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Diastereospecific Coupling of Imines by Low-Valent Titanium: An Experimental and Computational Study

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The reaction of phenylsilane ($PhSiH_3$) and titanium(IV) isopropoxide [Ti(O*i*Pr)$_4$] generates low-valent titanium alkoxides that reduce and reductively couple imines. The C–C coupling reaction is diastereospecific, with exclusive formation of the (±)-isomer. The yield is dependent on the concentration of titanium(IV) isopropoxide used. Using imines with varying electronic demand revealed that the coupling is most efficient for unsubstituted imines. The involvement of a trimeric titanium biradical species is invoked to explain the observed concentration dependence and diastereospecificity in the reaction. Multilayer ONIOM ("our own n-layered integrated molecular orbital and molecular mechanics") calculations were carried out on the plausible intermediates involved by using the Guassian 09 suite of programs. Formation of the trimeric biradical species leading to the formation of the (±)-isomer is more favored than formation of the trimeric biradical species, which leads to the *meso*-isomer. Similar calculations with dimeric intermediates do not predict the (±)-selectivity. Mass spectral analysis of the reaction mixture indicates the presence of a trimeric titanium alkoxide species.

Introduction

Vicinal diamines are extensively used as complexing agents for metal ions in a range of applications,[1] including catalysis and radiopharmaceuticals.[2] One of the most convenient routes to diamines is through the reductive coupling of imines using low-valent metal reagents.[3]

Electrochemical reduction results in the formation of diamines through coupling.[4] A more convenient way however, is to use electropositive metals as odd-electron reductants. Thus, alkali metals[5a–5e] mediate the reductive dimerization of *N*-benzylideneaniline, and it was observed that the use of crown ethers has a dramatic effect on the chemical yield.[5e] Group 13 elements, such as Al and In, have also been used in the synthesis of vicinal diamines.[6] The reaction is very fast with aluminum powder and proceeds at room temperature, whereas the same reaction takes much longer with bismuth powder. The coupling reaction using indium proceeds only under drastic conditions. In addition, bimetal redox systems such as Pb/Al are reported to mediate such reactions.[7] Lanthanides, such as Sm and Yb, are widely used for the reductive coupling of both carbonyl compounds and imines.[8]

Many transition metals mediate the coupling reaction in the low-valent state. Examples include Zn–Cu couples[9] and complexes of V,[10] Nb,[11] Mn,[12] Ni,[13] Zn,[14] Ti,[15] and Zr.[16] The reductive dimerization of imines[15a–15h] and carbonyl compounds[15i–15n] has also been accomplished using reduction of titanium in situ to give low-valent titanium (LVT) reagents. In these reactions, [Ti(O*i*Pr)$_4$] is reduced to a Ti^{II} species on treatment with a Grignard reagent, which in turn brings about the coupling of *N*-benzylideneaniline.[15a–15c] There have been a few reports in which titanium chloride has been used as a precursor for the low-valent metal species. Most of these reagents are generated in situ from $TiCl_4$–Mg[15d–15g] in tetrahydrofuran (THF), $TiCl_4$–Hg[15d–15g] in THF, and $TiCl_4$–Et_3N.[15h]

Recently, Vairaprakash and Periasamy reported the intramolecular diastereoselective and enantioselective coupling of diamines to give diarylpiperazines using a mixture of Zn and [Ti(O*i*Pr)$_2$Cl$_2$] in the presence of a chiral ligand.[3a,17] Sato and co-workers have achieved the heterocoupling of imines with 99% selectivity towards the *threo*-isomer.[15c] Excellent (±)-selectivity was also reported in the reaction with Sm, which proceeded under microwave conditions, albeit with poor yield.[8f] The catalytic reductive coupling of aldimines has been achieved with good yield and high *meso*-selectivity either by the use of a Cp_2VCl_2/$PhMe_2SiCl$/Zn system[10] or by using a combination of *n*-butyllithium and sulfur in THF.[5a] In this study, we report the use of a combination of titanium isopropoxide [Ti(O*i*Pr)$_4$] and phenylsilane ($PhSiH_3$) to generate low-valent Ti species. This combination brings about Pinacol-type coupling of

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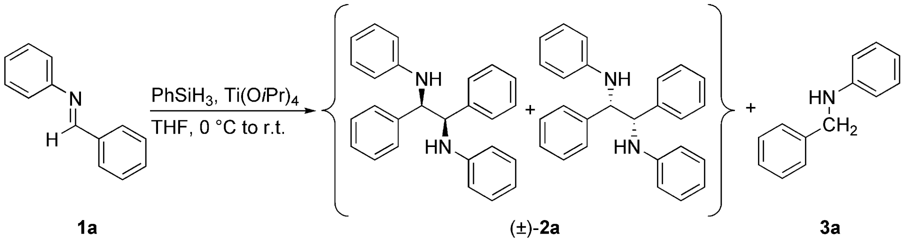


Scheme 1. Reduction of aldimine **1a** with $PhSiH_3$ mediated by [Ti(O*i*Pr)$_4$].

imines under ambient conditions. The coupling reaction was studied for imines with a range of electronic demands. The reaction is diastereospecific and only the (±)-isomer is obtained.

Results and Discussion

Reaction of Imine with Phenylsilane in the Presence of Titanium Isopropoxide

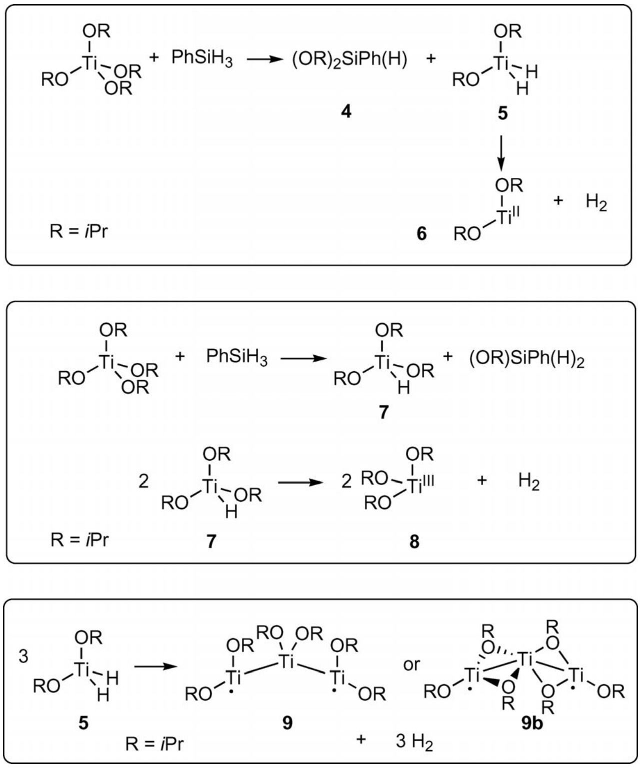
The reaction of *N*-benzylideneaniline (**1a**) was carried out with an equimolar amount of [Ti(O*i*Pr)$_4$] in THF (Scheme 1). The reaction mixture was cooled to 0 °C, an equimolar amount of phenylsilane ($PhSiH_3$) was added, and the reaction was brought to ambient temperature and stirred for 24 h.

Analysis of the products after work up of the reaction indicated the presence of a C–C-coupled product, (±)-*N*,*N′*,1,2-tetraphenyl-1,2-ethanediamine (**2a**) and the reduced imine *N*-phenylbenzenemethanamine (**3a**), in 71 and 22% yield, respectively (weight% with respect to imines).

The formation of **2a** was confirmed by analyzing the ^{1}H, ^{13}C NMR (both ^{1}H-coupled and ^{1}H-decoupled), and HRMS data. The NMR spectroscopic data of compound **2a** was also compared with reported values (Figure S1 in the Supporting Information).[4b,6d] Interestingly, the C–C coupling reaction was found to be diastereospecific, and only the (±)-isomer was obtained. Thus, a combination of [Ti(O*i*Pr)$_4$] and $PhSiH_3$ can be used to bring about a diastereospecific Pinacol-type coupling of imines under ambient conditions.

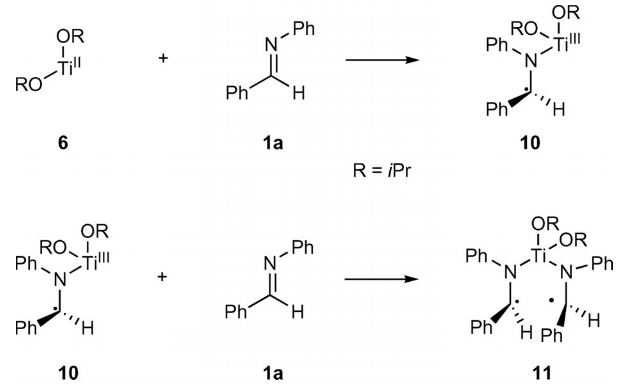
Possible Mechanism of the Reaction

Equimolar amounts of [Ti(O*i*Pr)$_4$] and $PhSiH_3$ were mixed in dichloromethane in a NMR tube at 0 °C in the absence of the substrate and the solution, was warmed to room temperature. Gas evolution was observed and the color changed to brownish black. ^{1}H NMR spectroscopic analysis of the sample revealed a singlet at δ = 4.6 ppm, indicating the presence of molecular hydrogen, which is significantly more downfield shifted than the Si–H proton of $PhSiH_3$, which is normally observed at δ = 4.2 ppm. A very broad signal was also observed in the negative region at δ = –8.6 ppm, suggesting the presence of a possible Ti–H intermediate, which is consistent with earlier reports.[18a,18b] The evolution of molecular hydrogen and the involvement of a Ti–H species suggests the reduction of [Ti(O*i*Pr)$_4$]. The low-valent titanium species that are possibly generated in this reaction are Ti^{II} **6** or Ti^{III} **8** species, shown in Scheme 2. Following the extensive work of Eisch and coworkers,[18c–18g] we propose the possibility of a trimeric biradical species **9/9b** (where **b** indicates a bridged isomer) in the presence of excess [Ti(O*i*Pr)$_4$] (Scheme 2).

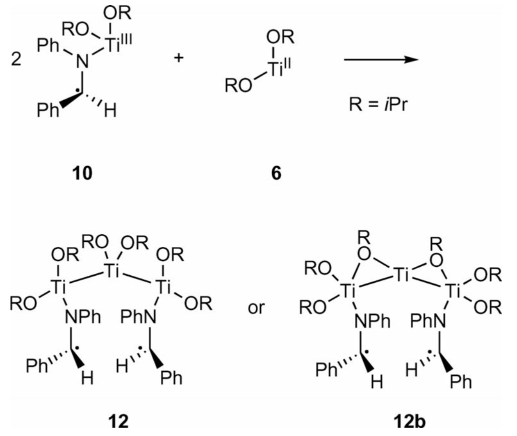


Scheme 2. Plausible reactions of [Ti(O*i*Pr)$_4$] with $PhSiH_3$.

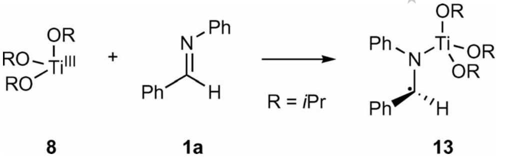
During the reduction process, if imine **1a** reacts with a Ti^{II} species such as **6** then it would lead to the formation of either a Ti^{III} species **10** or a Ti^{IV} species **11** (Scheme 3). The Ti^{III} species **10** can further react with two molecules of Ti^{II} species **6** to give mixed valent species **12/12b** (Scheme 4), which is a species derived from the trimeric biradical intermediate **9/9b**. Similarly, reaction of imine **1a** with Ti^{III} species **8** would result in the formation of a Ti^{IV} species **13** (Scheme 5). All intermediates (**11**, **12/12b**, and **13**) could lead to the coupled product **2a**.



Scheme 3. Intermediates formed in the reaction of low-valent titanium species **6** with imine **1a**.



Scheme 4. Formation of $\mathrm{Ti^{III}}$ species **12** in the reaction of **10** and **6**.



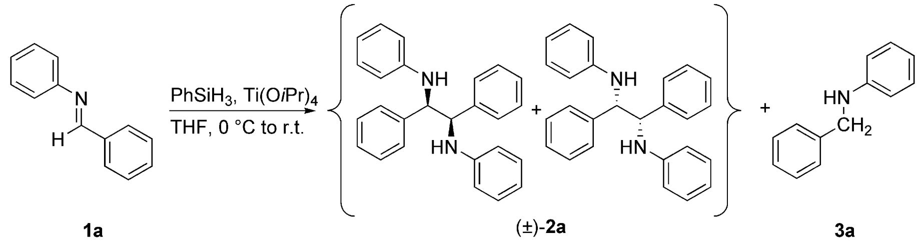
Scheme 5. Intermediates formed in the reaction of low-valent titanium species **8** with imine **1a**.

Reaction with Varying Amounts of Titanium(IV) Isopropoxide

The involvement of monomeric $\mathrm{Ti^{II}}$ and $\mathrm{Ti^{III}}$, or a trimeric biradical species can be distinguished by carrying out experiments with varying concentrations of $[\mathrm{Ti}(\mathrm{O}i\mathrm{Pr})_4]$. Thus, the ratio of imine **1a** to $\mathrm{PhSiH_3}$ was kept constant and the amount of $[\mathrm{Ti}(\mathrm{O}i\mathrm{Pr})_4]$ was varied. Reducing $[\mathrm{Ti}(\mathrm{O}i\mathrm{Pr})_4]$ to catalytic amounts did not give good yields (Table 1, entries 1, 2, and 3). However, when a stoichiometric amount of $[\mathrm{Ti}(\mathrm{O}i\mathrm{Pr})_4]$ was used, there was significant improvement in the yield of diamine **2** (Table 1, entry 4).

When more than stoichiometric amounts of $[\mathrm{Ti}(\mathrm{O}i\mathrm{Pr})_4]$ was used, diamine **2a** was obtained in excellent yields (Table 1, entries 5 and 6). Clearly, the yield of diamine **2a** was a function of the concentration of $[\mathrm{Ti}(\mathrm{O}i\mathrm{Pr})_4]$ used. The (±)-isomer was obtained exclusively in all cases. Hence, it is unlikely that the C–C coupling occurs through free organic radicals or a single titanium centre intermediate, such as **11**, which would not have such a concentration dependence. It is more likely that the C–C coupling reaction involves a multinuclear intermediate, such as **12**, resulting from either reaction of **9** with the imine, or the bimolecular coupling of intermediate **13** derived from $\mathrm{Ti^{III}}$ species **8**.

Table 1. Coupling of aldimine **1a** with varying amounts of $\mathrm{PhSiH_3}$ and $[\mathrm{Ti}(\mathrm{O}i\mathrm{Pr})_4]$.



Entry	$\mathrm{PhSiH_3}$ [equiv.]	$\mathrm{Ti}(\mathrm{O}i\mathrm{Pr})_4$ [equiv.]	Time [h]	Ratio of products [%][a]		Isolated yield [%][b]	
				2	**3**	**2**	**3**
1	1.0	0.01	24	–	–	–	–
2	1.0	0.1	24	50	50	5	5
3	1.0	0.5	24	53	47	29	20
4	1.0	1.0	24	66	34	71	22
5	1.0	2.0	24	86	14	89	7
6	1.0	2.5	24	91	9	94	ND

[a] Ratio of products determined from ^{1}H NMR spectroscopic analysis of the crude product. [b] Yields are wt.-% with respect to the imine.

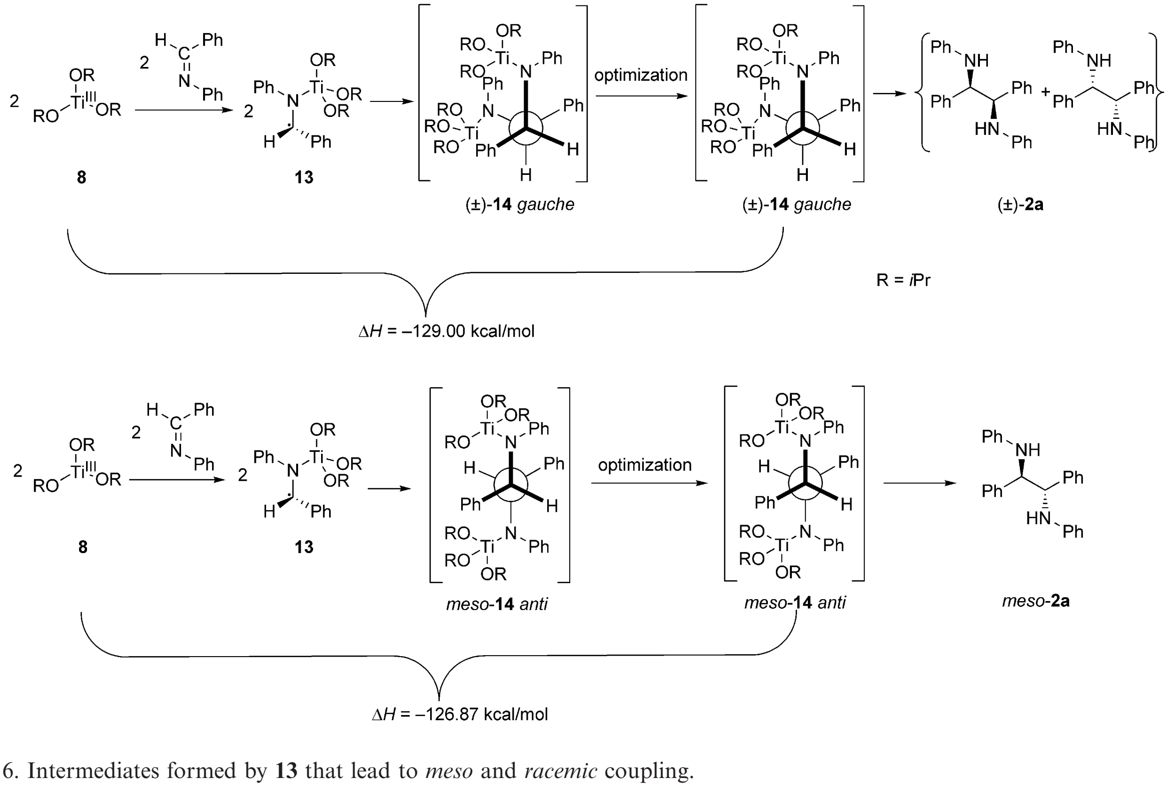
Computational Studies

To understand the observed diastereoselectivity in the C–C coupling reaction, the possible intermediates resulting from C–C bond formation were modeled. A multilayer ONIOM ("our own n-layered integrated molecular orbital and molecular mechanics") model (DFT and UFF molecular mechanics) calculation was carried out using the Gaussian 09 package to evaluate the relative stabilities of **14** and **15**.

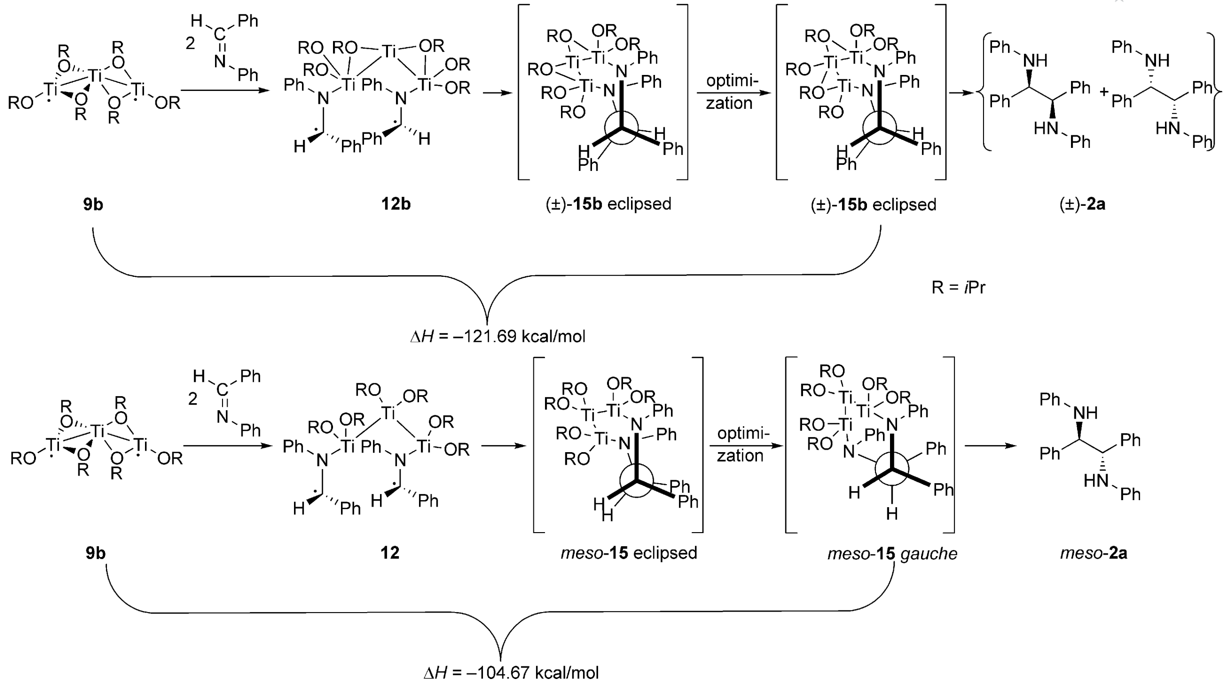
Two molecules of the intermediate **13** combined to give the C–C-coupled intermediate, (±)-**14** or *meso*-**14** (Scheme 6). Because we found the bridged intermediates to be more stable in some multinuclear complexes, alkoxy-bridged forms (±)-**14b** *gauche* and *meso*-**14b** *gauche* were also optimized (see the Supporting Information, Table S1 and Figure S2). All conformers (*gauche*, *anti*, and eclipsed forms) of the two isomers were examined. The most stable form of the coupled product arising from dimerization of **13** was the (±)-form (±)-**14** *gauche*, without bridges. However this form was stabilized by only 2 kcal/mol compared to the most favored *meso*-**14** *anti*. This energy is small enough to permit interconversion between the (±)- and *meso*-intermediates. The computed relative energies of various diastereoisomers are shown in Figure S2 in the Supporting Information. If indeed the intermediate **13**, derived from a Ti^{III} species **8**, was involved in the coupling reaction, one would expect formation of the (±)- and the *meso*-isomers in nearly equal amounts. Because this prediction is contrary to the observed result, one can exclude the involvement of species such as **13**.

However, if the possibility of a species such as **12**, which does not contain an alkoxy bridge, is invoked, the coupling would lead to the intermediates (±)-**15** *gauche* or *meso*-**15** *gauche*. In contrast, intermediate **12b**, which contains two alkoxy bridges, gives (±)-**15b** eclipsed or *meso*-**15b** *gauche*. Due to the cyclic form of intermediate **15**, only the eclipsed and *gauche* conformations are possible. Here, the coupling is more favored for formation of (±)-**15b** eclipsed, by 17 kcal/mol (Scheme 7, Table S2 and Figure S3 in the Supporting Information). This is in agreement with the experimental results, where exclusive formation of the (±)-isomer is observed. Hence, the intermediate proposed by Eisch et al. best fits the experimental results. Thus, we conclude that the diastereoselectivity arises from the involvement of a trimeric biradical species that contains two alkoxy bridges.

When the reaction mixture containing equivalent amounts of [Ti(O*i*Pr)$_4$] and PhSiH$_3$ in methanol was analyzed by ESI-MS, the major peak corresponded to the hydrolyzed product of the trimeric titanium complex (Figure 1). Several other minor peaks could also be assigned to different trimeric titanium species as shown in Figure S4 in the Supporting Information. These observations support, but do not confirm, our hypothesis that a multinuclear titanium intermediate is present in the reaction mixture and is probably responsible for the reaction.



Scheme 6. Intermediates formed by **13** that lead to *meso* and *racemic* coupling.



Scheme 7. Intermediates formed by **12/12b** that lead to *meso* and *racemic* coupling.

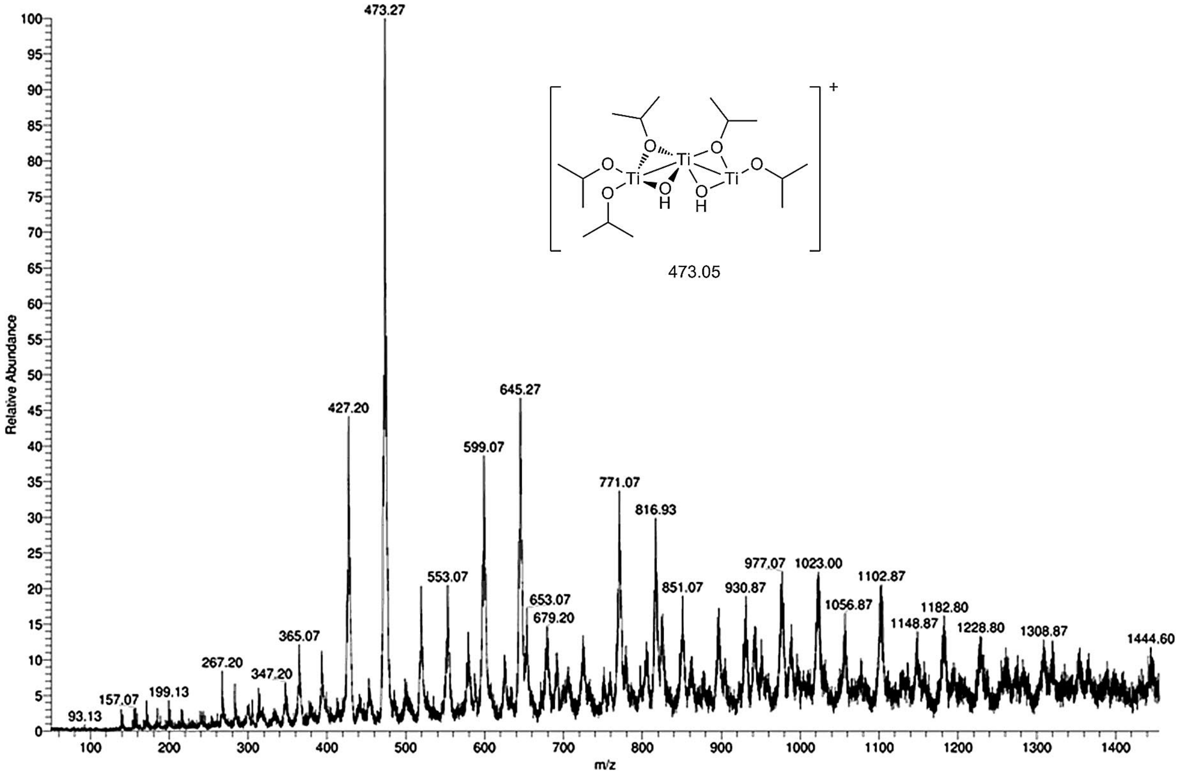
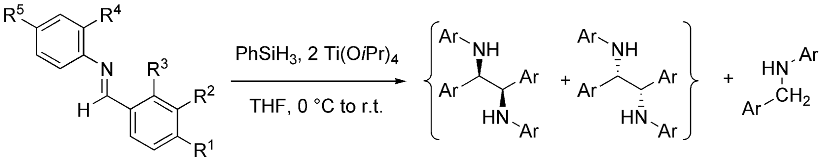


Figure 1. Mass spectrum of a methanol solution containing equivalent amounts of [Ti(O*i*Pr)$_4$] and PhSiH$_3$.

Reaction with Imines of Varying Electronic Demand

The reaction was carried out with aldimines with varying electronic demands. All reactions lead to exclusive formation of the (±)-isomer. Normally, the benzylic carbon of a (±)-isomer appears around δ = 63–65 ppm in the ^{13}C NMR spectra, whereas the corresponding carbon for a *meso* isomer appears around δ = 60–61 ppm.[4b,6d] For all the coupled products, a single benzylic carbon was observed in the ^{13}C NMR spectra at around δ = 64–65 ppm, which is in-

Table 2. Reductive coupling of aldimines with varying electronic demands mediated by two equivalents of titanium isopropoxide.



1a–j (±)-**2a–j** **3a–j**

Entry	Imine	R^1	R^2	R^3	R^4	R^5	Isolated yield [%][a]	
1	**1a**	H	H	H	H	H	89 (**2a**)	7 (**3a**)
2	**1b**	OMe	H	H	H	H	48 (**2b**)	47 (**3b**)
3	**1c**	OMe	H	H	H	F	30 (**2c**)	68 (**3c**)
4	**1d**	F	H	H	H	H	28 (**2d**)	70 (**3d**)
5	**1e**	H	H	H	H	F	32 (**2e**)	65 (**3e**)
6	**1f**	H	H	H	H	OMe	30 (**2f**)	60 (**3f**)
7	**1g**	H	H	H	OMe	H	16 (**2g**)	80 (**3g**)
8	**1h**	H	OMe	OH	H	H	–	86 (**3h**)
9	**1i**	H	H	OH	H	H	–	84 (**3i**)
10	**1j**	H	H	H	OH	H	–	72 (**3j**)

[a] All yields are wt.-% with respect to imines.

dicative of the presence of the (±)-isomer. The coupling reaction was found to proceed most efficiently in the case of the unsubstituted imine. Surprisingly, both electron-donating and electron-withdrawing groups decreased the yield of the C–C-coupled product (Table 2). Hence, the present method is best suited for imines that do not have strong electron-withdrawing or electron-donating substituents.

Conclusions

For the first time, a combination of $PhSiH_3$ and $[Ti(O\textit{i}Pr)_4]$ has been used to bring about the reduction and reductive coupling of aldimines. A striking feature of this reaction is that the C–C coupling is diastereospecific and the (±)-isomer is obtained exclusively. Among various models that were considered for the coupling reaction, the one that involves a trimeric biradical species explains the concentration dependence of the products in the reaction. Computational studies were useful to explain the (±)-selectivity. The formation of the (±)-isomer is computed to be more favorable than formation of the *meso* isomer. Mass spectral studies provide supporting evidence for the existence of a trimeric species in the reaction mixture. The coupling reaction proceeds more efficiently with unsubstituted imines.

Experimental Section

General: All manipulations were carried out under an inert atmosphere of dry nitrogen using a standard double manifold. Tetrahydrofuran was freshly distilled from sodium/benzophenone prior to use. $PhSiH_3$ and titanium(IV) isopropoxide were obtained from Aldrich U.S.A. The imines were prepared by a standard literature procedure.[19]

Physical Measurements: ^1H NMR, $^{13}C\{H\}$ NMR, were recorded with a Bruker AMX 400 spectometer operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR, with tetramethylsilane as internal reference. All spectra were recorded in $CDCl_3$. HRMS was recorded with a Micromass ESI-TOF MS instrument.

Reaction of *N*-Benzylideneaniline with $PhSiH_3$ in the Presence of 0.1 Equivalent of $[Ti(O\textit{i}Pr)_4]$: To a solution of *N*-benzylideneaniline (0.146 g, 0.81 mmol) in anhydrous THF (5.0 mL), was added titanium isopropoxide (0.1 equiv., 0.02 mL, 0.08 mmol). The reaction mixture was cooled to 0 °C in an ice bath and allowed to equilibrate for 30 min. To the above cooled solution was added dropwise phenylsilane (1.0 equiv., 0.1 mL, 0.81 mmol) with constant stirring. The colorless reaction mixture was warmed to room temperature, stirred for 24 h and then quenched by the addition of 1 N HCl (5.0 mL). The solution was filtered through a Celite pad and the filtrate was extracted with diethyl ether. The organic portion was separated and dried with anhydrous sodium sulfate. Solvent was then removed from the organic fraction to give a cream colored solid that contained compounds **2** and **3** in a ratio 1.0:1.0. The crude product was purified on a preparative TLC plate (petroleum ether/ethyl acetate/triethylamine, 98:1:1); yield of **2a**: 0.007 g (5%), yield of **3a**: 0.007 g (5%).

Reaction of *N*-Benzylideneaniline with $PhSiH_3$ in the Presence of 0.5 Equivalent of $[Ti(O\textit{i}Pr)_4]$: To a solution of *N*-benzylideneaniline (0.146 g, 0.81 mmol) in anhydrous THF (5.0 mL), was added titanium isopropoxide (0.5 equiv., 0.12 mL, 0.4 mmol). The reaction mixture was cooled to 0 °C in an ice bath and allowed to equilibrate for 30 min, then phenylsilane (1.0 equiv, 0.1 mL, 0.81 mmol) was added dropwise with constant stirring. The colorless reaction mixture became a brownish-black solution at room temperature on warming. After stirring at room temperature for 24 h the reaction was quenched by the addition of 1 N HCl (5.0 mL). The solution was then filtered through a Celite pad and the filtrate was extracted with diethyl ether. The organic portion was separated and dried with anhydrous sodium sulfate. Solvent was then removed from the organic fraction to give a cream colored solid that contained compounds **2** and **3** in the ratio 1.1:1.0. The crude product was purified on a preparative TLC plate (petroleum ether/ethyl acetate/triethylamine, 98:1:1); yield of **2a**: 0.043 g (29%), yield of **3a**: 0.029 g (20%).

Reaction of *N*-Benzylideneaniline with $PhSiH_3$ in the Presence of 1 Equivalent of $[Ti(O\textit{i}Pr)_4]$: To a solution of *N*-benzylideneaniline (0.146 g, 0.81 mmol) in anhydrous THF (5.0 mL), was added titanium isopropoxide (1.0 equiv., 0.24 mL, 0.81 mmol). The reaction mixture was cooled to 0 °C in an ice bath and allowed to equilibrate for 30 min. To the above cooled solution was added phenylsilane (1.0 equiv., 0.1 mL, 0.81 mmol) dropwise with constant stirring. The colorless reaction mixture, when warmed to room temperature, attained a brownish-black color. It was stirred at room temperature for 24 h and then quenched by the addition of 1 N HCl (5.0 mL). The solution was then filtered through a Celite pad and the filtrate was extracted with diethyl ether. The organic portion was separated and dried with anhydrous sodium sulfate. Solvent was then removed from the organic fraction to give a cream colored solid that contained compounds **2** and **3** in the ratio 1.9:1.0. The crude product was purified on a preparative TLC plate (petroleum ether/ethyl acetate/triethylamine, 98:1:1); yield of **2a**: 0.104 g (71%), yield of **3a**: 0.032 g (22%).

Reaction of *N*-Benzylideneaniline with $PhSiH_3$ in the Presence of 2 Equivalents of [Ti(O*i*Pr)$_4$]: To a solution of *N*-benzylideneaniline (0.146 g, 0.81 mmol) in anhydrous THF (5.0 mL), was added titanium isopropoxide (2.0 equiv., 0.48 mL, 1.62 mmol). The reaction mixture was cooled to 0 °C in an ice bath and allowed to equilibrate for 30 min. To the above solution was added phenylsilane (1.0 equiv., 0.1 mL, 0.81 mmol), dropwise with constant stirring. The colorless reaction mixture, when warmed to room temperature, attained a brownish-black color. The reaction mixture was stirred at room temperature for 24 h and then quenched by the addition of 1 N HCl (5.0 mL). The solution was then filtered through a Celite pad and the filtrate was extracted with diethyl ether. The organic portion was separated and dried with anhydrous sodium sulfate. Solvent was then removed from the organic fraction to give a cream colored solid that contained compounds **2** and **3** in the ratio 6.1:1.0. The crude product was purified on a preparative TLC plate (petroleum ether/ethyl acetate/triethylamine, 98:1:1); yield of **2a**: 0.131 g (89%), yield of **3a**: 0.011 g (7%).

Reaction of *N*-Benzylideneaniline with $PhSiH_3$ in the Presence of 2.5 Equivalents of [Ti(O*i*Pr)$_4$]: To a solution of *N*-benzylideneaniline (0.146 g, 0.81 mmol) in anhydrous THF (5.0 mL) was added titanium isopropoxide (2.5 equiv., 0.60 mL, 2.00 mmol). The reaction mixture was cooled to 0 °C in an ice bath and allowed to equilibrate for 30 min. To the above cooled solution was added phenylsilane (1.0 equiv., 0.1 mL, 0.81 mmol), dropwise with constant stirring. The colorless reaction mixture, when warmed to room temperature, gave a brownish-black solution. After stirring at room temperature for 24 h, the reaction was quenched by the addition of 1 N HCl (5.0 mL). The solution was then filtered through a Celite pad and the filtrate was extracted with diethyl ether. The organic portion was separated and dried with anhydrous sodium sulfate. Solvent was then removed from the organic fraction to give a cream colored solid that contained compounds **2** and **3** in the ratio 10.1:1.0. The crude product was purified on a preparative TLC plate (petroleum ether/ethyl acetate/triethylamine, 98:1:1); yield of **2a**: 0.138 g (94%).

The same procedure was followed for imines **1b–j** with $PhSiH_3$ in the presence of [Ti(O*i*Pr)$_4$] (2 equiv.).

***N*,*N′*,1,2-Tetraphenyl-1,2-ethanediamine (2a):** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.21 (m, 10 H), 7.06 (t, *J* = 8.0 Hz, 4 H), 6.66 (t, *J* = 8.0 Hz, 2 H), 6.52 (d, *J* = 8.0 Hz, 4 H), 4.55 (br. s, 4 H, 2CH, 2NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 64.15, 114.58, 118.59, 127.85, 128.03, 128.91, 129.61, 140.41, 147.54 ppm. HRMS: calcd. for $C_{26}H_{25}N_2$ [M + H]$^+$ 365.2025; found 365.1973.

1,2-Bis(4-methoxyphenyl)-*N*,*N′*-diphenyl-1,2-ethanediamine (2b): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.24 (m, 8 H), 6.75 (m, 4 H), 6.66 (t, *J* = 8.0 Hz, 2 H), 6.50 (d, *J* = 8 Hz, 4 H), 4.50 (br. s, 4 H, 2CH, 2NH), 3.79 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 55.67, 63.71, 114.26, 114.56, 118.44, 128.95, 129.58, 132.30, 147.59, 159.33 ppm. HRMS: calcd. for $C_{28}H_{28}N_2NaO_2$ [M + Na]$^+$ 447.2048; found 447.2015.

***N*,*N′*-Bis(4-fluorophenyl)-1,2-bis(4-methoxyphenyl)-1,2-ethanediamine (2c):** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.99 (m, 4 H), 6.75 (m, 8 H), 6.42 (m, 4 H), 4.38 (br. s, 4 H, 2CH, 2NH), 3.75 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 55.67, 64.37, 114.32, 115.48, 115.55, 115.91, 116.13, 126.01, 128.89, 131.98, 143.84, 155.38, 157.72, 159.40 ppm. HRMS: calcd. for $C_{28}H_{26}F_2N_2NaO_2$ [M + Na]$^+$ 483.1854; found 483.1860.

1,2-Bis(4-fluorophenyl)-*N*,*N′*-diphenyl-1,2-ethanediamine (2d): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.04 (m, 8 H), 6.92 (m, 4 H), 6.72 (m, 2 H), 6.52 (m, 4 H), 4.58 (s, 2 H, 2NH), 4.47 (s, 2 H, 2CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 64.05, 114.58, 115.78, 115.99, 118.92, 129.35, 129.42, 129.69, 135.93, 147.14 ppm.

***N*,*N′*-Bis(4-fluorophenyl)-1,2-diphenyl-1,2-ethanediamine (2e):** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.22 (m, 6 H), 7.13 (m, 4 H), 6.74 (t, *J* = 8.0 Hz, 4 H), 6.41 (m, 4 H), 4.47 (br. s, 4 H, 2CH, 2NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 65.10, 115.48, 115.53, 115.93, 116.15, 127.77, 128.16, 128.99, 140.11, 143.77, 155.03, 157.76 ppm. HRMS: calcd. for $C_{26}H_{23}F_2N_2$ [M + H]$^+$ 401.1821; found 401.1829.

***N*,*N′*-Bis(2-methoxyphenyl)-1,2-diphenyl-1,2-ethanediamine (2g):** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.15 (m, 9 H), 6.65 (m, 8 H), 6.31 (m, 1 H), 4.58 (s, 2 H, 2CH), 3.83 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 56.08, 64.48, 109.83, 110.54, 117.10, 121.74, 127.60, 128.00, 129.06, 138.55, 140.76, 147.75, 149.99 ppm. HRMS: calcd. for $C_{28}H_{28}N_2NaO_2$ [M + Na]$^+$ 447.2048; found 447.2076.

***N*-Phenylbenzenemethanamine (3a):** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.37 (m, 4 H), 7.18 (t, *J* = 8.0 Hz, 2 H), 6.72 (t, *J* = 7.6 Hz, 2 H), 6.63 (d, *J* = 8.4 Hz, 2 H), 4.34 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 48.35, 112.87, 117.60, 127.27, 127.55, 128.68, 129.31, 139.45, 148.18 ppm.

4-Methoxy-*N*-phenylbenzenemethanamine (3b): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.28 (d, *J* = 8.0 Hz, 2 H), 7.17 (t, *J* = 8.0 Hz, 2 H), 6.87 (d, *J* = 8.0 Hz, 2 H), 6.63 (d, *J* = 8.0 Hz, 2 H), 6.17 (t, *J* = 8.0 Hz, 1 H), 4.24 (s, 2 H), 3.79 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 47.91, 55.33, 112.90, 114.06, 117.62, 128.88, 129.21, 131.24, 148.07, 158.81 ppm.

***N*-(4-Fluorophenyl)-4-methoxybenzenemethanamine (3c):** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.19 (m, 2 H), 6.81 (m, 4 H), 6.49 (m, 2 H), 4.14 (s, 2 H), 3.74 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 48.89, 55.78, 114.07, 114.14, 114.52, 116.01, 116.23, 129.26, 131.67, 145.01, 159.38 ppm. HRMS: calcd. for $C_{14}H_{13}FK_2NO$ [M + 2K – H]$^+$ 308.0255; found 308.1554.

4-Fluoro-*N*-phenylbenzenemethanamine (3d): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.36 (m, 2 H), 7.19 (m, 2 H), 7.046 (t, *J* = 8.8 Hz, 2 H), 6.74 (t, *J* = 8.0 Hz, 1 H), 6.35 (d, *J* = 7.6 Hz, 2 H), 4.32 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 48.06, 113.38, 115.82, 116.03, 118.21, 129.44, 129.52, 129.77, 135.57, 148.40 ppm.

***N*-(4-Fluorophenyl)benzenemethanamine (3e):** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.32 (m, 5 H), 6.87 (t, *J* = 8.0 Hz, 2 H), 6.55 (m, 2 H), 4.28 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 48.42, 113.05, 115.15, 126.79, 126.96, 128.13, 138.65, 143.94, 155.21 ppm.

***N*-(4-Methoxyphenyl)benzenemethanamine (3f):** ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.55 (m, 5 H), 7.06 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 4.46 (s, 2 H), 3.92 (s, 3 H) ppm. ^{13}C

NMR (100 MHz, $CDCl_3$, 25 °C): δ = 49.50, 56.12, 114.63, 115.41, 127.75, 128.11, 129.23, 140.56, 143.14, 152.65 ppm.

***N*-(2-Methoxyphenyl)benzenemethanamine (3g):** ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.3 (m, 5 H), 6.82 (m, 2 H), 6.72 (m, 1 H), 6.61 (m, 1 H), 4.36 (s, 2 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 48.51, 55.89, 110.06, 112.10, 116.66, 117.36, 121.53, 127.98, 128.66, 137.73, 140.76, 147.27 ppm.

2-Hydroxy-3-methoxy-*N*-phenylbenzenemethanamine (3h): ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.09 (t, J = 8.0 Hz, 4 H), 6.73 (m, 4 H), 4.29 (s, 2 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 44.71, 56.51, 110.41, 114.20, 118.61, 120.00, 121.09, 129.68, 144.56, 147.22, 148.59 ppm. HRMS: calcd. for $C_{14}H_{15}NNaO_2$ $[M + Na]^+$ 252.1000; found 252.1000.

2-Hydroxy-*N*-phenylbenzenemethanamine (3i): ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.18 (s, 1 H), 7.28 (m, 5 H), 6.97 (m, 4 H), 4.45 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 46.37, 112.61, 115.36, 116.05, 119.23, 126.20, 127.99, 128.64, 129.33, 149.38, 155.41 ppm.

Computational Details: For theoretical studies, the imine **1a**, titanium intermediates **8**, **9**, **12**, and **13** were modeled. All structures were optimized using DFT (B3LYP/LANL2DZ)/UFF molecular mechanics calculations. The multilayer ONIOM model was used where the Ti, N, O, and C atoms (involved in C–C coupling and methine C atom of isopropoxide) were considered as the high layer and the rest of the atoms were defined as a low layer (see the Supporting Information). Atoms considered as high layer are represented as "ball and stick", whereas atoms in the low layer are represented as "tubes". The high layer was optimized using DFT at the B3LYP/LANL2DZ level of theory and the low layer was optimized using molecular mechanics calculation with the UFF forcefield. The Gaussian 09 program package was used for all calculations.[20]

Supporting Information (see footnote on the first page of this article): Cartesian coordinates of optimized structures and total energies, along with the energy profiles, and mass spectral data.

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