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Rhodium Carbenoid-Initiated Claisen Rearrangement: Scope and Mechanistic Observations

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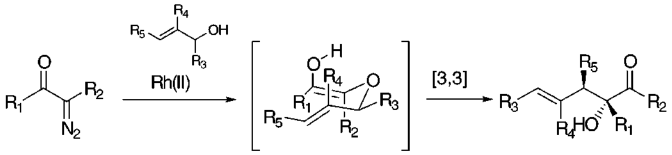
ABSTRACT



It has been shown that α-diazoketones react with allylic alcohols in the presence of Rh(II) catalysts to furnish intermediate enols which subsequently undergo Claisen rearrangement to α-hydroxyketones. Herein we report (1) studies into the mechanism of this transformation which establish that Claisen rearrangement is neither rhodium- nor acid-catalyzed but a reaction intrinsic to the intermediate enols that proceeds at a rate governed by enol substituents (R_3, R_4, R_5) and (2) the reaction of α-diazoketones with propargylic alcohols and preliminary investigations into its scope and mechanism.

Earlier this year we reported that α-keto rhodium carbenoids react with allylic alcohols to stereoselectively furnish α-hydroxy ketones.[1] In that study, a combination of experiments performed with spectroscopic monitoring demonstrated that the reaction proceeds via initial formation of a Z-enol which subsequently undergoes Claisen rearrangement faster than ketonization (e.g., **1** → **2** → **3**, Table 1).[2,3] In addition, the reaction was found to be general with regard to both diazo and alcohol substrate. Intrigued by the ease with which the derived enols (e.g., **2**) undergo rearrangement, we decided to extended our investigations by exploring the kinetics of the Claisen chemistry. As herein reported, these latter efforts clearly demonstrate the reactive nature of the enol intermediates and have led to further experiments which extend the scope of this process.

To facilitate the planned kinetic studies, we sought a series of enols that would undergo rearrangement over a broad temperature range. We thus became interested in a report describing the preparation and crystallographic analysis of **6**, a stable enol that is produced by reacting a methanol solution of azibenzil (**5**) with H_2SO_4.[4] Hoping to extend our Rh(II) conditions to this system, we treated a CH_2Cl_2 solution of **5** (1.0 equiv) and CH_3OH (1.1 equiv) with $Rh_2(TFA)_4$ (0.01 equiv) and were delighted to observe the rapid and selective formation of **6** (Scheme 1).[5,6] Importantly, similar

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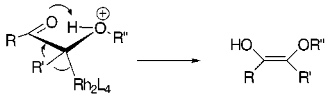
[1] Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748.

[2] The highly selective formation of a *Z*-enol suggests the reaction proceeds via intramolecular proton transfer to oxygen (i.e., **i** → **ii**).

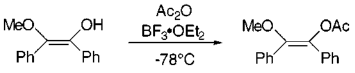


i **ii**

[3] For recent reviews on the chemistry of enols, see: (a) Hart, H. *Chem. Rev.* **1979**, *79*, 515. (b) Kresge, A. J. *CHEMTECH* **1986**, *16*, 250. (c) Capon, B.; Guo, B.; Kwok, F. C.; Siddhanta, A. K.; Zucco, C. *Acc. Chem. Res.* **1988**, *21*, 135. (d) Rappoport, Z.; Biali, S. E. *Acc. Chem. Res.* **1988**, *21*, 442. (e) Kresge, A. J. *Acc. Chem. Res.* **1990**, *23*, 43.

[4] McGarrity, J. F.; Pinkerton, A. A.; Schwartzenbach, D.; Flack, H. D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 405.

[5] As reported by McGarrity (ref 4), **6** can be isolated via crystallization or converted to several derivatives. To confirm the stability of the enol geometry under the conditions of derivatization, we prepared the corresponding acetate (**ii**) and established the structure by single-crystal X-ray analysis (see Supporting Information).



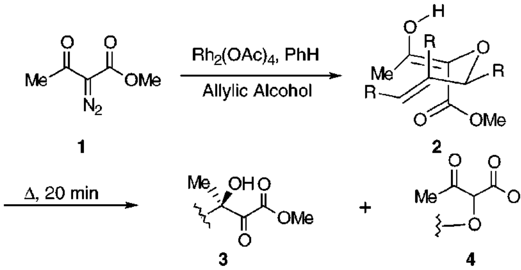
6 **ii**

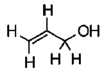
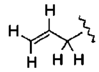
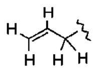
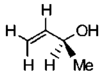
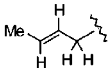
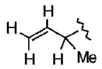
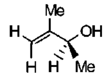
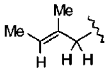
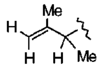
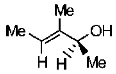
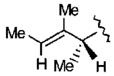
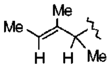
[6] A study of the tautomerization of this enol has recently been reported, see: Jefferson, E. A.; Kresge, A. J.; Wu, Z. *Can. J. Chem.* **1998**, *76*, 1284.

[7] (a) Our interest in this possibility derived from the known Lewis acidity of some Rh(II) catalysts, see: Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919. For a leading reference describing Lewis acid promotion of the Claisen rearrangement, see: Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205.

10.1021/ol990697x CCC: $18.00

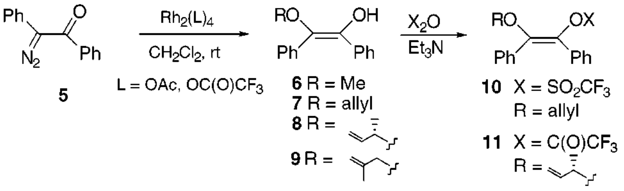
Table 1. Reaction of Doubly Stabilized α-Diazoketones with Various Substituted Allylic Alcohols[1]



Entry	Allylic Alcohol [ee]	[3,3] Product (yield) [ee]	Insertion Product (yield)
a		 (45)	 (34)
b	 [98]	 (77) [95]	 (0)
c	 [82]	 (70) [77]	 (8)
d	 [92]	 (63) [90]	 (12)

conditions using either $Rh_2(OAc)_4$ or $Rh_2(TFA)_4$ were found to promote the coupling of **5** with a range of allylic alcohols. With primary allylic alcohols, both catalysts afforded a single enol (e.g., **7** and **9**, observed by ^1H NMR). Decomposition of **5** with $Rh_2(OAc)_4$ in the presence of 3-buten-2-ol afforded enol **8** as a single isomer whereas catalysis of the same reaction with $Rh_2(TFA)_4$ results in a 7:1 mixture of isomers. As with **6**, derivatization of **7**−**9** is possible and in the case of **7** the corresponding triflate **10** proved amenable to single-crystal X-ray analysis (see Supporting Information).

Scheme 1

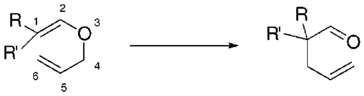


Having accessed enols **6**−**9**, we began investigating the possibility that rhodium was promoting the facile Claisen chemistry.[7] For these studies we used **8** as a representative substrate and observed first-order kinetics over a range of 5−90% conversion. In addition we found the rate to be independent of the ligand on rhodium and unaffected by either catalyst concentration or the presence of Proton Sponge (1.0 equiv, Table 2).[8] Thus, the propensity of allyloxy enols to undergo Claisen chemistry appears to be intrinsic and not the result of conditions present during their formation.

Table 2. Influence of Reaction Conditions on the Rearrangement of Allyloxy Enol **8** in CD_2Cl_2 at 298 K

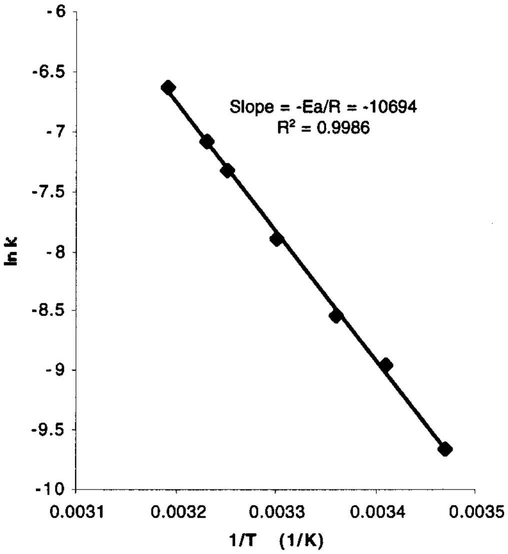
Reaction Conditions	$k(s^{-1}) \times 10^4$	$t_{1/2}$ (min)
1 mol % $Rh_2(OAc)_4$	-2.3	50
1 mol% $Rh_2(TFA)_4$	-2.5	46
5 mol% $Rh_2(TFA)_4$	-2.4	48
1 mol% $Rh_2(TFA)_4$ + 1 equiv proton sponge	-2.4	48

Scheme 2



12 R, R' = H
13 R = OH, R' = H
14 R = H, R' = OH

Qualitatively, these observations are consistent with a computational study by Houk which predicts enthalpies of activation for the Claisen rearrangement of enols **13** and **14** to be 1−2 kcal/mol lower than those of the parent allyl vinyl ether (**12**, Scheme 2).[9] Variable temperature kinetic experiments performed with enol **8** revealed a $\Delta H^{\ddagger}$ of 20.6 kcal/mol, corresponding to a $\Delta\Delta H^{\ddagger}$ of −4.8 kcal/mol between **8** and **12** (see Figure 1). This difference is substantially larger

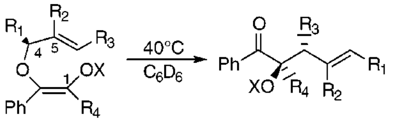


T(°C)	$k(s^{-1}) \times 10^4$	$t_{1/2}$(min)
15	0.64	180
20	1.3	89
25	2.0	58
30	3.8	30
35	6.7	17
37	8.5	14
40	13	8.8

Figure 1. Arrhenius plot for allyloxy enol **8**.

than the computed $\Delta\Delta H^{\ddagger}$ values for **13** and **14**, a discrepancy we attributed to the presence of rate-enhancing substituents in **8**. As illustrated in Table 3, this latter notion is supported by the kinetic behavior of **7**−**9** which clearly illustrates the significant influence of substituents on the rate of Claisen rearrangement. In accord with other reports,[10] we found that alkyl substituents at C4 enhance the Claisen rate relative to the parent allylic system **7**, whereas substrates containing analogous subtituents at C5 (i.e., **9**) rearrange more slowly. With regard to the substituents on the enol-baring carbons, the kinetics of **15** indicate that the aromatic group at C1 does not offer any significant acceleration relative to an alkyl group at this position; however, the rearrangement rate was dramatically retarded when electron donation from the enol hydroxyl was reduced by derivatization as the corresponding trifluoroacetate **11**.[11] In addition to illustrating the importance of substituent effects, these investigations serve to explain the different Claisen/OH-insertion ratios observed with some substrate combinations.[1] This product distribution derives from a delicate balance between ketonization and rearrangement that is clearly reflected by the data in Table 1 where one sees that ketonization can become competitive when the Claisen rearrangement is slowed by allylic alcohol substrates either lacking accelerating (entry a) or containing retarding (entry c and d) substituents.[12,13]

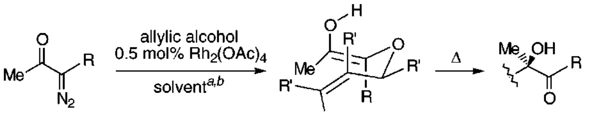
Table 3. Substituent Effects on the Rearrangement Rate of Allyloxy Enols in C_6D_6 at 313 K



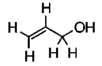
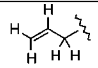
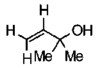
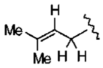
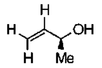
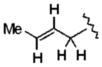
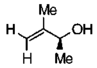
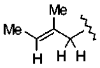
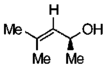
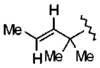
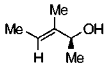
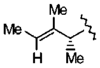
Substrate	$t_{1/2}$
7: R_1, R_2, R_3, X = H, R_4 = Ph	118 min
8: R_1 = Me; R_2, R_3, X = H; R_4 = Ph	8.8 min
9: R_1, R_3, X = H; R_2 = Me; R_4 = Ph	18 h
11: R_1 = Me; R_2, R_3 = H; X = TFA	14 h
15: R_1 = Me; R_2, R_3, X = H; R_4 = Me	9.2 min

Having established the importance of allylic alcohol substitution, attention was turned to the issue of substituent effects on enol stability. In our studies to date we had utilized α-diazoketones that furnish enols conjugated to either an aryl or carbonyl moiety. To determine if enol conjugation was a prerequisite for the success of this reaction, we extended our investigation to include α-diazoketones **16a** and **16b**. As shown in Table 4, **16a** and **16b** are both excellent substrates that combine with a variety of allylic alcohols to furnish the corresponding α-hydroxy ketones with chirality transfer equivalent to their conjugated counterparts. In addition, the successful use of **16b** serves to illustrate that competing intramolecular events such as carbonyl ylide formation will not inhibit conversion to the enol.

Table 4. Reaction of Monostabilized α-Diazoketones with Various Substituted Allylic Alcohols[13]



16a: R = Me
16b: R = $CH_2CH_2CO_2Et$
17

Entry	Allylic Alcohol [ee]	[3,3] Product (yield) [ee]
1a		 (51)
1b		(58)
2a		 (59)
2b		(49)
3a	 [98]	 (64) [93]
3b		(51)
4a	 [82]	 (59) [79]
4b		(51)
5a	 [75]	 (60) [41]
5b		(49)
6a	 [92]	 (60) [91]
6b		(53)

[a] Reactions with **16a** were performed in pentane. [b] Reactions with **16b** were performed in benzene

Intrigued by both the intrinsic reactivity of the allyloxy enols and the generality of the reaction with regard to both diazo and alcohol substrate, we have been considering applications of other similarly derived reactive enols.[14] To this end we explored the coupling of **16a** and **18** with several propargylic alcohols. As shown by the data presented in Table 5, the intrinsic enol reactivity is again manifest and the expected allenic α-hydroxyketones are produced in good yields under very mild conditions.[15]

In contrast to our experiences with allylic alcohols, the reaction course with propargylic substrates was found to be

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(8) The experiments with Proton Sponge indicated that protonation of the incipient enol is not promoting the Claisen rearrangement. Experiments with other amine bases such as Et_3N resulted in rapid tautomerization of the intermediate enol to the α-allyloxy ketone (i.e., the formal O−H insertion product).

(9) (a) Yoo, H. Y.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 2877. (b) We thank Professor Houk for providing unpublished results regarding the *Z*-enol **14**.

(10) Ziegler, F. E.; *Chem. Rev.* **1988**, *88*, 1423. Wipf, P. In *Comprehensive Organic Syntheses*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 5, p 827 and references therein.

(11) A similar effect was noted by Koreeda in the anionic variant of this reaction, see: Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572.

(12) The delicate balance between ketonization and rearrangement is further illustrated by a deuterium isotope study wherein allyl alcohol OD was found to combine with **1** and funish a 6:1 ratio of Claisen/OD insertion products.

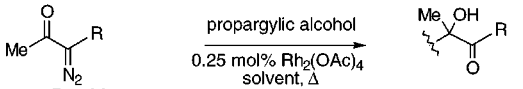
(13) The structure assigned to each new compound is in accord with its infrared and high-field ^1H (500 MHz) and ^{13}C (125 MHz) spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry.

(14) For a recent application of reactive enols in synthesis, see: Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. *J. Am. Chem. Soc.* In Press.

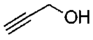
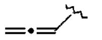
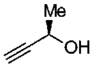
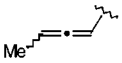
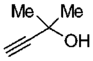
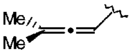
(15) For a review of pericyclic reactions of acetylenic compounds, see: Viola, A.; Collins, J. J.; Filipp, N. *Tetrahedron* **1981**, *37*, 3765.

(16) For a similar application, see the preceding Letter in this issue (Jung, M. E.; Pontillo, J. *Org. Lett.* **1999**, *1*, 367). We thank Professor Jung for sharing this information prior to publication.

Table 5. Reaction of α-Diazoketones with Propargylic Alcohols[13]

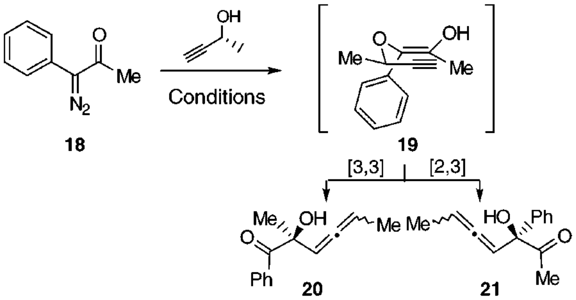


16a: R = Me
18: R = Ph

Entry	Substrate	Propargylic Alcohol	[3,3] Product (yield)
1a	**16a**		 (47)[a,c]
1b	**18**		(26)[b,d]
2a	**16a**		 (59)[a]
2b	**18**		(46)[b,e]
3a	**16a**		 (60)[a]
3b	**18**		(54)[b]

[a] Reactions were performed in refluxing pentane. [b] Reactions were performed in refluxing benzene. [c] A 21% yield of OH-insertion product was also obtained. [d] A 28% yield of OH-insertion product and a 7% yield of [2,3]-rearranged product were also obtained. [e] A 4% yield of [2,3]-rearranged product was also isolated

Table 6. Effect of Reaction Conditions on [2,3]/[3,3] Ratio Observed with α-Diazoketone **18** and 3-Butyn-2-ol



Entry	Conditions	20:21
1	0.25 mol% $Rh_2(OAc)_4$, PhH, Δ	10.5 : 1
2	1.0 mol% $Rh_2(OAc)_4$, PhH, Δ	2.3 : 1
3	5.0 mol% $Rh_2(OAc)_4$, PhH, Δ	1 : 1.6
4	0.25 mol% $Rh_2(OAc)_4$, PhH, rt	1.3 : 1
5	0.25 mol% $Rh_2(TFA)_4$, PhH, Δ	1 : 57

highly dependent upon conditions. Specifically, as indicated in Table 6, the reaction conditions influence a competition between paths leading to either [3,3] or [2,3] rearrangement.[16] Of particular note is the dramatic difference between reactions run with the acetate and trifluoroacetate ligands (cf. entries 1 and 5), an observation which suggests the involvement of rhodium in the [2,3] process and stands in stark contrast to the reactivity of the allyloxy enols (see Table 2). Attempting to rationalize this difference in behavior, we explored the possibility that the [2,3]- and [3,3]-derived products might not be linked by a common enol intermediate. In the event, monitoring experiments by ^{1}H NMR revealed that treatment of diazoketone **18** and 3-butyn-2-ol with 1 mol % of $Rh_2(OAc)_4$ results in clean and rapid formation of an enol (**19**) (Table 6) which, upon continued monitoring, undergoes conversion to both the [3,3] and [2,3] rearrangement products **20** and **21**, respectively ($t_{1/2}$ for [2,3] = 210 min at 40 °C).[17] In contrast, when 1 mol % of $Rh_2(TFA)_4$ is used the substrates combined to form the [2,3]-rearranged product (**21**) before a single spectrum could be acquired. Upon slowing this reaction by using only 0.1 mol % of $Rh_2(TFA)_4$, one again observes enol **19** which, upon continued monitoring, undergoes rapid [2,3] rearrangement to **21** in a (pseudo) first-order sense ($t_{1/2}$ = 5.4 min, 25 °C) and to the exclusion of **20**. Importantly, a side-by-side experiment was performed wherein two equimolar solutions of **18** and 3-butyn-2-ol in C_6D_6 at 25 °C were each treated with 1 mol % of $Rh_2(OAc)_4$ to effect diazo decomposition. Once complete (as evidenced by decolorization and cessation of N_2(g) release, about 1 min), 1 mol % of $Rh_2(TFA)_4$ was added to one mixture. Analysis of aliquots after 5 min (^{1}H NMR) revealed complete conversion of **19** to **21** in the $Rh_2(TFA)_4$-treated case and less than 5% conversion in the control. Taken together, these observations clearly support a mechanism wherein enol **19** bifurcates between rearrangement pathways and only the [2,3]-path is dramatically facilitated by Rh(II).

In summary, we have established that the coupling of α-diazoketones with allylic alcohols under Rh(II) catalysis furnishes allyloxy enols which, due to the electron-donating hydroxyl group, are intrinsically predisposed to undergo Claisen rearrangement. Importantly, this predisposition enables the Claisen chemistry to compete with ketonization, a delicate reactivity balance which can be influenced by substituent effects. An additional level of difficulty arises with enols derived from propargylic alcohols since these intermediates undergo [2,3] rearrangement in competition with the two aforementioned processes. Fortunately, proper choice of reaction conditions enables selection among the possible pathways. Further efforts to manipulate α-ketocarbenoid-derived enols in a variety of synthetically useful ways are ongoing.

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

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[17] Neither [3,3]-product **20** nor [2,3]-product **21** undergoes a [1,2] shift upon either silica gel chromatography or treatment with 5 mol % of $Rh_2(OAc)_4$ in refluxing benzene for 3 h.