Tetrahedron Letters,Vol.30,No.10,pp 1189-1192,1989
Printed in Great Britain

0040-4039/89 $3.00 + .00
Pergamon Press plc

Use of Organometallic Complexes of Ruthenium in the Lewis Acid Catalyzed Hetero Diels-Alder Reaction

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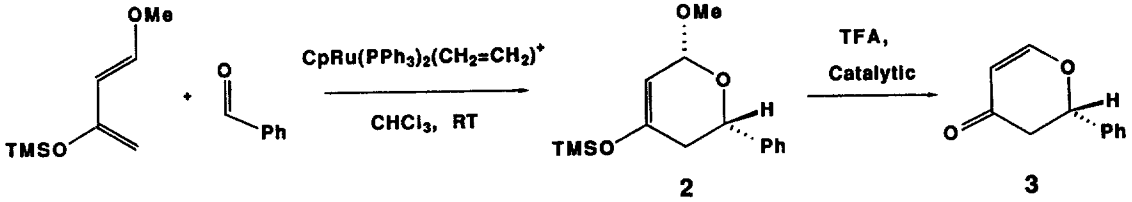
Summary. The hetero Diels-Alder reaction between benzaldehyde and a functionalized diene can be catalyzed by the Lewis acid transition metal complexes, $[CpRuLL'(CH_2{=}CH_2)]PF_6$ (L = L' = PPh_3, or LL' = 1,2-bis-diphenylphosphinoethane, (-)-DIOP or (S,S)-CHIRAPHOS).

The hetero Diels-Alder cycloaddition of aldehydes to 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) has been used as a key step in the synthesis of sugar derivatives.[1] This reaction is catalyzed by Lewis acids, such as lanthanide shift reagents,[2] main group and transition metal halides,[3] BF_3,[4] and aluminum complexes.[5] Owing to their potential applications in asymmetric synthesis, we now report that the reaction is also catalyzed by organo-transition-metal cations, specifically cyclopentadienyl-bis(phosphine) complexes of ruthenium.

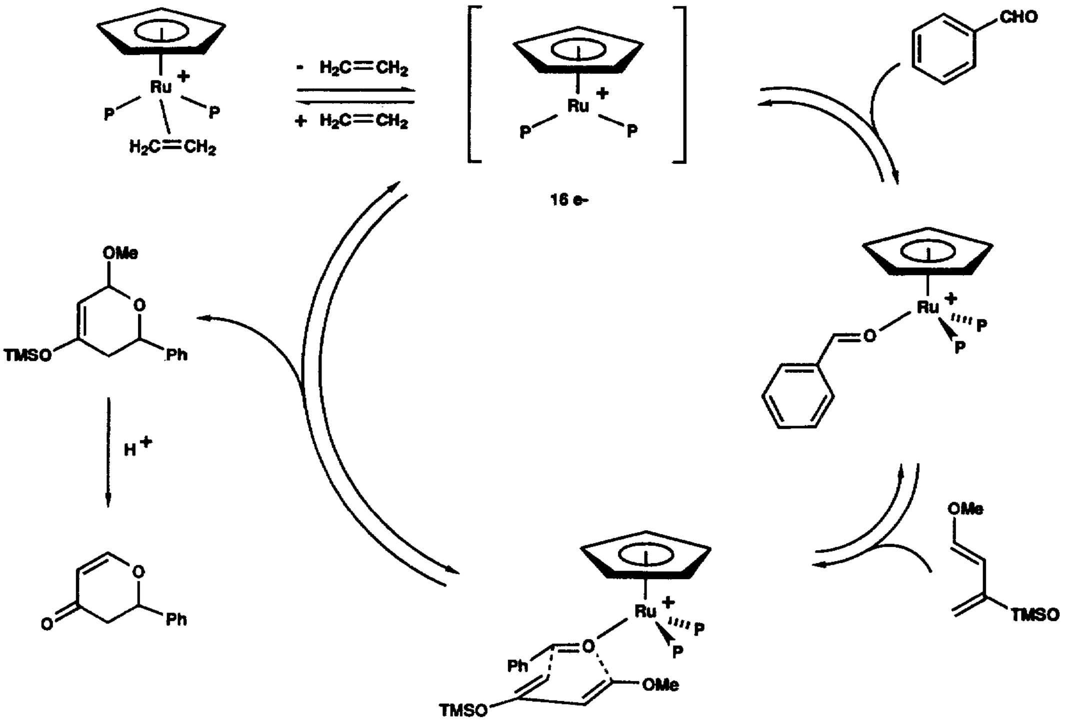
The ruthenium Lewis acid precursors were obtained from air stable $CpRu(PPh_3)_2Cl$, 1, which was prepared by a published method,[6] but is available commercially. Homochiral complexes were prepared by ligand exchange[7] of 1 with the chiral chelating bis-phosphines (-)-DIOP[8a] and (-)-(S,S)-CHIRAPHOS.[8b] The chlorides were converted to the cationic ethylene complexes by treatment with NH_4PF_6 in the presence of ethylene.[9]

The catalyses of the hetero Diels-Alder reaction by lanthanide reagents have been extensively studied in $CHCl_3$ at room temperature,[1,2] and these conditions provide a convenient standard for comparison of rates and selectivities for the ruthenium reagents. The reaction goes to completion in the presence of 0.5 - 5.0 mol% of ruthenium catalyst;[10] however, the best overall yields of the cycloaddition product were obtained when the catalyst concentrations were 5.0 mol% or greater. Owing to the increased rate under higher catalyst concentrations, the effects of competitive side reactions (most notably hydrolysis of the Danishefsky diene to the corresponding enone) are minimized. The yield of the Diels-Alder adduct was 78% when $[CpRu(PPh_3)_2(CH_2{=}CH_2)]PF_6$ was used and the reaction was complete after 24 h with 5 mol% catalyst. The reaction may take up to 48 h, depending on catalyst concentration. Loss of starting material due to hydrolysis could be reduced by the rigorous exclusion of water.

As has been observed for some lanthanide catalysts, we were able to observe the initial cycloaddition product **2** by NMR. However, the corresponding pyrone **3** is significantly more stable, and for the purpose of measuring isolated yields, the initial adduct was converted to the pyrone by addition of a catalytic amount of trifluoroacetic acid.



The cationic olefin complexes are 18-electron compounds and have no Lewis acid character as such. Formation of the Lewis acid occurs by dissociation of olefin from the precursor complex yielding the coordinatively unsaturated active species. Indeed, proton NMR studies show that initial formation of the cycloadduct is preceded by observation of free ethylene. Since no NMR evidence indicates the formation of a diene complex in the absence of aldehyde, we propose the next step in the catalytic cycle to be coordination of a molecule of aldehyde to the ligand deficient metal to give a transient aldehyde complex. The activated aldehyde would then readily react with the diene in the 2 + 4 cycloaddition reaction. Dissociation of the complexed cycloadduct would regenerate the organometallic Lewis acid and complete the catalytic cycle.



It is interesting to note that although 5 mol% of catalyst is used, only a small fraction of that amount actually participates in the catalytic cycle. When the reaction is complete, over 85% of the olefin complex can be recovered. Assuming that ethylene dissociation is relatively irreversible owing to some loss of free ethylene from the reaction system, this indicates that of the catalyst added, < 15% is directly involved in the Diels-Alder catalysis.

Asymmetric Induction. Recently, Gladysz has shown extremely high enantiofacial selectivity in the complexation of carbonyl compounds to chiral rhenium complexes.[11] However, the aldehyde is π-bound in these rhenium complexes and a σ-bonded aldehyde is likely to be required for a Diels-Alder reaction. This suggested to us the possibility that homochiral $[CpRuL_2]^+$ Lewis acids might act as effective asymmetric hetero Diels-Alder catalysts. The use of commercially available enantiomerically pure chelating phosphines allowed straightforward preparation of the homochiral $CpRu(LL')(CH_2{=}CH_2)]PF_6$ complexes, **4** and **5**, where (LL′ = (S,S)-CHIRAPHOS and (-)-DIOP respectively). These complexes were also used to catalyze the cycloaddition of benzaldehyde to the Danishefsky diene under the same conditions described above.

In general, the overall yields using **4** and **5** were somewhat lower (60-65%) with a commensurate increase in the amount of diene which was hydrolyzed to the enone. However, measurement of the optical rotation of the isolated pyrone indicated that moderate asymmetric induction *had* occurred. Enantiomeric excesses were measured by comparing the observed specific rotations to that of an enantiomerically pure sample.[12] When **4** is the catalyst, the observed specific rotation is +24.5°, 25% ee; when compound **5** is used, the $[\alpha]_D^{23}$ is +15.4°, 16% ee.

Under similar conditions (temperature, solvent, and catalyst concentration) the highest ee observed for the best lanthanide catalyst is 18% in the case where the reagents are benzaldehyde and the Danishefsky diene.[1] This ee was significantly improved upon in subsequent studies where the nature of the alkoxy group of the diene was modified to include a second center of chirality, thus invoking the effect of double diastereoselectivity.[13]

We anticipate that the same trend of improvement of the ee would result in the use of a homochiral diene in this ruthenium system. Alternatively, the ruthenium system presents the possibility of improving the selectivity by changing the nature of the chirality at the metal. In the present case the chirality at the metal (arising from use of the chiral chelating bis-phosphines) is manifested as a steric difference in the approaches of the diene to the different enantiofaces of the aldehyde. We are currently investigating ruthenium carbonyl phosphine complexes, more closely related to Gladysz′ rhenium compounds, in which the asymmetry at the metal arises from both steric and electronic effects. However, **4** and **5** have the advantage that the chirality originates in the ligand backbone and is imparted to the metal center via the orientation of the phenyl groups of the ligand; hence, the asymmetry cannot be lost at the pseudo-tetrahedral metal center in the intermediates and the catalyst will not racemize even if the phosphine ligand were to dissociate.[14]

These results show that the hetero Diels-Alder reaction can be catalyzed by Lewis acids derived from organotransition-metal compounds, and that the catalytic activity, regioselectivity (NMR indicates only one isomer of **2**), and stereoselectivity can be comparable to or better than that seen for the widely used lanthanide reagents. Variations of reaction temperature, solvent, and elaboration of ligands has allowed the aluminum binaptholate system[5] to be optimized for increased enantiomeric yield of **3** (56% ee, -20° C, nonpolar solvent, triphenylsilyl substituents). These ruthenium reagents offer an alternative to lanthanide and aluminum reagents and we anticipate that they have a similar potential for optimization. Furthermore, they are not particularly sensitive to moisture and have the advantage of being quickly and easily prepared from commercially available materials.

Acknowledgement. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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(8) a) (-)-DIOP = (-)-2,3-O-isopropylidine-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane.
b) (-)-CHIRAPHOS = (-)-(2S,3S)-bis(diphenylphosphino)butane.

(9) At room temperature, ethylene was slowly bubbled through a stirred solution of $CpRu(PPh_3)_2Cl$ (0.030 g., 0.041 mmol) and NH_4PF_6 (0.015 g., 0.092 mmol) in 25 mL MeOH for one h. *Cf.* Consiglio, G.; Morandini, F., *J. Organomet. Chem.* **1986**, 310, C66.

(10) Compound **1** and the phosphines can be purchased from Aldrich. For example: a 10 mL flask was charged with PhCHO (0.025 mL, 0.25 mmol), Danishefsky's diene (0.050 mL, 0.26 mmol), $[CpRu(PPh_3)_2(CH_2CH_2)]PF_6$ (0.0245 g., 0.028 mmol), and 5 mL $CDCl_3$. The mixture was stirred for 24 h at room temperature under an atmosphere of dry nitrogen. After treatment with TFA, the pure pyrone was obtained by chromatography on silica (cyclohexane:EtOAc 85:15).

(11) a) Fernandez, J.A.; Emerson, K.; Larsen, R.D.; Gladysz, J.A. *J. Am. Chem. Soc.*, **1986**, 108, 8268.
b) *Idem.*, *J. Chem. Soc. Chem. Commun.* **1988**, 37.

(12) For optically pure (R)-3, $[\alpha]_D^{23}$ = -96.0 degrees.[1]

(13) For examples of applications and discussion of double diastereoselectivity, see:
a) Heathcock, C.H.; White, C.T. *J. Am. Chem. Soc.* 1979, 101, 7076.
b) Masamune, S. in "Organic Synthesis Today and Tomorrow", Trost, B.M. and Hutchinson, C.R., eds., Pergamon Press: New York, **1981**, 197 and references cited therein.

(14) Monodentate phosphine exchange occurs with $t_{1/2}$~1h in boiling benzene. Bidentate phosphine exchange would be much slower.

(Received in USA 16 November 1988)