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Enantioselective diarylcarbene insertion into Si–H bonds induced by electronic properties of the carbenes

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ABSTRACT: Catalytic enantioselection usually depends on differences in steric interactions between prochiral substrates and a chiral catalyst. We have discovered a carbene Si–H insertion in which the enantioselectivity depends primarily on the electronic characteristics of the carbene substrate, and the log(*er*) values are linearly related to Hammett parameters. A new class of chiral tetraphosphate dirhodium catalysts was developed that shows excellent activity and enantioselectivity for the insertion of diarylcarbenes into the Si–H bond of silanes. Computational and mechanistic studies show how the electronic differences between the two aryls of the carbene lead to differences in energies of the diastereomeric transition states. This study provides a new strategy for asymmetric catalysis exploiting the electronic properties of the substrates.

INTRODUCTION

Enantiomers of chiral molecules often exhibit biological activities distinct from one another due to the homochirality of biological molecules (e.g. L-amino acids and D-saccharides). As a result, industrial compounds such as pharmaceuticals, pesticides, flavors and fragrances often must be a single enantiomer.¹ In the past several decades, asymmetric catalysis has become a reliable method for the synthesis of enantiomerically-enriched chiral compounds.² Most current methods of asymmetric catalysis rely on the spatial interactions between the catalyst and substrate for enantiocontrol. Many sterically crowded chiral catalysts have been developed that utilize this principle to achieve high enantioselectivity.³ For unsaturated substrates, the chiral catalyst is often able to achieve enantiocontrol by discriminating between the two prochiral faces of the substrate.⁴ It is difficult to identify prochiral faces when the reactive center is attached to two sterically similar substituents (Fig. 1A). For this reason, only limited successes have been achieved in the catalytic enantioselective reactions such as hydrogenations of diaryl⁵ or dialkyl ketones,⁶ or of diaryl or dialkyl ethylenes,⁷ and cycloadditions of diaryl ethylenes.⁸

Many active intermediates of organic reactions, such as carbocations, carbon radicals, carbenes, and conjugated carbanions have planar structures. Asymmetric reactions that proceed via these active intermediates often rely on the steric differences between the substituents connected to the prochiral center.⁹ Catalytic enantiocontrol by discriminating substituent electronics is very rare.¹⁰ Recently, Fürstner and coworkers¹¹ studied the structures of rhodium-diphenylcarbenes by X-ray single crystal diffraction: the electron-rich phenyl ring (4-Me₂NC₆H₄) adopts a coplanar orientation with carbene plane ($\Theta = 0.9^\circ$) to maximize the overlap of the π cloud of phenyl ring with the (empty) carbene *p* orbital. The electron-deficient phenyl ring (4-CF₃C₆H₄) lies orthogonal to the carbene plane (Θ

$= -94.7^\circ$) to stabilize the lone pair of the carbene that also donates to the Rh *d*_{z² orbital. In this way, the electronic properties of the substituents determine the degree of the conjugation between the aryl rings and the *p* or lone pair orbitals of the carbene center. Based on this property, we speculated that enantioselective transformation could be achieved by a chiral catalyst that distinguishes the conformations of a prochiral carbene intermediate. This strategy provides a new method for the enantiocontrol for chiral transformations of substrates which have sterically similar substituents. While stereoselectivity has been achieved in carbene reactions catalyzed by Cu, Fe, and Rh catalysts,¹² the carbenes generally have one ester group and one aryl or alkenyl group, or in the work by Shaw, very different substitution patterns on the two aryl groups of diaryl carbenes that cause large steric differences.¹³ We have now found that dirhodium catalysts modified with chiral spiro phosphate ligands (Fig. 1B, Rh₂(SPA)₄) can differentiate the conformations of diarylcarbenes to achieve highly enantioselective transformations even though the substituents are in positions where they have no different direct interactions with the catalyst.}

Transition-metal-catalyzed carbene insertion into Si–H bonds is a powerful method for the synthesis of optically active silanes. However, high enantioselectivity has only been achieved using carbenes with markedly different substituents (e.g. one substituent is an alkyl, alkenyl, or aryl group and the other substituent is an electron-withdrawing group).¹⁴ Enantioselective Si–H bond insertion of diarylcarbenes remains undeveloped. The challenge in the enantioselective Si–H bond insertion of diarylcarbene stems from the difficulty of precisely distinguishing the *Re* and *Si* faces of the carbene. We sought to overcome this limitation using a chiral catalyst capable of distinguishing the electronic-induced conformations of the prochiral carbene intermediate (Fig. 1B).

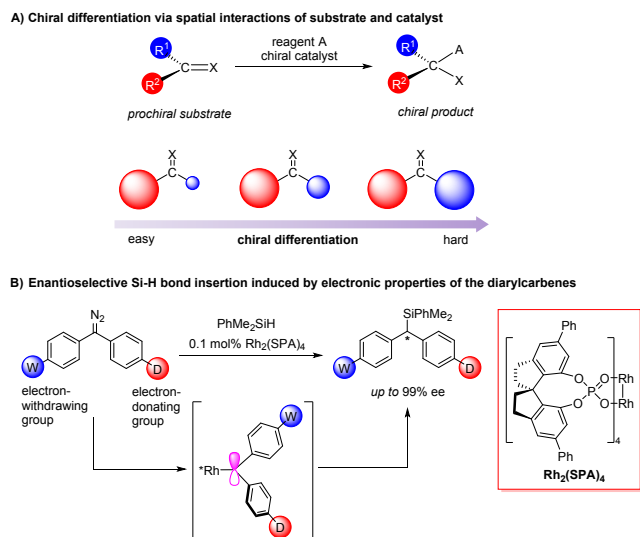
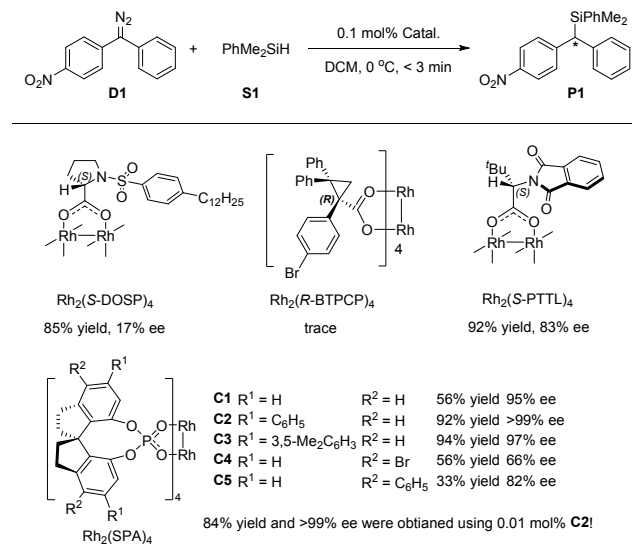


Figure 1. Chiral differentiations of prochiral faces and enantioselective diarylcarbene insertion into Si-H bonds.

RESULTS AND DISCUSSION

The insertion of 4-nitrophenyl phenyl diazomethane (**D1**) into dimethylphenylsilane (**S1**) was performed using several chiral dirhodium catalysts commonly used in asymmetric carbene transformations¹⁵ (see the Supporting Information for more details). The best performing catalyst for this reaction, $\text{Rh}_2(\text{S-PTTL})_4$, gave high yield but only modest enantioselectivity, prompting further investigation. A new type of dirhodium catalysts was developed which contain spiro phosphate ligands **C1**–**C5** (see Supporting Information for details).¹⁶ Of the spiro phosphate dirhodium catalysts, **C2** afforded both good yield and the highest enantioselectivity (Scheme 1). Even 0.01 mol% catalyst is sufficient for excellent results.

Scheme 1. Enantioselective Si-H Bond Insertion of 4-Nitrophenylphenyl Diazomethane Catalyzed by Chiral Dirhodium Catalysts^a



^a Reaction conditions: Catal/**D1**/**S1** = 0.0002:0.2:0.24 (mmol), 1 mL solution of **D1** was dropped into 2 mL solution of **S1** and catalyst at 0 °C, < 3 min, isolated yield.

A variety of diphenyl diazomethylenes **D1**–**D12** bearing electronically different *para* substituents were evaluated in the reaction with silane **S1** catalyzed by **C2** (Table 1). The substrates with a strong electron-withdrawing group or a strong electron-donating group at the *para* position of one phenyl ring exhibited high enantioselectivity (entries 1–4 and 12), while the substrates having a moderate or weak electronic effect exhibited lower enantioselectivity (entries 5–11). Moreover, the substrates with electron-withdrawing groups (**D3**, R = CF₃) or electron-donating groups (**D11**, R = OMe) afforded Si-H bond insertion products with opposite absolute configurations (entry 3 and entry 11). When the Hammett substituent constant (σ_p)¹⁷ differences of the *para* substituents of two phenyl rings are over 0.5, the ee values of the corresponding Si-H bond insertion products are over 90%. Moreover, a plot of log(er) values against Hammett's σ_p values is shown in Figure S1 (slope 2.86, R² = 0.96). These results clearly indicate that the enantioselectivity of this reaction is directly related to the electronic properties of carbene intermediates.

Table 1. Rhodium-Catalyzed Enantioselective Si-H Bond Insertions of Diphenyl Diazomethylenes **D1**–**D12**

entry ^a	R	$\Delta\sigma_p$ (R-H) ^b	product	yield (%)	ee (%)
1	NO ₂	0.78	P1	92	>99
2	CN	0.66	P2	96	98
3 ^c	CF ₃	0.54	P3	91	95 (<i>S</i>) ^d
4 ^c	SCF ₃	0.50	P4	68	97
5 ^c	OCF ₃	0.35	P5	66	76
6	Cl	0.28	P6	95	66
7	Br	0.23	P7	79	77
8	I	0.18	P8	62	82
9 ^c	F	0.06	P9	88	25
10	Me	−0.17	P10	51	18
11	OMe	−0.27	P11	47	64 (<i>R</i>) ^d
12	NMe ₂	−0.60	P12	45	91

^a Reaction conditions: Condition A (for entries 1–3, 6–7, and 10–11): diazo compound (0.2 mmol), PhMe₂SiH (1.2 equiv), **C2** (0.1 mol%), DCM, 0 °C; Condition B (for entries 4, 5, 8, 9 and 12): hydrazone (0.2 mmol), MnO₂ (3.5 equiv), MgSO₄, DCM, rt, 5–6 h; then, PhMe₂SiH (1.2 equiv), **C2** (0.1 mol%), DCM, 0 °C. Isolated yields were given. The ee values were determined by chiral HPLC.

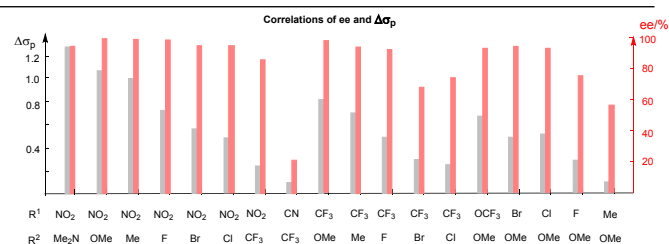
^b Hammett substituent constant for *para* substituents. ^c The ee value was determined by the corresponding alcohol obtained through the oxidation of Si-H insertion product. ^d The absolute configuration was assigned by analogy with the reported data (see Supporting Information for details).

Next, various diphenyl diazomethanes bearing different *para* substituents were studied (Table 2). These results show that the enantioselectivity of the reaction is directly correlated with the differences in substrate electronics. Again, when the difference of Hammett substituent constant of the two *para* substituents is equal or greater than 0.5, the ee of the corresponding Si-H bond insertion product is equal or greater than 90% (entries 1–6, 9–11, and 14–16). Moreover, sterically similar substituents (e.g. *para*-NO₂ vs *para*-NMe₂, entry 1; *para*-CF₃ vs *para*-CH₃, entry 10; *para*-OCF₃ vs *para*-OCH₃, entry 14) were precisely

differentiated indicating that the observed enantioselectivity is not a result of steric effects.

Table 2. Rhodium-Catalyzed Enantioselective Si–H Bond Insertion of Diphenyl Diazomethanes D13–D30

entry ^a	R ¹	R ²	$\Delta\sigma_p$ (R ¹ -R ²) ^b	product	yield(%)	ee (%)
1	NO ₂	NMe ₂	1.38	P13	66	96
2	NO ₂	OMe	1.05	P14	78	99
3	NO ₂	Me	0.95	P15	87	99
4	NO ₂	F	0.72	P16	86	98
5	NO ₂	Br	0.55	P17	80	95
6	NO ₂	Cl	0.5	P18	88	96
7	NO ₂	CF ₃	0.24	P19	58	86
8	CN	CF ₃	0.12	P20	42	36
9	CF ₃	OMe	0.81	P21	78	98
10 ^c	CF ₃	Me	0.71	P22	85	94(<i>S</i>)
11 ^c	CF ₃	F	0.48	P23	63	92
12 ^c	CF ₃	Br	0.31	P24	71	67
13 ^c	CF ₃	Cl	0.26	P25	73	76(<i>R</i>)
14	OCF ₃	OMe	0.62	P26	58	93
15	Br	OMe	0.50	P27	58	94
16	Cl	OMe	0.55	P28	59	93
17 ^c	F	OMe	0.33	P29	43	77(<i>R</i>)
18	Me	OMe	0.10	P30	40	56

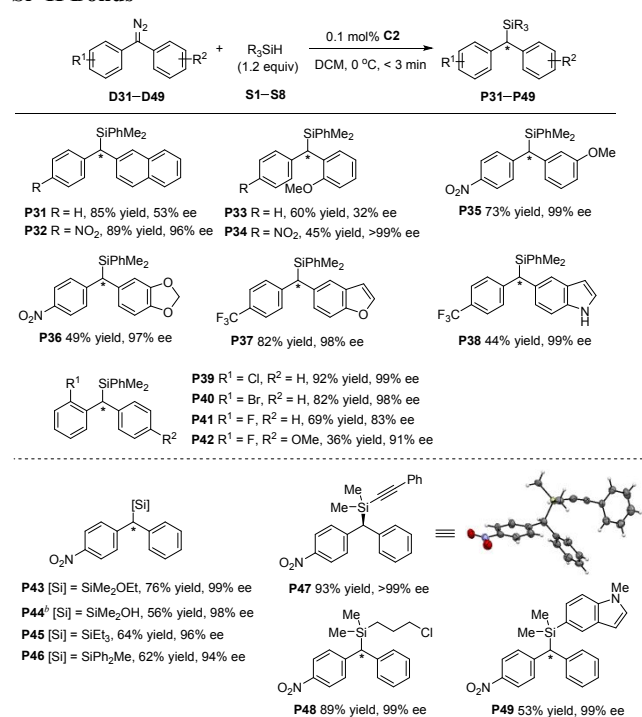


^a Reaction conditions: hydrazone (0.2 mmol), MnO₂ (3.5 equiv), MgSO₄, DCM, rt, 5–6 h; then, PhMe₂SiH (1.2 equiv), **C2** (0.1 mol%), DCM, 0 °C. Isolated yields were given. The ee values were determined by chiral HPLC analysis. ^b The Hammett substituent constant difference for *para* substituents. ^c The ee value was determined by the corresponding alcohol obtained through the oxidation of Si–H insertion product. A plot of log(*er*) vs $\Delta\sigma_p$ (R¹-R²) is shown in Figure S2.

The chiral spiro phosphate dirhodium catalyst **C2** is also efficient for the enantioselective Si–H bond insertion of other diazo compounds containing two different aryl groups (Scheme 2). In every case, the electronic property of the substituents on the aryl rings significantly affected the enantioselectivity of reaction. For instance, the naphthyl phenyl diazomethane afforded the Si–H bond insertion product **P31** with 53% ee; however, introducing a *para*-NO₂ at the phenyl ring dramatically increased the ee value of product **P32** to 96%. Similarly, 4-nitrophenyl 2'-methoxyphenyl diazomethane provided much higher enantioselectivity (**P34**, >99% ee) than 2-methoxyphenyl phenyl diazomethane (**P33**, 32% ee). Moreover, if one aryl ring of the substrates has a strong electron-withdrawing *para* substituent (e.g. NO₂ or CF₃), and the other aryl ring is a heteroaryl ring (**P36–P38**), excellent

enantioselectivity can be obtained. Excellent enantioselectivity can also be achieved when the diaryl diazomethane substrates have an *ortho* substituent (**P39** and **P40**). Presumably due to small radius of fluorine atom, the 2-fluoro-substituted diazo compound afforded relatively lower ee (83% ee, **P41**). However, the enantioselectivity can be increased by introducing an electron-donating group (4-OMe) at the other aryl ring of the substrate (91% ee, **P42**). In addition to dimethylphenylsilane (**S1**), other silanes can also be used in the Si–H bond insertion reaction with diaryl diazomethane **D1**, affording Si–H bond insertion products with excellent enantioselectivity (**P43–P49**). It is worth mentioning that the alkynyl silane underwent Si–H bond insertion reaction, giving the corresponding product **P47** with high yield (93%) and excellent enantioselectivity (>99% ee). The absolute configuration of (*S*)-**P47** was determined by a single crystal X-ray diffraction analysis.

Scheme 2. Substrate Scope of Diarylcarbene Insertion into Si–H Bonds^a



^a Reaction conditions: hydrazone (0.2 mmol), MnO₂ (3.5 equiv), MgSO₄, DCM, rt, 5–6 h; then, PhMe₂SiH (1.2 equiv), **C2** (0.1 mol%), DCM, 0 °C. Isolated yields were given. The ee values were determined by chiral HPLC analysis. ^b Dimethylchlorosilane was used and the hydrolysis product was isolated after work-up.

MECHANISTIC STUDIES

A kinetic isotopic study was carried out; in a competition experiment using dimethylphenylsilane and deuterated dimethylphenylsilane, the kinetic isotope effect (KIE) was found to be 1.5 (see Supporting Information for details). This result is similar to the values reported in the Si–H insertions of aryl diazoesters catalyzed by transition metals such as Ir^{14c}, Rh^{14d} and Cu¹⁸; these reactions proceed through concerted three-center transition states. In order to gain insights about the origin of enantioselectivity from the catalyst and the electronic effects of substrates, we also conducted a computational investigation. **C1** was used as the model catalyst.¹⁹ X-ray structure analysis of the catalyst **C1** reveals that the presence of

four identical chiral ligands around the dirhodium core results in a rigid catalyst with higher symmetry (D_4 symmetry) than the ligands themselves (C_2 symmetry).¹⁶ This symmetry causes both sides of the dirhodium catalyst to be identical, limiting the number of possible conformations for the transition state of Si-H insertion.

Initially, a dirhodium-tetraformate catalyst ($Rh_2(O_2CH)_4$) was computed to observe transition state geometries in the absence of any steric effects caused by the ligands (see Supporting Information for details). Fig. 2A shows that the Si-H insertion proceeds via a concerted three-center transition state. Calculated transition state geometries for diphenyl carbene insertion into the Si-H bond of dimethylphenylsilane show that one aryl ring rotates to a near-coplanar orientation with the carbene empty p orbital while the other phenyl ring rotates to a near orthogonal orientation. For substituted diphenyl carbenes, two transition state geometries are possible depending on whether the substituted aryl ring is conjugated (TS-1) or orthogonal (TS-2) to the empty p orbital. These two transition states are not equal in energy and the favored transition state always results when the electron-rich aryl ring is nearly coplanar with carbene plane. Plotting the energy difference ($\Delta\Delta G^\ddagger$) vs the corresponding Hammett substituent constant σ_p shows a linear correlation (Fig. 2A), indicating that this energy difference is greater when the electronic difference between aryl rings is more pronounced.

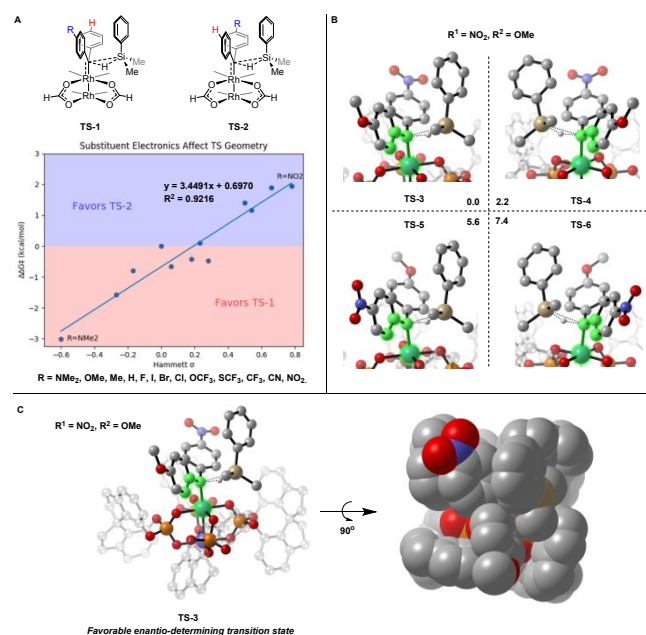


Figure 2. Computational studies. **A)** Optimized transition state structures for carbene insertion into Si-H bond with a tetraformate dirhodium ($Rh_2(O_2CH)_4$) as a model catalyst. **B)** Structures of optimized transition states for the Si-H bond insertion of asymmetrically substituted diphenyl carbene formed from **C1**. ONIOM partitioning of the transition state geometry, with the atoms shown opaque modelled with density functional theory (DFT), and the atoms shown transparent modelled with the universal force field (UFF). The relative Gibbs free energies with single point corrections are given in kcal mol⁻¹. **C)** Favorable enantio-determining transition state structure for the Si-H bond insertion of asymmetrically substituted diphenyl carbene ($R^1 = NO_2$, $R^2 = OMe$) formed from **C1**.

In the chiral environment of **C1**, the transition state for the Si-H bond approaching to the asymmetrical diphenyl carbene

($R^1 = NO_2$, $R^2 = OMe$) from its *Re* face (**TS-3**) is the lowest in energy (Fig. 2B, 2C). This transition state is favored by 5.6 kcal mol⁻¹ over TS-5 due to the different steric effects of the two aryl substituents on carbene; this steric difference originates from the electronic effects of substituents that orients electron-rich and electron-deficient aryl rings differently. Moreover, **TS-3** is favored by 2.2 kcal mol⁻¹ over **TS-4** (which would lead to the opposite enantiomer) due to steric effects the chiral catalyst has on the transition state conformations. In these structures, the electron-rich aryl ring ($R^2 = OMe$) is able to adopt a more coplanar orientation in **TS-3** ($\theta = 19.5^\circ$) than in **TS-4** ($\theta = 31.6^\circ$). The last possible transition state, **TS-6**, is 7.4 kcal mol⁻¹ higher in energy than **TS-3** due to both unfavorable electronics and steric clashes with the catalyst. Moreover, when two aryls of the carbene have similar electronic property, as in the case for $R^1 = CN$, $R^2 = CF_3$, the energy difference between **TS-3** and **TS'-5** is smaller (2.4 kcal/mol), which is consistent with the low enantioselectivity observed in the experiment (see Supporting Information for details).²⁰

These calculations show that the chiral environment of the catalyst **C1** can fix the conformations of the transition state in the Si-H bond insertion reaction. On this basis, the energy difference of the transition states, which relates to the enantioselectivity of reaction, is primarily due to the electronic difference between two aryls of carbene.

CONCLUSION

In summary, we have achieved a method for highly enantioselective carbene insertion into Si-H bonds that relies primarily on the electronic properties of the substrates. It represents the first highly enantioselective diarylcarbene insertion into the heteroatom-hydrogen bonds. A new class of D_4 -symmetric dirhodium catalysts bearing chiral spiro phosphate ligands was developed, and computational studies demonstrate that the chiral environment of these catalysts can differentiate the various possible transition state conformations. The chiral induction observed in this study not only enables the unprecedented enantioselective transformations of carbenes having spatially similar groups, but also inspires the development of new strategies for chiral transformations of charged active intermediates, such as carbocations, carbanions, as well as carbon radicals.

ASSOCIATED CONTENT

Supporting Information.

The data supporting the findings of this study are available within the paper and its Supplementary Information. Geometrical parameters for the structure of reagents **C3** and **P47** (see Supplementary Information) are available from the Cambridge Crystallographic Data Centre (<https://www.ccdc.cam.ac.uk/>) under reference numbers CCDC 1888695 and CCDC 1888689, respectively. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing interests.

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