Communications to the Editor

Catalyst-Based Control of [2,3]- and [3,3]-Rearrangement in α-Diazoketone-Derived Propargyloxy Enols

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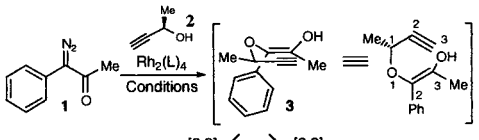
Recent studies in these laboratories have revealed that α-diazoketones (e.g., **1**) undergo rhodium(II)-catalyzed coupling with alcohols to selectively deliver (*Z*)-alkoxy enols (e.g., **3**, Scheme 1).[1,2] When generated under these neutral conditions, alkoxy enols are sufficiently stable to enable their manipulation in a number of synthetically useful ways. In particular, we have been interested in the sigmatropic chemistry of enols derived from allylic alcohols, which undergo exceptionally facile Claisen rearrangement to furnish tertiary α-hydroxy carbonyl compounds.[1−3] Recently, we reported the extension of this tandem enol formation/Claisen process to furnish tertiary α-hydroxy allenes.[2,4] In that study, it was found that the standard Claisen conditions, when applied to propargylic alcohols, also gave rise to a byproduct derived from an apparent [2,3]-rearrangement (e.g., **5**, Scheme 1). Furthermore, the amount of **5** coproduced was dependent both on catalyst load and ligand. In this communication, we describe investigations that establish the [2,3]-rearrangement as a versatile, Lewis acid-catalyzed process that can be selectively promoted or suppressed. In addition, enantioselective [2,3]-rearrangement can be realized using a chiral Lewis acid promoter.

Extensive catalyst screening further clarified the relationship between catalyst structure and reaction course (i.e., **1**→**4** vs **1**→**5**, Scheme 1), revealing a substantial dependence on electronics (cf., $Rh_2(cap)_4$ vs $Rh_2(tfa)_4$).[5,6] However, at the outset, it was unclear if the observed catalyst dependence derived from perturbation of the primary sigmatropic event or catalysis of a secondary [1,2]-α-ketol rearrangement (i.e., **4**→**5**, Scheme 1). Our studies with allyloxy enols, which undergo [3,3]-rearrangement regardless of the Rh(II) catalyst employed, first led us to speculate that the latter process was more likely. In an effort to substantiate this hypothesis, we devised the isotope-labeling study shown in Scheme 2.

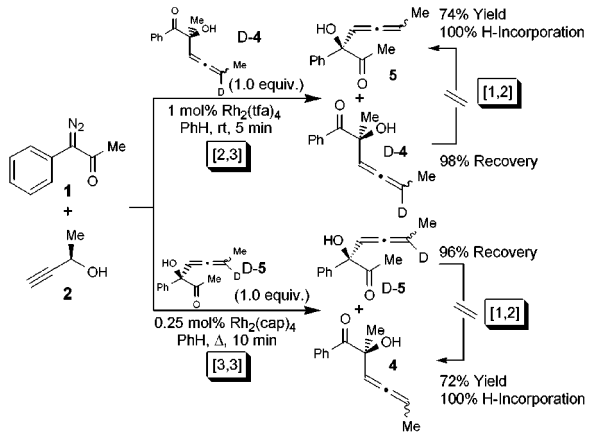
Diazoketone **1** was combined with 3-butyn-2-ol (**2**) under both [3,3]-selective (i.e., $Rh_2(cap)_4$) and [2,3]-selective (i.e., $Rh_2(tfa)_4$) conditions. Incorporated in each reaction was the independently prepared, deuterium-labeled analogue of the unanticipated regioisomer. Use of $Rh_2(tfa)_4$ in the presence of D-**4** gave rise to the apparent [2,3]-product **5** free of deuterium incorporation.

Scheme 1

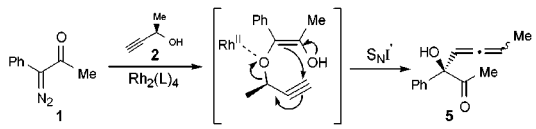


Conditions	4 : 5
0.25 mol% $Rh_2(OAc)_4$, Benzene, Δ	10.5 : 1
1.0 mol% $Rh_2(OAc)_4$, Benzene, Δ	2.3 : 1
5.0 mol% $Rh_2(OAc)_4$, Benzene, Δ	1 : 1.6
0.25 mol% $Rh_2(tfa)_4$, Benzene, rt	1 : 57
0.25 mol% $Rh_2(cap)_4$, Benzene, Δ	30 : 1

Scheme 2



Scheme 3



Similarly, use of $Rh_2(cap)_4$ in the presence of D-**5** gave exclusively protic [3,3]-product **4**, illustrating that the anticipated [1,2]-α-ketol rearrangement process was not operative.

Having demonstrated that rearrangement products **4** and **5** arise via independent pathways, we began to favor a mechanism wherein the rhodium(II) catalyst adopts a dual role, promoting both enol formation and [2,3]-rearrangement. In this scenario, coordination of Rh(II) to the enol ether oxygen promotes an S_NI' process (Scheme 3). Attenuating the Lewis acidity of the Rh(II) catalyst (i.e., $Rh_2(cap)_4$ vs $Rh_2(tfa)_4$) would therefore be expected to slow this process, enabling thermal [3,3]-rearrangement to predominate. Initial support for this hypothesis was found in the reaction kinetics, which showed that [2,3]-rearrangement of **3** in the presence of 0.1 mol % $Rh_2(tfa)_4$ ($t_{1/2}$ = 5.4 min, 25 °C) was dramatically accelerated relative to that in the presence of 1 mol % $Rh_2(OAc)_4$ ($t_{1/2}$ = 3.5 h, 40 °C). To demonstrate that this rate enhancement derived from interaction of the enol with Rh(II), we treated a solution of **1** and **2** (1.2 equiv) with 1 mol % $Rh_2(OAc)_4$, cleanly generating enol **3** (Scheme 4, observed by ^1H

(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) Wood, J. L.; Moniz, G. A. *Org. Lett.* **1999**, *1*, 371.
(3) 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.* **1999**, *121*, 6326.
(4) For recent synthetic applications of allenes, see: (a) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470. (b) Jonasson, C.; Horvath, A.; Backvall, J.-E. *J. Am. Chem. Soc.* **2000**, *122*, 9600. (c) Wender, P. A.; Zhang, L. *Org. Lett.* **2000**, *2*, 2323.
(5) For a discussion of the electron-rich nature of the $Rh_2(cap)_4$ catalyst, see: Doyle, M. P.; Westrum, L. J.; Wolthuis, W. N. E.; See, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958.
(6) For discussions of the electron-deficient nature of the $Rh_2(tfa)_4$ catalyst, see: (a) Doyle, M. P.; Colsman, M. R.; Chinn, M. S. *Inorg. Chem.* **1984**, *23*, 3684. (b) Davies, H. M. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol 4, p 1031. (c) Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797.

10.1021/ja015727h CCC: $20.00
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Scheme 4

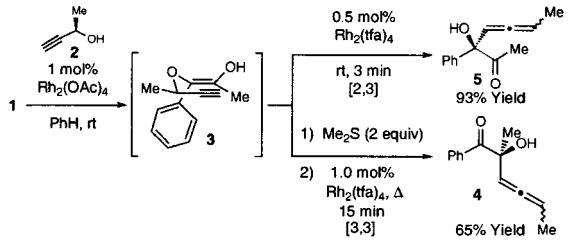
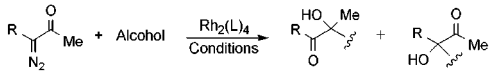


Table 1. Examples with Doubly Stabilized α-Diazoketones[11]



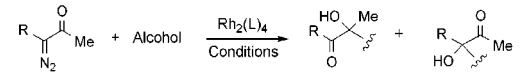
Entry	Alcohol	Diazoketone	Conditions	Yield [3,3]	Yield [2,3]
1a		**1**	A[a]	22%[c]	-
			B[b]	-	87%
1b		**6**	A	-	-
			B	-	62%
2a		**1**	A[d]	-	-
			B	-	68%
2b		**6**	A	-	-
			B	-	61%
3a		**1**	A	81%	-
			B	-	82%
3b		**6**	A	-	-
			B	-	60%
4a		**1**	A	52%	-
			B	-	50%
4b		**6**	A	-	-
			B	-	43%

[a] Conditions A: 0.5 mol % $Rh_2(cap)_4$, PhH, reflux, 10 min. [b] Conditions B: 0.25 mol % $Rh_2(tfa)_4$, PhH, 10 min rt (**1**) or reflux (**6**). [c] A 44% yield of tautomerized product was also isolated. [d] An 83% yield of tautomerized product was isolated exclusively.

NMR).[7] Treatment of the enol solution with 0.5 mol % $Rh_2(tfa)_4$ resulted in rapid [2,3]-rearrangement at room temperature, a process that could be completely suppressed by prior addition of dimethyl sulfide (2 equiv) to yield only [3,3]-rearrangement product **4** upon heating.[8]

Having established the basis for the divergent reactivity of enol **3**, we explored our ability to manipulate reaction outcome in related substrates. As shown in Tables 1 and 2, similar control can be achieved with a number of α-diazoketones and propargylic alcohols affording a variety of substituted allenes in good to excellent yield. With doubly stabilized α-diazoketones (i.e., **1** and **6**), use of $Rh_2(tfa)_4$ affords exclusively the product of [2,3]-rearrangement. Use of $Rh_2(cap)_4$ generates the [3,3]-product with **1**; however, this catalyst does not efficiently dediazotize **6**. The identical conditions ($Rh_2(cap)_4$, benzene, reflux) are employed to effect exclusive [3,3]-rearrangement with monostabilized α-diazoketones (i.e., **7** and **8**, Table 2), while the harsher $Rh_2(tfa)_4$ catalyst is replaced by a higher catalyst loading of the more mild $Rh_2(oct)_4$ to furnish the [2,3]-product.[9] In accord with our studies of allyloxy enols, tautomerization of propargyloxy enols is observed to compete with [3,3]-rearrangement in certain substrates due to a substituent-controlled reduction in [3,3] rate.[2] However, this competition is not observed with [2,3]-rearrangement. Reduced yields are observed for both processes with 2-methyl-3-butyn-2-ol (cf., entries 4a,b) due to inefficient carbenoid capture.[10]

Table 2. Examples with Monostabilized α-Diazoketones[11]



Entry	Alcohol	Diazoketone	Conditions	Yield [3,3]	Yield [2,3]
1a		**7**	A[a]	64%	-
			B[b]	-	60%
1b		**8**	A	68%	-
			B	-	62%
2a		**7**	A	66%	-
			B	-	68%
2b		**8**	A	67%	-
			B	-	66%
3a		**7**	A	60%	-
			B	-	65%
3b		**8**	A	69%	-
			B	-	60%
4a		**7**	A	41%	-
			B[c,d]	-	40%
4b		**8**	A[e]	38%	-
			B[f]	-	-

[a] Conditions A: 0.25 mol % $Rh_2(cap)_4$, PhH, reflux, 10 min. [b] Conditions B: 5 mol % $Rh_2(oct)_4$, PhH, reflux, 10 min. [c] 20 mol % $Rh_2(oct)_4$ was employed. [d] An 11% yield of enone **i** (ref 10) was also isolated. [e] A 5% yield of enone **ii** (ref 10) was also isolated. [f] Only enone **ii** (ref 10) was isolated in 25% yield.

Table 3. Effect of Lewis Acid Additives on Rearrangement of Enol **3**[a]

Lewis acid additive/conditions	**5**:**4**[b]	yield, %
no additive, PhH, Δ, 10 min	1:2.3	78
1 equiv $CuSO_4$, PhH, Δ, 10 min	2.5:1	70
5 mol % $AgBF_4$, PhH, rt, 2 min	60:1	80
15 mol % [Sn−((*S*,*S*)-Ph-pybox)](OTf)$_2$ (**9**), CH_2Cl_2, rt, 35 min	>100:1	76
2.5 mol % [Cu−((*S*,*S*)-Ph-pybox)](OTf)$_2$ (**10**), PhH, rt, 5 min	>100:1	67

[a] Generated in all cases by treatment of **1** and **2** with 1 mol % $Rh_2(OAc)_4$, rt, 5 min. [b] Ratios determined by integration of ^{1}H NMR resonances.

The determination that $Rh_2(tfa)_4$ was functioning in a Lewis acidic capacity to facilitate [2,3]-rearrangement led to an investigation of other Lewis acid additives for similar activity. As can be seen in Table 3, enol **3** is successfully intercepted by several Lewis acids, including (pybox)-Sn(II) (**9**) and (pybox)-Cu(II) (**10**) catalysts which afford, at room temperature and with low catalyst loadings, the [2,3]-product (**5**) via a *three-step, two metal-catalyzed process*.[12]

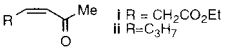
The success of Lewis acids **9** and **10** prompted us to explore the possibility of asymmetric induction in the [2,3]-rearrangement (Scheme 5). We were delighted to find that treatment of α-diazoketone **1** and propargyl alcohol (1.2 equiv) with 1 mol % $Rh_2(OAc)_4$ affords enol **11**, which, upon treatment with [Cu(*S*,*S*)-Ph-pybox$(H_2O)_2$](OTf)$_2$ (**12**), affords (*R*)-**13** in 61% yield[13] and

(7) <10% [2,3]-rearrangement of enol **3** is observed after 1 h in the presence of 1 mol % $Rh_2(OAc)_4$ at 25 °C.

(8) This catalyst inhibition experiment illustrates the Rh(II)-dependent nature of the [2,3]-rearrangement and the catalyst independence of the [3,3]-rearrangement. The selection of dimethyl sulfide was based on the large K_{eq} reported for binding of tetrahydrothiophene to $Rh_2(but)_4$, see: Drago, R. S.; Bilgrien, C. J. *Polyhedron* **1988**, *7*, 1453.

(9) Use of $Rh_2(tfa)_4$ with monostabilized α-diazoketones leads, in general, to intractable mixtures of products. The $Rh_2(oct)_4$ catalyst is electronically similar to $Rh_2(OAc)_4$ with solubility equivalent to $Rh_2(tfa)_4$.

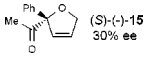
(10) The principal byproduct in reactions with 2-methyl-3-butyn-2-ol is the corresponding (*Z*)-enone (e.g., **i**, **ii**) which arises via β-hydride elimination of the uncaptured carbenoid, see: Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908.



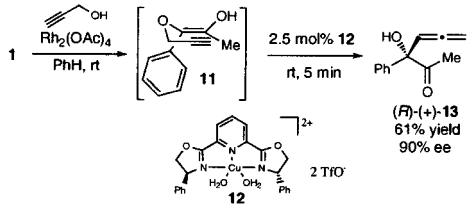
(11) The structure assigned to each compound is in accord with its infrared and high-field ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra as well as with appropriate parent ion identification by high-resolution mass spectrometry.

(12) For the preparation of bis(oxazolinyl)pyridine catalysts **9** and **10**, see: (a) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859. (b) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669.

(13) (*S*)-(−)-**15** is isolated as a byproduct of this reaction (30% yield); however, isotope-labeling studies prove that **15** is not derived from **13** (see Supporting Information). Rather, it is believed to arise from the same complex **14** via a proton-transfer event.



Scheme 5



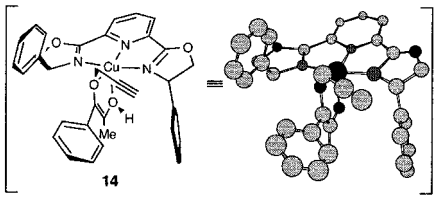


Figure 1. Computational structure of enol complex **14**.

90% ee. The sense of stereochemical induction is predicted by enol complex **14** (Figure 1), which represents the calculated global minimum conformation of this complex by Monte Carlo methods, further minimized by PM3 level calculations.[14,15]

In summary, we have shown that (*Z*)-propargyloxy enols are capable of undergoing rearrangement to allenyl α-hydroxyketones via thermal [3,3]-rearrangement and Lewis acid-catalyzed [2,3]-rearrangement pathways. The latter has proven amenable to asymmetric catalysis, affording [2,3]-rearrangement product in good yield and high % ee. Further studies into asymmetric catalysis of the [2,3]-rearrangement and the chemistry of alkoxy enols are in progress.

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Supporting Information Available: Spectral data, experimental data, and stereochemical proofs pertaining to all products illustrated in Schemes 2, 4, and 5 and Tables 1 and 2 as well as details regarding the computation of complex **14** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA015727H

(14) This stereochemical model is based upon those of Evans and co-workers, see: Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686.

(15) The opposite enantiomer, (*S*)-(−)-**13,** can be prepared using the [Cu(*R, R*)-Ph-pybox$(H_2O)_2$]$(OTf)_2$ catalyst in equivalent yield and enantiomeric excess.