 py	1.5	CH_2Cl_2	19 (2.5)
$[Cp^*RuCl]_4$	bpy	1.5	CH_2Cl_2	100 (>19)[b]
$[Cp^*RuCl]_4$	TMEDA	4	CH_2Cl_2	100 (9.1)
$[Cp^*RuCl]_4$		4	THF	100 (14)[c]
$[Cp^*RuCl]_4$	bpy	4	THF	100 (10.7)
$[Cp^*RuCl]_4$		1.5	CH_3CN (50 °C)	66 (3)
4	bpy	16	THF (65 °C)	100 (0.5)
4		16	CH_2Cl_2 (40 °C)	nr
4	bpy	16	CH_2Cl_2 (40 °C)	nr
5	bpy	16	CH_2Cl_2	49 (10)

[a] Ratios of branched (**2**) to linear (**3**) product were determined at complete conversion. [b] Minor isomer was not detected by ^1H NMR spectroscopy. [c] 1.25 mol % catalyst was used.

reaction and resulted in quantitative conversion to the [3,3] rearrangement product in 1.5 h at room temperature. Addition of 10 or 20 mol % pyridine led to smaller rate increases. It appears that the role of the ligand is to form a monomeric ruthenium species from the tetrameric precatalyst; however, strongly coordinating solvents such as CH_3CN are deleterious to the rates. Other ruthenium(II) sources such as $(CH_2CMeCH_2)_2Ru(COD)$ (**4**) and $CpRu(NCCH_3)_3PF_6$ (**5**) were not as effective.

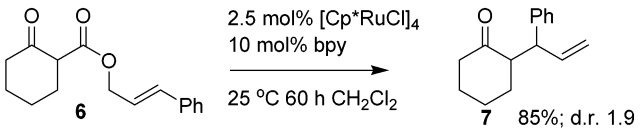
A brief study of substituent effects shows that electron-donating groups on the aryl substituent accelerate the reaction and the reactions are more sluggish with electron-withdrawing substituents (Table 2). Importantly, substituted nucleophiles react smoothly but require longer reaction times and the diastereoselectivities are low (Scheme 3).

Table 2. Ruthenium-Catalyzed Carroll Rearrangements[a]

substrate	R_1	R_2	time	yield
1a	Ph	H	1.5 h	94
1b	*p*-tolyl	H	2 h	96
1c	*o*-tolyl	H	5 d	81
1d	*p*-C_6H_4OMe	H	15 min	91
1e	*o*-C_6H_4OMe	H	15 min	93
1f		H	30 min	91
1g	*p*-C6H4Cl	H	4 h	96
1h	*p*-C6H4CF3	H	40 h	90
1i	H	Ph	1.5 h	93
1j	Ph	Ph	1 h	67

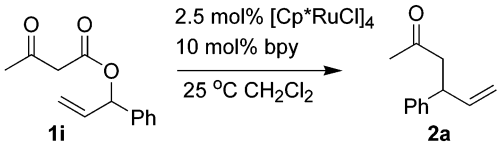
[a] Reaction times and isolated yields for 0.2 M substrate, 2.5 mol % $[Cp^*RuCl]_4$, and 10 mol % bipyridine in CH_2Cl_2 at 25 °C.

Scheme 3



Next, the rearrangement of **1i** (the regioisomer of **1a**) was shown to give **2a**, the product of formal [1,3] rearrangement (Scheme 4). This experiment demonstrates that the ruthenium-catalyzed rearrangement is highly regioselective but not regiospecific like the uncatalyzed Carroll rearrangement. This observation is most simply interpreted in terms of an intermediate ruthenium π-allyl complex, which exhibits a

Scheme 4

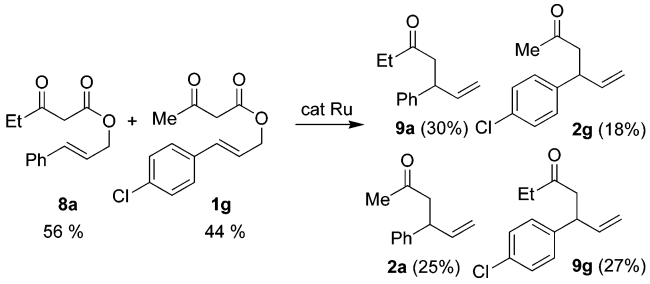


(6) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422.
(7) (a) Roper, W. R.; Wright, L. J. *J. Organomet. Chem.* **1982**, *234*, C5−C8. (b) Casey, C. P.; Singer, S. W.; Powell, D. R. *Can. J. Chem.* **2001**, *79*, 1002−1011.
(8) (a) Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.; Takahashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10405−10406. (b) Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059−1061. (c) Renaud, J. L.; Bruneau, C.; Demerseman, B. *Synlett* **2003**, *3*, 408−410. (d) Kondo, H.; Kageyama, A.; Yamaguchi, Y.; Haga, M.; Kirchner, K.; Nagashima, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1927−1937.

large preference for addition of the enolate to the more substituted allyl terminus.[8]

To further probe the mechanism of this transformation, we tested whether the reaction proceeds intra- or intermolecularly. Thus, a 1:1 mixture of allyl-β-ketoesters **8a** and **1g** were treated under the standard reaction conditions (Scheme 5). Gas chromatographic and mass spectrometric

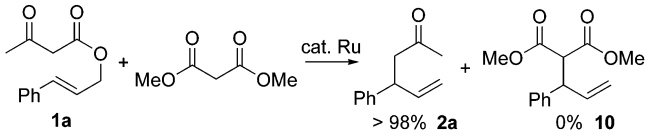
Scheme 5



analysis of the resulting mixture shows approximately equal quantities of products **2g**, **9a**, and crossover products **2a** and **9g**. This result indicates that freely diffusing enolates are formed, which then add to ruthenium π-allyl complexes.[9] The observation that **9a** and **9g**[10] are the only products derived from the propionyl acetate **8a** demonstrates that the regiochemistry of enolate generation is preserved. In fact, treatment of **8a** under the standard reaction conditions produced only **9a**, confirming that enolate formation is under kinetic control.

Next, the reaction was run in the presence of dimethylmalonate in order to probe the lifetime of the enolate. If the enolate is long-lived, it should be protonated by the more acidic malonate, ultimately providing **10** as the product (Scheme 6). The fact that the reaction is unhampered by the

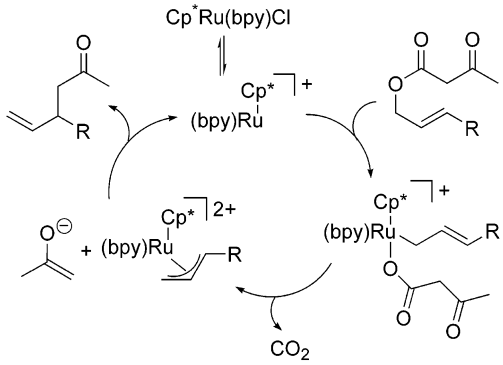
Scheme 6



addition of 1 equiv of dimethylmalonate shows that the addition of enolate to the allyl ligand is much faster than deprotonation of the acidic malonate.

Investigation of the ruthenium speciation by ^{1}H NMR spectroscopy showed that under the conditions of catalysis ruthenium exists as a 1:1 complex with bipyridine. On the basis of this evidence and the known coordination chemistry of $[Cp^*RuCl]_4$,[11] we suggest that Cp*Ru(bpy)Cl is responsible for the catalysis (Scheme 7). This 18 e$^-$ complex likely ionizes to catalytically active 16 e$^-$ Cp*Ru(bpy)$^+$, consistent with the previously reported rapid ionization of Cp*Ru(TMEDA)Cl [TMEDA = tetramethylethylenediamine].[12] Activation by ionization is also consistent with the poor reactivity of these catalysts in acetonitrile, which will disfavor formation of a coordinatively unsaturated cationic ruthenium complex. This ruthenium complex reacts with the allyl-β-ketoester resulting in ruthenium allyl formation. The decarboxylation of the resulting acetoacetate requires further mechanistic investigation; however, ruthenium is likely involved in this process because acetoacetate anion does not spontaneously decarboxylate at ambient temperature.[5a,13]

Scheme 7



In conclusion, Cp*Ru(bpy)Cl is a selective catalyst for the decarboxylative rearrangement of allyl-β-ketoesters to γ,δ-unsaturated ketones. The mechanism of catalysis likely involves ruthenium-π-allyl intermediates that are selectively attacked at the more substituted allyl terminus. In this regard, the reaction is equivalent to the allylation of nonstabilized ketone enolates, an important goal of allylation chemistry.[6,14] Currently, use of boron or tin enolates has allowed use of ketone enolates for palladium-catalyzed allylic alkylation of allyl acetates; however these reactions result in substitution at the least hindered allyl terminus. Therefore, the reaction described here broadens the scope of allylic alkylations and eliminates the need for boron or tin additives. Extension of this methodology to the asymmetric rearrangement is currently underway.

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Supporting Information Available: Experimental procedures and spectroscopic data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Bimolecular addition of a ruthenium enolate to a ruthenium allyl remains a possibility.

(10) The structure of **9g** is tentatively assigned as shown based only on the observation of its molecular ion. The regiochemistry is assumed to be the same as all other substrates investigated.

(11) Koelle, U. *Chem. Rev.* **1998**, *98*, 1313−1334.

(12) Gemel, C.; Mereiter, K.; Schmid, R.; Kirchner, K. *Organometallics* **1997**, *16*, 5601−5603.

(13) We are grateful to a reviewer for pointing out this fact.

(14) (a) Braun, M.; Laicher, F.; Meier, T. *Angew. Chem., Int, Ed.* **2000**, *39*, 3494−3497. (b) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759−6760.