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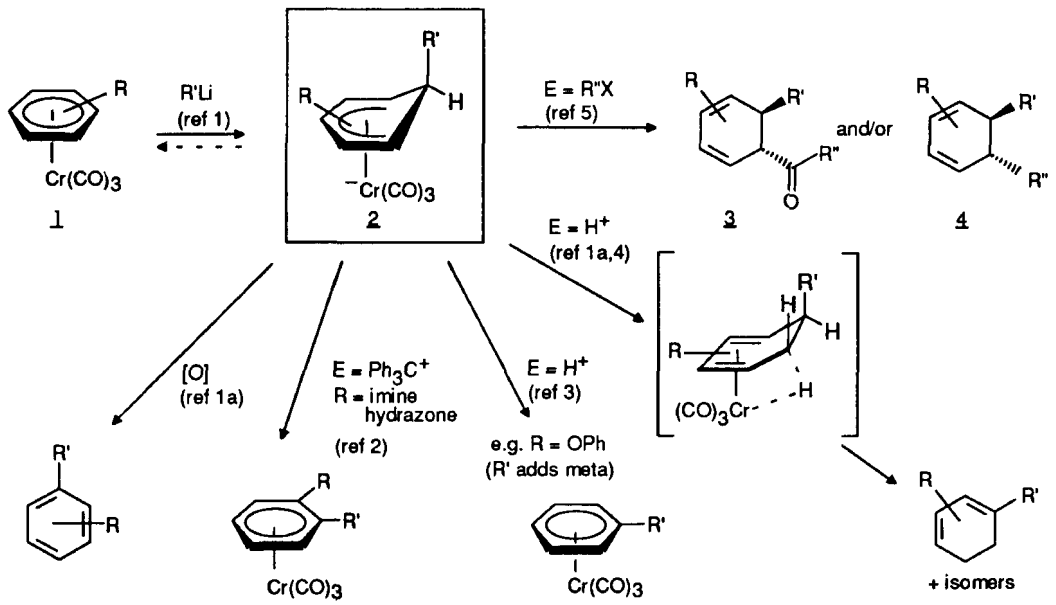
Chiral CO-emulating ligands: From arene chromium chemistry to enantioselective catalysis

E. P. Kündig, A. Quattropani, M. Inage, A. Ripa, C. Dupré, A. F. Cunningham, Jr. and B. Bourdin

Département de Chimie Organique, Université de Genève, 30 quai Ernest Ansermet, CH-1211 Geneva 4, Switzerland

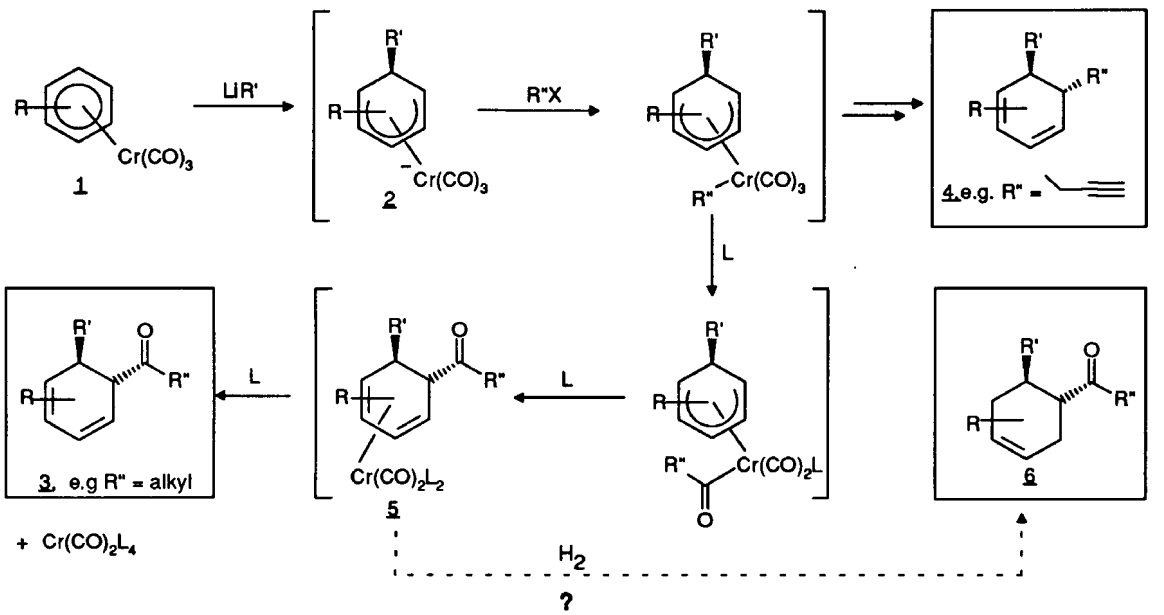
Abstract: A one pot nucleophile/electrophile addition/hydrogenation sequence was applied to [(benzene)$Cr(CO)_3$] to give predominantly the 4,5-trans-disubstituted cyclohexene. Several asymmetric modifications of the sequential addition of C-nucleophiles and C-electrophiles to (arene)$Cr(CO)_3$ complexes are discussed. A mechanistically intriguing route involves the use of chiral phosphorous ligands to control the diastereoselectivity in the migratory CO insertion step and/or the reductive elimination step in the sequence. Ephedrine and norephedrine derived ligands gave product ee of up to 69 %. New C_2-chiral bidentate ligands (L*) which emulate some of the bonding characteristics of CO were synthesized and briefly considered for this application. The main interest in these ligands concerns their potential in catalytic C-C bond forming reactions; a first application to the Lewis acid $[CpFeL^*]^+$ catalyzed Diels-Alder reaction between enals and dienes was successfully realized.

The readily accessible, air stable (arene)$Cr(CO)_3$ complexes 1 react with carbanions by addition to the arene exo-face to afford anionic η^5-cyclohexadienyl complexes 2. *In situ* reaction with the appropriate electrophile gives access to aromatic and alicyclic products as shown in Scheme 1 (1-5).



Scheme 1. Products resulting from the sequential addition of a C-nucleophile and an electrophile to an (arene)$Cr(CO)_3$ complex.

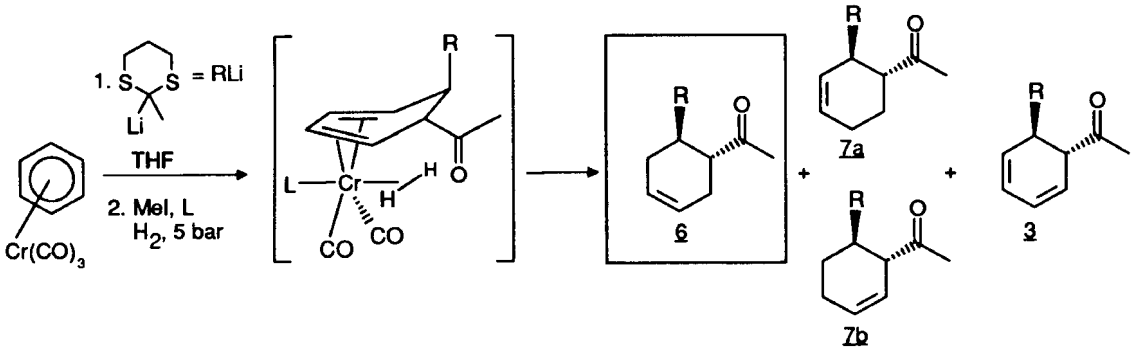
If we turn our attention to the transformation 1 → 3 and 4, we note that two new stereogenic centers are created by the sequential addition of a carbon nucleophile and a carbon electrophile (5). Competitive pathways, leading to either 3 or 4, are shown in Scheme 2. Product distribution depends on the relative rate of migratory CO insertion and of reductive elimination and these in turn depend primarily on the nature of R". With R"X = propargyl bromide, the reaction gives selectively the product without CO insertion (4), whereas with R"X = alkyl iodide, 3 largely predominates (5d). Second in importance is the nature of the arene substituent R. With allyl bromide as electrophile, the benzene complex leads exclusively to 3, but with R = oxazoline or aldimine, 4 is formed with good to excellent selectivity. Before discussing asymmetric routes to enantioenriched 3 and 4, let us focus briefly on an extension of this one pot reaction sequence. (Arene)$Cr(CO)_3$ complexes are precatalysts for the selective hydrogenation of dienes to Z-alkenes (6). A (η^4-diene)$Cr(CO)_3(H_2)$ complex is a likely intermediate in this reaction (7). In view of this, the C-C bond forming sequence in Scheme 2 suggested the possibility of intercepting the putative intermediate 5 with H_2 to give 6 regio- and stereoselectively. Cyclohexene 6 is the formal product of a Diels-Alder reaction between a diene and an E-alkene.



Scheme 2. Proposed mechanism for the formation of products 3 and 4. Possibility of interception of 5 by hydrogen.

This was realized as shown in Scheme 3. Diene hydrogenation requires an intermediate capable of coordination or oxidative addition of H_2. With 5 bar H_2, product selectivity varied with the nature of the coligand L which was added to compensate for the CO consumed in the preceding step. Addition of CO itself led exclusively to the reductive elimination product 3. Hydrogenation was the major or exclusive pathway in its absence. In addition to the expected cyclohexene 6, the isomeric alkenes 7a and 7b were also formed. These unexpected products could be formed *via* a competitive 1,2-hydrogenation of the diene intermediate 5 or *via* a 1,4-hydrogenation preceded by a diene isomerization step (note a). In order to address this question, the reaction was carried out with $(C_6D_6)Cr(CO)_3$. The ^{1}H-NMR of products 7 so obtained showed no signals associated with H-C(4) or H-C(5) (the substituted positions) and this ruled out the diene isomerization /1,4-hydrogenation pathway. Subsequently, L was varied in order to suppress this undesired side-reaction. Satisfactory product selectivity was obtained when L was a nitrile ligand.

Note a: Diene isomerization in the absence of H_2 is catalyzed by [(naphthalene)$Cr(CO)_3$] (6).



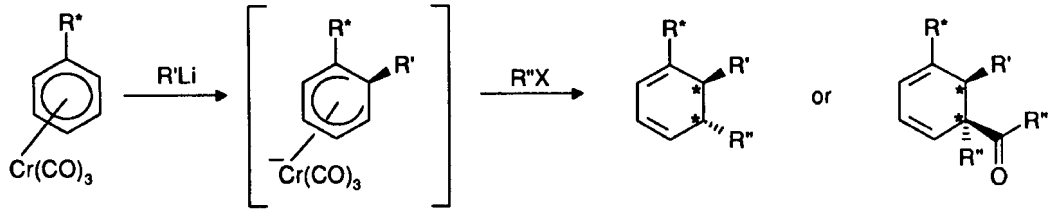
L	Yield	Product distribution		
		6	7a + 7b[a]	3
THF/CO (1 bar)	68	0	0	100
THF	50	74	26	0
THF/HMPA (4 : 1)	68	29	71	0
THF/PhCN (1 equiv.)	58	84	16	0
THF/MeCN (1 : 1)	89	75	9	16

[a]Products 7a and 7b were formed in approximately equal quantities.

Scheme 3. Benzene $Cr(CO)_3$: Nucleophile addition / acylation / hydrogenation

With efficient methods for the regio- and stereoselective transformation of arenes into substituted alicyclic compounds in hand, we focused on asymmetric methodologies. Four different approaches are depicted in Scheme 4.

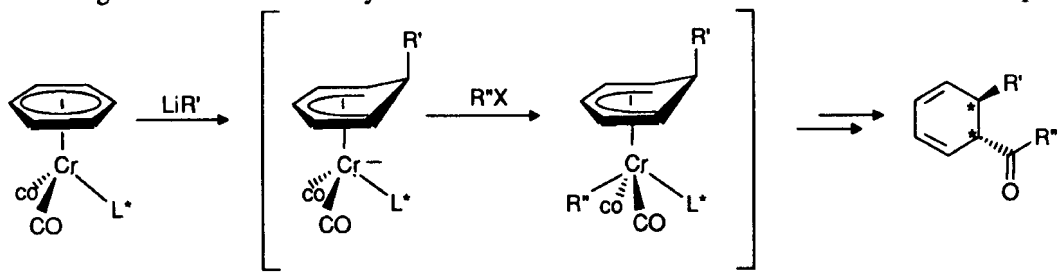
a) Chiral auxiliary on the arene: diastereoselectivity in the nucleophile addition step



b) Chiral nucleophile (e.g. RLi + chiral N or O-ligands): diastereoselectivity in the nucleophile addition step.

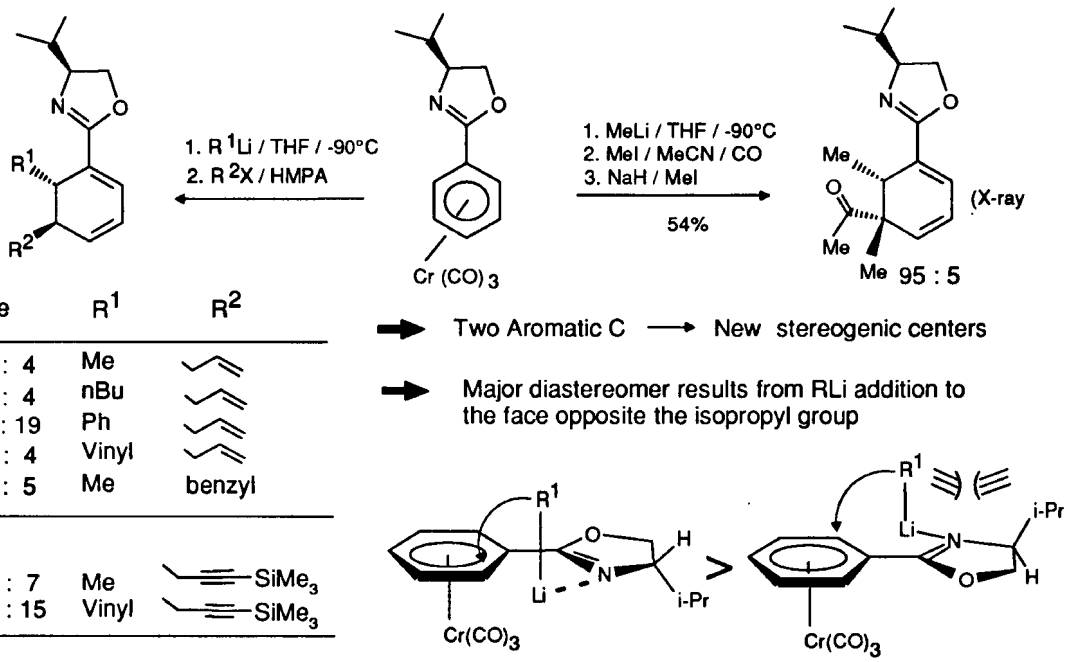
c) Planar chiral starting complex: diastereoselectivity in the nucleophile addition step.

d) Chiral ligand: diastereoselectivity in the CO insertion and/or in the reductive elimination step.



Scheme 4. Nucleophile/electrophile addition: asymmetric approaches

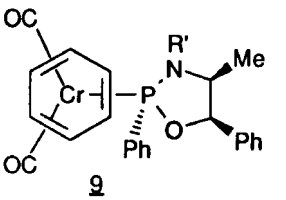
In the first three approaches, asymmetry is generated in the nucleophile addition step. An example of approach a), using as chiral auxiliary an oxazoline derived from L-valinol, is shown in Scheme 5 (8). In several examples diastereoselectivity exceeds 90%. An exception is PhLi which only gave a 4:1 mixture of diastereomers. The observed diastereoselectivity can be ascribed to the bulky i-Pr group which prevents the N-coordinated R^1Li addition. This interpretation is supported by the observation that replacement of the i-Pr group by a t-Bu group substantially increases diastereoselectivity. Single diastereomers were obtained in most cases and even PhLi added to give a product with 90 % de (8).



yield	de	R^1	R^2
61	96 : 4	Me	
54	96 : 4	nBu	
60	81 : 19	Ph	
48	96 : 4	Vinyl	
51	95 : 5	Me	benzyl
77	93 : 7	Me	$SiMe_3$
86	85 : 15	Vinyl	$SiMe_3$

Scheme 5. Diastereoselective nucleophile/electrophile addition to a chiral (phenyl oxazoline)$Cr(CO)_3$ complex.

Approach d) in Scheme 4 differs from the other three in that asymmetry is introduced not in the nucleophile addition step but in either the migratory CO insertion step, or the reductive elimination step, or in both. This approach is primarily of mechanistic interest. To our knowledge, the question of diastereoselectivity in migratory insertion of an R group *trans* to a chiral ligand in a square planar or square pyramidal coordination environment has not yet been investigated. Scheme 6 shows some results and trends in this sequence (9). Enantioselectivities are modest but are best with the ephedrine and nor-ephedrine derived ligands 8. Following nucleophilic addition to the arene in 9 and Cr-alkylation trans to the P-ligand, a stereochemically rigid intermediate is generated in which one carbonyl group is eclipsed with O and the other with NR'. As expected, the data shows that product enantioselectivity is sensitive to the size of R' but at this stage it is not clear if the product ee is entirely due to this difference or if the ensuing reductive elimination step, which is also a diastereoselective process, further modifies the result (10).



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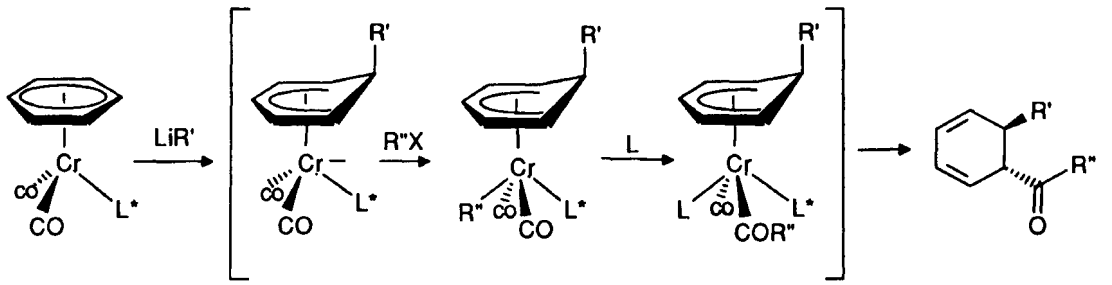
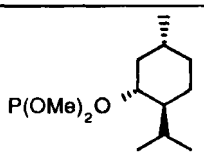
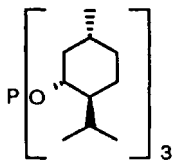
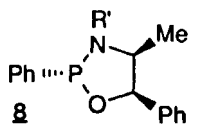
We next considered the use of C_2-chiral bidentate ligands in this sequence. They would have the advantage of avoiding some of the problems discussed above such as the presence of diastereotopic CO ligands. It quickly became clear that for the purpose of synthesis and of arene activation, the bidentate ligands required must mimic CO. Unlike electron rich bidentate chiral phosphorous ligands (11), analogs with elec-

tron poor P-substituents are scarce (12). While of potential use in (arene)Cr(CO)L chemistry, the primary interest of these new chiral ligands lies in their application in enantioselective catalysis and the last topic discussed in this lecture is an example from this area.

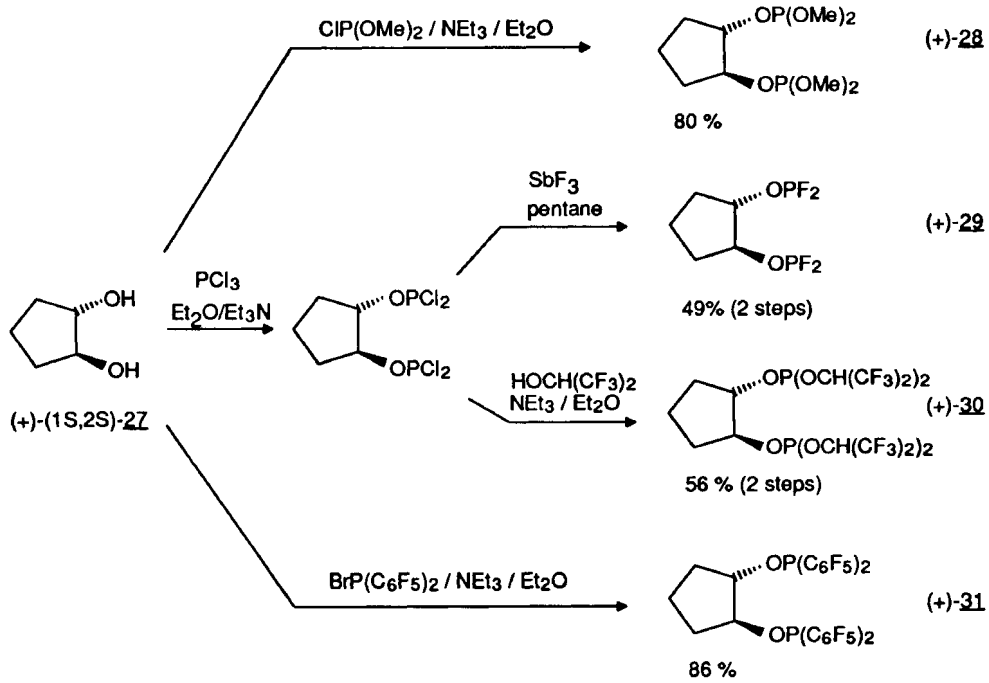


L*		Yield [%]	ee [%]	abs. config.
	R" = Et, L = CO	82	26	RR
	R" = Me L = $P(OPh)_3$	70	31	SS
 8	R" = Me, L = CO	R' = Me	71	41	SS
		Cy	60	56	SS
		i Pr	50	69	SS

Scheme 6. Ligand mediated asymmetric transformation of benzene into a disubstituted cyclohexadiene

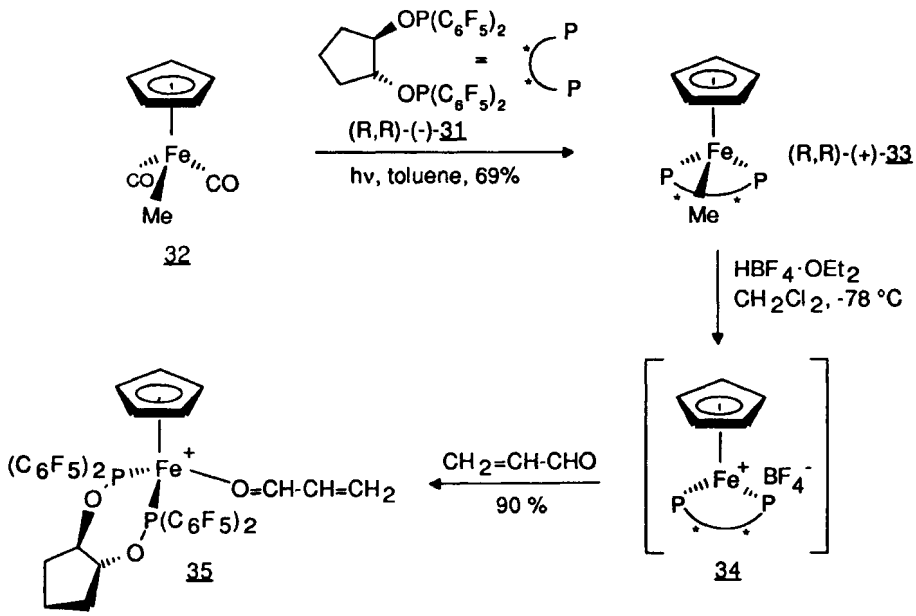
Scheme 7 shows our synthesis of the (S,S)-(+)-enantiomers of ligands 28-31 (13). Highly enantioenriched trans-cyclopentanediol ((+)-27) provided the backbone of the ligands. Both enantiomers of this diol are accessible by either chemical synthesis from diethyltartrate (12a) or by enzymatic enantioselective ester hydrolysis or acetyl transfer (14). IR-Spectral comparison of complexes (benzene)Cr(CO)L incorporating 28-31 showed that electronically these ligands bridge the gap between donor phosphine and acceptor carbonyl ligands (13).

As a first test we chose (R-R)-(-)-31 and the organometallic fragment $[CpFeL]^+$. *Hersh and coworkers* have reported that the complex $[CpFe(CO)_2(THF)][BF_4]$ catalyzes the Diels-Alder reaction between acroleins and cyclopentadiene (15). Rate comparison between the reactions under catalytic and stoichiometric conditions indicated the former to be much faster than expected and this cast some doubt on the role of the iron complex in catalysis. More recently, *Hossain and coworkers* reported that the substitution of one CO ligand by PPh_3 completely suppressed catalytic activity in this reaction (16). Some activity remained, however, with the less electron rich complex $[CpFe(CO)_2\{P(OMe)_3\}(THF)][BF_4]$. These reports set the stage for our investigation which was to answer the three questions: 1. Does the iron center in the weak Lewis acid $CpFe(CO)_2^+$ play a role in Diels-Alder catalysis? 2. Is the ligand 31 an adequate substitute for CO ? and 3. Does the substitution of CO by (R-R)-(-)-31 result in an enantioselective catalyst ? Titanium and copper complexes apart, only three reports of asymmetric transition metal catalysts for the Diels-Alder reaction have appeared (17- 21).



Scheme 7: Synthesis of C_2-chiral π-acceptor ligands

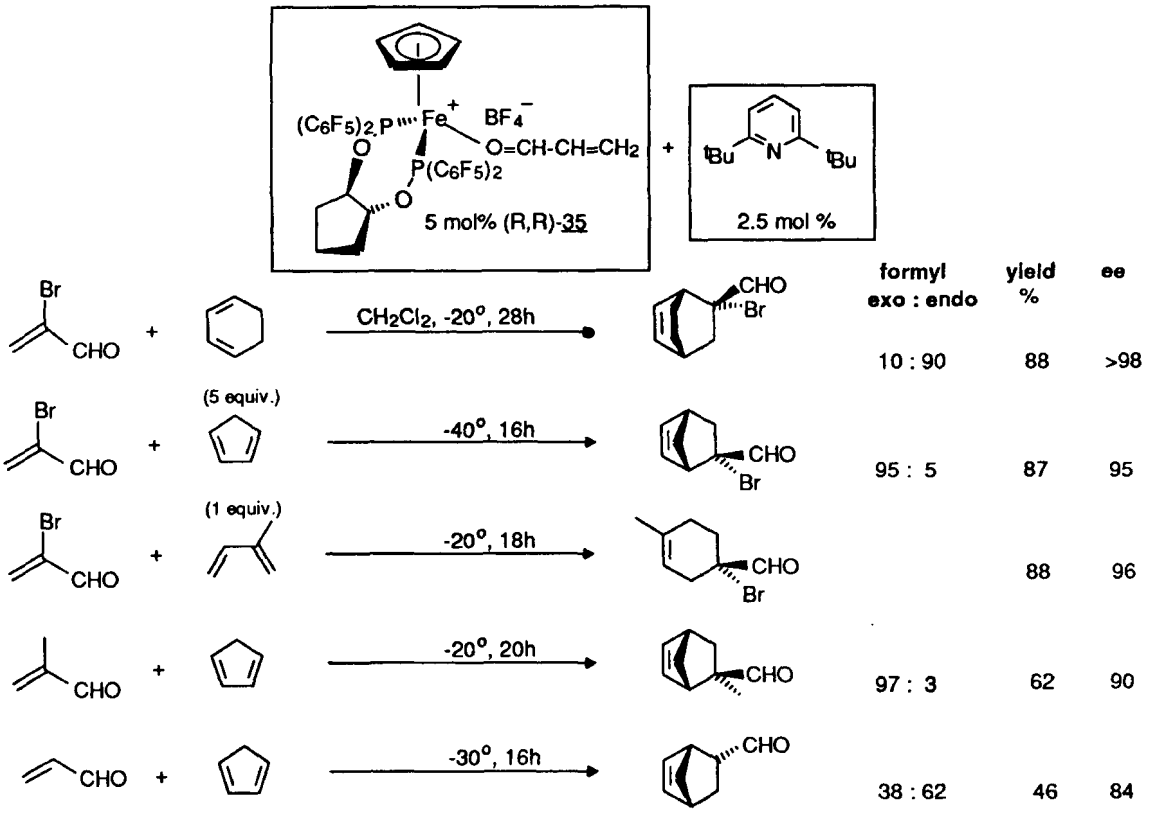
Complex [CpFe(L)Me] (33) was readily prepared by photolytic ligand substitution in the dicarbonyl complex 32 (Scheme 8). Reaction with HBF_4 generated the Lewis acid intermediate 34. On addition of acrolein, complex 35 was isolated in nearly quantitative yield (22).



Scheme 8: Synthesis of the chiral Lewis acid catalyst 34 and its acrolein adduct 35.

In CH_2Cl_2 solution, and in the presence of 2,6-di-tert-butylpyridine to trap residual acid impurities, complex (R,R)-35 catalyzed asymmetric Diels-Alder reactions between dienes and enals (Scheme 9)(22).

Due to the low Lewis acidity of the iron complex and its limited stability in solution (ca. -20 °C), the reaction is confined to reactive enals and dienes. Asymmetric inductions are uniformly high, though, and vie with those obtained with the very efficient boron based catalysts (23). Catalysis with a chiral iron based Lewis acid with chirality in the P(III) ligand is new. Modification and fine tuning of the catalyst will undoubtedly benefit from the structural characterization of the immediate catalyst precursor 33.



Scheme 9. Asymmetric Diels-Alder reactions catalyzed by (R,R)-35

Based on structural data of the acetonitrile adduct of complex 33 , ^{1}H-NMR data for the acrolein complex 35 and the crotonaldehyde complex, and stereochemistry of the cycloaddition product, a transition state model was proposed in which the diene approaches the olefin Cα-si-face of the s-trans-conformer of the coordinated enal (22).

The results on the catalytic Diels-Alder reaction with the Lewis acid 35 confirm the hypothesis that chiral ligands that model the bonding properties of CO are attractive for asymmetric synthesis. We are confident that this concept can be extended to other Lewis acid catalyzed processes as well as other catalytic reactions where π-acceptor ligands are of advantage.

ACKNOWLEDGMENTS

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