Figure 2. Mean rate constants for formation of alkali metal cation-bound dimers of 15-crown-5 and tetraglyme. Error bars are ± 1 standard deviation. The points for Li$^+$ are upper limits; dimer formation was not observed on the time scale of our experiment.

rate calculated using Langevin theory.[13] It is possible that complex formation occurs on every collision, and that differences between the observed complexation rates and the calculated collision rates are largely due to inaccuracies in our pressure measurements. If the rates do prove to be collision-limited, measurement of the complex formation rates will be a useful means of accurately determining the neutral ligand pressure in the trapping cell, which will enable more accurate absolute rate measurements for other reactions such as the formation of cation-bound dimers described below.

As we have previously noted,[14] the initially formed metal–ligand complexes undergo reaction with a second ligand to form metal-bound dimer species. For reaction times less than 500 ms, some curvature is evident in the plots of log (reactant intensity) versus time, suggesting that the reactant monomer complexes are incompletely cooled at short reaction times. Rate constants determined by fitting the later, linear portion of the plots are shown in Figures 1 and 2 for the four- and five-oxygen ligands, respectively. It is immediately apparent that rates for the macrocyclic ligands are approximately an order of magnitude faster than those for the glymes. In addition, the macrocycles show much more selective kinetics than the corresponding acyclic ligands, with rates peaking strongly for the first cation significantly larger than the ligand cavity. Thus, the maximum rate for formation of the alkali cation-bound dimer of 12-crown-4 occurs for Na$^+$, while for the 15-crown-5 ligand the rate is fastest for K$^+$. Rates for the glymes, which do not have a well-defined binding cavity, are much less cation-dependent and peak for the next larger alkali metal cation than do those for the crowns. This is consistent with the acyclic glymes being more flexible than the crowns in their ability to adopt configurations favorable for binding the larger metals. We are currently investigating cation–ligand binding affinities in the gas phase as a function of size and ligand cyclization, and it will be interesting to see whether or not there is any correlation between the reaction kinetics and energetics in these systems.

These results can be understood in terms of the relative ease with which the cyclic and acyclic ligands can accommodate cation guests. For example, molecular mechanics calculations[15] indicate that the intrinsic interaction energies of 18-crown-6 and penta-

glyme with K$^+$ are similar. However, to convert the "all-trans" minimum energy conformation[16] of pentaglyme to the approximately D_{3d} conformation which provides optimum bonding to the cation, approximately 15 kcal mol^{-1} more energy is required than is needed for 18-crown-6 to adopt an optimal conformation.

Experimental proton affinity measurements also suggest that entropic effects are important. In the gas-phase protonation of crowns and acyclic polyethers, ΔS is much more favorable for macrocycles than for the corresponding glymes (12-crown-4, −8.3 cal K^{-1} mol^{-1}, vs triglyme, −18.3 cal K^{-1} mol^{-1}; 15-crown-5, −11.1 cal K^{-1} mol^{-1}, vs tetraglyme, −20.7 cal K^{-1} mol^{-1}).[17] Our data so far do not allow us to distinguish whether energetic or entropic effects dominate in explaining the differences between the cyclic and acyclic ligands.

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High Enantioselectivity for Intermolecular Cyclopropenation of Alkynes by Diazo Esters Catalyzed by Chiral Dirhodium(II) Carboxamides

Marina N. Protopopova[1] and Michael P. Doyle*

*Department of Chemistry, Trinity University
San Antonio, Texas 78212*

Paul Müller* and Doina Ene

*Département de Chemie Organique
Université de Genève, 30 quai Ernest-Ansermet
CH-1211, Genève, Switzerland*

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Functionalized cyclopropenes are viable synthetic intermediates whose applications,[2] which extend to a wide variety of carbocyclic and heterocyclic systems, are largely ignored because of the relative inaccessibility of these strained compounds. However, recent advances in the synthesis of cyclopropenes, particularly from rhodium(II) carboxylate catalyzed reactions of diazo esters in the presence of alkynes,[3–5] have made available an array of stable 3-cyclopropenecarboxylate esters. Previously, copper catalysts provided low to moderate yields of cyclopropenes in reactions of diazo esters with disubstituted acetylenes,[3a,6] but the higher temperatures required for these carbenoid reactions often led to thermal or catalytic ring opening and products derived from

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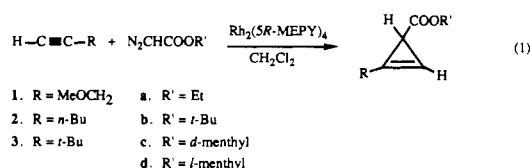
2756 *J. Am. Chem. Soc., Vol. 114, No. 7, 1992*

Communications to the Editor

Table I. Enantioselective Cyclopropenation of Representative Alkynes Catalyzed by Rh₂(5R-MEPY)₄[a]

diazoacetate, R′ =	1-alkyne, R =	cyclopropene	yield, %[b]	ee, %[c]
Et	CH₃OCH₂	1a	73 (65)	69
t-Bu	CH₃OCH₂	1b	56 (38)	78
d-menthyl	CH₃OCH₂	1c	43 (28)	98
l-menthyl	CH₃OCH₂	1d	45	43
Et	n-Bu	2a	70 (58)	54
t-Bu	n-Bu	2b	69 (60)	53
d-menthyl	n-Bu	2c	46 (32)	86
l-menthyl	n-Bu	2d	46	20
Et	t-Bu	3a	85 (69)	57
t-Bu	t-Bu	3b	57 (37)	70
d-menthyl	t-Bu	3c	51 (30)	77
l-menthyl	t-Bu	3d	50 (29)	56

[a] Reactions were performed by the addition of the diazo compound (1.0 mmol) in 5 mL of CH₂Cl₂ over a 5-h period to a solution of the alkyne (10.0 mmol) and catalyst (0.01 mmol) in 10 mL of CH₂Cl₂. Average values from 2–4 separate experiments are reported. [b] Yield of product following chromatographic separation of catalyst and, in parentheses, product yield of the homogeneous sample after distillation (2a) or column chromatography (silica gel: hexane/ethyl acetate). [c] Determined from integration of the olefinic proton with use of chiral NMR shift reagent Eu(tfc)₃[10a] and for 2a and 1b–3b also by chromatographic separation on a Chiraldex γ-cyclodextrin trifluoroacetate column (±2% from separate experiments). Diastereomeric excesses for 1c–3c and 1d–3d were obtained by direct NMR analysis (±3%).

vinylcarbene intermediates.[7,8] Potential uses of the cyclopropene ring as a template in enantiocontrolled synthesis have been recognized,[2a] but until now synthetic chiral cyclopropene derivatives have been accessible only from natural products[9] or through resolution.[10]

Chiral rhodium(II) carboxamides are exceptional catalysts for highly enantioselective intermolecular cyclopropenation reactions. With a series of diazo esters and propargyl methyl ether, use of dirhodium(II) tetrakis[methyl 2-oxopyrrolidine-5(R)-carboxylate], Rh₂(5R-MEPY)₄,[11] in catalytic amounts (≤1.0 mol %) results in the formation of 1 (eq 1) with enantiomeric excesses (ee's) of

$$H{-}C{\equiv}C{-}R \; + \; N_2CHCOOR' \xrightarrow[CH_2Cl_2]{Rh_2(5R\text{-}MEPY)_4} \quad (1)$$

1. R = MeOCH₂   a. R′ = Et
2. R = n-Bu   b. R′ = t-Bu
3. R = t-Bu   c. R′ = d-menthyl
                     d. R′ = l-menthyl

69% (1a, R′ = Et), 78% (1b, R′ = t-Bu), and 98% (1c, R′ = d-(1S,2R,5S)-menthyl) and in moderate yields (43–73%). Virtually identical results, except in the opposite stereochemical sense, are obtained with the use of Rh₂(5S-MEPY)₄. Carbene dimers and azine are the principal byproducts, but dimer formation can be minimized by using higher alkene/diazo ester ratios and by decreasing the rate of addition. In reactions with menthyl

diazoacetate, intramolecular carbon–hydrogen insertion[12] competes with cyclopropenation.

Table I reports results from cyclopropenation reactions of representative 1-alkynes using Rh₂(5R-MEPY)₄ as the catalyst. Enantioselectivities increase with the steric size of the diazo ester, and the size and polarity of the alkyne substituent also appear to influence enantiocontrol. That percent ee's of cyclopropenes from reactions with propargyl methyl ether are higher than those from reactions with 1-hexyne and 3,3-dimethyl-1-butyne suggests that polar interactions of the alkyne with ligands of the catalyst may be operative. Indeed, propargyl acetate, from reactions with l-menthyl diazoacetate catalyzed by Rh₂(5S-MEPY)₄, yielded the corresponding cyclopropene (R = CH₂OAc, 30% isolated) with a diastereoisomeric excess equal to that obtained from the same reaction with propargyl methyl ether (98% de).

The use of Rh₂(5R-MEPY)₄ and Rh₂(5S-MEPY)₄ for reactions with menthyl diazoacetates (MDA) also produces an enormous double diastereoselection not previously observed to the same degree in cyclopropanation reactions.[13-15] With methyl propargyl ether, for example, Rh₂(5R-MEPY)₄-catalyzed reactions of d-MDA yield 1c in 98% diastereomeric excess (de), but l-MDA produces 1d in only 40% de; with Rh₂(5S-MEPY)₄, l-MDA gives the higher de (98%) and d-MDA gives the lower de (43%). Similar results are obtained from reactions of MDA with 1-hexyne and 3,3-dimethyl-1-propyne. With Rh₂(OAc)₄ as the catalyst, reactions of these alkynes with d- or l-menthyl diazoacetate yield the corresponding cyclopropane products with de's ≤10%. The diazocarboxylate substituent obviously plays a critical role in establishing the more effective carbene orientation within the chiral catalyst environment for addition to the alkyne.

Alternative rhodium(II) carboxamide catalysts derived from 4(R)-benzyloxazolidinone (4R-BNOXH) and 4(S)-isopropyl-oxazolidinone (4S-IPOXH)[13] provided only a fraction of the enantioselection obtained with Rh₂(MEPY)₄ catalysts. Whereas cyclopropenation of 1-hexyne with ethyl diazoacetate in the presence of Rh₂(5R-MEPY)₄ resulted in 2a with 54% ee, Rh₂(4R-BNOX)₄ gave 2a in 5% ee and Rh₂(4S-IPOX)₄ gave 2a in 6% ee. Dipolar influences from the Rh₂(MEPY)₄ ligand's carboxylate substituents are primary determinants of enantiocontrol in these intermolecular reactions.

With disubstituted acetylenes, enantioselectivities were low and so were reaction efficiencies. 1-Phenylpropyne underwent Rh₂(5S-MEPY)₄-catalyzed cyclopropenation with ethyl diazoacetate to produce 4a in 39% yield with 16% ee; with methyl diazoacetate, the corresponding cyclopropene was isolated in 26% yield with an enantiomeric excess of 20%. Even lower enantiocontrol was
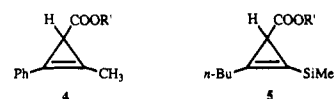
observed from reactions with 1-(trimethylsilyl)-1-hexyne: 28% isolated yield of 5a (<2% ee) with ethyl diazoacetate and a 15% yield of the corresponding methyl ester (<2% ee) from reactions with methyl diazoacetate. In these cases it is likely that steric factors inhibit close approach of the alkyne to the metal carbene.

Preliminary results with a chiral semicorrin copper catalyst,[16] established by Pfaltz and co-workers as highly effective for asymmetric intermolecular cyclopropanation reactions,[17] showed

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10% ee of **2a** in reactions of 1-hexyne with ethyl diazoacetate; low product yields were obtained that reflected the significant dependence of carbenes derived from the action of this catalyst on substrate reactivity. The chiral Rh₂(MEPY)₄ catalysts appear to have unique design features[18] for asymmetric cyclopropenation that are not present in the semicorrin copper catalysts, and efforts are underway to optimize these features for further enhancement of percent ee's. We are also working toward establishing the absolute configuration of these chiral cyclopropene derivatives.

Supplementary Material Available: Listings of experimental details for catalytic reactions and product characterization (4 pages). Ordering information is given on any current masthead page.

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Glycopeptide Binding Site Spied through Transferred Heteronuclear NOE: [1-¹³C]Ac-D-Ala-D-Ala Bonded to Vancomycin and Ristocetin A
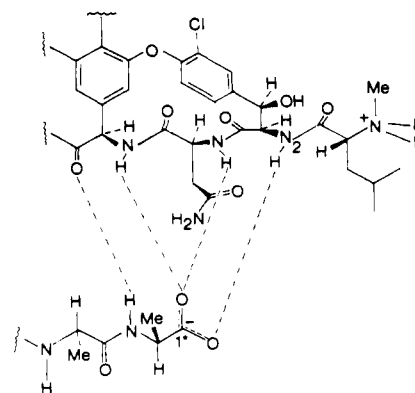
Gy. Batta,*,† K. E. Kövér,‡ Z. Székely,† and F. Sztaricskai*,†

*Research Group for Antibiotics of the Hungarian
Academy of Sciences, Lajos Kossuth University
P.O. Box 70, Debrecen, Hungary H-4010
BIOGAL Pharmaceutical Works
Debrecen, Hungary H-4042*

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The structure[1] and binding[2] of glycopeptide antibiotics[3] to cell wall analogue oligopeptides are mostly characterized by high-field 1D and 2D homonuclear NMR spectroscopy. On the basis of these studies it is safely proved that, among other interactions, a strong hydrogen-bonding network exists between the binding pocket of the antibiotic and the carboxylate anion at the C-terminal of Ac-D-Ala-D-Ala.[4]

In this communication, we present a direct method—the transferred heteronuclear NOE—for the assignment of inter-molecular H-bonding.[5] The ¹³C-{¹H} NOE method[6] alone has

†Lajos Kossuth University.
‡BIOGAL Pharmaceutical Works.

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Figure 1. N-terminal region of vancomycin and the C-terminal part of a bacterial cell wall peptide analogue Ac-D-Ala-D-Ala. Intermolecular hydrogen bonds are indicated according to the structure of the complex.

some inherent difficulties when biomolecules are investigated, since in the slow motion regime the theoretical maximum of the signal enhancement is only ca. 15%. The effect may be buried in the noise, especially in the presence of chemical exchange.

To increase the sensitivity, we employed a [1-¹³C]-labeled dipeptide as a guest with the hosts vancomycin or ristocetin A. Moreover, these compounds were dissolved in a cryogenic solvent DMSO-d_6:CCl₄ = 10:3 at 5 °C to ensure slow chemical exchange between the free and bonded states of the guest. We assume that the relevant structures of the complexes are maintained in the cryogenic media.[3b] The Ac-D-Ala-D-Ala concentration was 20 mM/L while the antibiotic concentration was held constant at 12.5 (vancomycin) or 20 mM/L (ristocetin A). It should be mentioned that the mixture also contained ca. 30% impurity arising from the inactive[2] D,L compound of the dipeptide, which resulted in a 16 ppb downfield shift in the ¹³C NMR spectrum as compared to the active D,D component. When the D,D component is bonded to its host, the chemical shift of the labeled C-1 carbon is shifted downfield by more than 1 ppm! (The D,L compound may be used as an internal standard.)

Figure 1 shows the well-known partial structure of the heter-oaggregate of vancomycin. A 2D ¹³C–{¹H} NOE[6c] experiment indicated, surprisingly, a correlation between the *bonded* 2-NH of the antibiotic and the C-1 atom of the *free* dipeptide (Figure 2). This phenomenon can be explained by a chemical exchange mediated[7] ¹³C magnetization transfer which follows the hetero-nuclear NOE. Since in the free state the C-1 signal is much sharper, it renders the detection of small NOE more feasible. ¹³C–¹³C EXSY[8] and the initial buildup rate of cross peaks verified the presence of exchange for both antibiotics and, in the case of ristocetin A, gave an estimate of 2 s for the average lifetime for the exchanging sites. In a 1D ¹³C–{¹H} NOE experiment (Figure 3) we observed C-1 signals due to both bonded and nonbonded states. Semiquantitative evaluation (saturation efficiency is estimated to be 60%) gives approximately half of the theoretical maximum NOE. This fact suggests a short NH⋯CO distance (<250 pm) in accordance with predictions.[3e] In the case of ris-tocetin A, similar results are obtained; however, their interpretation is difficult since, besides the monomer, at least two other different

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