Chiral Cooperativity: The Nature of the Diastereoselective and Enantioselective Step in the Gold(I)-Catalyzed Aldol Reaction Utilizing Chiral Ferrocenylamine Ligands

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Mechanistic aspects of the gold(I)-catalyzed aldol reaction of aldehydes with α-isocyanoacetate esters in the presence of a chiral ferrocenylamine ligand possessing both planar and central chirality were investigated. The synthesis of (*S*)-*N*-[2-(*N*,*N*-dimethylamino)ethyl]-*N*-methyl-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine [(*S*)-(*S*)-**4**] is described. Analysis of the ^1H and $^{31}P\{^1H\}$ NMR spectral data of (*S*)-(*S*)-**4** and (*R*)-(*S*)-**4** suggested that their preferred time-averaged conformations in solution are different. Similar observations were made for the *N*,*N*-dimethylamine-substituted precursors, (*S*)-(*S*)-**11** and (*R*)-(*S*)-**11**, of **4**. The ^1H NMR spectral data of the phenylseleno- and phenylthio-substituted analogues, **8a,b**, of (*R*)-(*S*)-**4** suggested that their conformations were different from that of (*R*)-(*S*)-**4** in solution and, furthermore, that the phenyl substituents on the ligand donor groups are important in the stereoselective step of the gold(I)-catalyzed aldol reaction. The preferred conformer of (*R*)-(*S*)-**4** in solution proposed from the ^1H NMR spectral data is similar to that of the X-ray crystal structure of the gold(I) complex of (±)-(*R**)-(*S**)-**4**. The reaction of benzaldehyde (**1a**) with methyl α-isocyanoacetate (**2a**) catalyzed by bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate (**3**) in the presence of the chiral ferrocenylamine ligand (*R*)-(*S*)-**4** gave a mixture of the *trans*- and *cis*-oxazolines **5a** and **6a** in which (4*S*,5*R*)-**5a** was the predominant diastereomer, formed in 91% enantiomeric excess. The use of (*S*)-(*S*)-**4** as a ligand demonstrated that not only does a change in the absolute configuration of the stereogenic carbon atom (a change in central chirality) from *R* to *S* result in both a reduction of the product trans:cis ratio but also *the opposite trans-oxazoline enantiomer is formed in enantiomeric excess.* Furthermore, the ee of the *cis*-oxazoline increased upon changing the absolute configuration of the stereogenic carbon atom from *R* to *S*. These results indicate that the insensitivity of product stereochemistry to the central chirality of the stereogenic carbon atom in the ferrocenylamine side chain previously observed for Grignard cross-coupling reactions cannot be generalized to other reaction types involving chiral ferrocenylamine ligands. *The highest diastereo- and enantioselectivity of the trans-oxazoline 5 is obtained when the central and planar chirality are opposite as defined by the Cahn–Ingold–Prelog sequence rules. This constitutes the first example in a chiral transition-metal ligand containing both central and planar chirality of internal cooperativity of chirality in the control of product diastereo- and enantioselectivity.* Variable-temperature $^{31}P\{^1H\}$ NMR spectra, kinetic isotope, and linear free energy studies suggest that prior coordination of aldehyde is not involved in the stereoselective transition state as previously supposed, but rather the rate-determining step of the gold(I)-catalyzed aldol reaction is attack of the aldehyde upon a gold(I) complex of ferrocenylamine ligand and α-isocyanoacetate ester. A stereoselective transition-state model that correctly predicts the correct enantiomer of the dominant *trans*-oxazoline formed was developed. An electronic effect of the substrate upon product stereoselectivity was demonstrated for certain heteroaldehydes and trifluoromethyl-substituted benzaldehydes.

The development of synthetic methodology that preferentially leads to the formation of a single enantiomer of a targeted chiral compound is today a topic of fundamental importance. It is widely recognized that the manufacture of agricultural and pharmaceutical compounds containing only the correct biologically active enantiomer is desirable because not only is the other enantiomer usually biologically less effective or inactive but it may be antagonistic or, at worst, toxic.[1] Of particular importance are C–C bond-forming reactions whose diastereo- and enantioselectivity are derived through the use of catalytic quantities of chiral transition-metal catalysts.[2-6]

In 1986, Ito and Hayashi reported an elegant synthesis of oxazolines utilizing a gold(I)-catalyzed aldol reaction in the presence of chiral ferrocenylamine ligands that possess both planar and central chirality.[7] For example, the reaction of **1a** with **2a** catalyzed by bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate (**3**)[8] in the presence of the chiral ferrocenylamine ligand (*R*)-(*S*)-**4** gave a mixture of the *trans*- and *cis*-oxazolines **5a** and **6a**, respectively[9] (Scheme I). The trans isomer **5a** illustrated was the dominant isomer, formed in 91% enantiomeric excess (ee).[10] In a series of reports largely from the laboratories of Hayashi and Ito, the usefulness of this reaction and chiral ferrocenylamine ligands in general was demonstrated for the transition-metal-catalyzed asymmetric synthesis of natural products or their precursors. Despite the importance of the enantioselective C–C bond-forming reactions using chiral ferrocenylamines, detailed mechanistic studies directed toward elucidation of both the mechanism

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‡ A preliminary account of part of this work has appeared: Pastor, S. D.; Togni, A. *J. Am. Chem. Soc.* **1989**, *111*, 2333–2334.

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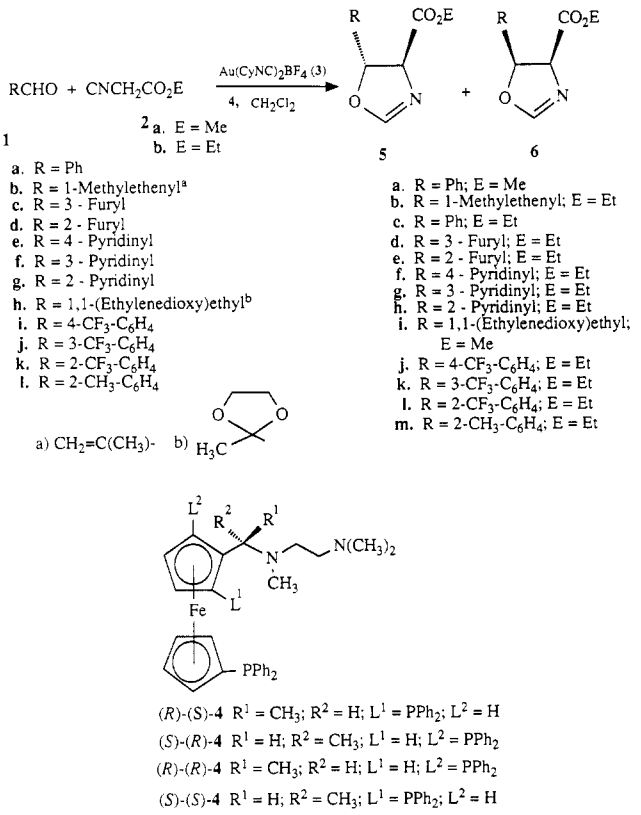
(10) The original ee of 94% was revised in a subsequent paper by Ito et al. to 91%, which is in agreement with our results; see: Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 6215–6218.

0022-3263/90/1955-1649$02.50/0

Scheme I



and transition-state (TS) structure are lacking.

Kumada et al. investigated the effect of the central chirality of the stereogenic carbon atom of **4** upon the product diastereo- and enantioselectivity of transition-metal-catalyzed Grignard cross-coupling reactions. Kumada came to the reasonable conclusion from the experimental data obtained that the planar chirality of **4** plays the dominant role in determining product stereochemistry.[11,12]

Based largely upon the results of the transition-metal-catalyzed Grignard cross-coupling studies of Kumada and co-workers, subsequent studies on the gold(I)-catalyzed aldol reaction and other transition-metal-catalyzed reactions have implicitly presumed that the planar chirality of **4** plays the major role in determining *product* stereochemistry.[13-28] In a recent communication of results from our laboratory, we have shown that this is *not* the case.[29] Contrary to what was previously believed, a change of the absolute configuration of the stereogenic carbon atom central chirality) from *R* to *S* on the side chain of **4** with constant *S* planar chirality results not only in a reduction of both the trans-to-cis product ratio and ee of the trans isomer but also in the formation of the opposite *trans*-oxazoline enantiomer of **5a** in 41% enantiomeric excess. Furthermore, our previous communication[29] provided the first example in a chiral transition-metal ligand containing both planar and central chirality of *internal cooperativity of chirality in the control of product diastereo- and enantioselectivity* similar in concept to the strategy of double stereodifferentiation (external cooperativity of chirality) advocated by Masamune and others.[30]

In their initial and subsequent reports, Hayashi and Ito furnished a working model for the TS of the stereoselective step of the gold(I)-catalyzed aldol reaction.[7,27] The following constitute major conclusions drawn from their hypothetical stereoselective TS model: (1) The gold(I) cation is coordinated to the two phosphorus atoms of **4**, the carbon of the α-isocyanoacetate ester, and the carbonyl oxygen atom of the aldehyde. (2) The enolate anion of the α-isocyanoacetate ester is formed by proton abstraction by the terminal nitrogen atom (the pendant *N,N*-dimethylamino group) of **4**. (3) The reactive π-face of the enolate formed is determined by electrostatic bonding (or possibly hydrogen bonding) of the enolate to the protonated terminal nitrogen atom. It should be noted that gold(I) generally favors linear coordination,[31,32] and the coordination of gold(I) suggested by Hayashi and Ito is quite unusual. Our reported X-ray crystal structure of racemic **4** with Au(I) suggested that a refinement of the proposed TS structure is needed.[33]

In this paper we report full details of our investigations on the observed cooperativity of central and planar chirality in **4** along with further mechanistic studies directed toward developing a model of the stereoselective transition state (TS) that correctly predicts the absolute configuration of the major enantiomer formed.

Results and Discussion

Synthesis of Model Compounds. Elucidation of the nature of the steric and electronic interactions that take place in the stereoselective step of the gold(I)-catalyzed aldol reaction required the preparation of model ferroce-

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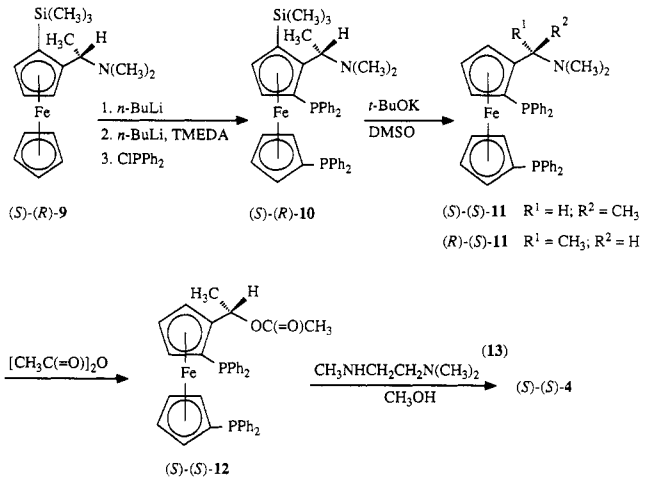
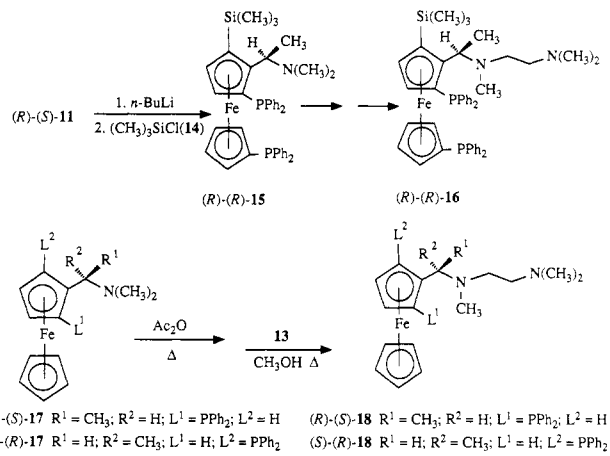
Scheme II

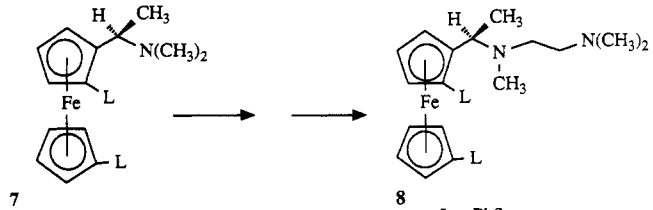


Scheme III



nylamine ligands in which certain structural features were modified. Specifically, a change from the diphenylphosphino donor substituents to group-15 donor atoms, the synthesis of ferrocenylamine ligands with the central and planar chirality having the same absolute configuration as defined by the Cahn–Ingold–Prelog sequence rules, and the introduction of additional steric restraints into the ferrocenylamine ligand were required.

Ample research efforts have been reported that were directed toward the synthesis of ferrocenylamines with sulfur, selenium, and tellurium donor atoms.[34] Quite recently, Brubaker and co-workers have described the synthesis of chiral ferrocenylamines containing a single thio or seleno donor substituent, which were effective catalysts for Grignard cross-coupling and hydrogenation reactions.[35] The synthesis of the required chiral ferrocenylamines (*R*)-(*S*)-**8a,b**, which are the sulfur and selenium analogues of (*R*)-(*S*)-**4**, were prepared from **7a,b** as described previously in a report from our laboratory.[36]



7
a. L = PhSe-
b. L = PhS-

8
a. L = PhSe-
b. L = PhS-

The elucidation of the role of central chirality in the stereoselective step of the gold(I)-catalyzed aldol reaction required the synthesis of (*S*)-(*S*)-**4**. The details of the synthesis of (*S*)-(*S*)-**4** are as follows, which represents a significant improvement in the procedure to a key intermediate previously described by Kumada et al.[37] The silylated ferrocenylamine (*S*)-(*R*)-**9** was prepared by the method described by Ugi et al. for the corresponding enantiomer.[38] Kumada reported that the diphosphinated derivative of the corresponding *R*-*S* enantiomer of **9** could be prepared in very low yield by using a two-step procedure.[37] We anticipated that (*S*)-(*R*)-**10** could be prepared in a single step from dilithiated (*S*)-(*R*)-**9**.[39] Indeed, sequential lithiation of (*S*)-(*R*)-**9** with *n*-butyllithium (*n*-BuLi) followed by a *n*-BuLi/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) mixture and the reaction of the resultant dilithiated species with 2 equiv of chlorodiphenylphosphine gave a mixture of the desired (*S*)-(*R*)-**10** (75%) and the corresponding monophosphinated compound (25%) (Scheme II). This reaction was not optimized, and further improvement in the yield of the diphosphinated product can be expected. The resultant mixture of (*S*)-(*R*)-**10** and monophosphinated compound was not purified, but rather converted directly to (*S*)-(*S*)-**11** by removal of the trimethylsilyl group with potassium *tert*-butoxide in DMSO. The key intermediate (*S*)-(*S*)-**11** was obtained in an overall yield of 25% from (*S*)-(*R*)-**9** as yellow crystalline needles with $[\alpha]^{22}_{D}$ −429.5 (c = 0.559, $CHCl_3$), which is a considerable improvement to the literature procedure (4% overall yield). Furthermore, both the physical form (oil) and the optical rotation reported for the enantiomeric (*R*)-(*R*)-**11** suggest that the compound reported in the literature was in a lower state of purity.[37]

The (*S*)-(*S*)-**11** was converted to (*S*)-(*S*)-**4** in a conventional manner. The reaction of (*S*)-(*S*)-**11** with acetic anhydride gives the corresponding acetate (*S*)-(*S*)-**12** with retention of conformation at carbon.[37,38,40] The desired (*S*)-(*S*)-**4** was prepared by the reaction of (*S*)-(*S*)-**12** with *N*,*N*,*N*′-trimethylethylenediamine (**13**) in methyl alcohol at reflux temperature.[37]

Silylated derivatives such as **16** were anticipated to provide interesting model ligands in which the additional sterically bulky trimethylsilyl substituent would perturb the geometry of the stereoselective step. The lithiation of (*R*)-(*S*)-**11** with 2 equiv of *n*-BuLi followed by reaction with trimethylsilyl chloride (**14**) gave a mixture of the desired silylated product (*R*)-(*R*)-**15** (73%) and at least two isomeric disilylated products (27%) (Scheme III). The ratio of mono- to disilylation was determined by integration of the peak areas for the appropriate resonances in

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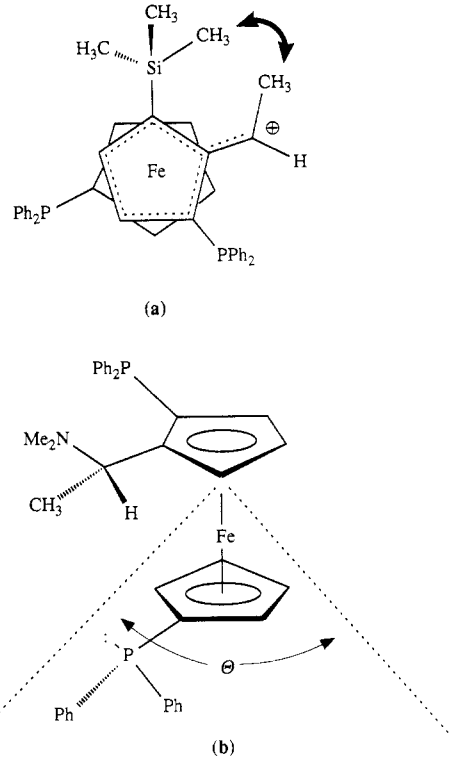

Figure 1.

the ^{1}H NMR spectrum of the mixture. The strong molecular ions observed at 697 (monosilylated) and 769 (disilylated) mass units were consistent with this interpretation. No evidence was observed in the mass spectrum of the mixture for trisilylated products. The elemental analysis of the mixture was consistent with the 73:27 product ratio found by integration of the ^{1}H NMR peak areas.

Much to our surprise, no acetate formation was observed under the standard reaction conditions upon heating (*R*)-(*R*)-**15** with acetic anhydride. Although we did not pursue this reaction further, a reasonable explanation of the failure of (*R*)-(*R*)-**15** to react with acetic anhydride under standard reaction conditions is provided by the reaction mechanism proposed by Ugi et al. to explain the observed retention of configuration at carbon during the substitution of the *N*,*N*-dimethylamino group.[38] The electrophile-assisted loss of the nucleofugal dimethylamino group in (*R*)-(*R*)-**15** with incipient carbenium ion or ion-pair formation requires a change of hybridization at carbon from sp^3 to sp^2. The examination of a Dreiding model suggests that this process will result in a severe steric interaction of the methyl group bound to the carbon undergoing rehybridization with the nearby trimethylsilyl group (Figure 1a). Watts reported a similar destabilization of an α-ferrocenyl-substituted carbenium ion by a sterically less demanding methyl group.[41] The diphenylphosphine substituents normally do not interfere with this process because the phenyl groups and the C_{Cp}–P bond can rotate to avoid this interaction. This is not the case with the trimethyl-substituted silyl moiety.

It is worthwhile noting at this point that retention of configuration is observed during substitution of the dimethylamino group by acetate in **11**. Although backside assistance to the leaving group by interannular electron participation has been reported,[42] a significant steric obstruction to backside attack (the inversion process) by the nucleophile is similarly expected.[43] The iron atom and the lower substituted cyclopentadienyl ring[44] (the cyclopentadienyl group *without* the chiral aminoalkyl side chain) are expected to exert a significant steric effect to direct nucleophilic attack away from the rear side of the carbon atom. The iron atom and the lower substituted cyclopentadienyl ring together can be modeled as a single sterically bulky substituent. If it is assumed that there is free rotation of the lower substituted cyclopentadienyl ring, a considerable area will be swept out by the diphenylphosphino substituents. Representing the effective area of the lower cyclopentadienyl group as in Figure 1b, a cone angle Θ can be defined as illustrated that is similar to that defined by Tolman for phosphorus ligands.[45] It can be appreciated that if the lower phenyl groups bonded to phosphorus rotate in such a manner that they point away from the iron atom [the lone pair of electrons properly oriented to coordinate to the gold(I) cation in the enantioselective TS proposed by Ito and Hayashi], the defined cone angle is expected to be large. This large steric effect has not been implicitly recognized in the TS models proposed for the stereoselective step of the gold(I)-catalyzed aldol reaction using chiral ferrocenyl ligands, although the steric bulk of the ferrocenyl group has been noted by Cullen in catalytic hydrogenation reactions.[46]

Steric effects imposed by a metal and its ligands are often of paramount importance in arguments for a particular stereoselective TS model proposed for an asymmetric synthesis.[47] For example, a shielding effect was observed on one face of the *o*-methoxyacetophenone complexed to chromium tricarbonyl in reactions with Grignard reagents.[48]

To further test the contention that the lower diphenylphosphino substituent can play an important role both sterically and as a donor atom required the synthesis of a model compound without the presence of the diphenylphosphino group on the lower cyclopentadienyl ring.

Table I. Product Stereoselectivity in the Gold(I)-Catalyzed Aldol Reaction of 1a with 2a as a Function of Ferrocenylamine Donor Atom

entry[a]	ligand	ligand:3 molar ratio	% yield	% *trans*-**5a** (ee)	% *cis*-**6a** (ee)
1	(*R*)-(*S*)-**4**	1.1:1	99	90 (91)	10 (7)
2	(*R*)-(*S*)-**8a**	1.1:1	63	69 (0)	31 (0)
3	(*R*)-(*S*)-**8b**	1.1:1	74	72 (0)	28 (0)
4	(*R*)-(*S*)-**8b**	2.2:1	82	72 (0)	28 (0)
5	Ph_3P/TMEDA	*b*	80	67 (0)	33 (0)

[a] Dichloromethane solvent; 20 h at room temperature. [b] Ph_3P:TMEDA:3 molar ratio, 2:1:1.

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(42) For a discussion on the stability, structure, and possible modes of charge delocalization in ferrocenyl-substituted carbenium ions, see: (a) Watts, W. E. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; pp 1052–1055 and references therein. (b) Vogel, P. *Carbocation Chemistry*; Elsevier: Amsterdam, 1985; pp 430–437 and references therein.

(43) Reference 42a, p 1059.

(44) Throughout this paper, the cyclopentadienyl group *without* the chiral aminoalkyl side chain will be referred to as the lower cyclopentadienyl group.

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(47) For a discussion, see: Davis, S. G. *Organotransition Metal Chemistry: Applications to Organic Synthesis*; Pergamon: Oxford, 1982; pp 10–12.

(48) (a) Besancon, J.; Tirouflet, J.; Card, A.; Dusausoy, Y. *J. Organomet. Chem.* **1973**, *59*, 267. (b) For a discussion, see: Hegedus, L. S. In *Comprehensive Carbanion Chemistry, Vol. 5b*; Buncel, E.; Durst, T., Ed.; Elsevier: Amsterdam, 1984; pp 55–56.

Table II. Selected Nuclear Magnetic Resonance Spectral Data

entry[a]	ligand	^{1}H NMR: δ					^{31}P{^{1}H}-NMR: δ
		CpCH(C*H*$_3$)N	CH$_3$N	(CH$_3$)$_2$N	NCH$_2$CH$_2$N	CpC*H*(CH$_3$)N	
1	(*R*)-(*S*)-**4**	1.15	1.69	2.03	1.69 (2 H), 2.24 (1 H), 2.40 (1 H)	4.14	−23.5, −17.0
2	(*S*)-(*S*)-**4**	1.23	2.10	2.07	2.19 (2 H), 2.30 (1 H)	3.64	−21.5, −17.0
3[b]	(*R*)-(*S*)-**8a**	1.39	1.95	2.02	1.94 (2 H), 2.34 (2 H)	4.04	
4[b]	(*R*)-(*S*)-**8b**	1.33	2.17	2.19	1.87 (2 H), 2.33 (2 H)	4.05	
5	(*R*)-(*S*)-**11**	1.12		1.73		4.09	−23.0, −16.9
6	(*S*)-(*S*)-**11**	1.32		2.05		3.47	−20.8, −16.9
7	(*R*)-(*R*)-**15**	1.67		1.87		3.32	
8	(*R*)-(*S*)-**17**	1.25		1.76		4.15	−22.4
9	(*S*)-(*R*)-**18**	1.27	1.72	2.18	1.64 (2 H), 2.27 (1 H), 2.43 (1 H)	4.25	−23.0
10[c]	(*R*)-(*S*)-**19**	1.22		2.04		3.84	
11[c]	(*R*)-(*S*)-**19**	1.18		2.33		3.33	

[a] ^{1}H and ^{31}P NMR spectra obtained in CDCl$_3$. [b] Reported in ref 36. [c] Reported in ref 38.

The required derivative (*R*)-(*S*)-**18** was prepared by the reaction of (*R*)-(*S*)-**17**[37] with acetic anhydride followed by reaction of the obtained acetate with **13** in methyl alcohol at reflux (85% column chromatographed). The enantiomer (*S*)-(*R*)-**18** ferrocenylamine ligand was prepared in an identical manner starting from (*S*)-(*R*)-**17**.

Conformation in Solution: NMR Spectral Studies. Examples in the literature for the use of NMR spectroscopy to study the conformation of a particular compound in solution are legion. The conformational analysis of selected chiral ferrocenylamines was expected to provide valuable information regarding the possible structure of the TS for the stereoselective step of the gold(I)-catalyzed aldol reaction.

In our initial work, we investigated the effect of the substitution of the phosphorus donor atoms in **4** by sulfur and selenium upon product stereoselectivity in the gold(I)-catalyzed aldol reaction.[36] The known ability of both sulfur and selenium to function as ligands in complexes of gold(I)[49,50] suggested that **8a,b** would be effective ligands for a stereoselective aldol reaction. The aldol reaction of **1a** with **2a** was investigated by using the in situ formed catalyst from **3** and **8a,b** (Table I). Interestingly, no asymmetric induction was observed. Furthermore, the cis:trans product ratios obtained were only slightly better than that obtained in the control reaction (Table I, entry 5), in which a 2:1 ratio of triphenylphosphine/TMEDA was used with **3** as a catalyst.

Far more revealing, however, is the comparison of the ^{1}H NMR spectral data of the ligands **8a,b** with that of (*R*)-(*S*)-**4** (Table II). In the ^{1}H NMR spectrum of **8a** and **8b**, singlet resonances were observed at δ 1.95 and 2.17, respectively, which were assigned to the protons of the *N*-methyl group bonded to the stereogenic carbon atom. The chemical shift observed is in the region expected for the protons of a methyl group bonded to nitrogen. The analogous methyl group protons of (*R*)-(*S*)-**4** are significantly upfield (δ 1.15). Strikingly, the corresponding methyl group protons of (*S*)-(*S*)-**4**, which gives the opposite trans enantiomer of **5** in ee in the gold(I)-catalyzed aldol reaction, resonates downfield (δ 1.23). Similar differences were observed for the methine proton of the stereogenic carbon atom of (*R*)-(*S*)-**4** (δ 4.14) and (*S*)-(*S*)-**4** (δ 3.64). Although in both **4** and **8a,b** the observed resonances for the protons of the pendant dimethylamino substituents are in the region expected, the methylene protons of (*R*)-(*S*)-**4** displayed a significantly greater degree of nonequivalence than the methylene protons of either (*S*)-(*S*)-**4** or **8a,b**.

Differences in the environment of the phosphorus atom were similarly observed in the ^{31}P{^{1}H} NMR spectrum of (*R*)-(*S*)-**4** and (*S*)-(*S*)-**4**. The differences observed (entries 1–4) suggest that both the phenyl groups bonded to phosphorus and the absolute stereochemistry at the stereogenic carbon atom (central chirality) can strongly affect the local environment where asymmetric induction occurs when these ligands are employed in catalysis.

The observed differences in the spectral characteristics can be reasonably explained if the preferred alkyl side chain conformations of **4** and **8a,b** are different. Similar trends in the simple *N,N*-dimethylamino-substituted ferrocenes **11** (entries 5 and 6) are apparent and suggest as a first approximation that the dimethylamino and the *N*-[2-(dimethylamino)ethyl]-*N*-methylamino groups can be considered sterically comparable. This reasoning is based upon the fact that in alkanes a longer alkane chain can rotate to minimize steric interactions, which accounts for the similar conformational energies of methyl ($-\Delta G°$ = 1.70 kcal/mol) and ethyl ($-\Delta G°$ = 1.75 kcal/mol) groups in substituted cyclohexanes.[51] This approximation cannot be extended to the TS model of the stereoselective step of the gold(I)-catalyzed aldol reaction where the conformation of the pendant (dimethylamino)ethyl group must also be considered. What is important to recognize is that *the preferred time-averaged conformation of* (*R*)-(*S*)-**4** *and* (*S*)-(*S*)-**4** (or the corresponding diastereomers of **11**) *are different.*

Understanding the steric interactions that lead to different preferred conformations of **4** requires an understanding of the steric requirements of the substituents present. The assignment of a large steric role to the lower diphenylphosphino-substituted cyclopentadienyl ring was discussed previously. A similar model has recently been applied by Collins et al. to the steric effect caused by substitution of a cyclopentadienyl ring bonded to titanium.[52] The diphenylphosphino group on the substituted cyclopentadienyl ring would be expected to rotate about the P–C$_{Cp}$ bond in such a manner that the phenyl groups point away from the lower cyclopentadiene ring. Interestingly, this places the lone pair of electrons on phosphorus in the proper orientation for metal in the TS model proposed by Ito and Hayashi.

The assignment of relative sizes of the alkylamino and methyl substituents is not as straightforward because the lone pair of electrons on nitrogen can be rotated to minimize the steric interactions of the dialkyl groups. Studies on the protonation of amino-substituted cyclohexanes suggest that the size of the lone pair of electrons on ni-

(49) For a review on gold(I) coordination chemistry, see: Puddephatt, R. J. In *Comprehensive Coordination Chemistry, Vol. 5*; Wilkinson, G., Ed.; Pergamon: Oxford, 1987; pp 861–923.
(50) Roulet, R.; Favez, R. *Chimia* **1975**, *29*, 346–348.
(51) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199–222.
(52) Collins, S.; Dean, W. P.; Ward, D. G. *Organometallics* **1988**, *7*, 2289–2293.

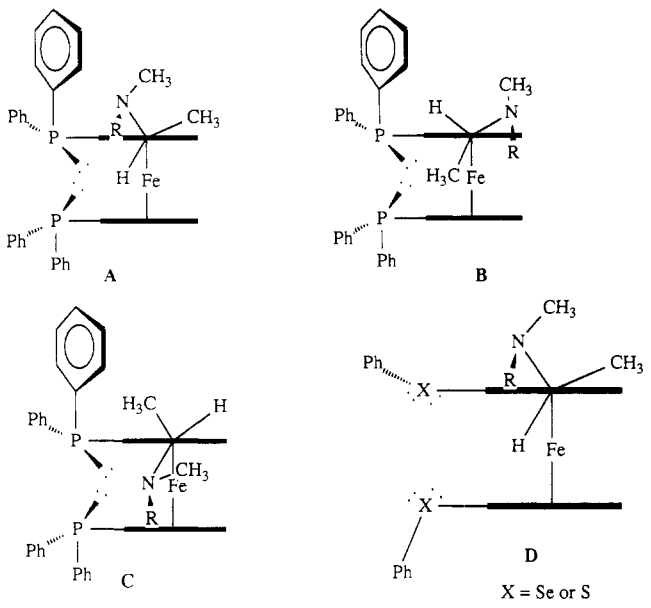


Figure 2.

trogen is somewhat less than that of hydrogen.[53] The conformational energy of a dimethylamino group ($\Delta G°_{293}$ = 2.1 kcal/mol; 80% methyl alcohol) is more than that of a methyl group (ΔG = 1.70 kcal/mol) and similar to that of a 2-propyl substituent (2.15 kcal/mol).[54,55]

Given these assumptions, a significant time-averaged population of conformer A in Figure 2 explains the observed ^{1}H NMR spectrum of (*R*)-(*S*)-**11** [or (*R*)-(*S*)-**4**]. In conformer A, the torsional angle defined by CH_3–C–C-$(1)_{Cp}$–$C(5)_{Cp}$ is approximately 10–20° to minimize the steric interactions of both the alkyl substituents on nitrogen with the phenyl substituents on phosphorus and the methyl group bonded to the stereogenic carbon atom with the adjacent hydrogen atom on the cyclopentadienyl ring. This suggested torsional angle, which is based upon steric considerations in a Dreiding model, is only approximate and could in reality be greater. Slight angle deformations of the bond angles about the stereogenic carbon atom to avoid these interactions are not energetically costly.[56] Quite recently, Togni et al. reported an X-ray crystal structure of a gold(I) complex of (±)-(*R**)-(*S**)-**4**.[33] Although caution must be exercised in extrapolating the conformational results found in the solid state to those in solution due to crystal-packing effects, the Cp–C rotamers found in the solid state corresponded to that illustrated in conformer A. An angle of 10° was found for the torsion angle defined by CH_3–C–$C(1)_{Cp}$–$C(5)_{Cp}$ in this X-ray crystal structure as compared to the 10–20° that was suggested by a consideration of Dreiding models and the accompanying NMR spectral data.

The phenyl ring bonded to phosphorus illustrated in conformation A is rotated in such a manner that the shielding π-face is directed toward the dialkylamino group. This explains the observed shielding of the methyl and methylene group protons bonded to nitrogen. Furthermore, the large observed nonequivalence of the methylene protons is explained. This model is strongly supported by the solid-state crystal structure of (*S*)-(*R*)-**17** reported by Einstein and Willis.[57,58]

The region lying in between the two cyclopentadienyl rings has been established to be strongly deshielding,[59,60] pertinent examples of which were reported by Rosenblum and Abbate.[61] In conformer A, the downfield resonance expected for the methine proton is in fact observed. A similar conformation in an α-(dimethylamino)ethyl-substituted η-arene chromium complex was established by NOE studies reported by Heppert and Aubé.[62] Quite interesting is the observation derived from a consideration of molecular models that when both diphenylphosphino substituents are in an eclipsed conformation (illustrated for conformer A), the lone-pair electrons are oriented properly for near linear coordination to a gold(I) cation as suggested in the Ito–Hayashi model.

A change in the absolute configuration at the stereogenic carbon atom is clearly expected to modify the conformational preferences of the molecule. This is reflected particularly in the change in chemical shifts of the methine and dimethylamino group protons of (*S*)-(*S*)-**11** and (*S*)-(*S*)-**4**. Although this simple proposed steric model ignores other conformational influences, for example, dipole–dipole repulsion, that must also play an important role in these highly functionalized ligands, this simple conformational model, nevertheless, provides a rational starting point for understanding the stereoselectivity of the gold(I)-catalyzed aldol reaction.

The examination of Table II entries 3 and 4 reveals the role of the phenyl group on the phosphorus atom in shielding the methyl and methylene protons in (*R*)-(*S*)-**4** which is absent in (*R*)-(*S*)-**8a,b**. That the downfield shifts observed in (*R*)-(*S*)-**8a,b** are not simply due to the inductive effects of either the selenium or sulfur atom, respectively, is shown by the similar chemical shifts observed in (*R*)-**20**. Simple steric considerations suggest that the single phenyl group on the selenium or sulfur substituent of (*R*)-(*S*)-**8a,b** can rotate away from the chiral side chain and does not contribute to the steric environment (Figure 2, conformer D). This model provides a ready explanation for the low product stereoselectivity observed in the gold(I)-catalyzed aldol reaction employing **8a,b** as ligands. It should be noted that the successful use of thio- and seleno-substituted ferrocenylamine ligands by Brubaker and co-workers[35] requires the use of transition metals that coordinate to both the phosphorus and nitrogen atoms, which is not the case for gold(I).

Several avenues exist for evaluating the usefulness of this steric model. Placing a large substituent in the unsubstituted position on the cyclopentadiene ring adjacent to the chiral side chain of (*R*)-(*S*)-**4** would be expected to perturb the favored geometry illustrated in conformer A.

(53) Nõgrâdi, M. *Stereochemistry: Basic Concepts & Applications*; Pergamon: Oxford, 1981; p 107.
(54) Sicher, J.; Jonáš, J.; Tichy, M. *Tetrahedron Lett.* **1963**, 825–830.
(55) Eliel, E. L.; Della, E. W.; Williams, T. H. *Tetrahedron Lett.* **1963**, 831–835.
(56) (a) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 252–253. (b) Kagan, H. *Organic Stereochemistry*; Edward Arnold: London, 1979; p 26. (c) Riddell, F. G. *The Conformational Analysis of Heterocyclic Compounds*; Academic Press: London, 1980; pp 12–13.
(57) Einstein, F. W. B.; Willis, A. C. *Acta Crystallogr.* **1980**, *B36*, 39–43.
(58) For other X-ray crystal structures supportive of this interpretation, see: (a) Battelle, L. F.; Bau, R.; Gokel, G. W.; Oyakawa, R. T.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 138–140. (b) Lou, Y. G.; Barton, R. J.; Robertson, B. E. *Can. J. Chem.* **1987**, *65*, 2756–2759.
(59) (a) Mulay, L. N.; Attalla, A. *J. Chem. Phys.* **1966**, *88*, 760. (b) Barr, T. H.; Lentzner, H. L.; Watts, W. E. *Tetrahedron* **1969**, *25*, 6001–6013. (c) Turbitt, T. D.; Watts, W. E. *Tetrahedron* **1972**, *28*, 1227–1235.
(60) In contrast, an alkyl group bonded directly to iron is strongly shielded; see: Piper, T. S.; Wilkinson, G. *J. Inorg. Nucl. Chem.* **1956**, *3*, 104–124.
(61) Rosenblum, M.; Abbate, F. W. *J. Am. Chem. Soc.* **1966**, *88*, 4178–4184.
(62) (a) Heppert, J. A.; Thomas-Miller, M. E.; Milligan, M. L.; Vander Velder, D.; Aubé, J. *Organometallics* **1988**, *7*, 2581–2584. (b) See also: Erker, G.; Nolte, R.; Tsay, Y.-H.; Krüger, C. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 628–629.

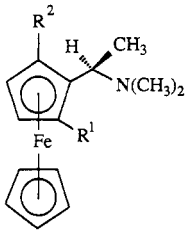
Table III. Product Stereoselectivity in the Gold(I)-Catalyzed Aldol Reaction

entry	ligand	aldehyde	ester	% yield[a]	reactn time, h	% trans (ee) 5	% cis (ee) 6
1[f]	(*R*)-(*S*)-4	1a	2a	99	18[b,d]	90 (91 [4*S*,5*R*]) 5a	10 (7 [4*S*,5*S*]) 6a
2[f]	(*S*)-(*R*)-4	1a	2a	72	18[b,d]	90 (90 [4*R*,5*S*]) 5a	10 (12 [4*R*,5*R*]) 6a
3[f]	(*S*)-(*S*)-4	1a	2a	90	18[b,d]	84 (41 [4*R*,5*S*]) 5a	16 (20 [4*S*,5*S*]) 6a
4	(*S*)-(*R*)-18	1a	2a	85	5[c,e]	74 (21 [4*R*,5*S*]) 5a	26 (4 [4*R*,5*R*)] 6a
5	(*R*)-(*S*)-4	1b	2b	69	20[c,e]	91 (78) 5b	9 (9) 6b
6	(*R*)-(*S*)-18	1b	2b	34	20[c,e]	77 (16) 5b	23 (1) 6b
7[g]	(*R*)-(*S*)-4	1a	2b	88	24[b,d]	89 (93) 5c	11 (18) 6c
8	(*R*)-(*S*)-4	1c	2b	80	18[c,e]	86 (87) 5d	14 (7) 6d
9	(*R*)-(*S*)-4	1d	2b	62	2.5[c,e]	68 (32) 5e	32 (83) 6e
10	(*R*)-(*S*)-4	1e	2b	38	4[c,e]	88 (75) 5f	12 (78) 6f
11	(*R*)-(*S*)-4	1f	2b	55	4[c,e]	88 (79) 5g	12 (62) 6g
12	(*R*)-(*S*)-4	1g	2b	45	4[c,e]	75 (6) 5h	25 (84) 6h
13	*h*	1g	2b	44	4[c,e]	78 (0) 5h	22 (0) 6h
14	*i*	1g	2b	95	8[b,d]	74 (0) 5h	26 (0) 6h
15	*j*	1g	2b	98	1[d,k]	94 (0) 5h	6 (0) 6h
16	(*S*)-(*R*)-4	1h	2a	28	28[b,e]	95 (51) 5i	5 (59) 6i
17	(*S*)-(*R*)-4	1i	2b	89	20[b]	85 (85) 5j	15 (57) 6j
18	(*S*)-(*R*)-4	1j	2b	92	18[b]	81 (84) 5k	19 (62) 6k
19	(*S*)-(*R*)-4	1k	2b	94	18[b,l]	84 (88) 5l	16 (86) 6l
20	(*S*)-(*R*)-4	1l	2b	72	18[b]	93 (92) 5m	7 (21) 6m

[a] Isolated Distilled yields. [b] Dichloromethane. [c] 1,2-Dichloroethane. [d] Room temperature. [e] Temperature, 50 °C. [f] Reference 29. [g] Reference 69. [h] Et_3N/DIPHOS. [i] TMEDA/PPh_3. [j] Procedure of Schöllkopf.[77] [k] Exothermic Reaction. [l] Determined by ^1H NMR with a chiral shift reagent.

Indeed, the introduction of a trimethylsilyl substituent leads to a significant change in the ^1H NMR spectrum of (*R*)-(*R*)-**15** and its chemistry (vide ante).

A more interesting example is provided by removing the lower diphenylphosphino substituent that is postulated to both provide an increase in steric bulk to the lower cyclopentadienyl ring and coordinate to the gold(I) atom. Indeed, the observed changes in chemical shifts in the ^1H NMR spectrum of (*S*)-(*R*)-**18** meet this expectation. Further support of this model is provided by a consideration of the ^1H NMR spectra reported by Ugi et al. of the silyl derivatives (*R*)-(*S*)-**19** and (*R*)-(*R*)-**19** (compare Table II, entries 9 and 10 with 5 and 6). The monodiphenyl-



(*R*)-(*S*)-**19** $R^1 = Me_3Si$-; $R^2 = H$
(*R*)-(*R*)-**19** $R^1 = H$; $R^2 = Me_3Si$-

phosphino ligands (*R*)-(*S*)-**18** and (*S*)-(*R*)-**18** are expected to be poor ligands in regard to product stereoselectivity in the gold(I)-catalyzed aldol reaction due to both their reduced steric requirements and monodentate character. This was observed to be the case (Table III, entries 4 and 6).

Role of Central Chirality. The conformational differences observed in solution for (*R*)-(*S*)-**4** and (*S*)-(*S*)-**4** strongly suggested that the stereogenic carbon atom of **4** should markedly affect the product stereoselectivity in the gold(I)-catalyzed aldol reaction. Indeed, this clearly proved to be the case (compare entries 1–3, Table III) in the gold(I)-catalyzed reaction of **1a** with **2a**. Changing the absolute configuration of the stereogenic carbon atom from *R* to *S* while maintaining the *S* planar chirality constant results in a dramatic change in product stereoselectivity. The examination of entries 1 and 3 of Table III reveals that not only does a change in the absolute configuration of the stereogenic carbon atom (a change in central chirality) from *R* to *S* result in a reduction of the product trans-to-cis ratio but also *the opposite trans-oxazoline enantiomer is formed in enantiomeric excess.* Furthermore, the ee of the *cis*-oxazoline increased upon changing the absolute configuration of the stereogenic carbon atom from *R* to *S*. These results indicate that the insensitivity of product stereochemistry to the central chirality of the stereogenic carbon atom in the ferrocenylamine side chain previously observed for Grignard cross-coupling reactions cannot be generalized to other reaction types involving chiral ferrocenylamine ligands. The change in conformational preferences observed for (*R*)-(*S*)-**4** and (*S*)-(*S*)-**4** (vide ante) strongly suggests that these changes in product diastereoselectivity are due to conformational differences in the transition-state structure of the stereoselective step proposed by Hayashi and Ito. The conformational changes in TS structure are the result of different steric interactions brought about by a change in the absolute configuration of the stereogenic carbon atom, vide infra.

The pioneering work of Heathcock and Kagan, and more recently Masamune, has led to the powerful synthetic strategy of matched and mismatched pairs in the control of product stereoselectivity (double stereodifferentiation).[30] This works suggests that the central and planar chirality of a ferrocenylamine ligand can act in either a cooperative or noncooperative sense in controlling product stereoselectivity. A consideration of entries 1–3 (Table III) shows this indeed to be the chase. *Both the highest diastereo- and enantioselectivity of the trans-oxazoline* **5** *are obtained when the central and planar chirality are opposite as defined by the Cahn–Ingold–Prelog sequence rules. This constitutes the first example in a chiral transition-metal ligand containing both central and planar chirality of internal cooperativity of chirality in the control of product diastereo- and enantioselectivity*, which can be compared to the principle of matched and mismatched pairs (*external cooperativity*) advocated by Masamune. Further studies supporting the concept of internal cooperativity of chirality will be reported at a later date.

Mode of Gold Coordination and the Rate-Determining Step. In the TS model of the stereoselective step proposed by Hayashi, coordination of the gold(I) cation to the two phosphorus atoms of **4** in a bidentate manner was proposed. The lack of coordination of the gold(I) cation to the nitrogen atoms in the chiral ferrocenylamine **4** was deemed essential for high stereoselectivity in the

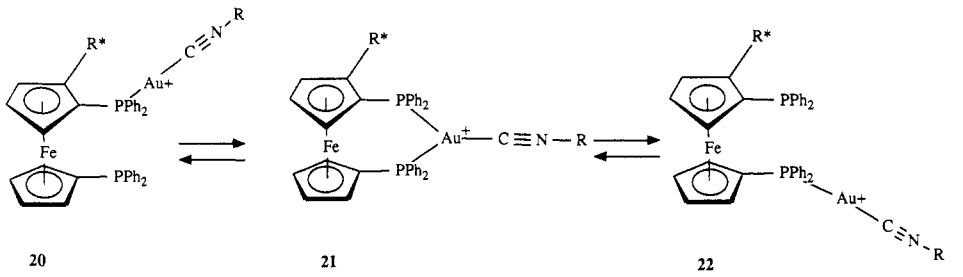


Figure 3.

products and accounted for the lower product stereoselectivity observed when gold(I) is replaced by either silver of copper(II).[7] Quite recently, a crystal structure of (±)-(*R**)-(*S**)-**4** with gold(I) chloride confirmed the lack of gold(I) coordination to the nitrogen atoms, although a trinuclear species was observed in which two molecules of (±)-(*R**)-(*S**)-**4** functioned as bridging monodentate ligands.[33]

The structure of the gold(I) complex of (*R*)-(*S*)-**4** was studied by variable-temperature ^{31}P NMR spectroscopy. The gold(I) complex was prepared by mixing bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate (**3**) with (*R*)-(*S*)-**4** and the resultant complex (dissolved in dichloromethane-d_2) was studied spectroscopically without attempted purification.[99] In the $^{31}P\{^1H\}$ NMR spectrum of the uncomplexed ligand (*R*)-(*S*)-**4**, two singlet resonances were observed at δ −23.5 and −17.0, which were assigned to the two nonequivalent phosphorus atoms bonded to the upper and lower cyclopentadienyl ring, respectively. These assignments are based upon the comparison of chemical shifts of **4** with **11**, **17**, and **18**. In the $^{31}P\{^1H\}$ NMR of the gold(I) complex of (*R*)-(*S*)-**4**, an AB quartet pattern was observed for the coordinated phosphorus atoms. The upfield and downfield arms of the AB quartet were observed at δ 32.0 and 34.8, respectively, with $^2J_{P(1)P(2)}$ = 90.3 Hz. The observed downfield shift of the phosphorus resonances is that expected upon complex formation.[63] The observation of $^2J_{PP}$ coupling demonstrates that both phosphorus atoms are coordinated to the gold(I) atom and provides the first reported evidence in solution for the lack of nitrogen complex formation in **4** to gold(I).[64]

Upon addition of either 1 equiv or an excess of **2b** to the gold(I) complex, a broad singlet resonance was observed in the ^{31}P NMR spectrum *with the loss of P–P ^2J coupling.* A dynamic process must be taking place involving a rapid exchange on the NMR time scale of the phosphorus atoms in the coordination sphere of the gold(I) atom. This must be the case because J coupling is lost in an exchanging system when $1/\Upsilon_e > J$, where Υ_e is the lifetime at a particular site and J is the coupling constant in hertz.[65]

A reasonable process that is consistent with the known coordination chemistry of gold(I) is illustrated in Figure 3. The rapid equilibrium between structures **20**, **21**, and **22**, in which **21** is either an intermediate or TS for interconversion of the two limiting structures **20** and **22**, provides a ready rationale for the observed spectrum upon addition of **2b**. This dynamic exchange process was still rapid at −80 °C.

The addition of benzaldehyde (**1a**) to the gold(I) complex formed from (*R*)-(*S*)-**4** and **3** gave *no observable change* in the AB quartet found in the $^{31}P\{^1H\}$ NMR spectrum. This observation provides powerful evidence *against* any prior coordination of the aldehyde to gold(I) contrary to the TS structure suggested by Ito and Hayashi.

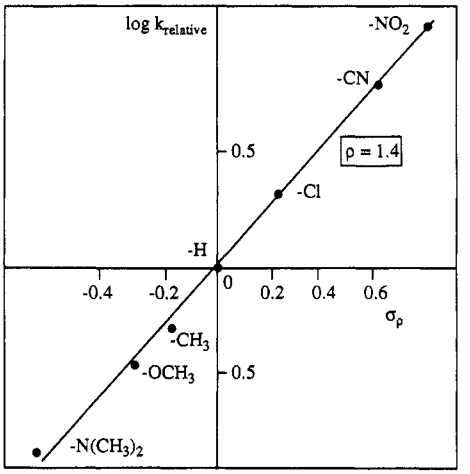


Figure 4. A Hammett plot of the reaction of para-substituted benzaldehydes with **2b**.

The rate-determining step of the gold(I)-catalyzed aldol reaction was identified by a Hammett study.[66] Furthermore, the observation of a linear free energy relationship in the reaction of substituted benzaldehydes and the preformed in situ gold(I)–α-isocyano ester complex provided supporting evidence against prior rate-determining coordination of an aldehyde to gold(I). If coordination of the oxygen atom of the aldehyde carbonyl is the rate-limiting step, one expects that the reaction rate would increase with electron-donating substituents on benzaldehyde. The results obtained show that this is clearly not the case (Figure 4). A linear Hammett plot was obtained with a positive slope (ρ = 1.4), indicative of increased electron density on the carbonyl carbon atom in the rate-determining step. The Hammett relationship obtained strongly suggests that *the rate-determining step of the gold(I)-catalyzed aldol reaction involves electrophilic attack of the aldehyde on the enolate π-face formed by proton abstraction from the α-isocyanoacetate ester.* The Hammett relationship obtained, of course, does not preclude coordination of the carbonyl oxygen prior to the rate-determining step, although the ^{31}P NMR spectral evidence, vide infra, strongly suggests that this is not the case.

The observed dynamic $^{31}P\{^1H\}$ NMR spectrum clearly suggests that the carbon atom of the enolate isocyano substituent coordinates to gold. The enolate or enol formed by either base-catalyzed proton abstraction or enolization, respectively, can in principle be bonded to the ferrocenylamine side chain by an electrostatic (enolate–

(63) Hartley, F. R. *The Chemistry of Platinum and Palladium*; Applied Science Publishers: London, 1973; pp 136–163.

(64) Coordination of both phosphorus atoms and a nitrogen atom of (*R*)-(*S*)-**4** would appear unlikely, although consistent with the observed spectra.

(65) Abragam, A. *The Principle of Nuclear Magnetism*; Clarendon: London, 1961; p 308.

(66) For a discussion of the Hammett linear free energy relationship, see: March, J. *Advanced Organic Chemistry*; Wiley-Interscience: New York, 1985; pp 242–250 and references therein.

ammonium ion attraction) or a hydrogen-bonding (enol proton hydrogen bonded to the nitrogen atom of the ferrocenylamine) interaction. Our previous observation of high diastereo- and enantioselectivity of **1a** with an α-isocyanomethylphosphonate[67] strongly suggests that the latter is not the case because enol structures of phosphonates are not expected.[68] These observations together provide the first experimental evidence for a stereoselective TS structure involving an enolate bonded both coordinatively through the α-isocyano carbon atom and electrostatically by the attractive interaction of the negatively charged enolate with the positively charged protonated tertiary amine group in the ferrocene side chain. Further support for an electrostatically bonded enolate structure is provided by a recent study by Hayashi using α-isocyanoacetamides in the gold(I)-catalyzed aldol reaction,[28] for which amidate structures are less stable than enolate structures because of the electron-donating ability of nitrogen.

The foregoing observations do not necessarily preclude a stereoselective TS in which the proton on the enolate carbon atom is partially transferred to the nitrogen atom in the ferrocenyl side chain. However, no significant kinetic isotope effect was observed ($k_H/k_D = 1 \pm 0.2$) in competition experiments between **2b** and ethyl 2,2-dideuterio-α-isocyanoacetate (**2b**-d_2).[100] This observation provides evidence against structures involving a significant stretching of the C–H bond in the rate-determining step.

Electronic Effects. Quite recently, Ito and Hayashi reported that the gold(I)-catalyzed reaction of paraformaldehyde with α-isocyanoacetates gave oxazolines in which a single stereogenic carbon atom was formed in high ee.[20] Quite clearly, the stereogenic C-4 carbon atom is formed *without* concurrent diastereomer formation (formation of a stereogenic C-5 atom). Ito and Hayashi reasonably attribute the observed product stereoselectivity to the enantioface selectivity of formaldehyde for the *si* and *re* π-faces of the *Z* enolate formed from the α-isocyanoacetate ionically and coordinatively bound in the chiral ferrocenylamine–gold complex. In cases where diastereomers are formed, Ito and Hayashi observed that high product diastereoselectivity is normally accompanied by high enantioselectivity in the major enantiomer formed. However, work in our laboratory provided examples to the contrary.[69] This was particulary seen to be the case in the reaction of the isomeric thiophenecarboxaldehydes with **2b**. Similar examples of unexpected stereoselectivity are found for the reaction of either the furancarboxaldehydes **1c,d** or the pyridinecarboxaldehydes **1e–g** with **2b** (Table III, entries 8–12).[70]

The normal pattern of high diastereo- and enantioselectivity for the *trans*-oxazoline product **5d** was observed for the reaction of **1c** with **2b**. In the case of the reaction of **1d** with **2c**, however, although the *trans*-oxazoline isomer was the major product formed, high enantioselectivity was observed in the minor *cis*-oxazoline product. The results obtained for the isomeric pyridinecarboxaldehydes were even more surprising. In the case of 4-pyridinecarboxaldehyde (**1e**), the reaction with **2a** gave an 88:12 trans:cis product ratio with high enantioselectivity in both the *trans*-oxazoline (75% ee) and *cis*-oxazoline (78% ee). Similar observations were made for the reaction of **1f** with

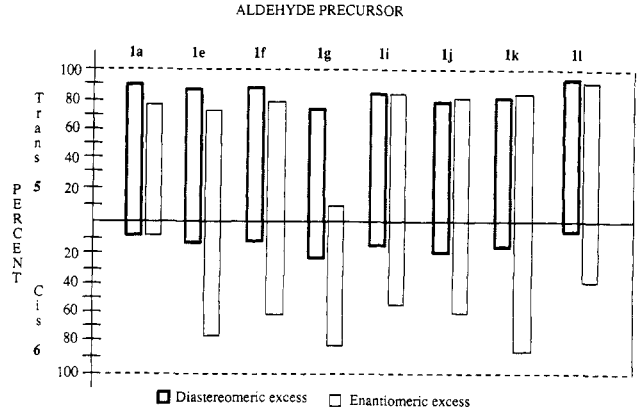


Figure 5. Product diastereo- and enantioselectivities observed for the reaction of certain aldehydes and **2b** in the gold(I)-catalyzed aldol reaction.

2b. Particularly striking were the results obtained in the reaction of 2-pyridinecarboxaldehyde (**1g**) with **2b**. Although a relatively high 75:25 trans:cis product ratio was obtained, the *cis*-oxazoline **6h** had a significantly greater ee (84% ee) than the *trans*-oxazoline **5h** (6% ee). These results are dramatically illustrated with a graphical representation in Figure 5.

The results obtained in the case of the isomeric pyridinecarboxaldehydes cannot reasonably be explained by a steric argument because the sizes of the aldehydes **1e–g** are essentially the same. Similarly, a comparison of the product stereoselectivity obtained in the reaction of **2b** with benzaldehyde (**1a**) (Table III, entry 7) with the selectivity obtained in the reaction of **2b** with the isomeric pyridinecarboxaldehydes strongly argues against a steric explanation of the results obtained because the phenyl and pyridyl rings have similar steric requirements. A consideration of the results obtained with **1h** suggests that the results are not limited to π systems.[71]

A change in product stereoselectivity due to coordination of the heteroatom with gold(I) seems equally unlikely. Both the oxygen atom of **1c,d** and the nitrogen atom of **1e–g** are known to be particularly poor ligands for gold(I).[31,72] Hayashi and Ito have noted that coordination of the gold(I) cation to the phosphorus atoms in **4** rather than the nitrogen atoms is important to the observed stereoselectivity of the gold(I)-catalyzed aldol reaction.[7] A recent X-ray crystal structure of a gold(I) complex of **4** reported by Togni et al. confirms this assertion[33] and, incidentally, provides the first direct evidence for the retention mechanism of substitution at the stereogenic carbon atom (vide ante) in the formation of (*R*)-(*S*)-**4**.

If the observed effects upon product stereoselectivity are not steric in origin, it follows that electronic effects are dominant. Indeed, the measured dipole moments of 2-thiophenecarboxaldehyde (3.28 D),[73] 2-furancarboxaldehyde (3.32 D),[73] and 2-pyridinecarboxaldehyde (3.33 D)[74] are significantly higher than those of their isomers. ^1H and ^{13}C NMR spectral studies, as well as other physical and theoretical studies, of the isomeric pyridinecarbox-

(67) Togni, A.; Pastor, S. D. *Tetrahedron Lett.* **1989**, *30*, 1071–1072.
(68) Kwart, H.; King, K. *d-Orbitals in the Chemistry of Silicon, Phosphorus and Sulfur*; Springer-Verlag: Berlin, 1977.
(69) Togni, A.; Pastor, S. D. *Helv. Chim. Acta* **1989**, *72*, 1038–1042.
(70) For a nonchiral synthesis of **5e** by a zinc(II)-catalyzed aldol reaction of **1d** with **2b**, see: Ito, Y.; Matsuura, T.; Saegusa, T. *Tetrahedron Lett.* **1985**, *26*, 5781–5784.
(71) The reaction of **2a** with the methyl ester of glyoxylic acid gave an 86:4 trans:cis product ratio with a low ee in both the *trans*-oxazoline (3% ee) and the *cis*-oxazoline (5% ee). Whether the low ee is the result of epimerization due to the presence of two carbomethoxy substituents in the product is presently unknown: ^1H NMR ($CDCl_3$) (major *trans*-oxazoline) δ 3.80 (s, 6 H), 4.72 (dd, 1 H), 5.10 (d, 1 H), 6.80 (d, 1 H).
(72) Reference 49, p 871.
(73) Cheng, C. L.; John, I. G.; Ritchie, G. L. D.; Gore, P. H.; Farnell, L. *J. Chem. Soc., Perkin Trans. 2* **1975**, 744–751.
(74) Cheng, C. L.; Ritchie, G. L. D. *J. Chem. Soc., Perkin Trans. 2* **1973**, 1461–1465.

Table IV. Effects of the Reaction Medium upon Product Enantioselectivity

entry	aldehyde	ester	solvent	dipole moment, D	oxazoline product: % trans (ee)	oxazoline product: % cis (ee)
1	**1g**	**2b**	$ClCH_2CH_2Cl$	1.20	75 (6) **5h**	25 (84) **6h**
2	**1g**	**2b**	CH_2Cl_2	1.60	74 (1) **5h**	26 (45) **6h**
3	**1g**	**2b**	diglyme	1.97	81 (2) **5h**	19 (20) **6h**
4	**1k**	**2b**	$ClCH_2CH_2Cl$	1.20	84 (92) **5l**	16 (87) **6l**
5	**1k**	**2b**	CH_2Cl_2	1.60	84 (88) **5l**	16 (86) **6l**
6	**1k**	**2b**	diglyme	1.97	90 (81) **5l**	10 (60) **6l**

[a] *Lange's Handbook of Chemistry*, 13th ed.; McGraw-Hill: New York, 1985; pp 10-103–10-117.

aldehydes show significant differences in the conformational preferences in solution.[73-76] This suggests that the observed changes in ee for the *trans*- and *cis*-oxazoline products for each individual group of isomeric hetero aldehydes is due to a destabilization and stabilization, respectively, of a particular conformation in the enantioselective transition state, vide infra. This electronic effect provides a ready explanation for the differences in diastereo- and enantioselectivity observed for **1e,f** and **1a**, in which the steric requirements should be similar. Obviously, however, this conformational effect in the enantioselective TS must include the chiral ferrocenylamine ligand. If this were not the case, the transition states would be equal in energy and enantioselectivity would be impossible.

The gold(I)-catalyzed aldol reaction of **1g** with **2b** in the absence of a chiral ferrocenylamine ligand (Table III, entries 13 and 14) gave a trans:cis product ratio that is similar to that obtained by using **4**. In contrast, the sodium cyanide catalyzed procedure reported by Schöllkopf[77] gave a 94:6 trans:cis product mixture (entry 15). The basic conditions of the Schöllkopf procedure are reported to result in the epimerization of the *cis*-oxazoline to the thermodynamically more stable *trans*-oxazoline.[78] Schöllkopf reported that the reaction of **1a** with **2b** gives only *trans*-oxazoline.[77] This result along with that of the present study suggests that the trans:cis ratio observed in the gold(I)-catalyzed aldol reaction is predominantly under kinetic control.[79] The similarity of the trans:cis product ratios observed for the reaction of **1g** with **2b** (Table III, compare entries 12–14) suggests that the structure of the chiral ferrocenylamine complex did not, in this case, strongly affect the product trans-to-cis ratio. We and others have, however, reported examples where this is not the case.

The contention that the effect of heteroarenecarboxaldehydes upon product enantioselectivity is due to an electronic perturbation by the heteroatom on the enantioselective TS can be tested by the reaction of appropriately substituted aldehydes with **2a**. The utilization of a trifluoromethyl substituent is particularly suitable because it is strongly electron withdrawing and, of course, noncoordinating. Toward this end, the reactions of 4-, 3-, and 2-(trifluoromethyl)benzaldehyde (**1i–k**) with **2b** were studied.

The observed enantioselectivities (Table III, entries 17–19) clearly support the contention that electronic effects are operative in controlling the observed product stereoselectivity. The observed results parallel those observed for the pyridinecarboxaldehydes. The results for the *o*-methyl-substituted **1l** support the argument that the results obtained with **1k** are *not* steric in origin. Both NMR spectral studies and theoretical calculations by Schaefer et al. indicate that the conformation preferences of **1k** and **1l** in solution are different. Whereas **1l** exists as a 55:45 mixture of O-syn to O-anti forms (305 K in CCl_4), the trifluoromethyl derivative **1k** exists in the O-anti form to the extent of at least 95% (305 K in benzene).[80] If the explanation is advanced that the strong dipole moments of the hetero aldehydes changed the preferred conformations in the stereoselective TS, a significant solvent effect is expected. Solvent effects on preferred conformations in solution are well-known, e.g., the stabilization of a particular conformation with a high dielectric constant in a polar solvent.[81] Indeed, significant effects of the solvent upon the ee of the *cis*-oxazoline are observed for the reaction of either **1g** or **1k** with **2b** (Table IV). A significant solvent effect was also observed for the *trans*-oxazoline **5l**. Interestingly, a significantly higher trans:cis ratio was observed when glyme was used as a solvent compared to 1,2-dichloroethane or dichloroethane.

It should be noted at this point that the ee of the products obtained from *p*- and *m*-(trifluoromethyl)benzaldehyde (**1i,j**) were determined both by GLC (Chirasil-L-Val column) and ^1H NMR spectroscopy using (+)-2,2,2-trifluoro-1-(9-anthryl)ethyl alcohol as a chiral solvating agent. The results of both methods agreed within experimental error (±2 for both ee and diastereoselectivity). In the case of the ortho aldehyde **1k**, the trans enantiomers could not be separated by GLC and the ee was measured by both ^1H and ^{19}F NMR spectroscopy using the chiral shift reagent (+)-2,2,2-trifluoro-1-(9-anthryl)ethyl alcohol. The use of the combination of (+)-2,2,2-trifluoro-1-(9-anthryl)ethyl alcohol with ^{19}F NMR spectroscopy for the determination of ee has not been previously reported and should find wider application in the future. Previously, Togni and Pastor reported the use of ^{31}P NMR spectroscopy in combination with (+)-2,2,2-trifluoro-1-(9-anthryl)ethyl alcohol for the determination of ee in a chiral oxazoline phosphonate derivative.[67]

One must remain cognizant of the fact that the polarity of the reaction medium can also result in changes in the enolate–ammonium ion electrostatic bonding in the stereoselective TS due to solvation effects and may be partly responsible for the changes in ee observed.

(75) (a) Galasso, V. *Mol. Phys.* **1973**, *26*, 81–89. (b) Drakenberg, T. *J. Chem. Soc., Chem. Commun.* **1974**, 1011–1012. (c) Drakenberg, T. *J. Chem. Soc., Perkin Trans. 2* **1976**, 147–149.

(76) For leading references, see: (a) Bertin, D.-M.; Robba, M.; Roques, B. *C. R. Seances Acad. Sci., Ser. C* **1966**, 36–39. (b) Lumbroso, H.; Bertin, D. M.; Cagniant, P. *Bull Soc. Chim. Fr.* **1970**, *5*, 1720–1728. (c) Bertin, D. M.; Chatain-Cathaud, C.; Fournie-Zaluski, M.-C. *C. R. Seances Acad. Sci., Ser. C* **1972**, 1112–1115. (d) Kuzharov, A. S.; Sheinker, V. N.; Derecha, E. G.; Osipov, O. A.; Movshovich, D. Y. *Zh. Obshch. Khim. (Engl. Transl.)* **1974**, *44*, 1971–1975. (e) John, I. G.; Ritchie, G. L. D.; Radom, L. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1601–1607. (f) Kao, J.; Radom, L. *J. Am. Chem. Soc.* **1979**, *101*, 311–318. (g) Grossee, C.; Mechetti, M.; Brito, P. *Can. J. Chem.* **1985**, *63*, 1031–1034.

(77) Hoppe, D.; Schöllkopf, U. *Justus Liebigs Ann. Chem.* **1972**, *763*, 1–16.

(78) Schöllkopf, U.; Schröder, R.; Stafforst, D. *Justus Liebigs Ann. Chem.* **1974**, 44–53.

(79) Reference 53, p 191.

(80) Schaefer, T.; Salman, S. R.; Wildman, T. A. *Can. J. Chem.* **1980**, *58*, 2364–2368.

(81) Allinger, J.; Allinger, N. L. *Tetrahedron* **1958**, *2*, 64–74.

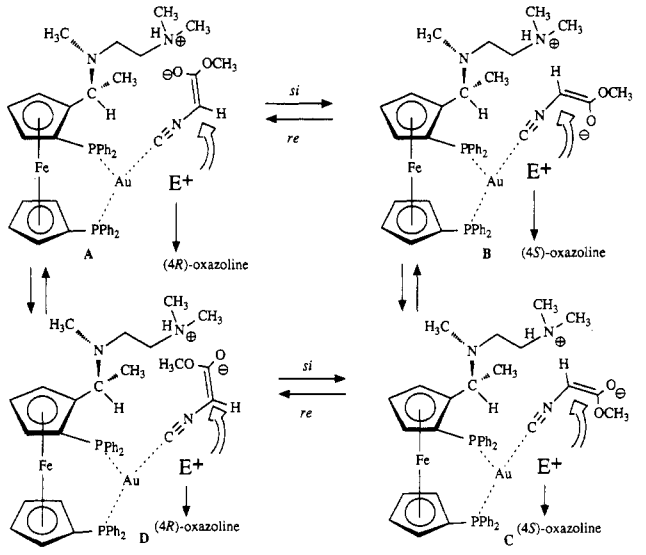


Figure 6. Transition-state model for the gold(I)-catalyzed reaction of an electrophile (E^+) with methyl α-isocyanoacetate using a chiral ferrocenylamine.

Transition-State Model for the Diastereoselective and Enantioselective Steps. On the basis of the observations made herein, a reasonable model of the intermediates and transition-state structures governing diastereo- and enantioselectivity can be constructed.[82] Initially, the stereochemical outcome of electrophilic attack upon the coordinated α-isocyano ester enolate will be considered.

On the basis of the previously discussed ^{31}P NMR experiments, the gold(I) cation is depicted to be in dynamic equilibrium with the two phosphorus donor atoms and the carbon atom of the isocyano substituent of the enolate (Figure 6). Prior coordination of the electrophile is not invoked, which avoids the unusual coordination of gold previously postulated.[83] Four possible intermediates A–D are illustrated, which differ both in regard to the enolate geometry (E or Z) and the reactive π-face (*si* or *re*) of the enolate exposed.[4,82] As reasonably postulated by Ito and Hayashi, one face of the enolate is shielded from attack by the electrophile by both the ferrocenyl moiety and the ferrocenylamine side chain that forms an ionic (electrostatic) bond to the enolate (vide ante). Helmchen has reported a conceptually similar approach in synthesizing sterically restrained molecules in which one π-face of a *covalently bonded* enolate is shielded from electrophilic attack.[84,85]

For clarity, the preferred orientations of the phenyl groups bonded to phosphorus that are surmised from our NMR spectral studies are not illustrated in Figure 6 (cf. Figure 2). One should remain cognizant of the fact that the orientations of these phenyl substituents provide considerable steric shielding of the reaction center. The phenyl substituent bonded to the phosphorus atom of the upper cyclopentadienyl ring, in particular, is expected to have a significant influence on the approach of the incoming electrophile. The orientation of the phenyl substituents on phosphorus ligands playing an important role in asymmetric induction is well documented.[86]

Consider first the electrophilic attack of a carbonyl group that contains a C_2 axis of symmetry (carbonyl π-faces are homotopic) upon the *re* and *si* faces of the *Z* enolate (intermediates A and B, respectively).[87,88] The choice of an electrophile containing these symmetry restraints results in the formation of a product containing only a single new stereogenic carbon atom. The attack of such an electrophilic carbonyl group on the *re* π-face of the enolate (intermediate A) results in the formation of an oxazoline whose absolute stereochemistry at C-4 is *R*, whereas attack upon the *si* π-face (intermediate β) leads to an oxazoline whose absolute stereochemistry at C-4 is *S*. The TS structure can be envisioned as the point of incipient bond formation of the electrophile with the enolate intermediates A–D.

An electrophile possessing these symmetry restraints, formaldehyde, has been reported by Ito and Hayashi. The gold(I)-catalyzed reactions of four different substituted isocyanoacetates with paraformaldehyde in the presence of the (*R*)-(*S*)-4 ligand all gave an oxazoline product with an *S* absolute configuration at C-4. Clearly, the absolute configuration at C-4 and the ee of the product are dependent on the rate of reaction of the electrophile with either intermediate A (*re* π-facial selectivity) or B (*si* π-facial selectivity). The Curtin–Hammett principle prevents conclusions concerning either the concentration or stability of either A or B.[89] The elegant work of Halpern provides an ample caveat in this regard.[90]

A similar consideration of the *E* enolate intermediates C and D leads to the conclusion that *the absolute configuration of the C-4 stereogenic carbon atom in the product is independent of the enolate geometry and is dependent only upon the π-facial selectivity of the electrophile.* This conclusion does not imply that, e.g., both B and C would react at the same rate with an electrophile to give (4*S*)-oxazoline product. Indeed, B and C no doubt have different rates of reaction with electrophiles. Neither is evidence available in regard to whether both B and C are present or, for that matter, whether the (4*S*)-oxazoline obtained is the result of electrophilic attack of the *si* face

(82) For leading references discussing aldol TS structure, see: (a) Heathcock, C. H. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1984; pp 177–237. (b) Evans, D. A.; Nelson, J. V.; Tauber, T. R. *Topics in Stereochemistry, Vol. 13*; Allinger, N. L., Eiliel, E. L., Wilen, S. H., Eds.; Wiley-Interscience: New York, 1982. (c) Heathcock, C. H. *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon Press: Oxford, 1983. (d) Heathcock, C. H. *Asymmetric Synthesis*, Vol. 3; Morrison, J. D., Ed.; Academic Press: New York, 1983. (e) Agami, C. *Bull. Soc. Chim. Fr.* **1988**, 499–507. (f) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3684–3686.

(83) (a) The possible existence of bonding between the gold(I) atom with orbitals of proper symmetry on the ferrocenyl iron atom is not implicitly considered. The existence of an Fe–Au bond would further reduce the conformational probability of the proposed stereoselective TS. See: Akabori, S.; Kumagal, T.; Shirahige, T.; Sato, S.; Kawazoe, K.; Tamura, C. *Organometallics* **1987**, *6*, 2105–2109. (b) A referee has pointed out that the Hammett and NMR studies do not necessarily rule out coordination of the carbonyl oxygen atom to the gold(I) atom in the transition state of the rate-determining step, i.e., rate-determining carbon–carbon bond formation occurs in a transition state containing a tetracoordinate gold(I) atom bonded to two phosphorus atoms, isocyanoacetate, and aldehydic oxygen. The lack of change in the ^{31}P NMR spectrum of the gold(I) complex of 4 upon addition of benzaldehyde suggests that prior coordination of the aldehydic oxygen does not occur.

(84) Helmchen, G.; Leikauf, U.; Taufer-Knöpfel, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874–875.

(85) For the development of mathematical models for the inherent steric congestion at a reaction center, see: (a) Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* **1974**, *96*, 299–301. (b) Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* **1976**, *98*, 8107–8118.

(86) For recent examples, see: (a) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310–312. (b) Evans, D. A.; Chepamn, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.

(87) For a discussion on topicity, see ref 4, pp 9–12.

(88) The *E*–*Z* convention used herein is the normal convention with the modification that is used in the excellent review by Evans, in that the negatively charged oxygen atom of the enolate has the highest priority regardless of the counterion. This nomenclature avoids ambiguity arising as to whether the counterion, e.g., in the present case, is a proton or the nitrogen atom of the ammonium ion. See: Evans, D. A. In *Asymmetric Synthesis*, Vol. 3; Morrison, J. D., Ed.; Academic: New York, 1983; pp 111–212.

(89) Reference 56a, pp 149–156.

(90) Halpern, J., in ref 2, pp 41–69.

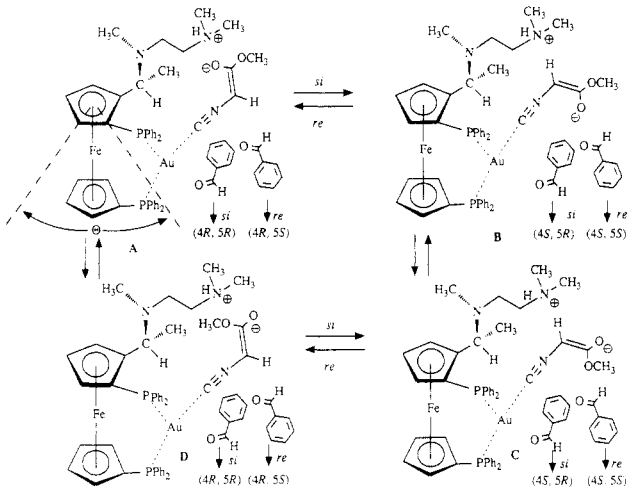


Figure 7. Transition-state model for the gold(I)-catalyzed reaction of benzaldehyde with methyl α-isocyanoacetate using a chiral ferrocenylamine.

of the *Z* enolate (B) and the (4*R*)-oxazoline is the result of the *re* π-facial attack on the *E* enolate (D). The important conclusion to be made is that the resultant stereochemistry at C-4 *is dependent on the π-facial selectivity of the electrophile and, to a first approximation, is independent of the diastereoselectivity obtained when the electrophile lacks the imposed symmetry constraints.*

To simplify the discussion of the model for the π-facial selectivity (diastereoface selection in the sense that the enolate is chiral due to bonding to the ferrocenylamine ligand) of a carbonyl electrophile without symmetry restraints (enantiotopic carbonyl π-faces), we will consider only the *Z* enolate intermediates A and B, remaining cognizant of the fact that the *E* enolates may also play a decisive role. The previously discussed results with formaldehyde suggest that the electrophilic attack on the *si* π-face of the enolate (intermediate B) leads to the dominant enantiomer of the oxazoline formed. If this is also the case with electrophiles lacking the before-mentioned symmetry constraints, then the approach of the electrophile will determine both the absolute configuration at C-5 and the diastereoselectivity of the oxazoline formed. This is illustrated in Figure 7 for the reaction of the enolate of **2a** with **1**. In the case of the TS from the reaction of intermediate B with **1**, steric grounds would dictate that the phenyl group of **1** would point away from the sterically dominant lower cyclopentadienyl group (vide ante), which would result in the formation of the (4*S*,5*R*)-*trans*-oxazoline **5a**. The formation of the (4*R*,5*S*)-*trans*-oxazoline isomer requires the sterically unfavorable approach of **1** with the phenyl group pointing toward the lower cyclopentadienyl ring. In fact, in all cases in which the absolute stereochemistry of the product is known, the (4*S*,5*R*)-*trans*-oxazoline isomer is formed in ee using the (*R*)-(*S*)-**4** ligand. Similar considerations suggest that the (4*R*,5*R*)-*cis*-oxazoline isomer should be formed in ee. This is in fact generally the case when a significant ee is observed for the *cis*-oxazoline. When the (4*S*,5*S*)-*cis*-oxazoline is formed, the ee is generally low.

This model, which is based upon *steric approach control* of the electrophilic reagent, strongly suggests that a change in absolute configuration of the stereogenic carbon atom of the ferrocenylamine ligand side chain should strongly influence the preferred enolate geometries and their resultant rate of reaction with electrophiles will be changed. Indeed, the reaction of **1a** with **2a** in the presence of (*R*)-(*S*)-**4** gives the *trans*-oxazoline with an absolute configuration at C-4 of *S*, while in the presence of (*S*)-(*S*)-**4**, the *R* configuration is obtained. The proposed model provides a rational interpretation of why both the planar and central chirality of the ferrocenylamine, vide infra, are important.

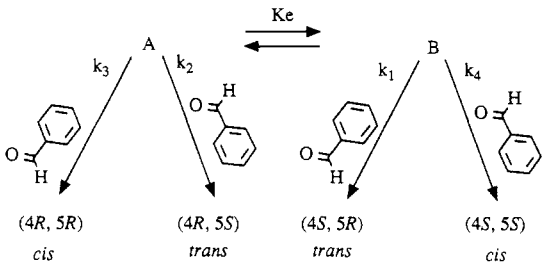


Figure 8.

Unfortunately, specific studies ascertaining the preferred geometry of enolates derived from α-isocyanoacetates are not available. It is not clear whether the product obtained from electrophilic attack on the intermediates A–D are under kinetic or thermodynamic control.[91] A comparison of the cis:trans ratio obtained for the reaction of **1g** with **2b** using the Schöllkopf procedure, in which based-catalyzed epimerization gives predominantly *trans*-oxazoline, with the results obtained in the gold(I)-catalyzed reaction (Table III, compare entries 12–15) strongly suggests, however, that the reaction is under kinetic control.

The unusual results obtained by using the hetero aldehydes **1e–k** deserve further comment. The high trans:cis diastereoselectivity observed for both the previously reported aldehydes and the hetero aldehydes **1e–k** suggest that a similar TS model is applicable. However, in the case of the hetero aldehydes **1e–k**, additional electronic (dipolar) effects favor TS conformations leading to higher ee in the *cis*-oxazolines (or both *cis*- and *trans*-oxazolines). Future work directed toward the determination of the absolute configuration of **6d–l** should prove rewarding. It is further suggested that the changes in the enantioselectivity of the cis enantiomer observed by Hayashi et al. when the pendant amino functionality was modified from morpholino to *N*-methylpiperidino must be due to changes in the preferred conformation of the ferrocenylamine side chain.[10] This change in conformational preference is reflected in the stereoselective TS and the resultant product stereoselectivity obtained.

Kinetic Considerations. The model discussed may be used to develop a simplified kinetic treatment (Figure 8), which ignores contributions from conformations C and D. The inclusion of conformations C and D, although leading to more complicated rate expressions, will not change the following conclusions. In Figure 7, k_1, k_2, k_3, and k_4 represent the rate constants for the formation of their respective *cis*- and *trans*-oxazoline enantiomers, and [A] and [B] are the concentrations of the *re* and *si* π-face enolates in the transition-state structures illustrated in Figure 7, respectively. The rates of formation of the two enantiomeric *trans*-oxazolines are given by eqs 1 and 2,[92] wherein [E] is the concentration of the electrophile.

$$d[(4S,5R)\text{-}\mathbf{5}]/dt = k_1[B][E] \quad (1)$$

$$d[(4R,5S)\text{-}\mathbf{5}]/dt = k_2[A][E] \quad (2)$$

(91) In principle, proton exchange of the product oxazoline with the chiral amine ligand could lead to a kinetic amplification of product ee; see: Bergens, S.; Bosnich, B. *Comments Inorg. Chem.* **1987**, *6*, 85–90. However, the reaction of **1b** with **2b** at 50 °C monitored every 10 min over a period of 2 h showed no significant change in ee.

(92) Reference 56a, pp 234–239.

The ratio of trans enantiomers obtained, P_T, which is dependent upon the ratio of their individuate rates of formation, is given by eq 3.[92]

$$P_T = k_1[B]/k_2[A] \quad (3)$$

From the definition of ee, eq 4 follows for the ee of the trans 4*S*,5*R* enantiomer, where the concentrations of A and E are functions of time.

$$\% \text{ ee} = \frac{\int_{T_0}^{T_\infty} k_1[B(t)][E(t)]\,dt - \int_{T_0}^{T_\infty} k_2[A(t)][E(t)]\,dt}{\int_{T_0}^{T_\infty} k_1[B(t)][E(t)]\,dt + \int_{T_0}^{T_\infty} k_2[A(t)][E(t)]\,dt} \times 100 \quad (4)$$

The ee of the *trans*-oxazoline produced is clearly dependent only upon this ratio and is independent of the rate of formation of *cis*-oxazoline. *No relationship* between the percent ee of the (4*S*,5*R*)-*trans*-oxazoline (or the ee of any other enantiomer) and the cis:trans ratio is to be expected. An examination of the results obtained in this and previous studies indicates that this is often the case. Implications in the literature that high trans diastereoselectivity is accompanied by high enantioselectivity in the trans isomer are misleading and incorrect. The observed cis:trans ratios and ee observed in the reaction of the aldehydes **1d** and **1g** with **2b** provide examples to the contrary. With these aldehydes, trans:cis ratios of 2.1 and 3.0 were obtained with a low ee in the the major *trans*-oxazoline product with an accompanying high ee in the minor *cis*-oxazoline product.

Further, if A and B are in rapid prequilibrium, an equilibrium constant K_{eq} can be defined for the equilibrium A $\rightleftharpoons$ B.

$$K_{eq} = [B]/[A] \quad (5)$$

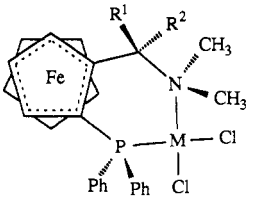
Solving eq 5 for [B], substitution into eq 3, and simplification gives eq 6.

$$P_T = k_1K_{eq}/k_2 \quad (6)$$

If this is the case, the ee obtained is dependent upon the magnitude of the individual rate constants and the size of K_{eq}.[90] Two individual steps in the pathway, namely, the equilibrium of the *re* and *si* π-facial enolates followed by rate-determining attack of the aldehyde, have an influence on the finally observed ee and cis:trans ratios. The often observed high trans diastereoselectivity accompanied by a high ee of the 4*S*,5*R* trans products suggests that K_{eq} favors the *si* π-face leading to this enantiomer. Although this may be the case in some instances, the Curtin–Hammett principle allows only the conclusion that the $\Delta G^{\ddagger}$ for the formation of this isomer is low. The factors that determine the relative magnitude of the individual rate constants and K_{eq} remain at present to be further elucidated. Furthermore, whether a dissociative or nondissociative mechanism of *re* and *si* enolate equilibration is involved remains to be established. If a dissociative mechanism is involved, the kinetic equations would become more complicated due to incorporation of terms for ligand exchange, but the fundamental conclusions should not change.

Conclusions

The stereochemical results of the gold(I)-catalyzed reaction of aldehydes with α-isocyanoacetates using chiral ferrocenylamine ligands can be rationalized by using a steric TS model (Figure 7). In the case of aldehydes possessing either an electronegative heteroatom or an electron-accepting substituent, an additional electronic effect upon the preferred stereoselective TS conformation must be considered.



(*R*)-(*S*)-**23** $R^1 = CH_3$; $R^2 = H$
(*S*)-(*S*)-**23** $R^1 = H$; $R^2 = CH_3$

Figure 9.

The proposed mechanistic TS model allows a ready rationalization as to why previous workers believed that the planar chirality of **4** played the dominant role in determining product stereoselectivity. Kumada and coworkers,[11,22] e.g., reported that the planar chirality of chiral ferrocenylamine ligands gave the same absolute product stereochemistry in Grignard cross-coupling reactions. In the stereoselective TS of Grignard cross-coupling reactions reported in the literature, the transition-metal atom is suggested to coordinate to both the phosphorus atom and the nitrogen atom in the ferrocenylamine side chain (Figure 9, M = transition-metal ion).[93] This mode of coordination is supported by reported X-ray crystal structures.[94] When the metal is coordinated to both phosphorus and nitrogen, the methyl group bonded to the stereogenic carbon atom in (*R*)-(*S*)- or (*S*)-(*S*)-**23** points away from the transition metal and catalytic reactions occur primarily in the chiral cavity due to the planar chirality of the ferrocenylamine. The central chirality of the ligand plays a minor role, in this case, because steric effects are attenuated by the fact that the methyl group points away from the catalytic center regardless of the absolute configuration of the ligand's stereogenic carbon atom. In an X-ray crystal structure of a palladium(II) complex of **11** reported by Hayashi, the metal ion was coordinated to both phosphorus atoms. The nitrogen atom of the alkyl side chain was not involved in coordination to the metal but pointed away from the metal center and is expected to have little effect upon product stereoselectivity. Hayashi noted that the conformation of the phenyl rings on the phosphorus donor atom controls product stereoselectivity.[95]

The presently proposed mechanistic TS model for the gold(I)-catalyzed aldol reaction based upon steric approach control clearly shows that both the central chirality and planar chirality of **4** play an important role in determining the conformation of the stereoselective TS. The nature of the observed *internal cooperativity of both the planar and central chirality of the ferrocenylamine ligand in controlling both the orientation of the α-isocyano ester enolate and the approach of the attacking electrophile* can be rationalized from the stereoselective TS proposed. When the absolute stereochemistry of the planar chirality and that of the central chirality (as defined by the Cahn–Ingold–Prelog sequence) are opposite, maximum diastereo-

(93) (a) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962–4963. (b) Hayashi, T.; Konishi, M.; Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195–2202.
(94) Appleton, T. D.; Cullen, W. R.; Evans, S. V.; Kim, T.-J.; Trotter, J. *J. Organomet. Chem.* **1985**, *279*, 5–21.
(95) Hayashi, T.; Kumada, M. *J. Organomet. Chem.* **1987**, *334*, 195–203.

and enantioselectivity are obtained for the major *trans*-oxazoline. Clearly, when the planar chirality and the central chirality are the same, a favorable transition state for the achievement of high enantioselectivity cannot be achieved.

Experimental Section

All melting points were determined in open capillary tubes and are uncorrected. ^1H (300.133 MHz), ^{19}F NMR (282.421 MHz), and ^{31}P (121.496 MHz) NMR spectra were taken on a Bruker 300 FT NMR spectrometer. ^{31}P NMR spectra were obtained with full proton decoupling. All ^1H chemical shifts are reported in parts per million relative to tetramethylsilane, where a positive sign is downfield from the standard. Significant ^1H NMR data are tabulated in the following order: multiplicity (br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dq, doublet of quartets), coupling constant in hertz, and number of protons. ^{31}P chemical shifts are reported in parts per million relative to 85% phosphoric acid (external), where a positive sign is downfield from the standard. All ^{19}F NMR chemical shifts are reported in parts per million relative to CCl_3F [$\delta(CF_3CO_2D) = -78.5$], where a positive sign is downfield from the standard. Reagents were purchased from commercial laboratory supply houses. Solvents were dried prior to use. Tetrahydrofuran (THF), diethyl ether, toluene, and benzene were distilled prior to use from a deep-blue solution of sodium ketyl under a nitrogen atmosphere. Reactions were carried out in dried apparatus under a dry inert atmosphere of argon, using standard inert atmosphere and Schlenk techniques. GLC analysis was performed on a 50-m Chirasil-L-Val column on a Carlo Erba Model HRGC 5300 GLC instrument. Woelm alumina N (activity IV), ICN Biomedicals alumina N (activity I), and Merck silica gel 60 (70–230 mesh) were used for column chromatography. Elemental analyses were performed by Analytical Research Services, Ciba-Geigy AG.

General Procedure of the Gold(I)-Catalyzed Aldol Reaction. The gold(I)-catalyzed aldol reaction of **1a** with **2a** is illustrative of the general method for the reaction of **1b–l** with **2a,b**. The reaction temperature, duration, and yield of product are listed in Table III. Spectral and analytical data for new compounds follow the general procedure.

To a solution of 37.5 mg (0.055 mmol) of **4** in 6 mL of dichloromethane was added 25.1 mg (0.05 mmol) of **3**. The reaction mixture was stirred for 10 min, and then to the resultant solution were added sequentially 0.45 mL (5 mmol) of **2a** and 0.56 mL (5.5 mmol) of **1a**. The reaction mixture was stirred for 18 h at room temperature. The solvent was removed in vacuo, and the residue was dissolved in 20 mL of diethyl ether. Any precipitate formed was removed by filtration, and the solvent was removed in vacuo. The residue was bulb-to-bulb distilled (Kugelrohr), to give a cis/trans mixture of oxazolines **5** and **6**, which was analyzed when possible both by GLC using a Chirasil-L-Val column and by ^1H NMR with the chiral shift reagent (+)-2,2,2-trifluoro-1-(9-anthryl)ethyl alcohol.[96]

***trans*-4-(Ethoxycarbonyl)-5-(1-methylethenyl)-2-oxazoline. 5b**: bp 57–58 °C (0.15 mm); $[\alpha]^{20}_D$ −162.9 ± 0.4° (*c* = 2.766, THF); ^1H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 1.74 (s, 3 H), 4.29 (m, 2 H), 4.43 (dd, $^3J_{HCCH}$ = 8 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 4.99 (s, 1 H), 5.09 (d, $^3J_{HCCH}$ = 8 Hz, 1 H), 5.10 (s, 1 H), 7.00 (d, $^4J_{HC=NCH}$ = 2 Hz, 1 H); MS, *m/z* 183 ($M^{\bullet+}$). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.63; H, 7.06; N, 7.81.

4-(Ethoxycarbonyl)-5-phenyl-2-oxazoline. 5c: ^1H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 4.31 (m, 2 H), 4.63 (dd, $^3J_{HCCH}$ = 8 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 5.68 (d, $^3J_{HCCH}$ = 8 Hz, 1 H), 7.11 (d, $^4J_{HC=NCH}$ = 2 Hz, 1 H), 7.38 (complex m, 5 H). **6c**: ^1H NMR ($CDCl_3$) δ 0.82 (t, 3 H), 3.67 (m, 2 H), 5.08 (dd, $^3J_{HCCH}$ = 11.5 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 5.74 (d, $^3J_{HCCH}$ = 11.5 Hz, 1 H), 7.26 (d, $^4JH_{C=NCH}$ = 2 Hz, 1 H), 7.38 (complex m, 5 H); MS, *m/e* 219 ($M^{\bullet+}$). Anal.[97] Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.68; H, 5.98; N, 6.55.

4-(Ethoxycarbonyl)-5-(3-furyl)-2-oxazoline. 5d: ^1H NMR ($CDCl_3$) δ 1.31 (t, 3 H), 4.28 (m, 2 H), 4.61 (dd, $^3J_{HCCH}$ = 8 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 5.68 (d, $^3J_{HCCH}$ = 8 Hz, 1 H), 6.40 (m, 1 H), 7.03 (d, 1 H), 7.46 (m, 1 H), 7.52 (m, 1 H). **6d**: ^1H NMR ($CDCl_3$) δ 1.04 (t, 3 H), 3.94 (m, 2 H), 4.98 (dd, $^3J_{HCCH}$ = 12 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 5.73 (d, $^3J_{HCCH}$ = 12 Hz, 1 H), 6.32 (m, 1 H), 7.14 (d, 1 H), 7.38 (m, 1 H), 7.46 (obscured m, 1 H); MS, *m/z* 209 ($M^{\bullet+}$). Anal.[97] Calcd for $C_{10}H_{11}NO_4$: C, 57.42; H, 5.30; N, 6.70. Found: C, 57.52; H, 5.26; N, 6.65.

4-(Ethoxycarbonyl)-5-(2-furyl)-2-oxazoline. 5e: ^1H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 4.28 (m, 2 H), 4.93 (dd, $^3J_{HCCH}$ = 8 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 5.73 (d, $^3J_{HCCH}$ = 8 Hz, 1 H), 6.40 (complex m, 2 H), 7.00 (d, 1 H), 7.48 (m, 1 H). **6e**: ^1H NMR ($CDCl_3$) δ 1.07 (t, 3 H), 3.99 (m, 2 H), 5.03 (dd, $^3J_{HCCH}$ = 12 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 5.76 (d, $^3J_{HCCH}$ = 12 Hz, 1 H), 6.50 (complex m, 2 H), 7.15 (d, 1 H), 7.40 (m, 1 H); MS, *m/z* 209 ($M^{\bullet+}$). Anal.[97] Calcd for $C_{10}H_{11}NO_4$: C, 57.42; H, 5.30; N, 6.70. Found: C, 57.34; H, 5.41; N, 6.73.

4-(Ethoxycarbonyl)-5-(4-pyridinyl)-2-oxazoline. 5f: ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H), 4.33 (complex m, 2 H), 4.56 (dd, $^3J_{HC}C_H$ = 8 Hz, $^4J_{HCN=CH}$ = 2.5 Hz, 1 H), 5.70 (d, $^3J_{HCCH}$ = 8 Hz, 1 H), 7.13 (d, 1 H), 7.28 (complex m, 2 H), 8.65 (complex m, 2 H). **6f**: ^1H NMR ($CDCl_3$) δ 0.87 (t, 3 H), 3.70 (m, 2 H), 5.13 (dd, $^3J_{HCCH}$ = 12 Hz, $^4J_{HCN=CH}$ = 2.5 Hz, 1 H), 5.71 (d, $^3J_{HCCH}$ = 12 Hz, 1 H), 7.28 (complex m, Ar H and OCH=N, 3 H), 8.65 (complex m, 2 H); MS, *m/z* 220 ($M^{\bullet+}$). Anal.[97] Calcd for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.50; N, 12.72. Found: C, 59.89; H, 5.54; N, 12.86.

4-(Ethoxycarbonyl)-5-(3-pyridinyl)-2-oxazoline. 5g: ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H), 4.33 (m, 2 H), 4.62 (dd, $^3J_{HCCH}$ = 8 Hz, $^4J_{HCN=CH}$ = 2.5 Hz, 1 H), 5.74 (d, $^3J_{HCCH}$ = 8 Hz, 1 H), 7.15 (d, 1 H), 7.38 (m, 1 H), 7.68 (m, 1 H), 8.63 (m, 2 H). **6g**: ^1H NMR ($CDCl_3$) δ 0.85 (t, 3 H), 3.72 (m, 2 H), 5.14 (dd, $^3J_{HCCH}$ = 12 Hz, $^4J_{HCN=CH}$ = 2.5 Hz, 1 H), 5.79 (d, $^3J_{HCCH}$ = 8 Hz, 1 H), 7.28 (d, 1 H), 7.31 (m, 1 H), 7.61 (m, 1 H), 8.55 (m, 2 H). Anal.[97] Calcd for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.50; N, 12.72. Found: C, 59.79; H, 5.57; N, 12.89.

4-(Ethoxycarbonyl)-5-(2-pyridinyl)-2-oxazoline. 5h: ^1H NMR ($CDCl_3$) δ 1.34 (t, 3 H), 4.31 (m, 2 H), 5.01 (dd, $^3J_{HCCH}$ = 7 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 5.81 (d, $^3J_{HCCH}$ = 7 Hz, 1 H), 7.08 (d, 1 H), 7.28 (m, 1 H), 7.41 (d, 1 H), 7.75 (m, 1 H), 8.65 (m, 1 H). **6h**: ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H), 3.77 (m, 2 H), 5.19 (dd, $^3J_{HCCH}$ = 12 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 5.84 (d, $^3J_{HCCH}$ = 12 Hz, 1 H), 7.24 (d, 1 H), 7.28 (m, 1 H), 7.38 (d, 1 H), 7.71 (m, 1 H), 8.57 (m, 1 H); MS, *m/z* 220 ($M^{\bullet+}$). Anal.[97] Calcd for $C_{11}H_{12}N_2O_3$: C, 60.00; H, 5.50; N, 12.72. Found: C, 60.14; H, 5.57; N, 12.66.

***trans*-5-[1,1-(Ethylenedioxy)ethyl]-4-(methoxycarbonyl)-2-oxazoline. 5i**: ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 3.80 (s, 3 H), 4.02 (s, 4 H), 4.60 (dd, $^3J_{HCCH}$ = 8 Hz, $^4J_{HCN=CH}$ = 2.5 Hz, 1 H), 4.73 (d, $^3J_{HCCH}$ = 8 Hz, 1 H), 6.92 (d, 1 H). Anal. Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09: N, 6.51. Found: C, 49.74; H, 6.00; N, 6.29.

4-(Ethoxycarbonyl)-5-[4-(trifluoromethyl)phenyl]-2-oxazoline. 5j: ^{19}F NMR ($CDCl_3$) δ −63.47; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H), 4.33 (m, 2 H), 4.59 (dd, $^3J_{HCCH}$ = 7 Hz, $^4J_{HCN=CH}$ = 2.1 Hz, 1 H), 5.76 (d, $^3J_{HCCH}$ = 7 Hz, 1 H), 7.13 (d, 1 H), 7.48 (d, 2 H), 7.68 (d, 2 H). **6j**: ^{19}F NMR ($CDCl_3$) δ −63.55; ^1H NMR ($CDCl_3$) δ 0.80 (t, 3 H), 3.69 (m, 2 H), 5.12 (dd, $^3J_{HCCH}$ = 11.3 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 5.79 (d, $^3J_{HCCH}$ = 11.3 Hz, 1 H), 7.26 (d, 1 H), 7.14 (d, 2 H), 7.63 (d, 2 H). Anal.[97] Calcd for $C_{13}H_{12}F_3NO_3$: C, 54.36; H, 4.21; N, 4.88. Found: C, 54.21; H, 4.23; N, 4.89.

4-(Ethoxycarbonyl)-5-[3-(trifluoromethyl)phenyl]-2-oxazoline. 5k: ^{19}F NMR ($CDCl_3$) δ −63.51; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3 H), 4.33 (m, 2 H), 4.53 (dd, $^3J_{HCCH}$ = 8 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 5.76 (d, $^3J_{HCCH}$ = 8 Hz, 1 H), 7.14 (d, 1 H), 7.58 (complex m, 4 H). **6k**: ^{19}F NMR ($CDCl_3$) δ −63.53; ^1H NMR ($CDCl_3$) δ 0.84 (t, 3 H), 3.67 (m, 2 H), 5.13 (dd, $^3J_{HCCH}$ = 11 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 5.80 (d, $^3J_{HCCH}$ = 11 Hz, 1 H), 7.28 (d, 1 H), 7.58 (complex m, 4 H). Anal.[97] Calcd for $C_{13}H_{12}F_3NO_3$: C, 54.36; H, 4.21; N, 4.88. Found: C, 54.34; H, 4.26; N, 4.80.

4-(Ethoxycarbonyl)-5-[2-(trifluoromethyl)phenyl]-2-oxazoline. 5l: ^{19}F NMR ($CDCl_3$) δ −59.13; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3 H), 4.28 (m, 2 H), 4.52 (m, $^3J_{HCCH}$ = 7 Hz, 1 H), 6.15 (m,

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(97) Analysis on the diastereomeric mixture.

$^3J_{HCCH}$ = 7 Hz, $^5J_{HF}$ = 1 Hz, 1 H), 7.20 (d, 1 H), 7.50–7.68 (complex m, 4 H). **6l**: ^{19}F NMR ($CDCl_3$) δ −59.58; ^{1}H NMR ($CDCl_3$) δ 0.77 (t, 3 H), 3.62 (m, 2 H), 5.08 (m, $^3J_{HCCH}$ = 11 Hz, 1 H), 6.06 (d, $^3J_{HCCH}$ = 11 Hz, 1 H), 7.30 (d, 1 H), 7.50–7.68 (complex m, 4 H). Anal.[97] Calcd for $C_{13}H_{12}F_3NO_3$: C, 54.36; H, 4.21; N, 4.88. Found: C, 54.04; H, 4.27; N, 4.83.

4-(Ethoxycarbonyl)-5-(2-methylphenyl)-2-oxazoline. 5m: ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3 H), 2.35 (s, 3 H), 4.29 (m, 2 H), 4.56 (dd, $^3J_{HCCH}$ = 7.5 Hz, $^4J_{HCN=CH}$ = 2.1 Hz, 1 H), 5.95 (d, $^3J_{HCCH}$ = 7.5 Hz, 1 H), 7.14 (d, 1 H), 7.23 (complex m, 4 H). **6m**: ^{1}H NMR ($CDCl_3$) δ 0.79 (t, 3 H), 2.36 (s, 3 H), 3.62 (m, 2 H), 5.08 (dd, $^3J_{HCCH}$ = 11.5 Hz, $^4J_{HCN=CH}$ = 2 Hz, 1 H), 5.91 (d, $^3J_{HCCH}$ = 11.5 Hz, 1 H), 7.23 (overlapping m, 5 H). Anal.[97] Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.92; H, 6.48; N, 6.06.

(*S*)-*N*,*N*-Dimethyl-1-[(*R*)-2-(trimethylsilyl)ferrocenyl]-ethylamine [(*S*)-(*R*)-9]. To a solution of 57.4 g (200 mmol) of (*S*)-(−)-*N*,*N*-dimethyl-1-ferrocenylethylamine in 400 mL of diethyl ether was added dropwise 145 mL (232 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. The reaction mixture was stirred for 1 h at 26–28 °C, and then to the resultant reaction mixture was added dropwise over a 15-min period 38.0 mL (300 mmol) of trimethylchlorosilane, during which time the reaction temperature was maintained below 30 °C. The reaction mixture was stirred for 3 h at room temperature. To the reaction mixture cooled to 0 °C was added dropwise 300 mL of a saturated aqueous solution of sodium bicarbonate. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2 × 100 mL). The combined organic phases were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel; 89.5:9.5:1 hexane/2-propyl alcohol/trimethylamine eluent) followed by distillation, to give 38.6 g (59%) of an orange-red liquid: bp 122–128 °C (0.009 mm); $[\alpha]^{22}_D$ −12.86° (*c* = 1.586, ethyl alcohol).

(*S*)-*N*,*N*-Dimethyl-1-[(*R*)-2-(trimethylsilyl)-1′,5-bis(diphenylphosphino)ferrocenyl]ethylamine [(*S*)-(*R*)-10]. To a solution of 6.58 g (20 mmol) of (*S*)-(*R*)-**9** in 30 mL of diethyl ether was added dropwise 15 mL (24 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. The reaction mixture was stirred at 30–32 °C for 2 h, and then to the resultant reaction mixture was added dropwise a separately prepared solution of 2.65 g (22.8 mmol) of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, which was dried over calcium hydride, 16.3 mL (26 mmol) of a 1.6 M solution of *n*-butyllithium in hexane, and 20 mL of diethyl ether. The reaction mixture was stirred at 32–34 °C for 5 h. To the resultant reaction mixture cooled to 0 °C was added dropwise 11.1 mL (60 mmol) of chlorodiphenylphosphine. The reaction mixture was heated at reflux for 18 h, and then to the resultant reaction mixture cooled to 0 °C was added 40 mL of a saturated aqueous solution of sodium carbonate. The reaction mixture was diluted with 50 mL of toluene and 50 mL of water. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2 × 50 mL). The combined organic phases were dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel; 1:1 dichloromethane/ethyl acetate followed by neutral alumina, activity IV; 2:1 hexane/toluene eluent), to give 12.7 (87%) of a mixture of monophosphinated (25%) and diphosphinated (75%) product, which was used without further purification.

(*S*)-*N*,*N*-Dimethyl-1-[(*S*)-1′,2-bis(diphenylphosphino)-ferrocenyl]ethylamine [(*S*)-(*S*)-11]. To a solution of 12.1 g (17.4 mmol) of impure (*S*)-(*R*)-**10** dissolved in 150 mL of dimethyl sulfoxide at 30 °C was added 2.1 g (18.6 mmol) of potassium *tert*-butoxide. The reaction mixture was heated at 40 °C for 2 h and then cooled to 0 °C. The reaction mixture was diluted with 200 mL of toluene and 100 mL of water. The organic phase was separated, and it was extracted with saturated sodium chloride solution (4 × 50 mL). The organic phase was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel; diethyl ether eluent), and the resultant solid was recrystallized from ethyl alcohol, to give 4.17 g (38%) of yellow needles: mp 141.9–142.1 °C; $[\alpha]^{22}_D$ −429.5° (*c* = 0.5590, $CHCl_3$); ^{31}P{^{1}H} NMR ($CDCl_3$) δ −16.9 (s), −20.8 (s); ^{1}H NMR ($CDCl_3$) δ 1.32 (d, CpCHCH_3, 3 H), 2.05 (s, N(CH_3)$_2$, 6 H), 3.47 (q, CpC*H*CH$_3$, 1 H), 3.51 (m, CpH, 2 H), 4.02 (m, CpH, 1 H), 4.11 (m, CpH, 1 H), 4.23 (m, CpH, 1 H), 4.36 (m, CpH, 1 H), 4.43 (m, CpH, 1 H), 7.11–7.46 (m, 20 H). Anal. Calcd for $C_{38}H_{37}FeNP_2$: C, 73.0; H, 6.0; N, 2.2. Found: C, 72.9; H, 5.8; N, 2.1.

(*S*)-1-[(*S*)-1′,2-Bis(diphenylphosphino)ferrocenyl]ethyl Acetate [(*S*)-(*S*)-12]. A mixture of 13.1 g (20.9 mmol) of (*S*)-(*S*)-**11** and 60 mL of acetic anhydride was heated for 1 h at 100 °C. The volatiles were removed in vacuo, and the residue was dissolved in 200 mL of diethyl ether. The ether solution was extracted with water (5 × 100 mL), and the organic phase was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, to give 13.35 g (99%) of a viscous orange-red liquid. An analytical sample was prepared by rapid filtration through silica gel: $[\alpha]^{22}_D$ −300.4° (*c* = 0.513, $CHCl_3$); IR ($CHCl_3$) ν 1725 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (d, CpCHCH_3, 3 H), 2.07 (s, C(=O)CH_3, 3 H), 3.58 (m, CpH, 1 H), 3.62 (m, CpH, 1 H), 4.04 (m, CpH, 1 H), 4.09 (m, CpH, 1 H), 4.16 (m, CpH, 1 H), 4.46 (m, CpH, 2 H), 5.93 (dq, CpC*H*CH$_3$, 1 H), 7.08–7.52 (m, 20 H). Anal. Calcd for $C_{38}H_{34}FeO_2P_2$: C, 71.2; H, 5.4. Found: C, 70.8; H, 5.4.

(*S*)-*N*-[2-(*N*,*N*-Dimethylamino)ethyl]-*N*-methyl-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine [(*S*)-(*S*)-4]. A mixture of 1.92 g (3 mmol) of **12** and 30.6 g (300 mmol) of **13** in 30 mL of methyl alcohol was heated at reflux for 18 h. The volatiles were removed in vacuo, and then a solution of the residue in 50 mL of diethyl ether was extracted with water (3 × 50 mL). The organic phase was dried over anhydrous magnesium sulfate. The volatiles were removed in vacuo, and the residue was purified by column chromatography (neutral alumina, activity IV, toluene followed by 19:1 toluene/diethyl ether eluent), to give 1.11 g (54%) of a viscous orange-red liquid: $[\alpha]^{22}_D$ −360.0° (*c* = 0.420, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 3 H), 2.07 (s, N(CH_3)$_2$, 6 H), 2.10 (s, NCH_3, 3 H), 2.19 (m, 2 H), 2.30 (m, 2 H), 3.37 (m, 1 H), 3.44 (m, 1 H), 3.64 (dq, CpC*H*CH$_3$, 1 H), 3.96 (m, 1 H), 4.04 (m, 1 H), 4.18 (m, 1 H), 4.32 (m, 1 H), 4.38 (m, 1 H), 7.04–7.43 (complex m, 20 H). Anal. Calcd for $C_{41}H_{44}FeN_2P_2$: C, 72.1; H, 6.5; N, 4.1. Found: C, 72.0; H, 6.8; N, 4.1.

(*R*)-*N*,*N*-Dimethyl-1-[(*R*)-2-(trimethylsilyl)-1′,5-bis(diphenylphosphino)ferrocenyl]ethylamine [(*R*)-(*R*)-15]. To a solution of 3.13 g (5 mmol) of (*R*)-(*S*)-**11** in 50 mL of diethyl ether was added dropwise 6.25 mL (10 mmol) of a 1.6 M solution of *n*-BuLi in hexane. The reaction mixture was stirred for 3 h at room temperature, and then at 20 °C 3.17 mL (25 mmol) of **14** was added dropwise. The reaction mixture was heated at reflux for 2 h, and then it was cooled to 0 °C. To the cooled reaction mixture was added sequentially 20 mL of a 30% aqueous solution of sodium hydroxide, 30 mL of water, and 30 mL of toluene. The organic phase was separated and was dried over anhydrous magnesium sulfate. Unreacted (*R*)-(*S*)-**11** was removed by fractional recrystallization from ethanol, and the residue that was obtained by concentration of the mother liquor in vacuo was purified by column chromatography (180 g of silica gel, ethyl acetate eluent), to give 0.79 g of an orange solid, which analyzed for a 73:27 ratio of (*R*)-(*R*)-**15**:disiylated products: ^{1}H NMR ($CDCl_3$) δ 0.40 (s, 9 H), 1.67 (d, 3 H), 1.87 (s, 6 H), 3.10 (m, 1 H), 4.30–4.62 (complex overlapping m, 4 H), 7.10–7.46 (complex m, 20 H); MS, *m*/*z* 697 ($M^{\cdot+}$). Calcd for a 73:27 $C_{41}H_{45}FeNP_2Si$:$C_{44}H_{53}FeNP_2Si_2$ mixture: C, 70.0; H, 6.6; N, 2.0. Found: C, 69.6; H, 6.8; N, 1.9.

(*S*)-*N*-[2-(*N*,*N*-Dimethylamino)ethyl]-*N*-methyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine [(*S*)-(*R*)-18]. By the procedure used to prepare compound (*S*)-(*S*)-**4**, compound (*S*)-(*R*)-**18** was prepared from 1.14 g (2.5 mmol) of the acetate derivative[37] of (*S*)-(*R*)-**17** and 22 mL (169 mmol) of **13** in 50 mL of methyl alcohol (18 h at reflux temperature). The product was purified by column chromatography (neutral alumina, activity I, diethyl ether eluent), to give 580 mg (47%) of a viscous orange-red liquid: $[\alpha]^{22}_D$ +315.0° (*c* = 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 3 H), 1.64 (m, 1 H), 1.72 (s, NCH_3, 3 H), 2.04 (s, N(CH_3)$_2$, 6 H), 2.27 (m, 1 H), 2.43 (m, 1 H), 3.82 (m, 1 H), 3.94 (m, 5 H), 4.24 (m, 1 H), 4.25 (dq, CpC*H*CH$_3$, 1 H), 4.38 (m, 1 H), 7.15 (m, 5 H), 7.35 (m, 3 H), 7.56 (m, 2 H). Anal. Calcd for $C_{29}H_{35}FeN_2P$: C, 69.88; H, 7.08; N, 5.62. Found: C, 69.9; H, 7.0; N, 5.7.

(*R*)-*N*-[2-(*N*,*N*-Dimethylamino)ethyl]-*N*-methyl-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethylamine [(*R*)-(*S*)-18]. By the procedure used to prepare (*S*)-(*R*)-**18**, compound (*R*)-(*S*)-**18** was prepared from 595 mg (1.3 mmol) of (*R*)-(*S*)-**17**, 11.4 mL (87.8 mmol) of **13**, and 30 mL of methyl alcohol (18 h

at reflux temperature). The residue was purified by column chromatography (neutral alumina, activity I), to give 553 mg (85%) of a viscous orange liquid: $[\alpha]^{22}_D$ -308.0° (c = 0.4, $CHCl_3$). The spectral data were identical in every respect with that obtained for (*S*)-(*R*)-**18**, although the lower optical rotation obtained suggests that it was in a slightly lower state of purity.

Procedure for Relative Rate Determination (Hammett Study). To a solution of 0.050 mmol of **3** and 0.055 mmol of (*R*)-(*S*)-**4** in 2.5 mL of 1,2-dichloroethane was added a solution of 5.0 mmol of freshly distilled **2b**, 5.0 mmol of **1a**, and 5.0 mmol of the para-substituted benzaldehyde in 2.5 mL of 1,2-dichloroethane. The reaction mixture was heated to 50 °C and the disappearance of starting materials monitored by GLC using a 25-m capillary fused-silicon DB 17/30 W column (HP Model 5890A gas chromatograph). The peak areas of the starting material were calibrated from the known starting concentration prior to addition of the catalyst. When a change in concentration of **2b** was no longer observed, the molar concentrations of unreacted aldehydes were used to calculate the relative rate constant. The ^1H NMR spectra and GLC results of the products were examined to insure that concurrent reactions leading to the disappearance of aldehyde did not occur.

Ethyl 2,2-Dideuterio-α-isocyanoacetate (2b-d_2). To 20 mL of deuterium oxide in a Schlenk tube, which was previously rinsed with deuterium oxide and dried, was added sequentially a solution of 1.1 mL (10 mmol) of **2b** in 10 mL of deuteriochloroform and 50 μL triethylamine. The reaction mixture was stirred at room temperature, and the exchange reaction was monitored by the disappearance of the methylene group protons at δ 4.18 in the ^1H NMR spectrum. After the exchange reaction was complete, the organic phase was separated and then was stirred for an additional 1 h with 20 mL of fresh deuterium oxide. The aqueous phase was separated, and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was distilled, to give 0.95 g of a colorless liquid, bp 95 °C.

Kinetic Isotope Effect. To a solution of 20 mg (0.029 mmol) of (*R*)-(*S*)-4 and 14 mg (0.027 mmol) of **3** in 2.5 mL of 1,2-dichloroethane was added sequentially 152 μL (1.4 mmol) of 2-d_2, 153 μL (1.4 mmol) of **2**, and 140 μL (1.4 mmol) of **1**. The reaction mixture was heated to 50 °C and was held at this temperature for 18 h. The solvent was removed in vacuo, and the residue was dissolved in 20 mL of diethyl ether. Any precipitate formed was removed by filtration with the aid of Hi-flow, and the solvent was removed in vacuo. The residue was bulb-to-bulb distilled (Kugelrohr) and the mixture analyzed by ^1H NMR (250 MHz) and MS.[98]

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(99) **Note Added in Proof**: The [Au((*R*)-(*S*)-4)]BF_4 complex was formed in methylene chloride and freed of cyclohexyl isocyanide by precipitation with diethyl ether, filtration, and washing with pentane.

(100) **Note Added in Proof**: A statistical mixture of the four possible isotopomeric oxazolines was formed, also indicating a rapid H/D scrambling of the starting materials **2b** and **2b**-d_2.

Notes

Properties of the Zinc-Nickel Chloride-Deuterium Oxide System: A Simple Method for Deuterium Addition to Carbon-Carbon and Carbon-Oxygen Double Bonds

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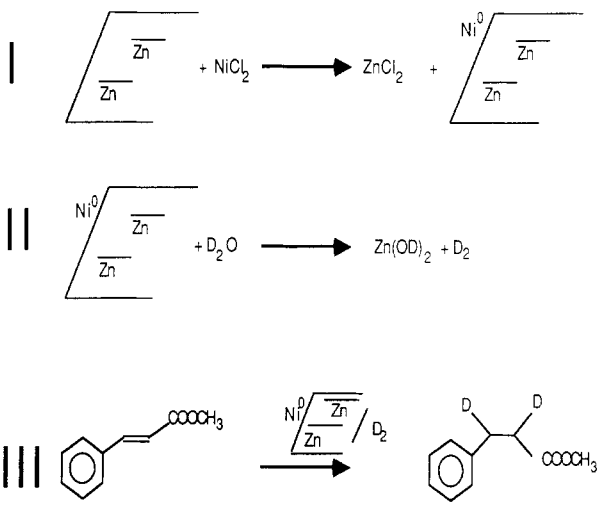
We previously reported that zinc-nickel chloride in deuterium oxide solution can be used to carry out selective deuterium addition on the olefinic bond of methyl cinnamate.[1] This incorporation is not the result of an electron transfer that is generally involved in equivalent systems.[2] In the mechanism proposed for the conjugated deuteration of methyl cinnamate (Scheme I) the nickel chloride is reduced to nickel metal, which coats the zinc surface (I). The zinc, assisted by nickel, reduces deuterium oxide to dideuterium (II). The nickel-activated surface catalyzes this reduction (III).

Several compounds have been tested and the results examined both to check the utility and validity of the method and to bring additional informations to the discussion of the reaction pathways.

Scheme I



Results and Discussion

Results obtained for several compounds are displayed in Table I. Deuterated products were isolated in high yield and are characterized by a good to high degree of deuterium addition.

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