Effective and Highly Stereoselective Coupling with Vinyldiazomethanes To Form Symmetrical Trienes

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Abstract: Diazo coupling reactions are capable of forming *E*,*E*,*E*-trienes from cinnamaldehydes in good yield. An efficient methodology is reported for the production of styryldiazomethanes that are subsequently used with catalysis for coupling and for cyclopropanation. A vast difference in product selectivity is seen with styryldiazomethane generated from the corresponding hydrazone via manganese dioxide oxidation and that formed in situ by treatment of the tosylhydrazone sodium salt of cinnamaldehyde with transition metal catalysts. This observation impacts understanding of the reaction mechanism for diazo decomposition.

The formation of alkenes from diazo compounds by catalytic methods shows potential as a viable synthetic transformation.[1,2] However, the vast majority of examples for what is commonly regarded as "carbene dimer formation" originate from diazocarbonyl compounds in intermolecular reactions.[3,4] An early report by Shankar and Shechter constitutes the only comprehensive examination of catalyst and substrate substituent effects with aryldiazomethanes,[5] and there has not been a report of coupling from vinyldiazomethanes despite their obvious synthetic potential for the synthesis of symmetrical trienes (eq 1). Furthermore, vinyldiazoacetates exhibit high diastereocontrol in cyclopropanation reactions,[6] but the stereoselectivity from vinyldiazomethanes is unknown. Symmetrical trienes have been previously prepared by Wittig reactions,[7] palladium-catalyzed coupling reactions,[8] and by other methods.[9] We now report a highly efficient method for the synthesis of symmetrical trienes from cinnamaldehydes, the highly stereoselective trapping of vinyl carbene intermediates with styrene, and mechanistic considerations related to the method for formation of vinyldiazo compounds.

Scheme 1

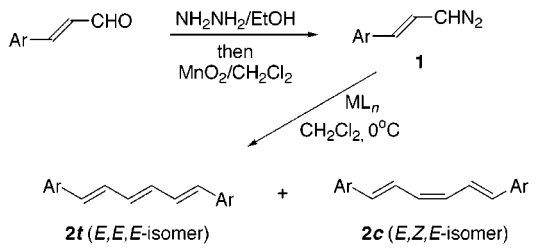
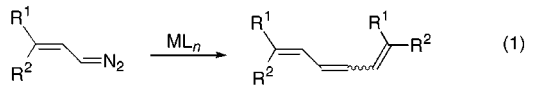


Table 1. Carbene Coupling Reactions of Arylvinyldiazomethanes[a]

Ar	catalyst	yield of **2**,[b] %	**2t**:**2c**[c]
C_6H_5	$Rh_2(OAc)_4$	52	98:2
	$Cu(MeCN)_4PF_6$	55	78:22
	$Rh_2(5S\text{-MEPY})_4$	50	68:32
p-$NO_2C_6H_4$	$Rh_2(OAc)_4$	65	>98:2

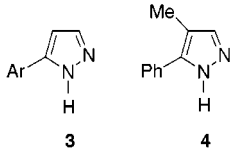
[a] Reactions performed at 0 °C in dry CH_2Cl_2 with 1.0 mol % catalyst. [b] Isolated yield of purified **2** following column chromatography. [c] Determined by ^1H NMR analysis.



(1)

A general procedure was developed for the synthesis of vinyldiazomethanes from the corresponding aldehydes via hydrazone intermediates that are oxidized with activated manganese dioxide (Scheme 1).

Treatment with representative catalysts in dichloromethane at 0 °C produced the results that are reported in Table 1. There is an obvious catalyst dependence on the product ratio, and use of $Rh_2(OAc)_4$ provides optimum results with exceptionally high stereocontrol for the *E*,*E*,*E*-isomer. Yields reported in the table are those from the initial cinnamaldehyde reactant since intermediates were not isolated before their use in subsequent steps. Major byproducts were the cinnamaldehyde that was the initial reactant, possibly re-formed during MnO_2 oxidation, and pyrazole **3,** which was produced by rearrangement of the initially formed vinyldiazo compound. Attempts to form branched trienes through the use of α-methylcinnamaldehyde produced only pyrazole **4** after treatment of the intermediate hydrazone with MnO_2.



3 **4**

The use of **1** for catalytic cyclopropanation reactions was also explored. Here styrene in 5-fold molar excess

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Scheme 2

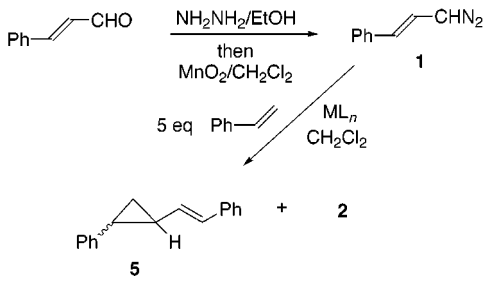
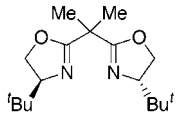


Table 2. Competitive Catalytic Cyclopropanation of Styrene with (*E*)-Styryldiazomethane[a]

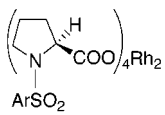
catalyst	yield of **5** + **2**,[b] %	**5**:**2**[c]	**5c**/**5t**[c]	% ee of **5c**[d]
$Rh_2(OAc)_4$	50	8:92	7	
$Cu(MeCN)_4PF_6$	57	92:8	22	
$CuPF_6$/**6**	17	88:12	14	25
Rh_2(*S*-DOSP)$_4$	15	80:20	9	16

[a] Reactions performed at 0 °C in dry CH_2Cl_2 with 1.0 mol % catalyst and 5.0 molar equiv of styrene based on reactant cinnamaldehyde. [b] Isolated yield following column chromatography. [c] Determined by ^{1}H NMR analysis. [d] Obtained by GC on a Chiraldex B-PM column.

was used, and reactions were carried out in the same manner as those for the coupling process (Scheme 2), except that the diazo compound was added over 1 h rather than all at once. Rhodium(II) acetate gave mainly coupling product **2**, but use of $Cu(MeCN)_4PF_6$ resulted in the formation of mainly **5** whose cis/trans ratio was an exceptionally high 22 (Table 2). Attempted use of chiral catalysts, including $CuPF_6$/bis(oxazoline) **6**,[10] led to significant decreases in product yield (**5** + **2**) due to competitive formation of **3**, and the % ee of *cis*-**5** was low. The chiral dirhodium(II) carboxylate catalyst first reported by Davies,[11] Rh_2(*S*-DOSP)$_4$, was employed because its reactivity is reported to be at least as great as $Rh_2(OAc)_4$ and much greater than those for chiral dirhodium(II) carboxamidates.



6[10]



7: Rh_2(*S*-DOSP)$_4$[11]

High cis diastereoselectivity for the formation of cyclopropane products using phenyldiazomethane has been reported, but with styrene and $Rh_2(OAc)_4$ the *Z*/*E* ratio was only 3.3.[12] Higher *Z*-selectivities were reported for the cyclopropane product from stoichiometric reactions with $(CO)_5W{=}CHPh$ and related organometallic reagents[13] but none as high as that found with (*E*)-styryldiazomethane catalyzed by $Cu(MeCN)_4PF_6$.

Aggarwal has recently reported an alternative methodology for catalytic reactions with aryldiazomethanes via direct treatment of the sodium salt of the tosylhydrazone with rhodium(II) acetate.[14] When the method

Scheme 3

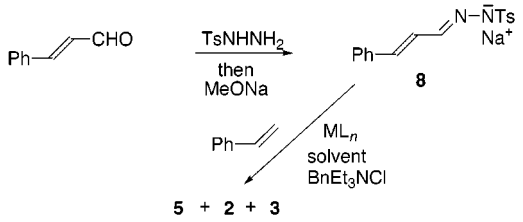


Table 3. Competitive Catalytic Cyclopropanation of Styrene with 8[a]

catalyst	solvent	temp, °C	yield of **5** + **2**,[b] %	**5**:**2**[c]	**5c**/**5t**[c]	% ee of **5c**[d]
$Rh_2(OAc)_4$	dioxane	35	14[e]	96:4	4.0	
$Cu(MeCN)_4PF_6$	dioxane	35	4[f]	90:10	0.8	
$Rh_2(OAc)_4$	CH_2Cl_2	reflux	38	98:2	6.0	
$Cu(MeCN)_4PF_6$	CH_2Cl_2	reflux	0			
Rh_2(4*S*-IBAZ)$_4$	CH_2Cl_2	reflux	2	87:13	1.4	34
Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	reflux	4	93:7	1.7	12

[a] Reactions were carried out with a ratio of styrene:**8**:$BnEt_3NCl$: catalyst = 5:1:0.1:0.01. [b] Isolated yield following column chromatography. [c] Determined by ^{1}H NMR analysis. [d] Obtained by GC on a Chiraldex B-PM column. [e] Pyrazole **3** was isolated in 32% yield. [f] Pyrazole **3** was isolated in 83% yield.

is applied to reactions with cinnamaldehyde (Scheme 3), the results obtained were quite different from those obtained directly from styryldiazomethane generated by MnO_2 oxidation (Table 3). The reported advantages of this methodology included minimization of carbene dimer formation, and this is evident in the comparison of results reported in Tables 2 and 3. Indeed, with $Rh_2(OAc)_4$ as the catalyst, **2** is virtually the exclusive product from **1** (**5**:**2** = 8:92) but not from **8** (**5**:**2** = 98:2). However, the production of **3** is much more dominant in reactions with **8**, and this could be due to the expected coordination of rhodium(II) with the amide nitrogen of **8** that becomes the terminal nitrogen of styryldiazomethane (Scheme 4). In this way rhodium(II) can be understood to activate the diazo compound to form **3** at a much faster rate than would occur if the diazo compound was generated prior to interaction with $Rh_2(OAc)_4$. The question of which site of diazomethane and its derivatives represents the more likely site of attack by Lewis acids is longstanding,[1] and the comparison of results from this study provides one measure of its operational characteristics.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were obtained as solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, δ) downfield from the internal standard, Me_4Si (TMS). Dichloromethane was distilled from calcium hydride prior to use. Manganese dioxide was commercially available and was oven dried before use. Dirhodium(II) acetate and copper(I) hexafluorophosphate[15] were crystallized prior to use. Bis(oxazoline) ligand **6**,[16] Rh_2(5*S*-MEPY)$_4$,[17] and Rh_2(4*S*-IBAZ)$_4$[18] were prepared by standard methods.

Synthesis of (*E*,*E*,*E*)-1,6-Diaryl-1,3,5-hexatrienes. The general procedure began with the addition of anhydrous hydra-

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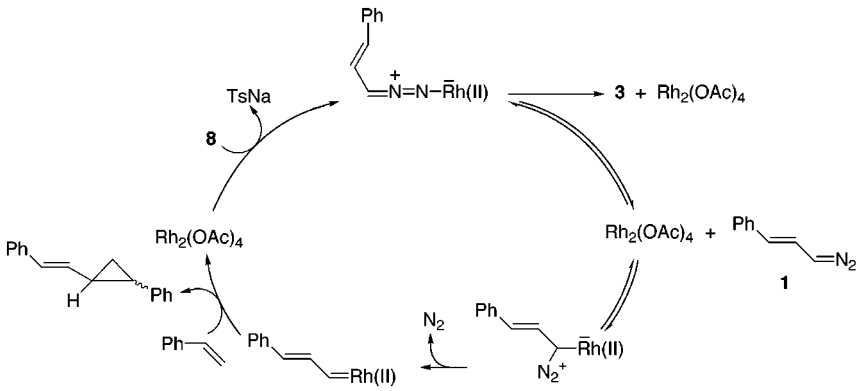
Scheme 4



zine (0.3 mL, 10 mmol, 5 equiv) to a solution of cinnamaldehyde (0.264 g, 2.00 mmol) and triethylamine (1.4 mL, 10 mmol, 5 equiv) in 10 mL of anhydrous ethanol at room temperature. After stirring of the mixture for for 1 h, solvent and excess reagents were removed at 0 °C under reduced pressure. The resulting colorless oil was dissolved in 10 mL of cold anhydrous CH_2Cl_2 that was then added to an ice-bath-cooled mixture of MnO_2 (1.68 g, 20 mmol, 10 equiv) and Na_2CO_3 (2.12 g, 20 mmol, 10 equiv) in 25 mL of CH_2Cl_2. The resulting mixture was stirred for 2 h at 0 °C. Excess MnO_2 was filtered through a layer of Celite to provide a red solution of the styryldiazomethane that was used immediately to minize formation of pyrazole **3**. The red solution was added in one portion to a solution of catalyst (0.020 mmol, 0.010 equiv) in 5 mL of ice-bath-cooled CH_2Cl_2, and stirring was continued at that temperature for an additional 30 min. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexanes:ethyl acetate = 100:1) to give the product triene. Products were identified by comparison to the spectral properties of the known compounds.[7–9] The (*E*,*Z*,*E*)-isomer has also been reported.[7b] Pyrazoles were identified by their characteristic NMR, IR, and mass spectral data.

Cyclopropanation of Styrene. The same procedure that was used for coupling was employed to prepare styryldiazomethane for cyclopropanation reactions. To a solution of catalyst (0.020 mmol, 1.0 mol %) and styrene (10 mmol, 5.0 equiv) in 5 mL of anhydrous dichloromethane at 0 °C was added the cooled solution of styryldiazomethane in dichloromethane by syringe pump over 1 h. The solution was then stirred at 0 °C for an additional 1 h, and the solvent was removed under vacuum. The residue was purified by column chromatography (hexane:EtOAc = 100:1) to give 1-styryl-2-phenylcyclopropane as a colorless oil. This compound (both cis and trans isomers) was compared spectrally with the authentic compound.[19]

Tosylhydrazone Sodium Salt Procedure.[14] The tosylhydrazone of cinnamaldehyde was converted to its sodium salt using sodium in methanol which was removed under vacuum to reveal a yellow solid. This solid (323 mg, 1.00 mmol), benzyltriethylammonium chloride (23 mg, 0.10 mmol), $Rh_2(OAc)_4$ (4.42 mg, 0.010 mmol), and styrene (0.57 mL, 5.0 mmol) were mixed with 5.0 mL of CH_2Cl_2, and the resulting mixture was refluxed for 6 h. After addition of water (7 mL), the resulting mixture was twice extracted with 10-mL portions of CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. Elution in column chromatography with hexane:EtOAc = 100:1 provided the cyclopropane product as a colorless oil, and continued elution with hexanes:EtOAc = 2:1 gave 3-phenylpyrazole[20] as a brown oil.

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