Homogeneous Catalysis

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Divergent Outcomes of Carbene Transfer Reactions from Dirhodium- and Copper-Based Catalysts Separately or in Combination**

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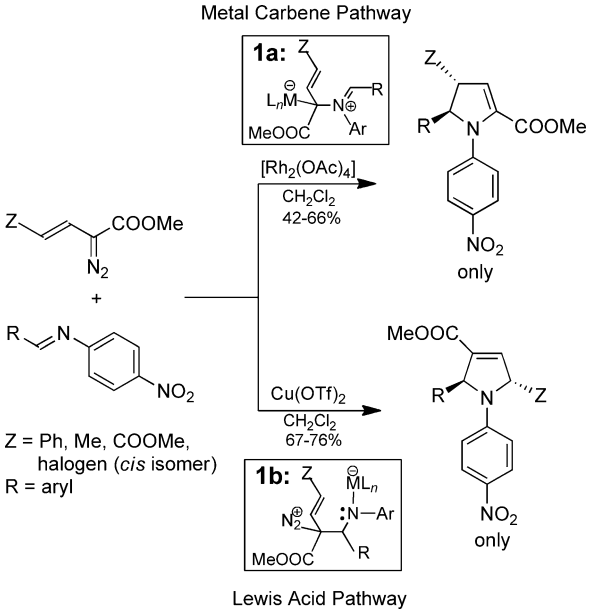
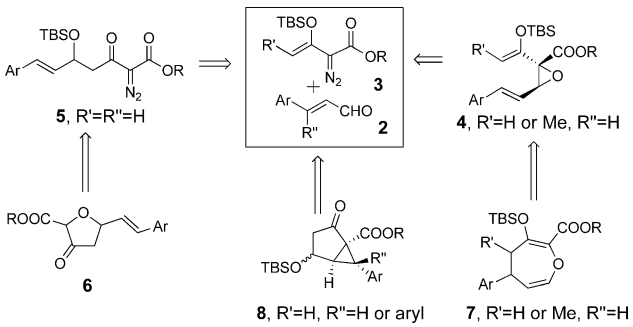
That a reaction pathway can be redirected to a different product by changing a reactant or reaction conditions is well known and widely practiced. Such processes are referred to as "divergent", and this term is broadly applied to methodology,[1] synthesis,[2] reactivity and selectivity,[3] among others.[4] However, processes in which the same reactant(s) form different products in synthetically meaningful yields by application of different catalysts are rare.[5] We and others have reported exceptionally efficient catalyst-dependent processes that occur with the same diazo substrates to form structurally different compounds.[5b,6–8] In the most well-documented cases, dirhodium(II) catalysts having different ligands differentiate between cyclopropanation and C–H insertion, ylide formation and aromatic substitution, or aromatic cycloaddition and C–H insertion with the same diazoacetates.[6] The exclusive formation of one of two regioisomeric dihydropyrroles in modest yields from the reactions between vinyldiazoacetates and imines using dirhodium(II) acetate or copper(II) triflate (Scheme 1), due to either electrophilic metal carbene formation (intermediate **1a** in the case of rhodium) or to initial iminium ion formation (intermediate **1b** in the case of copper),[7] exemplifies the critical role of catalyst in product selection. Other examples include the copper(I)/rhodium(II) product differences in macrocyclization with diazoacetates.[8] Although both dirhodium and copper catalysts are well established catalysts for dinitrogen extrusion from diazo compounds, there can be striking differences between them in product outcomes from the same reactant(s).

Here we report divergent copper- and/or dirhodium-catalyzed, synthetically relevant processes that occur between cinnamaldehydes and siloxyvinyl α-diazoacetates which clearly reveal fundamental differences between these two catalytic systems. Their applications include the syntheses of oxepin, furanone, and cyclopropane compounds by intramolecular cyclization (Scheme 2) with extraordinary efficiency and atom economy.



Scheme 1. Divergent pathways to isomeric dihydropyrroles from the same reactants, but different catalysts.

We have previously reported that methyl styryldiazoacetate undergoes ylide-induced epoxide formation in reactions with cinnamaldehydes catalyzed by dirhodium tetraacetate, but product yields were only modest, and mixtures were formed with the substituted aldehydes.[9] Consequently, we were surprised when treatment of methylsiloxyvinyldiazoacetate (**3-Me**) with 4-nitrocinnamaldehyde at room temperature, catalyzed by dirhodium carboxylates, gave epoxide **4a** with *trans*-divinyl substituents in excellent yield (Scheme 3).



Scheme 2. Divergent outcomes from copper- and rhodium-catalyzed reactions of **3** with cinnamaldehydes.

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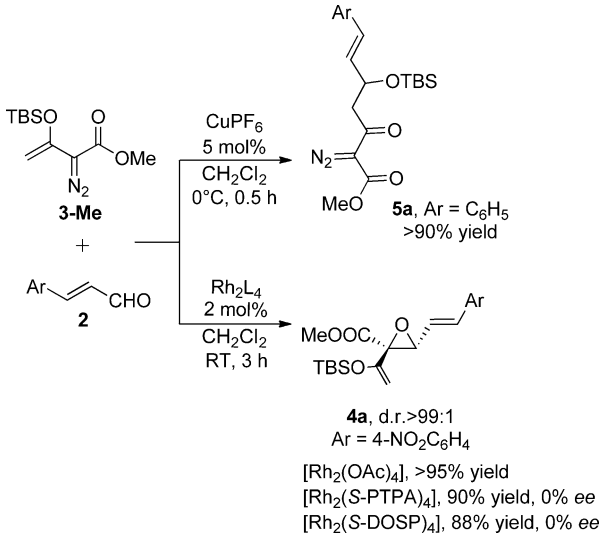


Scheme 3. Divergent catalyst-dependent pathways from cinnamaldehydes and methyl siloxyvinyldiazoacetate **3-Me**.

Use of chiral catalysts that included Hashimoto's [Rh_2(*S*-PTPA)$_4$][10] and Davies' [Rh_2(*S*-DOSP)$_4$][11] did not give evidence of enantiocontrol in this transformation, and dirhodium carboxamidates exhibited very low reactivity towards dinitrogen extrusion of **3**. Surprisingly, use of [Cu(CH_3CN)$_4$]PF_6, which is even more reactive towards dinitrogen extrusion from diazo compounds than is rhodium acetate,[12] gave the Mukaiyama-aldol addition product **5** in high yield when the reaction was performed at 0 °C without effecting diazo decomposition (Scheme 3).[13] In this case, $CuPF_6$ acts as Lewis acid for activation of the aldehyde towards electrophilic addition to **3** and does not cause decomposition of the diazoacetate in either the reactant or the product.

In contrast to their *cis*-divinylcyclopropane analogues that undergo [4+3]-cycloaddition at or below room temperature,[14] and have been key steps in several total syntheses,[15] *trans*-divinylepoxides are thermally stable at room temperature but slowly rearrange to 4,5-dihydrooxepins **7**.[16] This is obviously the reason why the conversion of **4** to dihydrooxepin does not occur under more moderate conditions. Hence a major challenge of this study has been to develop conditions suitable to form 4,5-dihydrooxepins in high yield. We initially applied thermal conditions to effect rearrangement of the *trans*-divinylepoxide **4a**, and this approach did provide the 4-nitrophenyl derivative **7a**, but the thermal transformation only occurred at or above 150 °C and required long reaction times. To find the catalytic version of this rearrangement, we investigated the effects of an array of Lewis acids ($CuPF_6$, CuOTf, $Cu(OTf)_2$, $Sc(OTf)_3$, $Zn(OTf)_2$) to discover that with the application of a catalytic amount of [$Cu(hfacac)_2$] (hfacac = hexafluoroacetylacetonate) the reaction temperature could be decreased to 100 °C while the reaction rate was drastically increased. Further optimization by carrying out the two-step reaction in one-pot by performing the catalytic epoxidation in dichloromethane, replacing that solvent with toluene, adding [$Cu(hfacac)_2$], and heating at 125 °C for 0.5 h

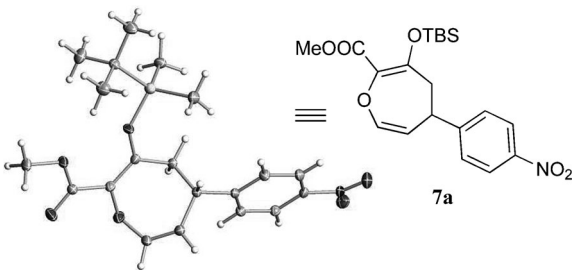
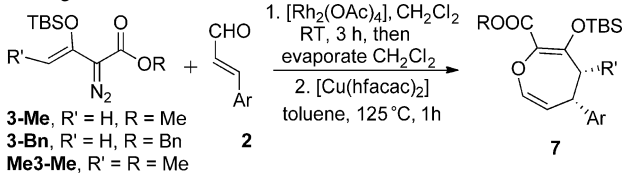


Figure 1. X-ray crystal structure of **7a**.

gave 4,5-dihydrooxepin **7a** in 95% isolated yield.[17] The structure of **7a** was confirmed by single-crystal X-ray diffraction analysis (Figure 1).

Using these optimum conditions we examined this rearrangement reaction for substrate generality in the two-step one-pot formal [4+3] cycloaddition of **3** with substituted cinnamaldehydes, and these results are summarized in Table 1. Product yields from reactions with cinnamaldehydes

Table 1: Substrate generality for the one-pot tandem epoxidation/rearrangement reaction.[a]



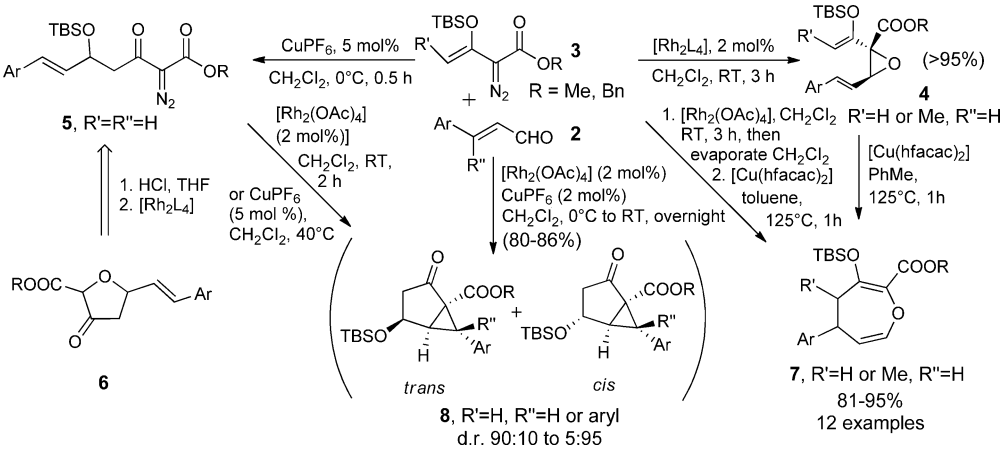
Entry	**3**	**2**, Ar	**7**	Yield [%][b]
1	**3-Me**	4-$NO_2C_6H_4$	**7a**	95
2	**3-Me**	3-$NO_2C_6H_4$	**7b**	95
3	**3-Me**	2-$NO_2C_6H_4$	**7c**	95
4	**3-Me**	C_6H_5	**7d**	82
5	**3-Me**	4-$CF_3C_6H_4$	**7e**	95
6	**3-Me**	4-BrC_6H_4	**7f**	90
7	**3-Me**	4-ClC_6H_4	**7g**	88
8	**3-Me**	4-FC_6H_4	**7h**	90
9	**3-Me**	4-MeC_6H_4	**7i**	81
10	**3-Bn**	4-$NO_2C_6H_4$	**7j**	95
11	**3-Bn**	2-$NO_2C_6H_4$	**7k**	95
12	**3-Bn**	C_6H_5	**7l**	85
13	**Me3-Me**	4-$NO_2C_6H_4$	**7m**	95[c]

[a] The reaction was carried out with **3** (0.36 mmol), aldehyde (0.30 mmol), [$Rh_2(OAc)_4$] (2 mol%), [$Cu(hfacac)_2$] (5 mol%), respective solvent (2 mL). [b] Yield of isolated **7** after chromatography. [c] The ^{1}H NMR spectrum of the reaction mixture showed only one diastereoisomer, whose stereochemistry was confirmed by NOE analysis (see the Supporting Information).

having electron-donating substituents were comparable to those from the nitrocinnamaldehydes (Table 1, entries 4–9). Benzyl ester analogues (**3-Bn**) underwent the same two-step process with isolated yields that were identical to those obtained with the methyl esters (Table 1, entries 10–12). That the reaction occurred with the stereospecificity of an electrocyclization reaction, whether from a direct Cope rearrangement of rearranged *cis*-divinyl epoxide[18] or from the corresponding ylide, with propenyldiazoacetate **Me3-Me** as

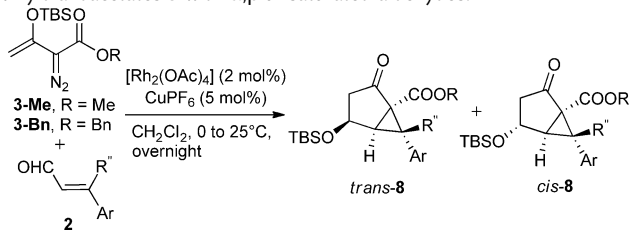
the reactant, *cis*-4,5-disubstituted-dihydrooxepine **7m** was formed stereospecifically in very high yield.

With the assumption that copper and rhodium catalysts act independently, so that the combination with vinyldiazoacetate **3-Me** and cinnamaldehydes could achieve the formation of **7** under one set of reaction conditions, we treated **3-Me** with cinnamaldehyde in the presence of catalytic amounts of rhodium acetate and copper(I) hexafluorophosphate at room temperature. However, instead of observing either epoxidation or dihydrooxepine products, use of this catalyst combination unexpectedly produced the two diastereoisomers[19] of bicyclo[3.1.0]hexane **8a**[20] in high yield (Table 2). Substrates with electron-donating substituents showed higher reactivity (Table 2, entries 2 and 3), and this reactivity pattern was opposite to that observed for epoxidation. Reversal of diastereoselectivity from up to 9:1 to < 1:20 was achieved by using a β-substituted cinnamaldehyde in this transformation (Table 2, entry 5); interaction with the *syn*-phenyl substituent that occupies position 6 in **8** forces the OTBS group to favor the *cis* geometry. With dirhodium catalysts and Ar = Ph, diastereoselectivity ranged from 82:18 (with rhodium caprolactamate) to 27:73 (with rhodium trifluoroacetate).



Scheme 4. Divergent outcomes from copper- and rhodium-catalyzed reactions of **3** with cinnamaldehydes.

Table 2: Cooperative rhodium- and copper-catalyzed bicyclization of vinyldiazoacetates **3** with α,β-unsaturated aldehydes.[a]



Entry	**3**	**2**, Ar/R″	**8**	d.r.[b] (*trans*/*cis*)	Yield [%][c]
1	**3-Me**	C_6H_4/H	**8a**	85:15	80
2	**3-Me**	4-$MeOC_6H_4$/H	**8b**	75:25	87
3	**3-Me**	2-$NO_2C_6H_4$/H	**8c**	90:10	32
4	**3-Bn**	C_6H_4/H	**8d**	70:30	86
5	**3-Bn**	C_6H_4/C_6H_4	**8e**	< 5:95	65

[a] Reaction in 0.3 mol scale: **3** (0.36 mmol), aldehyde (0.30 mmol), $[Rh_2(OAc)_4]$ (2 mol%), $CuPF_6$ (5 mol%), solvent (2 mL). [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Yield of isolated **8** (*trans* and *cis*) after chromatography.

Treatment of **3-Me** and cinnamaldehyde with both copper(I) and copper(II) compounds in catalytic amounts resulted in the formation of the Mukaiyama-aldol reaction product **5** to the complete exclusion of epoxide **4**. The product of the Mukaiyama-aldol reaction, catalyzed by $CuPF_6$, which gave optimum results, when treated with rhodium acetate gave cyclopropanation products **8a**. Alternatively, by performing the reaction of **3-Me** and cinnamaldehyde with $CuPF_6$ as catalyst at 40 °C (3 h), instead of at or below room temperature, the two-step process can be accomplished in one pot (77 % yield, d.r. = 90:10).[17] Obviously, the role of $CuPF_6$ as a Lewis acid in these reactions is pronounced, and the possibility exists that coordination of **5** with $CuPF_6$ inhibits its use as a catalyst for dinitrogen extrusion. The advantage of the cooperative rhodium- and copper-catalyzed bicyclization is that the overall transformation can be conducted at room temperature. Furanone **6** formation (Scheme 2) from diazoacetoacetates has been previously reported,[21] although not with the structural diversity that is available by this methodology.

In summary, the use of copper and rhodium catalysts separately and in combination directs the reaction between vinyldiazoacetates **3** and cinnamaldehydes to a broad diversity of products selectively and in high yield (Scheme 4). The basis for this catalyst-based selectivity lies in the differences in Lewis acidity between copper and rhodium catalysts and the bidentate coordinating ability of copper catalysts. That copper and dirhodium catalysts can work cooperatively for product formation is demonstrated.

Experimental Section

Diazo compound **3** (0.36 mmol) in CH_2Cl_2 (1.0 mL) was added over 1 h through a syringe pump at room temperature to an oven-dried flask containing a magnetic stirring bar, cinnamaldehyde **2** (0.3 mmol), and $[Rh_2(OAc)_4]$ (2.0 mol %) in CH_2Cl_2 (1.0 mL). The reaction mixture was stirred for another 2 h, then CH_2Cl_2 was removed under reduced pressure, and toluene (2.0 mL) was added. The solution was transferred to the reaction tube containing a magnetic stirring bar; the tube was suited for use under high pressure. The reaction tube was sealed after $[Cu(hfacac)_2]$ (5.0 mol %) was added, and the temperature of the reaction was warmed to 125 °C in an oil bath with stirring. After complete consumption of the intermediate epoxide **4** (about 1 h), monitored by ^{1}H NMR spectroscopy (epoxide and the product oxepin overlap on thin-layer

chromatography), the reaction mixture was purified by column chromatography on silica gel (eluent hexanes/EtOAc = 50:1 to 30:1) to give the pure products oxepin **7** in greater than 80% yield.

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