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Kinetic and stereoselectivity effects of phosphite ligands in dirhodium catalysis

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ABSTRACT

A phosphite additive that can act as an axial ligand for a dirhodium tetracarboxylate catalyst improves the enantioselectivity of silane insertion of a diazo substrate. A kinetic study enables measurement of the catalytic rate constant for the catalyst bound to an axial ligand. Although a single axial ligand has an inhibitory effect on reactivity at the distal rhodium center, axially-bound catalysts are the predominant active species in solution for phosphite concentrations above 6 mol % under our reaction conditions. We examine changes in product enantioselectivity as a function of ligand to shed light on the structure and kinetics of product formation steps.

1. Introduction

Dirhodium complexes are one of the most synthetically useful examples of homogenous catalysts containing multiple metal atoms.[1] A large number of enantioselective reactions have been developed through the design of chiral carboxylate and carboxamide ligands for the bridging equatorial sites of the dirhodium core, and these reactions play important roles in the synthesis of diverse classes of chiral targets. The development of selective dirhodium catalysts for diazo decomposition has typically treated a dirhodium complex as though it were a mono-metallic site. Reaction with diazo compounds is assumed to result in the formation of a metallocarbene intermediate with loss of dinitrogen. The reactive metallocarbene intermediate then undergoes reaction with substrate through X–H insertion, cyclopropanation, ylide formation, or other processes.[2] Because the two labile, axial coordination sites point in opposite directions, they are typically assumed to catalyze reactions independently. Homoleptic tetracarboxylate and tetraamidate complexes have an axis of symmetry through the metal–metal bond, and so the two metal sites are chemically equivalent as well. However, polymetallic complexes offer attractive targets for the development of selective catalysts precisely because metals can interact in diverse ways, allowing dual binding of substrate(s), or influencing the catalytic cycle through steric or electronic effects.

In the context of our work examining peptide ligands for enantioselective catalysis, we decided to examine the potential for improving the enantioselectivity through the addition of ligands. In pursuing this line of inquiry, we were mindful that added ligands almost certainly inhibit diazo decomposition (Fig. 1). Indeed, a previous kinetic study with other ligand classes concluded that ligated dirhodium complexes are not competent catalysts for diazo decomposition, even if one of the two rhodium atoms remains free of ligand.[3] Despite efforts to understand the mechanism of dirhodium-catalyzed diazo reactions,[3–5] mechanistic understanding of product-determining steps, which occur after the turnover-limiting diazo-decomposition step, is limited. The effects of the coordination environment of the distal rhodium atom on catalytic reactivity may be an important variable in determining catalytic selectivity and efficiency, yet is little studied. Sporadic evidence indicates that catalysis can be altered with solution additives,[6] including an observation that phosphate and phosphine-oxide additives can rescue enantioselectivity from the detrimental effects of trace water in asymmetric cyclopropanation reactions.[6b] Recently the catalytic activity of dirhodium complexes with exchange-inert NHC ligands bound to an axial site has been described.[7] In this paper, we describe a phosphite additive that improves the enantioselectivity observed in asymmetric silane insertion reactions[8,9] catalyzed by peptide–dirhodium complexes.[10,11] We present a kinetic analysis of the process to shed light on the equilibrium and kinetic parameters involved in the process.

Dirhodium metallopeptides are kinetically inert coordination complexes that are readily synthesized by direct metalation of a fully deprotected peptide ligand[10] and adopt discrete secondary

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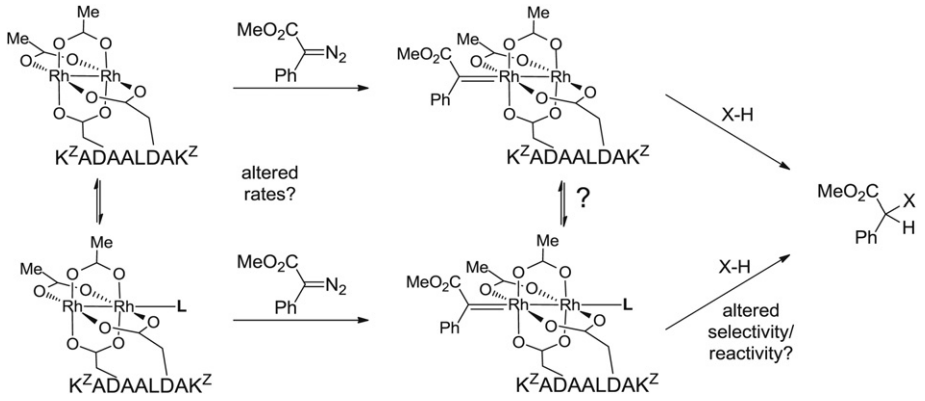
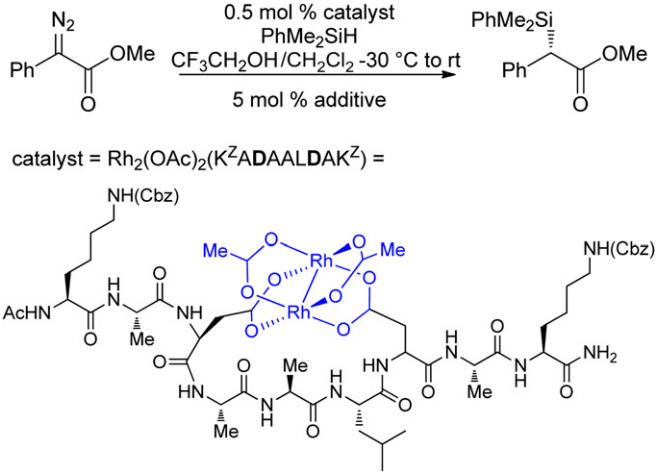


Fig. 1. Distal ligation and X–H insertion of dirhodium metallocarbene intermediates.

structures that are stabilized by chelate binding to the dirhodium center.[11] While four molecules of chiral ligand around the dirhodium center are typically employed for asymmetric catalysis, we have been interested in asymmetric catalysis with a single chelating bis-carboxylate peptide ligand at a rhodium center that also contains two (achiral) acetate ligands. In general, these mono-peptide catalysts provide modest stereoselectivity in silane insertion reactions (Table 1). Selectivity is improved in bis-peptide catalysts,[8a] but the development of selective mono-peptide catalysts is desirable for many purposes, including screening peptide ligands directly on solid support.

Table 1
Screen of additives for increased enantioselectivity



Additive	% ee
None	50
tris(2,4-di-*tert*-butylphenyl) phosphite	52
(PhO)$_3$P	**66**
(EtO)$_3$P	50
(MeO)$_3$P	53
DMSO	51
Et$_2$NOH	51
pyridine	48
(^{i}Pr)$_2$EtN	52
9-cyanoanthracene	42
PhCN	48
(biphenyl)(^{t}Bu)$_2$P	54
Ad$_2$PhP	53
(Ph)$_3$P	46

2. Results

2.1. Phosphite additives and enantioselectivity

Upon initial screening, the complex Rh$_2$(pep1)(OAc)$_2$, containing one chelating peptide ligand and two achiral acetate groups, catalyzes a silane insertion reaction of dimethylphenylsilane and ethyl phenyldiazoacetate with 50% ee (Table 1). We examined additives that might bind to the dirhodium core and affect enantioselectivity. Although most additives had a negligible or negative effect on enantioselectivity, the addition of triphenylphosphite improved the product ee to 66% (Table 1, bold entry).

The beneficial effect on product ee was general across a variety of peptide ligands; the addition of 10 equiv, relative to dirhodium, produced modest increases (5–18%) in ee across catalysts with a variety of peptide sequences (Table 2). The best results were observed with catalyst Rh$_2$(pep2)(OAc)$_2$, which afforded the product in 88% ee.

Table 2
Triphenylphosphite as an additive for enantioselective dirhodium reactions at 0 °C

Ligand	Sequence	ee %	
		No additive	P(OPh)$_3$
Pep1	K^{Z}ADAALDAK^Z	40	58
Pep2	K^{Z}TDAAIDAK^Z	77	88[a]
Pep3	K^{Z}TDGATDAK^Z	61	76
Pep4	K^{Z}NDAAIDAK^Z	82	87

[a] Scaled up reaction afforded 84% yield.

2.2. Kinetics

To shed light on the effect of phosphite on enantioselective dirhodium catalysis, we performed a kinetic analysis of the process. The loss of dinitrogen to form a metallocarbene is irreversible and turnover-limiting, so that the kinetics of the reaction can be expressed as a function of two ligand association constants (K_{i1} and K_{i2}), a rate constant for reaction in the absence of phosphite (k_c), and a constant (γ) that describes the catalytic power of the phosphite complex relative to the free catalyst, as shown in Fig. 2. The association constants were determined by fitting UV–vis absorption spectra as a function of phosphite concentration.[12,13] For Rh$_2$(pep1)(OAc)$_2$, log K_{i1} and log K_{i2} are 5.38 and 3.31, respectively (Table 2). These values are consistent with negative cooperativity typical of dirhodium complexes.[12,13]

The values for Rh$_2$(pep1)(OAc)$_2$ are somewhat lower than those for the parent compound, Rh$_2$(OAc)$_4$ (6.09 and 3.96, determined by the same method), indicating that the bulky peptide ligand disfavors axial ligation. The rate constant k_c can be measured for reactions without phosphite or fit numerically, while the constant γ is fit from kinetic data using non-linear least-squares protocols.

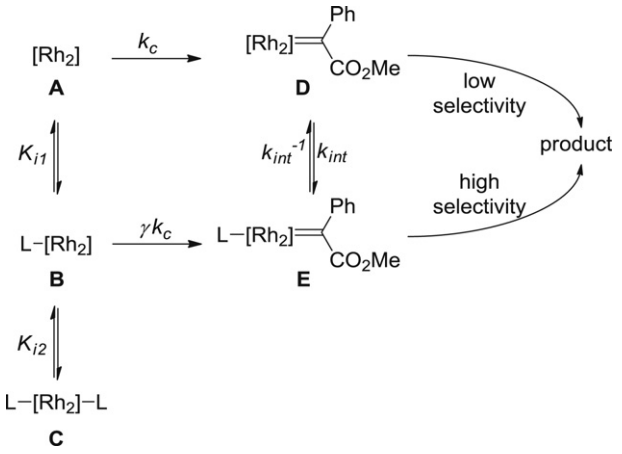


Fig. 2. Mechanism of dual-path enantioselective catalysis.

The relationship between phosphite concentration and reaction rate provides a plot of concentration versus 1/rate that allows determination of the reactivity ratio, γ. Disappearance of the diazo substrate was monitored by HPLC and/or UV absorption at varying concentrations of phosphite. Individual reactions displayed linear plots of $-\log([\text{diazo}]/[\text{diazo}]_0)$ versus time, indicative of clean kinetics that are first-order in substrate (see Supplementary data). The constant γ was obtained by fitting the rate constants to the kinetic data using a least-squares fitting method.[14] A value of 0.013 is obtained for γ (Table 3).

Table 3
Experimentally determined kinetic and thermodynamic parameters

$\log K_{i1}$ (M^{-1})	5.38
$\log K_{i1}$ (M^{-1})	3.31
k_c (M^{-1} s^{-1})	5.46
γ	0.013

3. Discussion

It is not apparent that ligand additives should be a successful strategy for altering selectivity in dirhodium catalysis. Each metal center contains a single open coordination site, so that ligand-bound rhodium atoms are necessarily catalytically inactive. In addition, the two axial sites of the dirhodium core point in opposite directions, projecting into very different regions of space. Finally, a previous kinetic study of dirhodium catalysis in non-polar solvent in the presence of weak ligands (such as THF) concluded that ligand-bound catalysts (Fig. 2, **B**) are not catalytically competent.[3] Nonetheless, it is clear that triphenylphosphite provides an enhancement in enantioselectivity with the dirhodium metallopeptide catalysts described here. The basis for this additive effect is difficult to establish. In the presence of a single peptide ligand, there is no twofold axis of symmetry through the Rh–Rh bond, and the two dirhodium sites are chemically non-equivalent. Part of the initial rationale for the use of added ligand was the belief that axial ligands might bind and change the site of catalysis. However, the association constants K_{i1} and K_{i2} are comparable to those observed with dirhodium tetraacetate, implying that the two non-equivalent rhodium atoms bind phosphite with similar affinity. Alternatively, electronic or steric effects of distal ligand binding may alter selectivity. NMR experiments (see Supplementary data) before and after addition of triphenylphosphite show shifts in aspartate Hβ and backbone Hα resonances, indicating close interactions of the phosphite and peptide that may affect peptide structure or dynamics.

Our kinetic data is inconsistent with $\gamma=0$, as would be the case if ligand-bound catalysts (Fig. 2, **B**) are not kinetically competent in diazo decomposition reactions. Least-squares fitting of the kinetic data provides a measured γ of 1.3% (Fig. 3). Fitting the data in Fig. 3 under the alternative assumption that $\gamma=0$ provides a model that is inconsistent with our data (Fig. 3, dashed curve). Indeed, the apparent linear relationship in Fig. 3 requires either that $\gamma=0$ and $K_{i2}=0$—reducing the system to simple, single-site inhibition, or else that both γ and K_{i2} are non-zero. This differs from a previous report, which determined that $\gamma=0$ for a series of weak oxygen donor ligands.[3] Despite the fact that ligand-bound catalysts are less reactive ($\gamma<1$), ligand-bound intermediates (**B**,**E**) can still be the predominant pathway in catalytic reactions. For example, in the reaction described in Table 1, ligand-bound intermediates (**B**,**E**) are on the predominant catalytic pathway (i.e., partition>0.5, see Fig. 4) for phosphite concentrations ≥6 mol %.

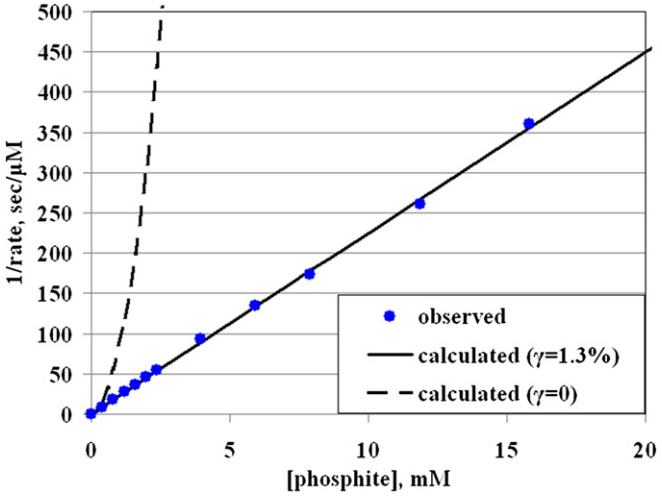


Fig. 3. Plot of kinetic data and fit for the reactivity ratio, γ.

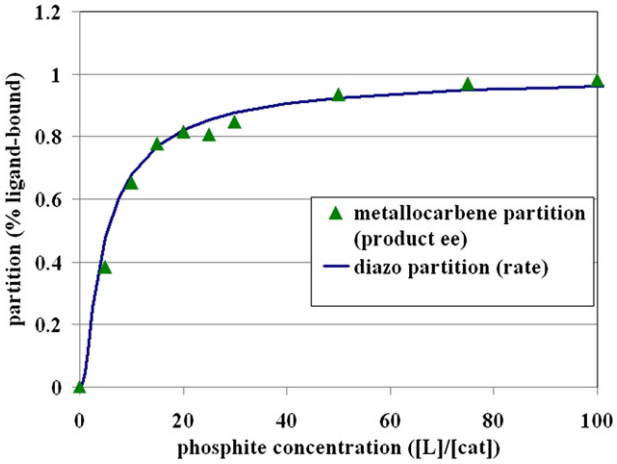


Fig. 4. Experimental measurement of partitioning between phosphite-bound and unligated catalyst for the two steps of the reaction, diazo decomposition and silane insertion. Diazo partition determined from kinetic data; metallocarbene partition determined from product ee.

Changes in product enantioselectivity as a function of phosphite concentration require that triphenylphosphite is involved in the enantio-determining step. Because the turnover-limiting step in dirhodium-catalyzed diazo reactions is irreversible diazo decomposition to afford the metallocarbene, it is difficult to use kinetic methods to probe the subsequent steps that determine product selectivity. Gleaning information about steps after the

formation of the metallocarbene requires creative substrate design to derive kinetic and mechanistic information from product ratios.[5]

Assuming two reactive metallocarbenes are involved in catalysis—a (less selective) free metallocarbene and a (more selective) phosphite-bound metallocarbene—it is possible to define a *metallocarbene partition*, the percentage of silane insertion that occurs though ligand-bound metallocarbene (Fig. 2, **E**). Examining the product ee as a function of ligand concentration provides a measure of this metallocarbene partition (Fig. 4). We can use our measurement of reaction kinetics to define a *diazo partition*—a function of catalyst and ligand concentration—that defines the percentage of diazo decomposition through ligand-bound catalyst, (Fig. 2, **B**). In a general sense, these two partitions will be rigorously identical only if silane insertion is faster than ligand exchange of the metallocarbene intermediate. However, coincidental overlapping partition curves is possible for individual reactions, even if insertion is not faster than ligand exchange, based on the rates of metallocarbene interconversion and product formation. As shown (Fig. 4), the *diazo partition*, derived from kinetics experiments, is identical to the *metallocarbene partition*. In other words, the fraction of substrate following the bottom path (Fig. 2) during diazo decomposition is the same as that during product formation. This observation implies that metallocarbene intermediates do not interconvert through ligand exchange, subject to the caveat of possible coincidental overlap described above. Future work with other substrates may enable us to address this possibility.

Our analysis carries with it a number of assumptions that could affect the results. The mono-ligated species, CL, as well as both metallocarbene intermediates, represent a mixture of ligand isomers. Because our kinetic analysis is based on the steady-state approximation, the ratio of these species must remain constant during a reaction and thus the existence of these isomers does not affect the kinetic results described here. Our analysis also ignores ligation to the axial sites by solvent molecules. Although trifluoroethanol certainly does bind to the axial sites, this binding is weak and transient and is accounted for under steady-state assumptions. Finally, a previous study modeled the diazo decomposition process as a combination of substrate binding and dinitrogen expulsion steps. This approach is compatible with the analysis presented here, and our reactivity ratio γ is equivalent to the ratio of two constants, β/α, used in that approach.[3]

4. Conclusion

We believe this work will spur the development of axial ligands as a control element in dirhodium catalysis. In the present context, a phosphite additive enables synthetically useful enantioselectivity in a dirhodium mono-peptide complex. In the absence of phosphite additives, achieving synthetically useful levels of enantioselectivity required the use of bis-peptide complexes, which require chromatographic separation of the two formed orientational isomers.[8a,11] Because axial ligands inherently inhibit catalysis through a two-state binding inhibition, it may be possible to build carboxylate ligands with a single pendant axial ligand to achieve improved selectivity with minimal sacrifice of reactivity.

Axial-bound dirhodium centers have been proposed in a few circumstances, beyond enantioselectivity questions, to play a role in chemoselectivity and reaction efficiency. However, it has been difficult to establish the role of added ligand and its presence on the catalytic pathway. In providing the first non-zero measurement of the reactivity ratio, γ, this paper provides a framework for investigating other instances of ligand effects and provides a foundation for the use of ligands to alter other selectivity types in dirhodium catalysis.

5. Experimental section

5.1. General

The synthesis, purification, and characterization of the metallopeptide complexes and the synthesis of starting materials have been described.[8a]

5.2. Ligand screening

General procedure for enantioselective silane insertion with phosphite additives: methyl phenyldiazoacetate (1 equiv, 7.8 μmol) was mixed with silane (2 equiv, 15.6 μmol) in trifluoroethanol (200 μL) and equilibrated to −30 °C; peptide catalyst (0.5%, 39 nmol) is dissolved and trifluoroethanol (100 μL) and ligand (5%, 390 nmol) was added in CH_2Cl_2 solution (200 μL). After equilibration of the catalyst solution to −30 °C, the mixture of starting materials was added and reaction proceeded overnight. The reactions were moved to ice (0 °C) and allowed to warm up to rt. The crude mixtures were dried under nitrogen jet and the product was isolated by silica-gel column, eluting with ether/hexanes (1:99). Enantioselectivity was determined by chiral HPLC (Phenomenex Lux 5μ, eluent: isopropanol–hexanes (10:90)).

5.3. Equilibrium constants

The equilibrium constants, K_{i1} and K_{i2}, were determined from UV–vis titration experiments according to the method of Bear.[12] Absorption values at 295 and 323 nm for varying phosphite concentrations were measured and the equilibrium constants, K_{i1} and K_{i2}, were fit with a non-linear least-squares method implemented in Excel.[15] Determining the concentration of free phosphite, [*L*], requires solving the third-degree polynomial obtained upon solving the equilibrium expressions:

$$K_{i1}K_{i2}[L]^3+(2[C]_0K_{i1}K_{i2}-[L]_0K_{i1}K_{i2}+K_{i1})[L]^2+([C]_0K_{i1}-[L]_0K_{i1}+1)[L]-[L]_0=0$$

for $[C]_0$=total metallopeptide concentration and $[L]_0$=total phosphite concentration. Solving this equation was accomplished with an add-in for Excel.[15]

Concentrations of free metallopepitde, [*C*]; the monophosphite complex, [*CL*]; and the bis-phosphite complex, [CL_2], were determined from the equations:

$$[CL]=\frac{K_{i1}[L][C]_0}{1+K_{i1}[L]+K_{i1}K_{i2}[L]^2}$$

$$[CL_2]=\frac{K_{i1}K_{i2}[L]^2[C]_0}{1+K_{i1}[L]+K_{i1}K_{i2}[L]^2}$$

$$[C]=\frac{[C]_0}{1+K_{i1}[L]+K_{i1}K_{i2}[L]^2}$$

5.4. Rate measurements

Methyl phenyldiazoacetate (1 equiv, 6.2 μmol) was mixed with silane (2 equiv, 12.4 μmol) in trifluoroethanol (160 μL) and cooled to 0 °C. In a separate vial, solid Rh_2(pep1)$(OAc)_2$ (0.5%, 31 nmol) was dissolved in trifluoroethanol (80 μL) and ligand (variable amounts) was added in CH_2Cl_2 (160 μL). After cooling to 0 °C, the solution of starting materials was added. Aliquots (10 μL) were taken from the reaction mixture at various times and quenched with acetonitrile (90 μL). The conversion of the reaction was determined by

analytical HPLC (Phenomenex Kinetex 2.6μ, water–acetonitrile gradient). Graphs of $-\log([\text{diazo}]/[\text{diazo}]_0)$ versus time were linear, indicating clean first-order kinetics (Supplementary data).

The reactivity ratio, γ, was fit using the least-squares method referenced above, according to the rate law,

$$rate = k_c[C] + \gamma k_c[CL]$$

where k_c=rate constant measured in the absence of phosphite and $[C]$ and $[CL]$ were determined from the equilibrium constants measured above.

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Supplementery data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.01.059. These data include MOL files and InChIKeys of the most important compounds described in this article.

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