

Highly Selective Catalyst-Directed Pathways to Dihydropyrroles from Vinyldiazoacetates and Imines

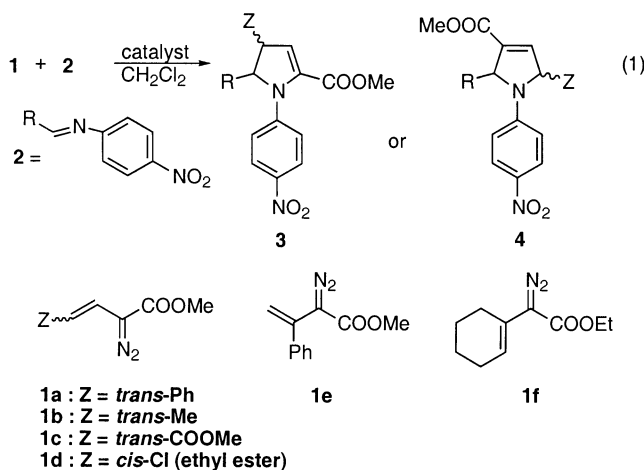
Michael P. Doyle,* Ming Yan, Wenhao Hu, and Luisa S. Gronenberg

Department of Chemistry, University of Arizona, Tucson, Arizona 85721-0041

Received December 13, 2002; E-mail: mdoyle@u.arizona.edu

Copper and dirhodium(II) catalysts have been remarkably effective for metal carbene reactions of diazo compounds. Their basic success is derived from their activities as Lewis acids for electrophilic addition to the diazo compound and in the stabilization of the metal carbene formed upon dinitrogen dissociation.¹ Recently, versatile catalytic approaches to ylide generation and reactions leading to heterocyclic compounds from aryl- and vinyldiazoacetates have been reported.^{2–4} Epoxides, aziridines, and, in selected examples, dihydropyrrolidines and dihydroazepines are among the compounds whose highly stereoselective syntheses have been demonstrated in $\text{Rh}_2(\text{OAc})_4$ -catalyzed reactions (Scheme 1).

In the course of investigating catalytic ylide-derived reactions of vinyldiazo compounds with imines, we surveyed a broad selection of catalysts that were suitable for ylide generation, including copper(I) hexafluorophosphate and triflate, and copper(II) triflate. Whereas $\text{Rh}_2(\text{OAc})_4$ and reactive chiral carboxylates and carboxamides of dirhodium(II) gave the anticipated dihydropyrrole **3** from the reaction between styryldiazoacetate **1a** and imine **2a** ($\text{R} = \text{trans-PhCH=CH}$) with high stereocontrol (100:0 *c:t*), use of copper catalysts, including those like CuPF_6 and CuOTf that normally operate through the same mechanistic pathway as rhodium(II) catalysts,¹ produced the isomeric dihydropyrrole **4** competitively (eq 1), and $\text{Cu}(\text{OTf})_2$ was optimum for this transformation (**3**:**4** = 0:100, 74% yield). The structures of these compounds were confirmed by 2-D and nOe NMR experiments. Formation of **3** occurred in competition with dihydroazepine production (32:68 **3**:dihydroazepine), and only its *cis*-stereoisomer was obtained; **4** was produced in a 70:30 *t:c* ratio.



This contrasting, highly stereoselective, behavior is also evident in reactions of a diverse set (Table 1) of vinyldiazoacetates (**1**) with imine **2b** ($\text{R} = \text{Ph}$) and led us to understand the alternative copper(II)-catalyzed pathway to **4** (and **9**) as being due to a Lewis acid-catalyzed process that is reminiscent of that used by W. Wulff for the efficient construction of aziridines with ethyl diazoacetate.⁵

Scheme 1

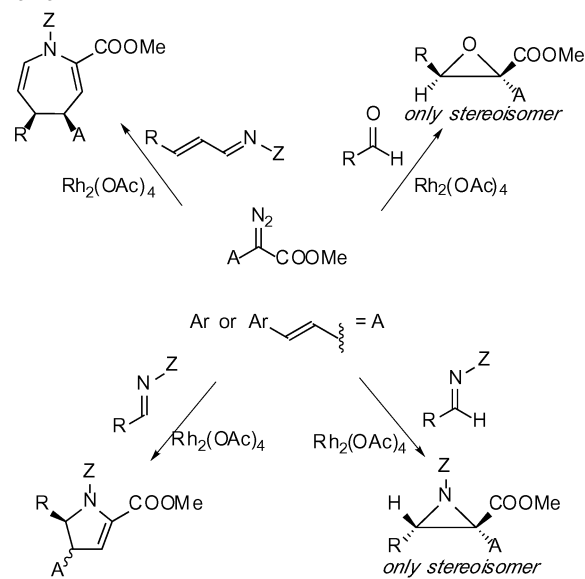


Table 1. Catalyst-Dependent Product Distributions from Reactions between **1** and **2b** ($\text{R} = \text{Ph}$)^a

catalyst	1	isolated yield, %	3 (<i>t:c</i>)	4 (<i>t:c</i>)
$\text{Rh}_2(\text{OAc})_4^b$	a	66 ^d	100 (<98:2)	0
	b	42	100 (90:10)	0
	c	51	100 (93:7)	0
	d	14 ^e	100	0
	f	64	100 (65:35)	0
	f	76	0	100 (91:9)
$\text{Cu}(\text{OTf})_2^c$	a	67	0	100 (91:9)
	f	76	0	100 (93:7)

^a Reactions performed in refluxing CH_2Cl_2 by adding **1** to an equal molar amount of **2b** over 1 h. ^b 1.0 mol %. ^c 5.0 mol %. ^d 1.2 equiv of **1a** was used in this case. ^e Yield of **5**.

Other Lewis acids were employed in efforts to develop the generality of the process,⁶ but only $\text{Sn}(\text{OTf})_2$ showed comparable product yield (but *t:c* = 84:16).

Accordingly, **3** is formed from a ylide originating with a metal carbene intermediate,³ whereas **4** is formed by a process in which the metal catalyst, acting as a Lewis acid, activates the imine for electrophilic addition to the diazo compound (Scheme 2). In previous investigations of copper-catalyzed aziridination reactions of ethyl diazoacetate, copper carbene species were the proposed intermediates.^{6,7} However, activation of imines for electrophilic addition by copper salts has recently been utilized in cycloaddition reactions.^{8,9} In the present case, addition is proposed to occur directly into the diazo carbon to generate an intermediate that is aligned for $\text{S}_{\text{N}}2'$ displacement of dinitrogen. Only **3** is formed with $\text{Rh}_2(\text{OAc})_4$ catalysis, and only **4** is obtained from reactions catalyzed by $\text{Cu}(\text{OTf})_2$.

Scheme 2

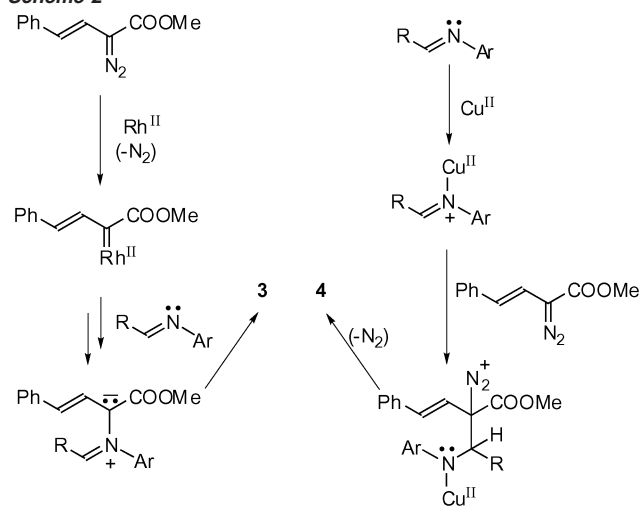
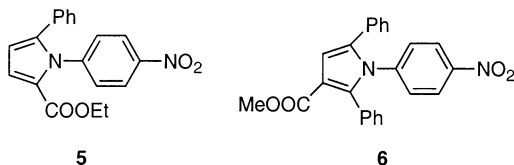


Table 2. Imine Substituent Effect on Product Yield and Selectivities in Reactions with Methyl Styryldiazoacetate^a

Ar in imine (7)	% yield 8 from Rh ₂ (OAc) ₄ -catal. ^b	% yield 9 from Cu(OTf) ₂ -catal. ^c
<i>p</i> -NO ₂ C ₆ H ₄	12	40 (98:2)
<i>p</i> -ClC ₆ H ₄	47	66 (96:4)
C ₆ H ₅	66	67 (91:9)
<i>p</i> -MeC ₆ H ₄	56	63 (88:12)
<i>p</i> -MeOC ₆ H ₄	62	74 (83:17)

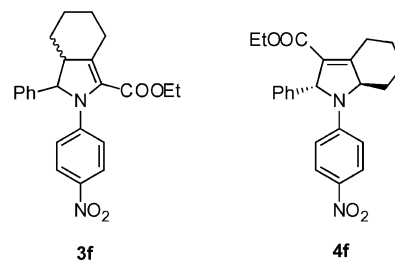
^a Reactions performed as in Table 1 with equimolar amounts of **1a** and **7**. ^b Only *trans*-**8** was obtained; a minor product having two units of the vinylcarbene and one of the imine was also obtained. ^c *Trans*:*cis* ratio in parentheses.

The dihydropyrrole product formed from **1d** with Rh₂(OAc)₄ catalysis was unstable and converted to the corresponding pyrrole (**5**) with loss of HCl. The product from **1a** with Cu(OTf)₂ was converted in 96% yield to pyrrole **6** by oxidation with DDQ, thus demonstrating the accessibility of this methodology to both dihydropyrroles and pyrroles. The *p*-nitrophenyl group is a suitable protective group that can be conveniently removed (reduction of NO₂/CAN oxidation).²

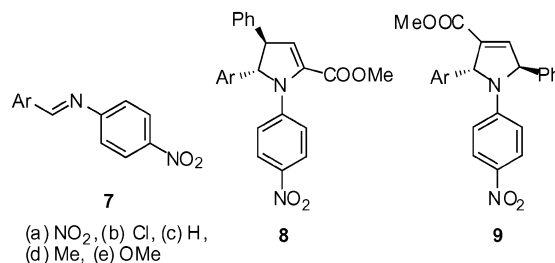


Vinyl diazoacetate **1e** was unresponsive in reactions catalyzed by either Rh₂(OAc)₄ or Cu(OTf)₂, and unreacted imine was recovered under the same conditions used with **1a–d,f**. However, the aliphatic vinyl diazoacetate **1f** was very effective in its catalytic applications, providing the requisite products (**3f** and **4f**) in high isolated yield. In the Cu(OTf)₂-catalysis series, neither **1b** nor **1c** formed product **4**; unreacted diazo compound was recovered.

Substituted benzalimines (**7**) fare well in these transformations. Thus, with methyl styryldiazoacetates, high product yields and selectivities were obtained from Ar = *p*-ClC₆H₄ through Ar = *p*-MeOC₆H₄ in Cu(OTf)₂-catalyzed reactions (Table 2). There was



no crossover in these transformations; Rh₂(OAc)₄ catalyzed the formation of **8**, and use of Cu(OTf)₂ led only to **9**. Stereoselectivity was high in both transformations, but in the rhodium(II)-catalyzed reactions only the *trans* isomer (**8**) was isolated. A substituent effect on stereoselectivity was evident in the formation of **9**.



Lewis acid catalysis of imine addition reactions is a recent development,^{5,10–12} and in most instances the activation mechanism is not known. The present study implicates imine coordination as an integral step in the addition process with accompanying stereocontrol. Efforts are underway to develop asymmetric catalytic analogues of these transformations.

Acknowledgment. Support for this research from the National Science Foundation and the National Institutes of Health (GM 46503) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and product analyses (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA029745Q