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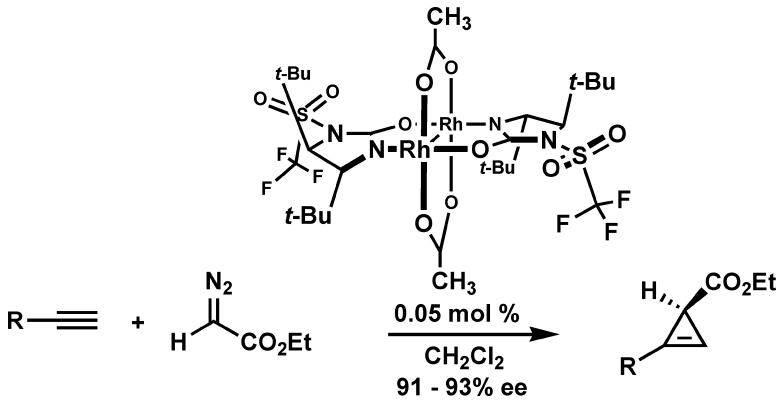

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Catalysis of Enantioselective [2+1]-Cycloaddition Reactions of Ethyl Diazoacetate and Terminal Acetylenes Using Mixed-Ligand Complexes of the Series $Rh_2(RCO_2)_n$ (L^*_{4-n}). Stereochemical Heuristics for Ligand Exchange and Catalyst Synthesis

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Abstract: This paper describes the synthesis of mixed Rh_2(II) complexes containing bridging acetate and *R,R*-diphenyl-*N*-triflylimidazolidinone (DPTI) ligands (**1**, **2**, and **9**−**19**), and their function as enantioselective catalysts for the conversion of ethyl diazoacetate and terminal acetylenes to chiral cyclopropenes. Of these catalysts, **1** and **10** functioned with the highest enantioselectivity, in accord with a mechanistic model in which one of the ligand bridges is broken in the intermediate Rh−carbene complex. The synthetic results allow conclusions with regard to kinetically and thermodynamically favored pathways for the synthesis of mixed acetate−DPTI complexes. A new C_2-symmetric complex having only two *anti*-DTBTI bridges (**23**) is shown to be a highly effective chiral catalyst, as expected from the model.

The use of Rh_2(II) salts, e.g., $Rh_2(OAc)_4$, as catalysts for C−C bond formation in [2+1]-cycloaddition reactions of olefins (or acetylenes) and α-diazo carbonyl compounds or in ring-forming C−H insertion reactions of the latter represents an important synthetic tool,[1] made even more powerful by the development of highly enantioselective versions using chiral Rh(II) catalysts. The most effective of these chiral catalysts thus far have been Rh_2-bridged dimers having four identical chiral bridging ligands, especially the ligands of McKervey/Davies (*N*-arylsulfonylproline),[1i,2] Doyle (chiral 2-oxopyrrolidines),[1a,b,3] and Hashimoto/Ikegami (*N*-phthaloyl-*tert*-butylglycine).[1e,4] The rate-limiting step for these catalytic reactions is the reaction of the α-diazo carbonyl with the Rh(II) catalyst, forming N_2 and a Rh(II) carbenoid complex.[5] The detailed nature of that complex and the subsequent product-forming step, which are both crucial to the understanding of the mechanistic basis for enantioselectivity, have been obscure, although the assumption that the carbenoid complex retains the framework of Rh_2L_4 has commonly been made for symmetrically bridged catalysts.[1,6] This assumption has also been used in the latest computational studies of the product-forming step.[7,8] We recently have described a different mechanistic model of the product-forming step with unsymmetrically bridged catalysts which is based on the idea that the Rh−carbenoid complex contains only three of the original ligand bridges of the starting Rh(II) catalyst and that the reaction proceeds by a [2+2]-cycloaddition of the C=C or C≡C linkage to Rh−carbenoid π-linkage.[9,10] On the basis of this hypothesis, we synthesized the chiral Rh(II) complex **1**,[10,11] having one acetate and three *R,R*-diphenyl-*N*-triflylimidazolidinone (DPTI) ligands, and compared it to the closely related complex with

(1) For reviews, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley: New York, 1998. (b) Doyle, M. P.; Ren, T. In *Progress in Inorganic Chemistry*; Karlin, K. D., Ed.; John Wiley: New York, 2001; pp 113−168. (c) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861−2908. (d) Forbes, D. C.; McMills, M. C. *Curr. Org. Chem.* **2001**, *5*, 1091−1105. (e) Hashimoto, S. *Farumashia* **2001**, *37*, 1095−1097. (f) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935. (g) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919−7946. (h) Kitagaki, S.; Hashimoto, S. *Yuki Gosei Kagaku Kyokaishi* **2001**, *59*, 1157−1168. (i) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617*−*618*, 47−55. (j) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459−2469.

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(3) (a) Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Watkins, L. M.; Eagle, C. T. *Tetrahedron Lett*. **1990**, *31*, 6613−6616. (b) Doyle, M. P.; Zhou, Q.-L.; Simonsen, S. H.; Lynch, V. *Synlett* **1996**, 697−698. (c) Doyle, M. P.; Winchester, W. R.; Protopopova, M. N.; Müller, P.; Bernardinelli, G.; Ene, D.; Motallebi, S. *Helv. Chim. Acta* **1993**, *76*, 2227−2235.

(4) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 5173−5174.

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(6) (a) Sheehan, S. M.; Padwa, A.; Snyder, J. P. *Tetrahedron Lett.* **1998**, *39*, 949−952. (b) Snyder, J. P.; Padwa, A.; Stengel, T.; Arduengo, A. J., III; Jockisch, A.; Kim, H.-J. *J. Am. Chem. Soc.* **2001**, *123*, 11318−11319.

(7) (a) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181−7192. (b) Yoshikai, N.; Nakamura, E. *Adv. Synth. Catal.* **2003**, *345*, 1159−1171.

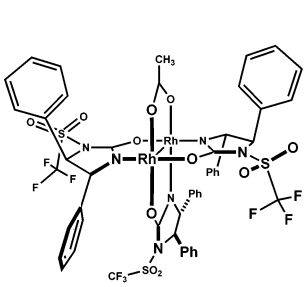
(8) Nowlan, D. T., III; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 15902−15911. These workers have also measured $^{12}C/^{13}C$ kinetic isotope effects for olefin cyclopropanation.

(9) For other studies of the conversion of acetylenes to cyclopropenes, see: (a) Petiniot, N.; Anciaux, A. J.; Noels, A.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1978**, 1239−1242. (b) Doyle, M.; Protopopova, M.; Müller, P.; Ene, D.; Shapiro, E. *J. Am. Chem. Soc.* **1994**, *116*, 8492−8498. (c) Protopopova, M.; Doyle, M.; Müller, P.; Ene, D. *J. Am. Chem. Soc.* **1992**, *114*, 2755−2757. (d) Müller, P.; Imogaï, H. *Tetrahedron: Asymmetry* **1998**, *9*, 4419−4428.

(10) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916−8919.

(11) The structure of this catalyst was confirmed by single-crystal X-ray diffraction analysis.

four DPTI ligands (**2**)[10,11] in the reaction of ethyl diazoacetate with terminal acetylenes. The chiral complex **1** efficiently



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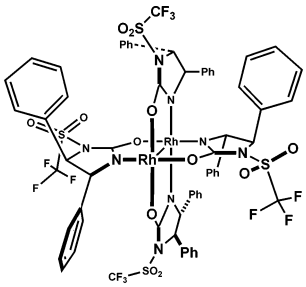

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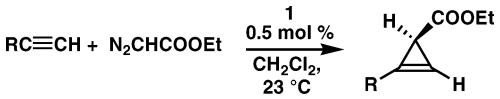
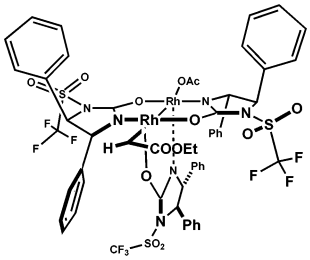
catalyzed the [2+1]-cycloaddition of ethyl diazoacetate to a variety of terminal acetylenes to form chiral (*S*)-cyclopropenes with enantioselectivities ranging from 39:1 to 24:1. These enantioselectivities were higher than those obtained



in parallel experiments using the $Rh_2(DPTI)_4$ catalyst **2** (ca. 9:1). The excellent results obtained with catalyst **1** are in accord with the triply bridged structure **3** for the Rh−carbenoid intermediate and reaction with the terminal acetylenic substrate by a pathway via assembly **4**, in which the more labile acetate bridge to the



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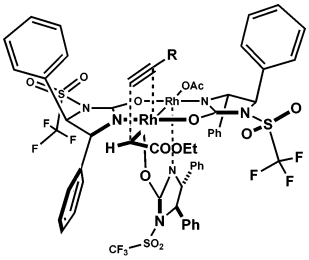
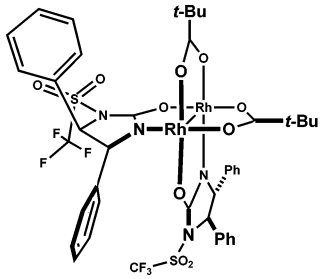


4

rhodium bearing the carbenoid fragment has been broken. The nonbridging acetate ligand in **3** and **4** is arbitrarily shown as monodentate, but it is likely to be attached to the rear rhodium in a bidentate mode. The [2+2]-cycloaddition step **3** → **4** involves the energetically more stable arrangement of the carbenoid fragment, HCCOOEt, with the bulky COOEt group *cis* to the Rh−O bond and opposite the bulkier N−CHPh group. The regiochemistry of the cycloaddition step is that expected for the carbenoid carbon, being more electrophilic than rhodium. In **3**, the Rh bearing the carbenoid has additional electron density in an orbital that can provide better Rh−carbenoid back-bonding than with the corresponding Rh(II) tetra-bridged structure. Even if the tetra-bridged structure were to predominate over the tri-bridged structure at equilibrium, the reaction with the acetylene would still proceed via **4** if the equilibration were relatively rapid and the reactivity of **4** were greater than that of the isomeric tetra-bridged intermediate.

The results obtained with **1** and **2** led us to prepare and examine the behavior of a catalyst containing only two DPTI ligands, specifically the dipivalate complex **5**.[10,11] The dipivalate was chosen for **5** instead of the corresponding diacetate because it could be prepared in much better yield due to the greater solubility of $Rh_2(t\text{-}BuCO_2)_4$ as compared to $Rh_2(OAc)_4$. Of great interest was the finding that **5** catalyzed the formation of *S*-cyclopropenes from ethyl diazoacetate with about the same enantioselectivity as catalyst **1**.[10] These results are consistent with a major reaction pathway via **6** (pivalate ligand possibly bidentate), very analogous to that proposed for the reaction with catalyst **1**. As described previously, there seems to be no logical explanation of the results obtained with catalyst **5** on the basis of a tetra-bridged carbenoid intermediate since the upper right quadrant of **5** is sterically the most accessible to the acetylene and is also effectively achiral.



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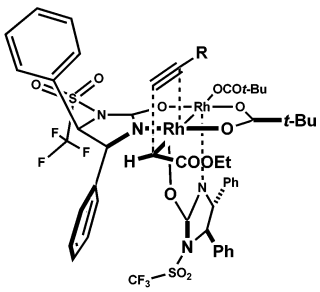
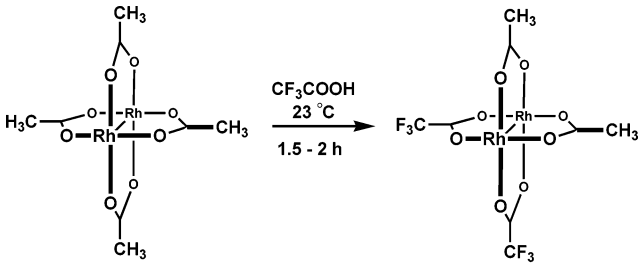


6

There are some important points that should be noted with regard to catalysts **1** and **5** and the tri-bridged carbenoid complexes derived therefrom. With regard to **1**, it is reasonable to believe that the attack by ethyl diazoacetate occurs at the rhodium having three oxygen substituents and one nitrogen substituent (front Rh in **1**), since that rhodium is sterically more available than the other (rear Rh in **1**). It is that selectivity which accounts for the preferential formation of the carbenoid complex **3**. With reference to catalyst **5**, the two Rh centers are equivalent, so it makes no difference which one attaches to the diazo ester. However, the formation of assembly **6** requires that the Rh−pivalate bond which breaks preferentially in the carbenoid complex is that which is *trans* to an oxygen ligand rather than to a nitrogen ligand. Alternatively, this preference may be summarized by stating that the carbenoid is more stable when there is an oxygen *trans* to the vacant Rh site than when there is a nitrogen. Regardless of the descriptive mode, the preference is a reasonable one, given that the driving force for bridge cleavage is the tendency for minimization of the formal Rh valance state in the carbenoid complex.

The present study was initiated with the following objectives: (1) to probe further the mechanistic details of the product-forming step in Rh(II)-catalyzed [2+1]-cycloaddition of ethyl diazoacetate to terminal acetylenes; (2) to test the above-described hypotheses regarding the basis for enantioselection using Rh(II) complexes with chiral *N*-triflylimidazolones, including DPTI and certain structural analogues; (3) to examine the enantioselectivity of [2+1]-cycloaddition for the entire series of mixed DPTI−carboxylate-containing Rh(II) complexes, i.e., the family $Rh_2(DPTI)_n(RCOO)_{4-n}$; (4) to examine the factors controlling ligand-exchange reactions of Rh_2(II) complexes to clarify the factors controlling the regio- and stereoselectivity; and (5) to identify useful new Rh_2(II) catalysts for enantioselective synthesis. The complex demands of rational design of mixed-ligand Rh_2(II) complexes have not previously been met with unsymmetrical ligands such as DPTI. Further, very little is known about the rational planning of syntheses of mixed Rh_2(II)−carboxylate γ-lactam complexes.

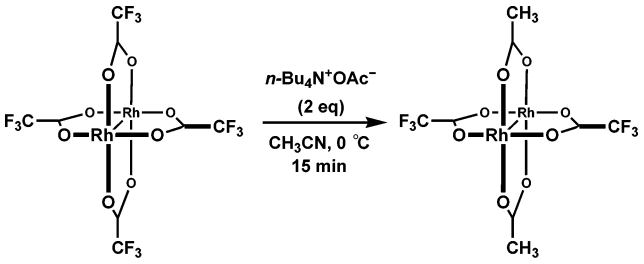
Synthesis of Mixed Complexes $Rh_2(OAc)_n(OCOCF_3)_{4-n}$. We carried out initial studies on the synthesis of mixed-ligand Rh_2(II) complexes with acetate and trifluoroacetate ligands as a simple model. The selection of this system was also guided by some important findings of J. L. Bear and colleagues on the reaction of $Rh_2(OAc)_4$ with trifluoroacetic acid.[12,13] These workers reported rate constants for the successive formation of mono-, di-, tri-, and tetratrifluoroacetates to be in the ratio 1:2:0.1 and 0.025.[12] It was of great interest to us that whereas the rate of the second exchange was somewhat faster than the first, the third and fourth exchanges were progressively much slower. Because of this, these researchers were able to isolate a pure mixed complex of composition $Rh_2(OAc)_2(OCOCF_3)_2$, which they considered to be the stereoisomer in which two identical ligands are *trans* to one another. Upon reinvestigation of this interesting reaction, we found that exposure of $Rh_2(OAc)_4$ to excess CF_3CO_2H at 23 °C for 1.5−2 h produced this major product which could be isolated in 51% yield after column chromatography on silica gel.[14] Recrystallization from 10%



7

CH_3OH in CH_2Cl_2 afforded monoclinic crystals which were subjected to X-ray crystallographic analysis and shown to be the *cis* isomer of $Rh_2(OAc)_2(OCOCF_3)_2$ (**7**)[15] rather than the *trans* isomer.[12] A simple explanation for this may be that the acetate bridge which is *trans* to the relatively electronegative trifluoroacetate in $Rh_2(OAc)_3(OCOCF_3)$ is bound more tightly than the other two and thus is more difficult to protonate (in the intermediate for ligand exchange, presumably having two nonbridging axial CF_3CO_2 ligands coordinated to the tetra-bridged $Rh_2(OAc)_3(OCOCF_3)$) and to displace. In any event, it is clear that the more electron-attracting CF_3CO_2 bridge disfavors displacement of the *trans*-CH_3CO_2 bridge relative to the two *cis*-CH_3CO_2 bridges.

These observations suggested a rational plan for the synthesis of *trans*-$Rh_2(OAc)_2(OCOCF_3)_2$ (**8**) that proved to be successful. Reaction of $Rh_2(OCOCF_3)_4$ in CH_3CN solution with 2 equiv of n-$Bu_4N^+OAc^-$ at 0 °C afforded, after column chromatography, 75% yield of **8**, the structure of which was proven by



8

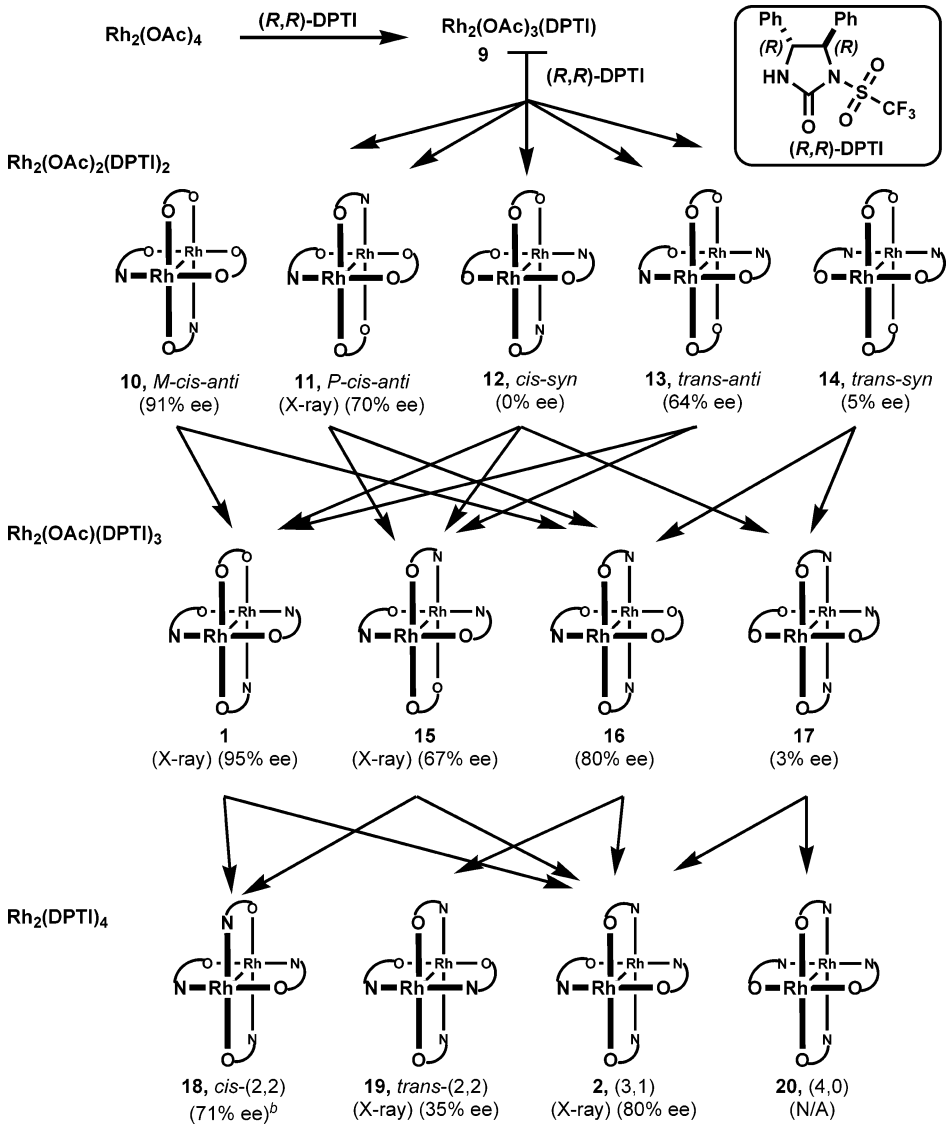
single-crystal X-ray diffraction analysis[15,16] (crystallized from CH_3CN/C_6H_6). This preparative route takes advantage of the more facile displacement of the *trans*-trifluoroacetate bridge in $Rh_2(OCOCF_3)_3(OAc)$ by AcO^- and also the obvious driving force for displacement of the more stabilized trifluoroacetate ion by the less stabilized acetate ion. The facile preparation of the *cis* (**7**) and *trans* (**8**) isomers of $Rh_2(OAc)_2(OCOCF_3)_2$ provided both a heuristic for synthetic planning and two very useful starting materials for the synthesis of mixed-ligand Rh_2(II) complexes.

Synthesis of Mixed-Ligand Rh_2(II) Complexes with DPTI and Acetate. There are 14 possible Rh_2(II)−DPTI complexes, including mixed-ligand complexes with acetate, having the formula $Rh_2(OAc)_n(DPTI)_{4-n}$. These are systematically displayed in Scheme 1 as a synthetic tree which shows the possible pathways of formation by unidirectional ligand displacement. We have been able to synthesize all but one of these, complex **20**. The structures of complexes **11**,[11] **1**,[10] **15**,[11] **19**,[11] and **2**[10] were determined by single-crystal X-ray diffraction analysis, as indicated in Scheme 1. Structure **10** is the acetate analogue of pivalate **5**, the structure of which was also determined by X-ray analysis,[10] and gave essentially identical ee values in [2+1]-cycloaddition reactions with terminal acetylenes. The ee values given in Scheme 1 represent those experimentally determined for the various complexes as catalysts for the reaction of ethyl diazoacetate and 1-heptyne in CH_2Cl_2 at 23 °C under the same standardized conditions. Structural assignments to the remaining complexes in Scheme 1 will be discussed below together with the method of synthesis.

A mixture of the three *cis* isomers of $Rh_2(OAc)_2(DPTI)_2$, **10**, **11**, and **12**, was synthesized in a logical way from the *cis* isomer of $Rh_2(OAc)_2(OCOCF_3)_2$ (**7**) by reaction with the sodium salt of DPTI (prepared by reaction of DPTI in THF with sodium hexamethyldisilazane, $NaN(TMS)_2$) in THF solution at 0 °C for 2 h and at 23 °C for 12 h, as shown in Scheme 2. Purification of the crude reaction product (ratio of **10**, **11**, and **12** ca. 4:2:1) by chromatography on silica gel (5% CH_3CN in CH_2Cl_2 for elution) afforded the following isolated yields: **10**, 43%; **11**, 23%; and **12**, 11%. The structure of **12** was obvious from the NMR spectrum, which shows nonequivalent DPTI ligands (e.g. two CF_3 peaks in the ^{19}F NMR spectrum in contrast to the spectra **10** and **11**, which show only a single sharp CF_3 peak), and from the fact that the cyclopropene that formed from ethyl diazoacetate and 1-heptyne with **12** as catalyst was completely racemic. A racemic product is to be expected since the Rh−carbenoid intermediate from **12** is expected to be that in which the carbene has attached to the Rh that initially had four oxygen ligands (the sterically most accessible and the most Lewis acidic Rh). Such a carbenoid clearly has a symmetric environment that would not lead to enantioselection in [2+1]-cycloaddition reactions. The structure of **10** follows logically not only by a process of elimination but also from its identical catalytic behavior with the dipivalate analogue **5**, to which that structure had been assigned unambiguously by X-ray analysis.[10]

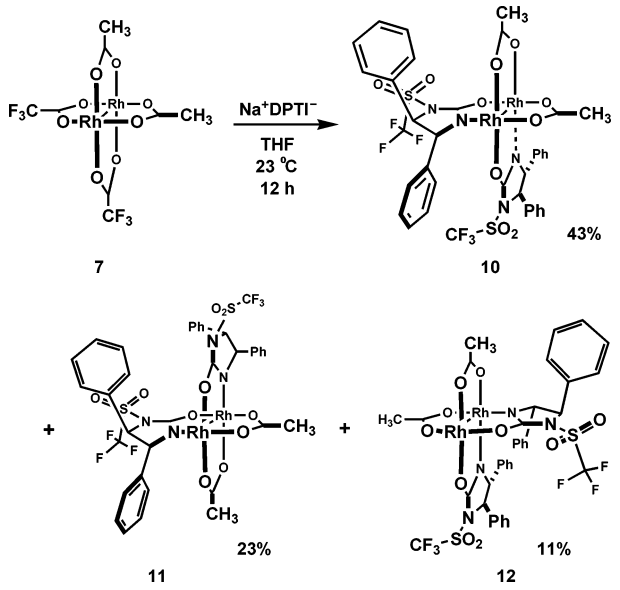
(12) Bear, J. L.; Kitchens, J.; Willcott, M. R., III. *J. Inorg. Nucl. Chem.* **1971**, *33*, 3479−3486.
(13) See also: Johnson, S. A.; Hunt, H. R.; Neumann, H. M. *Inorg. Chem.* **1963**, *2*, 960−962.
(14) Small amounts of $Rh_2(OCOCF_3)_3(OAc)$ and $Rh_2(OAc)_3(OCOCF_3)$ were also isolated from the reaction mixture by chromatography.
(15) For details on the determination of structure by single-crystal X-ray diffraction analysis, see Supporting Information.
(16) The only other reaction product was $Rh_2(OAc)_3(OCOCF_3)$.

Scheme 1. Synthetic Tree for Sequential Formation of $Rh_2(OAc)_n(DPTI)_{4-n}$ Complexes[a]



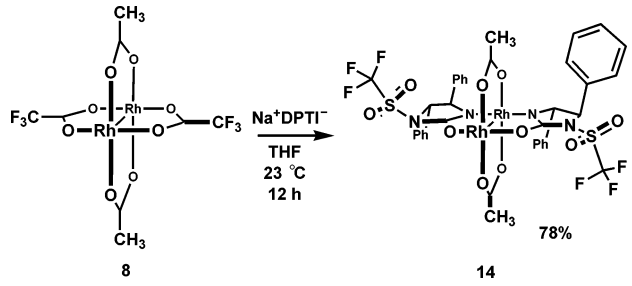
[a] The ee values shown in Scheme 1 refer to those measured for the catalyzed addition of ethyl diazoacetate to 1-heptyne (CH_2Cl_2 at 23 °C). [b] At 40 °C in CH_2Cl_2.

Scheme 2



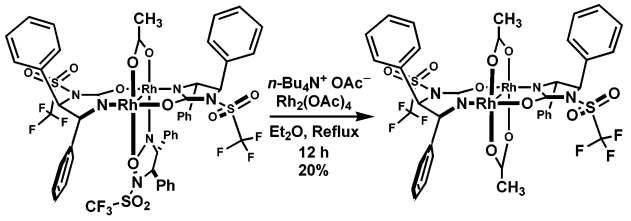
The *cis-anti* complexes **10** and **11** could also be prepared in one step from $Rh_2(OAc)_4$ by heating with 2 equiv of DPTI-H in chlorobenzene−acetic acid at reflux for 36 h. After chromatography of the crude reaction product, **10** was obtained in 25% isolated yield and **11** was obtained in 31% isolated yield. The remaining rhodium is accounted for as $Rh_2(OAc)_4$ and $Rh_2(OAc)_3(DPTI)$ under these conditions. The acetic acid cosolvent minimizes the amount of $Rh_2(OAc)(DPTI)_3$ formed under these conditions.

Reaction of *trans*-$Rh_2(OAc)_2(OCOCF_3)_2$ (**8**) with Na^+DPTI^- in THF at 23 °C gave cleanly *trans-syn*-$Rh_2(OAc)_2(DPTI)_2$ (**14**).



The preferential formation of the *trans-syn* isomer **14** over the *trans-anti* isomer **13**, which is thermodynamically more stable than **14**, is especially interesting (see below). In the conversion **8** → **14**, the anion of DPTI preferentially displaces trifluoroacetate rather than acetate because the former is a better leaving group.

Since *trans-anti*-$Rh_2(OAc)_2(DPTI)_2$ (**13**) was not available from **8**, an alternative route was devised for its synthesis starting from the readily available **1**. Upon heating of **1** with 10 equiv of *n*-$Bu_4N^+OAc^-$ and 1 equiv of $Rh_2(OAc)_4$ in Et_2O at reflux for 12 h, *trans-anti*-$Rh_2(OAc)_2(DPTI)_2$ could be obtained in 20% isolated yield after chromatographic separation on silica gel.



1 13

The remaining material from the reaction was the starting complex $Rh_2(OAc)(DPTI)_3$ (**1**). Subsequent to the development of this first preparation of **13**, it was discovered that the same compound could be made by isomerization of the less stable **14**. Thus, upon heating of **14** in chlorobenzene solution at reflux for 10 h, it was transformed into an 82:18 mixture of **13** and **14**, respectively. The structures of **13** and **14** followed from ^1H and ^{19}F NMR studies in the presence of pyridine.

Complex **13**, in which the two DPTI ligands are in the *trans-anti* relationship, coordinates with 1 equiv of pyridine to generate a mono-pyridine adduct that exhibits four distinct methine signals in the ^1H NMR spectrum. With excess pyridine a symmetrical bis-pyridine adduct is formed showing two methine signals. In contrast, complex **14**, in which the two DPTI ligands are in a *trans-syn* relationship, coordinates with 1 equiv of pyridine selectively to form a single mono-pyridine adduct that shows two methine signals, as expected for the complex of pyridine at the Rh having four oxygen ligands. The bis-pyridine complex of **14** also shows two methine proton signals, as expected for that structure. It is noteworthy that when **14** was employed as catalyst in the [2+1]-cycloaddition of ethyl diazoacetate to 1-heptyne, the cyclopropene carboxylic ester was produced with only 5% ee, as expected for *trans-syn*-$Rh_2(OAc)_2(DPTI)_2$.

The remaining rhodium−DPTI complexes that appear in Scheme 1 were readily synthesized. Reaction of either complex **10** or **11** with Na^+DPTI^- in THF at 50 °C afforded **16**, allowing assignment of its structure. Complex **17** was similarly prepared from **12** and Na^+DPTI^- in THF, which allowed assignment of the structure **17**. Complexes **18** and **19** were formed along with **2** by heating $Rh_2(OAc)_4$ with DPTI in chlorobenzene at reflux in a Soxhlet apparatus containing a mixture of CaH_2 and Celite 545 to remove HOAc from the reaction mixture. Chromatography of the mixture furnished **2** as major product, lesser amounts of **18**, and an even smaller amount of **19**. The structure of **18** followed clearly from the ^1H and ^{19}F NMR spectra, which showed two sets of peaks due to the two pairs of identical ligands (i.e., those *trans* to each other). Structure **20**, the only remaining possibility, would show only a single set of peaks from the four equivalent ligands. We have never observed **20** as a reaction product, in all likelihood because that structure is destabilized by strong steric repulsions between the substituents on the four bridges and also destabilized electronically (see below).

Table 1. Anionic Ligand Displacement of Acetate by DPTI Anion in THF: Observed Ratio of Product to Remaining Starting Material (**9**) as a Function of Time

t, min	9	10	11	12	13	14
10	1	0	0	0	0	0
30	1	0.02	0.03	0.02	0	0
60	1	0.04	0.05	0.03	0	0
120	1	0.09	0.12	0.05	0	0
180[a]	1	0.13	0.19	0.06	0.03	0.15
600[b]	1	0.31	0.53	0.10	0.20	0.49

[a] **1** (0.36) and **16** (0.03) also formed. [b] **1** (0.61) and **16** (0.16) also formed.

Enantioselectivity of the Reaction of Ethyl Diazoacetate with 1-Heptyne as a Function of Catalyst Structure with Complexes 1, 2, and 9−19. It is apparent from the data shown in Scheme 1 that the highest enantioselectivities in the catalytic test reaction of ethyl diazoacetate with 1-heptyne were observed with catalysts **1** (95% ee) and **10** (91% ee), as expected for a pathway via pre-transition-state complexes **4** and **6** (acetate instead of pivalate), respectively, and as discussed in the introductory section and in an earlier publication.[10] The lower enantioselectivities found for the catalyzed ethyl diazoacetate−heptyne reactions using the rhodium complexes **11**−**19** and **2** (summarized in Scheme 1) are also consistent with the proposed pathway. It is interesting that of all the Rh_2(II) catalysts shown in Scheme 1, the least reactive toward ethyl diazoacetate is the *cis*-(2,2)-**18**, in which every Rh−O bond is *trans* to an Rh−N bond. In the case of *trans-anti*-$Rh_2(OAc)_2(DPTI)_2$ (**13**) as catalyst, the 82:18 selectivity (64% ee) for formation of ethyl (1*S*)-2-*n*-amyl-2-cyclopropenylcarboxylate from 1-heptyne and ethyl diazoacetate—our mechanistic model—requires selectivity in the cleavage of one acetate bridge in the intermediate carbenoid (the upper acetate bridge of **13** in Scheme 1). This point is discussed further in the last section of this paper. The very low ee's (0−5%) that result from the use of catalysts **12**, **14**, and **17** are predictable from the mechanistic model.

Preferred Pathways for the Formation of $Rh_2(OAc)_n(DPTI)_{4-n}$ Complexes by $DPTI^-$ Displacement of Acetate. We have also carried out a kinetic investigation of selective formation of mixed acetate−DPTI complexes of Rh(II) using the displacement reaction of acetate by Na^+DPTI^- in THF solution. The greater stability of AcO^- vs $DPTI^-$ clearly provides the driving force for this process. The reaction of $Rh_2(OAc)_n(DPTI)_{4-n}$ with Na^+DPTI^- (from DPTI and sodium hexamethyldisilazane) in THF at 50−60 °C was monitored by HPLC analysis to determine quantitatively the rate of formation of the new complexes formed by ligand displacement. The complexes **9**−**19**, **1**, and **2** could all be distinguished by HPLC analysis using a standard elution protocol.[17] Some of the salient results of this study are presented in Tables 1 and 2. A more

(17) HPLC analysis was performed using a Microsorb MV silica column, 23 °C, detection at 254 nm, 1 mL/min flow rate, with the following solvent mixtures: 20/78/2 EtOAc−hexanes−CH_3CN (30 min); 80/18/2 EtOAc−hexanes−CH_3CN (30 min); then 20/78/2 EtOAc−hexanes−CH_3CN (10 min). The retention times of the isomers in Scheme 1 were determined to be as follows: **9**, 51 min; **10**, 39.8 min; **11**, 40.5 min; **12**, 41 min; **13**, 22 min; **14**, 25 min; **1**, 15.2 min; **15**, 13.7 min; **16**, 10.3 min; **17**, 30.3 min; **18**, 10.0 min; **19**, 6.1 min; **2**, 10.8 min; (*R*,*R*)-DPTI, 7.0 min.

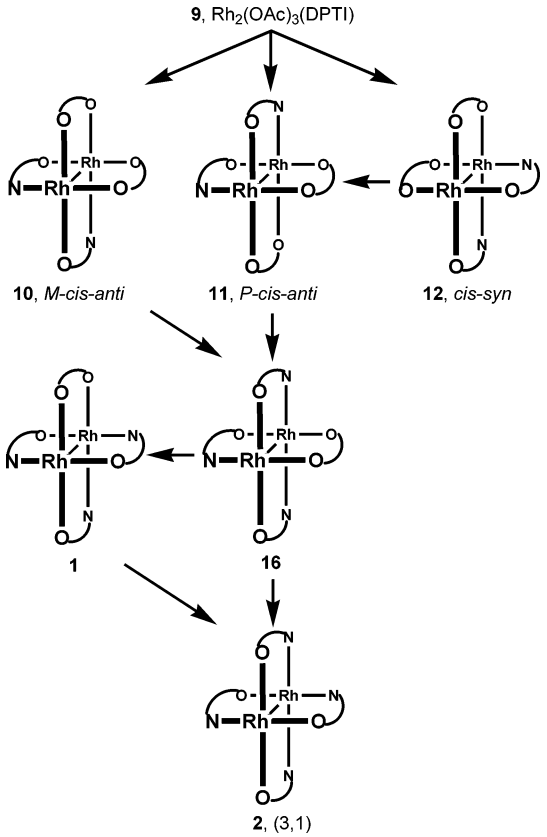
Table 2. Anionic Ligand Displacement of Acetate by DPTI Anion in THF: Observed Ratio of Product to Remaining Starting Material (**10**, **11**, or **12**) as a Function of Time

	a. From **10**			b. From **11**		
t, min	**10**	**1**	**16**	**11**	**16**	**2**
60	1	0	0.24	1	0	0
180	1	0	0.36	1	0.06	0
1440	1	0.76	11.4	1	0.39	0.41

	c. From **12**					
t, min	**10**	**11**	**1**	**15**	**16**	**17**
30[a]	0	1	0.08	0.47	3.2	0.88
60[a]	0.01	1	0.09	0.46	3.4	0.97
180[a]	0.02	1	0.12	0.49	3.5	0.95

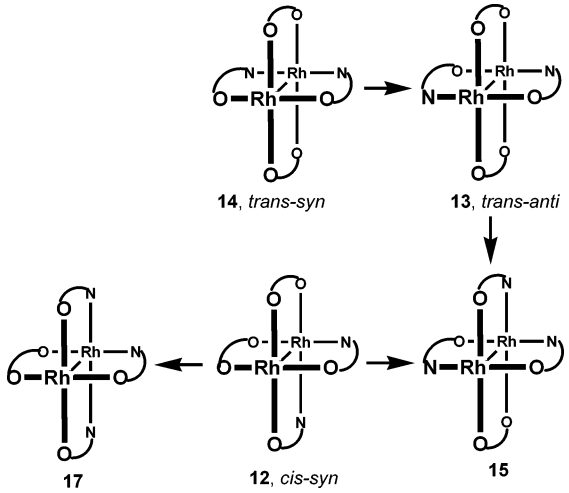
[a] No **12** remaining.

Scheme 3. Kinetically Preferred Pathways for Anionic Ligand Displacement of Acetate by DPTI Anion in THF



extensive summary of the data appears in the Supporting Information. From perusal of the information in Tables 1 and 2, it is evident that certain regio- and stereochemical preferences exist for the ligand displacement reactions and that some products are preferred over the other possibilities that are summarized in Scheme 1. These kinetically favored reaction pathways are shown in Scheme 3. Starting from $Rh_2(OAc)_3$(DPTI), the $Rh_2(OAc)_2(DPTI)_2$ isomers **10**, **11**, and **12**, all of which have a *cis* arrangement of ligands (two bridges are *cis* if they are at 90° angles to one another), are favored over the *trans* isomers **13** and **14**. At long reaction times **13** and **14** appear, evidently as secondary products formed by isomerization of **10**, **11**, and/or **12**. The $Rh_2(OAc)_2(DPTI)_2$ isomers **10** and **11** are both converted preferentially to **16** by acetate displacement. Complex **16** is then preferentially converted to **2** by displacement of acetate by $DPTI^-$. Our analyses also revealed

Scheme 4. Other Pathways for Anionic Ligand Displacement of Acetate by DPTI Anion in THF



that **16** can undergo an interesting isomerization to **1** and that **1** is converted preferentially to **2**. This isomerization of **16** to **1** indicates that it is possible for $DPTI^-$ to displace itself and to do so in a way that effects a *syn*/*anti* stereomutation. The behavior of the *cis-syn*-$Rh_2(OAc)_2(DPTI)_2$ complex **12** is also interesting. Upon heating with Na^+DPTI^- in THF, it is rapidly isomerized to the clearly more stable *P-cis-anti* complex **11**, another example of stereomutation by $DPTI^-$ at a rate that is fast relative to displacement of AcO^-.

Our kinetic studies have also revealed a number of interconversions that result from slower pathways for nucleophilic displacement of acetate by $DPTI^-$ in Rh(II) complexes. These slower pathways are summarized in Scheme 4. In addition to the isomerization process that converts **12** to **11**, **12** undergoes displacement to form **15** and **17**. The *trans-syn* complex **14** also is subject to isomerization to form the *trans-anti* complex **13** that then goes on to **15** by acetate displacement. It is of considerable interest that *trans-syn*-$Rh_2(OAc)_2(DPTI)_2$ (**14**) is less stable than the *trans-anti* isomer **13** because this difference in stability must be associated with intrinsically less favored bonding for DPTI ligands that are *syn* to one another as compared to *anti* since steric destabilization cannot be a factor here.[18] Our failure to synthesize complex **20** may be due to the occurrence in **20** of both electronic destabilization of the type operating in **14** and steric repulsion.

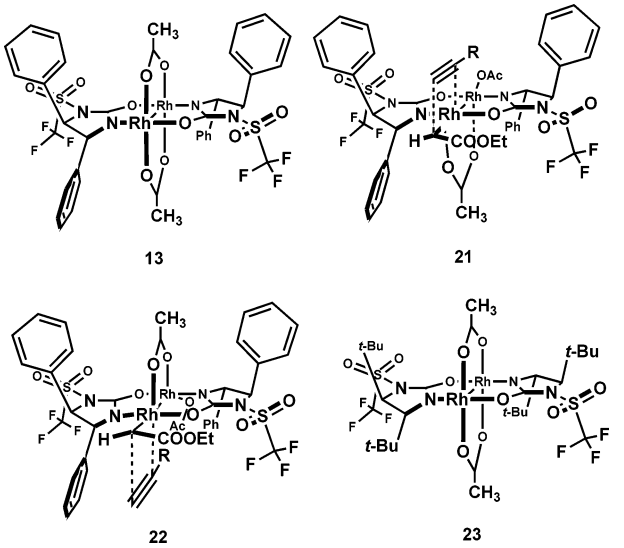
General Aspects of Rh_2(II) Ligand-Exchange Reactions. The results described above on the displacement of acetate in Rh_2(II) complexes by Na^+DPTI^- in THF at 50−60 °C point to some significant trends with regard to preferred pathways. First, the formation of *cis-anti* arrangements of DPTI ligands appears to be favored. Second, the displacements are kinetically controlled at low conversions. Third, Na^+DPTI^- can also cause isomerization of unstable to more stable structures in the $Rh_2(OAc)_2(DPTI)_2$ series, for example the conversion of **12** to **11**, or **14** to **13**.

The conventional method of synthesis of Rh_2(II) complexes with chiral ligands involves the thermal reaction of an achiral rhodium carboxylate, usually $Rh_2(OAc)_4$, with the chiral ligand

(18) It is possible that the *trans-anti* arrangement of DPTI ligands is energetically more favorable than the *trans-syn* alternative in Rh_2(II) complexes because the former allows the two Rh centers to have the same electron density and effective charge.

in refluxing solvent (e.g., C_6H_6 or C_7H_8). We have used this method extensively to synthesize $Rh_2(DPTI)_4$ and $Rh_2(OAc)(DPTI)_3$ complexes, generally using C_6H_5Cl as solvent at reflux with external CaH_2−Celite 545 for continuous removal of HOAc. Careful study of this thermal process by HPLC analysis of reaction mixtures as a function of time has demonstrated that this method generally leads to near-equilibrium mixtures of products (see Supporting Information).

Studies on *trans-anti*-$Rh_2(OAc)_2(DTBTI)_2$. As indicated in Scheme 1, *trans-anti*-$Rh_2(OAc)_2(DPTI)_2$ (**13**) catalyzes the reaction of ethyl diazoacetate and 1-heptyne to form ethyl (1*S*)-2-*n*-amyl-2-cyclopropenylcarboxylate of 64% ee (82:18 selectivity). Because this enantioselection can be explained by a preference for pre-transition-state assembly **21** over the alternative **22**, we were interested in testing whether the difference in stability of **21** and **22** (or their bidentate acetate equivalents) could be magnified by replacing the phenyl groups in catalyst **13** by the bulkier *tert*-butyl group, as shown in structure **23**.



That replacement would be expected to disfavor a pathway via the *tert*-butyl analogue of **22** vs that via the *tert*-butyl analogue of **21** for two reasons: (1) the steric repulsion between the acetylenic R group and *tert*-butyl in the analogue of **22** should be considerably greater than for phenyl in **22** and (2) the steric repulsion between the nonbridging acetate ligand in the *tert*-butyl analogue of **22** would be greater than for phenyl in **22**. Consequently, we have synthesized the *trans-anti* complex **23**, which we designate herein as *trans-anti*-$Rh_2(OAc)_2(DTBTI)_2$, where DTBTI stands for the ligand (*R*,*R*)-4,5-di-*tert*-butyl-*N*-triflylimidazolinone (**25**). The synthesis of the (*R*,*R*)-ligand **25** was carried out from (1*R*,2*R*)-1,2-di-*tert*-butylethylenediamine (**24**).[19] The route of synthesis is outlined in Scheme 5. The reaction of *trans*-$Rh_2(OAc)_2(OCOCF_3)_2$ with Na^+DTBTI^- in THF at 23 °C gave a mixture of *trans-anti*-$Rh_2(OAc)_2(DTBTI)_2$ (**23**) and *trans-syn*-$Rh_2(OAc)_2(DTBTI)_2$ in a ratio of ca. 1:2.[20] Pure **23** was obtained by chromatography of this mixture on silica gel (26% yield, unoptimized).[21]

Scheme 5

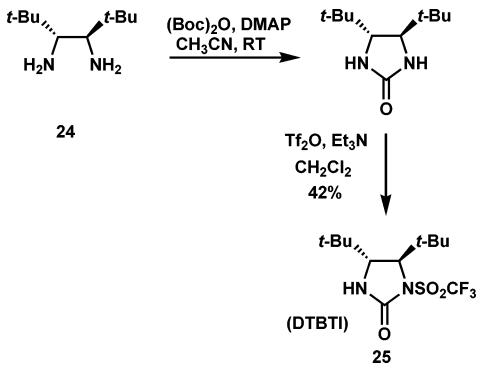
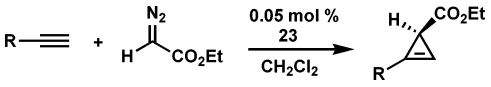


Table 3. Cyclopropenation of Ethyl Diazoacetate and Terminal Alkynes Catalyzed by **23**



entry	R	*T*, °C	yield, %	ee, %[a]
1	$CH_3(CH_2)_4$	23	87	89
2	$CH_3(CH_2)_4$	0	84	91
3	*t*-Bu	0	81	90
4	$MeOCH_2$	0	78	93

[a] Enantiomeric excess was determined by GC using a γ-TA column.[10]

As expected from our mechanistic model, *trans-anti*-$Rh_2(OAc)_2(DTBTI)_2$ (**23**) afforded substantially better enantioselectivity than *trans-anti*-$Rh_2(OAc)_2(DPTI)_2$ (**13**) for the reaction of ethyl diazoacetate with 1-alkynes. Table 3 summarizes the data obtained with catalyst **23** and three different alkynes which show enantioselectivities of approximately 20:1 for each case. We believe that these results provide additional evidence in support of a pre-transition-state model analogous to **21** (for the DPTI series).

Conclusions. The major objective of this work was the investigation of the synthesis and catalytic properties of a series of complexes of the type $Rh_2(OAc)_n(ligand)_{4-n}$. Both *cis*- and *trans*-$Rh_2(OAc)_2(OCOCF_3)_2$ have been synthesized, analyzed to demonstrate structure, and applied as starting materials to the synthesis of chiral Rh_2(II) complexes. Thirteen of the complexes $Rh_2(OAc)_n(DPTI)_{4-n}$, whose structures are systematically displayed in Scheme 1, have been made and characterized structurally and then applied as catalysts to determine their effectiveness in the synthesis of chiral ethyl 2-*n*-amyl-2-cyclopropenylcarboxylate from 1-heptyne and ethyl diazoacetate. As predicted from the mechanistic model described in the introduction, complexes **1** and **10** excel with regard to enantioselectivity, complexes **12**, **14**, **17**, and **19** are poor, and **2**, **11**, **13**, **15**, **16**, and **18** are mediocre (64−80% ee). Also as expected from the mechanistic model, *trans-anti*-$Rh_2(OAc)_2(DTBTI)_2$ (**23**) gave much better enantioselectivity (91%) than the DPTI

(19) Diamine **24** was prepared in this laboratory in 1988 by Dr. Po-Wei Yuen by addition of *tert*-butylmagnesium chloride and the Schiff base of benzylamine, glyoxal, followed by debenzylation with H_2 and Pd−C catalyst, and then resolution with *R*,*R*-tartaric acid, a method subsequently developed also by Roland et al. (Roland, S.; Mangeney, P.; Alexakis, A. *Synthesis* **1999**, 228−230).

(20) As described above, the corresponding reaction in the DPTI series gave selectively *trans-syn*-$Rh_2(OAc)_2(DPTI)_2$ (**14**).

(21) The structures of **23** and *trans-syn*-$Rh_2(OAc)_2(DTBTI)_2$ were determined by X-ray diffraction analysis. Interestingly, the latter forms only a mono-complex with either MeOH or pyridine, as shown by X-ray or ^1H NMR spectral analysis, respectively.

(22) After this paper was submitted for publication, a Communication appeared in which $^{12,13}C$ kinetic isotope effects were measured for $Rh_2(OAc)_4$ and $Rh_2(OAc)(DPTI)_3$ as catalysts for the reaction of $N_2CHCOOEt$ with 1-pentyne. See: Nowlan, D. T.; Singleton, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 6190−6191. These results and theoretical calculations were claimed to support the pathway involving tetrabridged Rh−carbenoid species, contrary to our proposal.[10] In our opinion, neither the kinetic isotope effect data nor the theoretical calculations provide an adequate basis for favoring one pathway over the other.

analogue **13** (64% ee). Preferred stereochemical pathways were identified for the anionic displacement of acetate by $Na^{+}DPTI^{-}$ in the synthesis of the complexes shown in Scheme 1. This work provides a basis for more rational planning of the stereocontrolled synthesis of complexes of the series $Rh_2(OAc)_n(ligand)_{4-n}$.[22]

Acknowledgment. We are grateful to Drs. Richard Staples and Robin Kloster for the X-ray crystallographic data.

Supporting Information Available: Synthetic procedures and characterization data for the new Rh_2(II) complexes reported herein (PDF); X-ray crystallographic data for compounds **1**, **2**, **7**, **8**, **11**, **15**, **19**, **23**, and *trans-syn*-$Rh_2(OAc)_2(DTBTI)_2$ (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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