Communications to the Editor

Development of a Rhodium Carbenoid-Initiated Claisen Rearrangement for the Enantioselective Synthesis of α-Hydroxy Carbonyl Compounds

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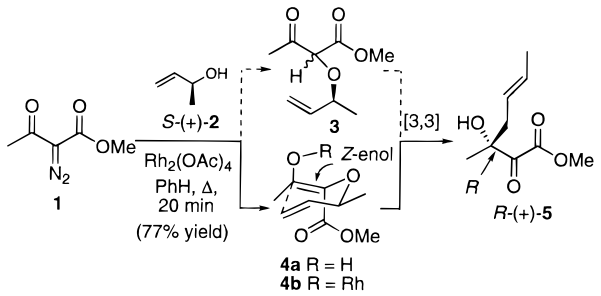
In the course of a recent total synthesis, we required a method for the stereocontrolled preparation of β-hydroxy ester **5**. Eventually we envisioned an asymmetric approach that called for the initial preparation of α-allyloxy-β-ketoester **3** (Scheme 1), a substrate we believed to be accessible from **1** via rhodium-mediated O−H insertion chemistry.[1,2] Based on reports by Koreeda we anticipated advancing **3** to **5** via a Claisen rearrangement.[3] In the event, we unexpectedly discovered that the $Rh_2(OAc)_4$-catalyzed dediazotization of **1** in the presence of *(S)*-(+)-3-buten-2-ol (**2**) directly produces *(R)*-(+)-**5** in what appeared to be an extraordinarily stereoselective tandem O−H insertion/[3,3] rearrangement process (i.e., **1** → **3** → **5**).[4] In this paper we describe investigations that establish this rhodium carbenoid-initiated Claisen rearrangement as a general stereoselective method for preparing tertiary alcohols. Additionally we report that this process occurs via a mechanism wherein the O−H insertion event delivers a reactive enol intermediate (i.e., **4a**) and not the anticipated ketone **3**, a finding which clearly suggests that rhodium-mediated O−H insertion reactions of α-diazo ketones proceed via initial proton transfer to oxygen.

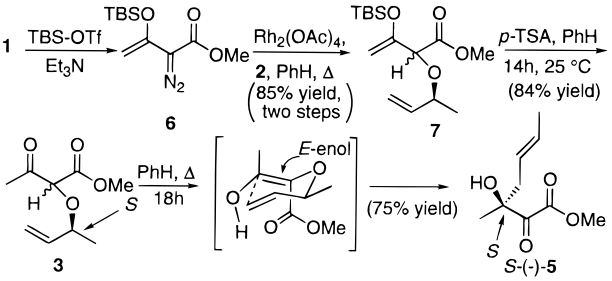
Intrigued by the facility with which **1** and **2** combine to produce **5**, we initiated investigations into the course of this transformation. Favoring an anion-accelerated mechanism[5] that would bypass the classical O−H insertion step by proceeding via a transient (*Z*)-rhodium enolate (i.e., **4b**), we set out to establish positive proof against the initially envisioned intermediate, **3** (Scheme 2). To this end, **1** was converted to TBS-enol ether **6** which, when combined with *(S)*-(+)-**2** in the presence of $Rh_2(OAc)_4$, was found to produce a mixture of diastereomeric O−H insertion products (**7**).[6−8] Although this mixture is separable by standard flash column chromatography, when individually advanced through the subsequent deprotection and purification steps, each isomer furnishes the same mixture of diastereomeric ethers (**3**). Interestingly, when exposed to reaction conditions that had previously furnished the Claisen product *R*-(+)-**5** (benzene at reflux for 20 min, Scheme 1), **3** produces only a trace of **5**. When the reaction time is increased to 18 h, the Claisen product can be isolated in 75% yield. However, under these conditions chirality transfer is diminished *and the opposite enantiomer [(S)-(−)-5] predominates* (47% ee). Additionally, **3** is recovered unchanged when incorporated as a substrate in the reaction of **1** with deuterated **2**.[9] Although these results clearly indicate that the rhodium-initiated reaction does not proceed via **3**, the novel pathway illustrated in Scheme 1 (i.e., **1** → **4a** → **5**) was not identified until we expanded our investigation to include a variety of substituted allylic alcohols, diazo substrates, and catalysts (vide infra).

As can be surmised from the data in Tables 1 and 2, our investigations into generality revealed that rhodium carbenoid-initiated Claisen rearrangements similar to that illustrated in Scheme 1 occur readily when either acyclic (Table 1) or cyclic (Table 2) diazo substrates are combined with a range of allylic alcohols. In some cases (e.g., Table 1, entry 1a) the classical O−H insertion product is coproduced in varying amounts. Transfer of stereochemistry from enantio-enriched allylic alcohols to the derived α-hydroxy ketones is in all cases consistent with the intermediacy of a chairlike transition state possessing a (*Z*)-enol

Scheme 1



Scheme 2



(1) For a recent review, see: Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811.

(2) For a recent and elegant stereoselective preparation of α-hydroxy carbonyls, see: Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893.

(3) (a) Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572. (b) Examples of both [2,3] and [3,3] rearrangement of α-allyloxy ketones have been reported, see: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423 and references therein.

(4) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1995**, *117*, 10413. In a typical experiment, a mixture of **1** (3.17 g, 22.3 mmol) and **2** (1.93 g, 26.8 mmol, 98% ee) is diluted in benzene (75 mL), treated with $Rh_2(OAc)_4$ (30 mg, 0.068 mmol), and heated to reflux. After 20 min at reflux the reaction is cooled, and the solvent removed in vacuo. Chromatographic purification (20% EtOAc/Hex) furnishes 3.20 g of **5** (77% yield, 95% ee).

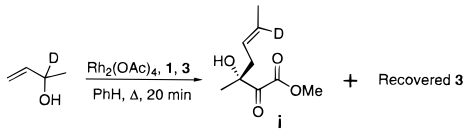
(5) Evans, D. A.; Golub, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

(6) 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 with appropriate parent ion identification by high-resolution mass spectrometry. Details regarding the assignment of relative and absolute stereochemistry are included as Supporting Information.

(7) For the preparation of **6**, see: Davies, H. M. L.; Houser, J. H.; Thornley, C. *J. Org. Chem.* **1995**, *60*, 7529.

(8) The reported yield for **7** includes three silylated products, see Supporting Information for details.

(9) This experiment eliminates the possibility that a transient species, generated in the presence of **1**, **2**, **3**, and $Rh_2(OAc)_4$, is responsible for promoting the formation of **5**. Deuterium incorporation into the Claisen product obtained from this experiment (i.e., **i**) was quantitative as determined by 500 MHz ^1H NMR.



10.1021/ja983294l CCC: $18.00
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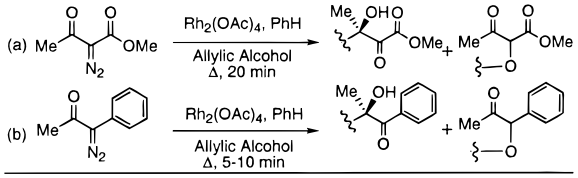
Table 1. Examples with Acyclic α-Diazoketones[6]



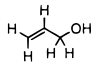
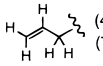
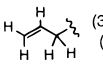
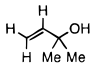
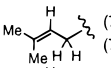
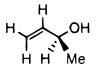
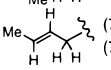
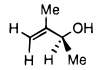
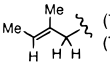
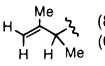
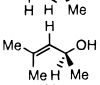
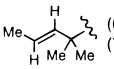
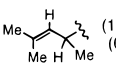
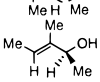
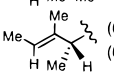
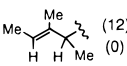
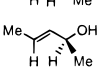
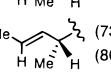
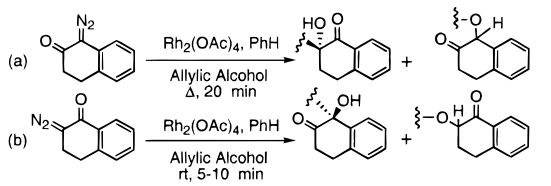
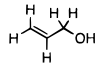
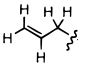
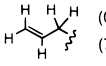
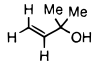
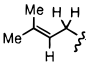
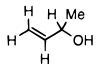
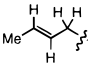
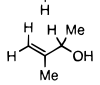
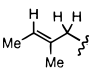
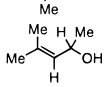
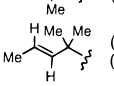
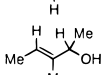
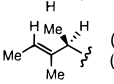
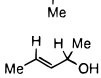
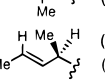
Entry	Allylic Alcohol [ee]	[3,3] Product (yield) [ee]	Insertion Product (yield)
1a		 (45)	 (34)
1b		(77)	(0)
2a		 (71)	--
2b		(72)	
3a	 [98]	 (77) [95]	--
3b	[98]	(77) [94]	
4a	 [82]	 (70) [77]	 (8)
4b	[82]	(76) [79]	(0)
5a	 [75]	 (68) [54]	 (12)
5b	[75]	(70) [45]	(0)
6a	 [92]	 (63) [90]	 (12)
6b	[92]	(67) [91]	(0)
7a	 [98]	 (73) [98]	--
7b	[98]	(80) [97]	

Table 2. Examples with Cyclic α-Diazoketones[6,10]

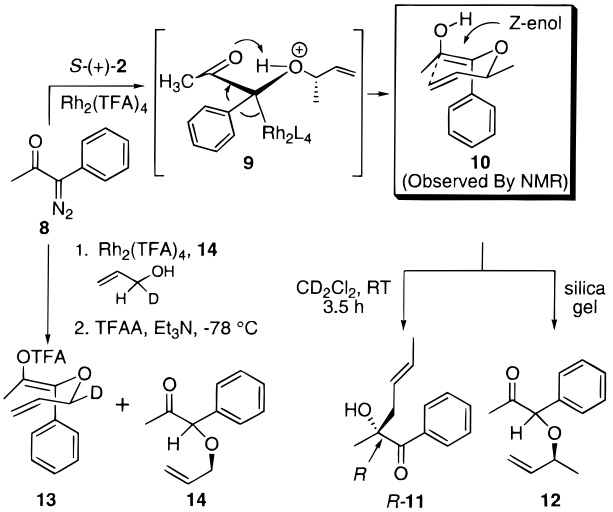


Entry	Allylic Alcohol	[3,3] Product (yield)	Insertion Product (yield)
1a		 (72)	 (0)
1b		(42)	(7)
2a		 (67)	--
2b		(60)	
3a		 (67)	--
3b		(73)	
4a		 (72)	--
4b		(52)	
5a		 (74)	--
5b		(66)	
6a		 (66)	--
6b		(52)	
7a		 (63)	--
7b		(66)	

and an equatorially disposed methyl substituent (e.g., **4a**, Scheme 1). The efficiency of stereochemical transfer is, with the exception of entry 5, excellent.

In furthering the investigation we began exploring various Rh(II) catalysts (Scheme 3). Although in general the reaction outcome was unaffected by changes in ligand, we did observe (by NMR) that within seconds after treating a solution of **8** and

Scheme 3



2 in CD_2Cl_2 with $Rh_2(TFA)_4$ (0.01 equiv) the substrates undergo rapid conversion to an intermediate which, in accord with our studies of **3** (vide supra), did not compare to an authentic sample of the classical O−H insertion product **12**. If left undisturbed this intermediate underwent slow conversion to the Claisen product (**11**). However, upon TLC or attempted isolation the intermediate rapidly furnished **12**. On the basis of these data we speculated that the initially formed carbenoid engages the allylic alcohol to form an intermediate rhodium stabilized ylide (**9**) which selectively furnishes the reactive (*Z*)-enol **10** via intramolecular proton transfer.[11,12] This suspicion was confirmed by a trapping study wherein **8** was converted to the enoltrifluoroacetate **13** in the presence of **14**.[13]

In summary, a novel rhodium carbenoid-initiated C−C bond forming reaction has been discovered and developed into an exceptionally useful method for the asymmetric construction of α-hydroxy carbonyl compounds. Particularly striking is the extent to which olefin geometry is controlled in the intermediate enols and the facility with which the latter undergo Claisen rearrangement. Further investigations into the intrinsic reactivity of these enols and the scope of this reaction are in progress.

Acknowledgment. We are pleased to acknowledge the support of this investigation by the NIH (1RO1GM54131). Eli Lilly, Glaxo-Wellcome, and Bristol-Myers Squibb provided additional support through their Junior Faculty Awards Programs. J.L.W. is a fellow of the Alfred P. Sloan Foundation.

Supporting Information Available: Spectral and experimental data pertaining to all products illustrated in Schemes 2 and 3 and Tables 1 and 2 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Experiments in this series were performed with racemic alcohol as substrate. Thus, where defined, the structures illustrate only relative stereochemistry.

(11) Although the transient species **9** can be envisioned with or without rhodium, the known influence of asymmetric rhodium catalysts on other sigmatropic rearrangements suggests its inclusion, see: Pierson, N.; Fernádez-Garciá; C.; McKervey, M. A. *Tetrahedron Lett.* **1997**, *38*, 4705.

(12) Acid-promoted tautomerization of **10** would account for observations of **12** by TLC.

(13) The inclusion and recovery of **14** in this experiment provides positive proof against its intermediacy en route to **13**. The structure of **13** was confirmed via chemical correlation, see Supporting Information.