Catalyst Design Insights from Modelling a Titanium-Catalyzed Multicomponent Reaction

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Syntheses of Titanium Complexes

Synthesis of Ti(OPh\(_2\)-t-butyl\(_4\))\(_4\) (6e) can be found in the manuscript. The syntheses and characterization data for the other derivatives are below.

*Synthesis of Ti(OPh\(_2\)-t-butyl\(_4\)-methyl\)\(_4\) (6b)*

In a glovebox, a Schlenk flask was charged with 70 mL benzene, Ti(O\(^{i}{\text{Pr}}\)\(_4\) (1.09 g, 3.84 mmol), and a stir bar. To this solution was added 2-tert-butyl-4-methylphenol (2.53 g, 15.4 mmol, 4 equiv). The flask was sealed and transferred to a Schlenk line, where it was attached to a reflux condenser under N\(_2\). The solution was refluxed for 24 h. The volatiles were removed in vacuo to provide a bright yellow residue. The flask was transferred back to the glovebox where the yellow solids were recrystallized from pentanes to provide pure 6b (2.16 g, 87\%). X-ray quality single crystals were grown from a concentrated solution in \(n\)-hexane at \(-35 \, ^{\circ}\)C. \( ^1 \)H NMR (500 MHz, benzene-\(d_6\)): 7.35 (d, \(J = 8.0\) Hz, 4H), 7.11 (d, \(J = 2.2\) Hz, 4H), 6.72 (dd, \(J = 8.2, 2.1\) Hz, 4H), 2.09 (s, 12H), 1.56 (s, 36H). \( ^{13} \)C NMR (126 MHz, chloroform-\(d\)): 161.80, 136.30, 131.70, 127.66, 127.17, 122.86, 34.85, 30.23, 21.20. Elemental Analysis calc. for TiC\(_{44}\)H\(_{60}\)O\(_4\): C, 75.41; H, 8.63; N, 0. Found: C, 74.93; H, 8.89; N, 0.10.
Synthesis of Ti(OPh$_{2}$-t-butyl-4-Br)$_4$ (6f)

The procedure provided for the preparation of 6b was followed to prepare 6f using Ti(OiPr)$_4$ (0.568 g, 2 mmol), 2-tert-butyl-4-bromophenol (1.83 g, 8 mmol), and benzene (70 mL). The product was recrystallized from pentanes at −35 °C to yield pure 6f (1.42 g, 74%). X-ray quality crystals were grown from pentanes at −35 °C. $^1$H NMR (500 MHz, benzene-$d_6$) 7.37 (d, $J$ = 2.5 Hz, 4H), 7.17 (dd, $J$ = 8.5, 2.4 Hz, 4H), 6.86 (d, $J$ = 8.5 Hz, 4H), 1.37 (s, 36H). $^{13}$C NMR (126 MHz, benzene-$d_6$) 162.52, 138.85, 130.26, 130.20, 124.12, 116.13, 34.70, 29.42, 28.89. Elemental Analysis calc. for TiC$_{40}$H$_{48}$O$_4$Br$_4$: C, 50.04; H, 5.04; N, 0. Found: C, 49.49; H, 4.58; N, 0.09.

Synthesis of Ti(OPh$_{2}$-t-butyl-4-F)$_4$ (6d)

The procedure provided for the preparation of 6b was followed to prepare 6d using Ti(OiPr)$_4$ (888 µL, 3 mmol), 2-tert-butyl-4-fluorophenol (2.00 g, 12 mmol), and benzene (70 mL). The product was recrystallized from pentanes at −35 °C to yield pure 6d (2.36 g, 90%). X-ray quality crystals were grown from n-hexane at −35 °C. $^1$H NMR (500 MHz, benzene-$d_6$): 7.06–7.01 (m, 4H), 6.96 (dt, $J$ = 10.6, 2.3 Hz, 4H), 6.58–6.43 (m, 4H), 1.29 (d, $J$ = 1.8 Hz, 36H). $^{13}$C NMR (126 MHz, benzene-$d_6$): 163.34–158.24 (m), 157.73, 139.02 (d), 123.69 (d), 114.27 (d), 113.77 (d), 35.11, 29.84. $^{19}$F NMR (470 MHz, benzene-$d_6$): –117.57 to −119.68 (m). Elemental Analysis calc. for TiC$_{40}$H$_{48}$O$_4$F$_4$: C, 67.04; H, 6.75; N, 0. Found: C, 66.36; H, 6.87; N, 0.24.
Synthesis of Ti(OPh<sub>2</sub>-<sub>t</sub>-butyl-4-methoxy<sub>4</sub>)<sub>4</sub> (6a)

The procedure provided for the preparation of 6b was followed to prepare 6a using Ti(O<sup>i</sup>Pr)<sub>4</sub> (1.09 g, 3.83 mmol), 2-<sub>t</sub>-tert-butyl-4-methoxyphenol (2.77 g, 15.4 mmol), and benzene (70 mL). The product was recrystallized from pentanes at −35 °C to yield pure 6a (2.21 g, 80%).<sup>1</sup>H NMR (500 MHz, benzene-<em>d</em><sub>6</sub>): 7.37 (dd, <em>J</em> = 8.6, 1.1 Hz, 4H), 7.04 (dd, <em>J</em> = 3.1, 1.1 Hz, 4H), 6.57–6.35 (m, 4H), 3.30 (s, 12H), 1.55 (d, <em>J</em> = 1.2 Hz, 36H). <sup>13</sup>C NMR (126 MHz, benzene-<em>d</em><sub>6</sub>): 158.50, 155.07, 137.82, 123.22, 113.52, 110.67, 54.66, 34.87, 29.86. Elemental Analysis calc. for TiC<sub>44</sub>H<sub>60</sub>O<sub>8</sub>: C, 69.05; H, 7.86; N, 0. Found: C, 69.10; H, 7.91; N, 0.09.

Synthesis of Ti(OPh<sub>2</sub>-<sub>t</sub>-butyl-4-trifluoromethyl<sub>4</sub>)<sub>4</sub> (6g)

The procedure provided for the preparation of 6b was followed to prepare 6g using Ti(O<sup>i</sup>Pr)<sub>4</sub> (340 µL, 1.12 mmol), 2-<sub>t</sub>-tert-butyl-4-trifluoromethylphenol (0.973 g, 4.46 mmol), and benzene (70 mL). The product was recrystallized from a 1:1 mixture of Et<sub>2</sub>O and pentanes at −35 °C to yield pure 6g (670 mg, 70%). X-ray quality crystals were grown from <em>n</em>-hexane at −35 °C. <sup>1</sup>H NMR (500 MHz, benzene-<em>d</em><sub>6</sub>): 7.69 (d, <em>J</em> = 2.2 Hz, 4H), 7.13 (d, <em>J</em> = 2.2 Hz, 4H), 7.08 (d, <em>J</em> = 8.3 Hz, 4H), 1.27 (s, 36H). <sup>13</sup>C NMR (126 MHz, benzene-<em>d</em><sub>6</sub>): 165.20, 137.67, 125.65 (d), 124.91 (q), 124.67 (d), 122.76, 116.21, 34.71, 29.32. <sup>19</sup>F NMR (470 MHz, benzene-<em>d</em><sub>6</sub>): −61.45. Elemental Analysis calc. for TiC<sub>44</sub>H<sub>48</sub>F<sub>12</sub>O<sub>4</sub>: C, 57.65; H, 5.28; N, 0. Found: C, 57.37; H, 5.41; N, 0.18.
Synthesis of Ti(OPh₂ᵗʰ-buty)₄ (6c)

The procedure provided for the preparation of 6b was followed to prepare 6c using Ti(OiPr)₄ (383 µL, 1 mmol), 2-tert-butylphenol (0.601 g, 4 mmol), and benzene (30 mL). The product was recrystallized from a 1:1 mixture of Et₂O and pentanes at −35 °C to yield 6c (389 mg, 60%). X-ray quality crystals were grown from a concentrated solution of the complex in toluene layered with n-hexane at −35 °C. ¹H NMR (500 MHz, benzene-d₆): 7.38 (dd, J = 7.9, 1.2 Hz, 4H), 7.20 (dd, J = 7.9, 1.7 Hz, 4H), 6.91 (td, J = 7.6, 1.7 Hz, 4H), 6.84–6.73 (m, 4H), 1.49 (s, 36H). ¹³C NMR (126 MHz, benzene-d₆): 163.70, 136.52, 127.38, 126.77, 122.97, 122.86, 34.68, 29.96. Elemental Analysis calc. for TiC₄₀H₅₂O₄: C, 74.52; H, 8.13; N, 0. Found: C, 75.06; H, 8.36; N, 0.17.

Synthesis of Chromium Complexes

The starting material NCr(NiPr₂)₃ was prepared using the literature procedure.¹ Substituted phenols were purchased from Sigma-Aldrich and were purified by sublimation prior to use.

Synthesis of NCr(NiPr₂)₂(OPh₄-methyl): A scintillation vial was charged with NCr(NiPr₂)₃ (50 mg, 0.14 mmol), a stir bar, and Et₂O (3 mL). The vial was chilled in a cold well with liquid nitrogen until the Et₂O solution was almost frozen. The chilled solution was stirred, and a solution of HOPh₄-methyl (15 mg, 0.14 mmol) in Et₂O was added dropwise. The solution went from beet-colored to red upon addition. The solution was warmed to room temperature and stirred for 2 h. The volatiles were removed in vacuo yielding a dark red residue. The residue was dissolved in a minimum amount of n-hexane, filtered through Celite, and chilled to −35 °C to yield crystals of NCr(NiPr₂)₂(OPh₄-methyl) (27 mg, 52%). ¹H NMR (500 MHz, chloroform-d): 6.97 (d, J = 7.8 Hz, 2H), 6.88 (d, J = 7.8 Hz, 2H), 5.02 (s, 2H), 3.73 (s, 2H), 2.24 (s, 3H), 1.83 (d, J = 6.3 Hz, 6H), 1.56–1.39 (m, 6H), 1.28–0.95 (m, 13H). ¹³C NMR (126 MHz, chloroform-d)
129.37, 128.29, 117.15, 58.26, 55.22, 30.45, 30.13, 21.42, 21.11, 20.78. Elemental Analysis calc. for CrC_{19}H_{36}ON_{3}: C, 61.10; H, 9.45; N, 11.25. Found: C, 61.47; H, 10.06; N, 11.42.

**Synthesis of NCr(NPr)_{2}(OPh^{4-bromo}):** A scintillation vial was charged with NCr(NPr)_{3} (50 mg, 0.14 mmol), a stir bar, and Et_{2}O (3 mL). The vial was chilled in a cold well with liquid nitrogen until the Et_{2}O solution was almost frozen. The chilled solution was stirred and a solution of HOPh^{4-bromo} (24 mg, 0.14 mmol) in Et_{2}O was added dropwise. The solution went from beet-colored to red upon addition. The solution was warmed to room temperature and stirred for 2 h. The volatiles were removed in vacuo yielding a dark red residue. The residue was dissolved in a minimal amount of toluene and was filtered through Celite. The filtrate was collected and layered with n-hexane. The layered solution was chilled to –35 °C for 1 week to yield crystals of NCr(NPr)_{2}(OPh^{4-bromo}) (38 mg, 62%). {^1}H NMR (500 MHz, chloroform-\textit{d}): 7.23–7.12 (m, 2H), 6.90–6.74 (m, 2H), 5.04 (septet, \(J = 6.5\ Hz, 2H\)), 3.75 (septet, \(J = 6.4\ Hz, 2H\)), 1.85 (d, \(J = 6.2\ Hz, 6H\)), 1.46 (d, \(J = 6.3\ Hz, 6H\)), 1.15 (d, \(J = 6.4\ Hz, 12H\)). {^{13}}C NMR (126 MHz, chloroform-\textit{d}): 165.93, 131.60, 119.56, 110.65, 58.46, 55.59, 30.50, 30.24, 21.48, 21.20. Elemental Analysis calc. for CrC_{18}H_{32}ON_{3}Br: C, 49.32; H, 7.36; N, 9.59. Found: C, 49.09; H, 7.41; N, 9.33.

**Catalytic Product Synthesis and Isolation**

**Synthesis of Iminoamination Product from aniline, 1-octyne, and tBuNC**

A 15 mL pressure tube was charged with Ti(dpm)(NMe_{2})_{2}(62 mg), toluene (1 mL), and a stir bar. To the stirred solution was added a 1 mL solution containing aniline (186 mg, 2 mmol, 1 equiv) in toluene. This mixture was stirred for 10 min at room temperature over which time the solution went from transparent bright orange to an opaque reddish-brown. Then a 1 mL solution containing tBuNC (184 mg, 2 mmol, 1 equiv) and 1-octyne (220 mg, 2 mmol, 1 equiv) in toluene was added to the solution in the pressure tube. The tube was sealed and transferred from the glovebox to a 110 °C oil bath. The tube was heated and stirred for 24 h. The tube was removed from the bath and allowed to ambiently cool. The volatiles were removed by rotary evaporation, and the resulting crude, dark brown oil was separated by column chromatography (Al_{2}O_{3}, hexanes with 1% TEA and gradient Et_{2}O from 0 to 30%). The isolated product was obtained as an
orange oil (310 mg, 54%), which proved to be a mixture of regioisomers (Table 1). $^1$H NMR (500 MHz, chloroform-$d$): (A) 9.97 (s, 1H), 4.72 (d, $J = 8.0$ Hz, 1H), 1.27 (s, 9H), 0.90 (m, 3H); (B) 10.83 (s, 1H), 7.77 (d, $J = 2.8$ Hz, 1H), 7.11 (d, $J = 2.8$ Hz, 1H), 1.32 (s, 9H), 0.84 (t, 3H); (A/B) 7.33–7.26 (m, 4H), 7.04 (d, $J = 7.7$ Hz, 2H), 7.03–6.97 (m, 1H), 6.85–6.78 (m, 3H), 2.37 (s, 1H), 2.22–2.09 (m, 3H), 1.48 (m, 5H), 1.18 (m, 8H). $^{13}$C NMR (126 MHz, chloroform-$d$): 171.01, 153.80, 151.55, 150.11, 146.87, 142.28, 129.06, 128.43, 122.66, 121.83, 121.38, 119.00, 103.60, 91.79, 52.60, 51.03, 33.68, 33.21, 32.91, 31.93, 31.80, 31.46, 30.36 (d, $J = 1.9$ Hz), 30.31, 29.47, 29.32, 28.74, 28.67, 27.73, 23.69, 22.72, 22.47, 14.15, 14.05.

High-Resolution MS: QTOF EI (positive ion) calc. for C$_{19}$H$_{31}$N$_2$: 287.2487; found: 287.2484. Elemental Analysis calc. for C$_{19}$H$_{30}$N$_2$: C, 79.66; H, 10.56; N, 9.78. Found: C, 79.88; H, 10.44; N, 9.44.

**Synthesis of 2,3-diaminopyrrole from aniline, 1-octyne, and 2 $^1$BuNC**

![Synthesis Scheme](image)

On several occasions, the product mass that corresponds to the coupling of 1 equiv aniline, 1 equiv alkyne, and 2 equiv of isonitrile (4-component coupling, 4CC) was observed by GC/MS in reactions catalyzed by homogeneous titanium catalysts. Typically, the amount of this product was relatively small. However, under certain conditions when reactions were carried out on large enough scales, substantial masses of the 4CC product were noted in various column fractions when isolating the iminoamination products by column chromatography. On one such occasion, a very clean fraction of the 4CC product was isolated from a 2 mmol scale reaction (H$_2$NPh, $^1$BuNC, 1-octyne) with 5 mol% Ti(dpm)(NMe$_2$)$_2$ as precatalyst. The 4CC product was the first compound eluted from an alumina column (93 mg, 0.25 mmol, 13% relative to 2 mmol H$_2$NPh as limiting reagent), basified with 1% TEA in hexane. Note, from the same column, the
iminoamination product was also isolated, but as a later fraction with the addition of Et₂O on a gradient from 0-30%.

The 4CC product was characterized by GCMS, HRMS, ¹H NMR, ¹³C NMR, and a few additional 2D NMR techniques. The above structural assignment seems to most closely match the characterization data for this product, in agreement with previous studies by our group.² ¹H NMR (500 MHz, benzene-d₆): 7.43 (d, J = 7.1 Hz, 2H), 7.13 (t, J = 7.8 Hz, 2H), 6.97 (t, J = 7.5 Hz, 1H), 6.53 (t, J = 0.9 Hz, 1H), 2.99 (s, 1H), 2.68–2.54 (m, 2H), 2.34 (s, 1H), 1.75 (pentet, J = 7.7 Hz, 2H), 1.52–1.42 (m, 3H), 1.40–1.29 (m, 6H), 1.23 (s, 12H), 0.92 (s, 15H). ¹³C NMR (126 MHz, benzene-d₆): 142.18, 128.80, 125.41, 125.16, 123.74, 122.06, 121.84, 113.63, 55.46, 54.53, 32.33, 30.66, 30.60, 30.54, 30.07, 26.37, 23.16, 14.41. HRMS: QTOF EI (positive ion) calc. for C₂₄H₄₀N₃⁺: 370.3222; found: 370.3218. Elemental analysis calc. for C₂₄H₃₉N₃: C, 77.99; H, 10.69; N, 11.37. Found: C, 78.09; H, 10.85; N, 11.11.
In Situ Investigations of Titanium Complex Nuclearity—DOSY Molecular Weight Determinations in C₆D₆

Note that D represents the diffusion coefficient, which is given in units of 1*10⁻⁴ m²/s.

Solution Molecular Weight of \{Ti(OArCH₂ArO)(µ-Ntolyl)\}_2·HNMe₂

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Solution Molecular Weight of Ti(OArCH₂ArO)I₂

MW Determination of Ti(OArCH₂ArO)I₂

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<th>log(D)</th>
<th>Error in Diffusion Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzene</td>
<td>72</td>
<td>1.86</td>
<td>27.9</td>
<td>1.45</td>
<td>0.33</td>
</tr>
<tr>
<td>Fc</td>
<td>186</td>
<td>2.27</td>
<td>16.7</td>
<td>1.22</td>
<td>0.14</td>
</tr>
<tr>
<td>TMS$_2$Si</td>
<td>321</td>
<td>2.51</td>
<td>12.7</td>
<td>1.10</td>
<td>0.32</td>
</tr>
<tr>
<td>Exper. Weight</td>
<td>465 ± 51</td>
<td>2.67</td>
<td>10.8</td>
<td>1.03</td>
<td>0.13</td>
</tr>
<tr>
<td>Calc. Monomer Weight</td>
<td>325</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calc. Dimer Weight</td>
<td>651</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

MW Determination of [Ti(Ntoly)(dpm)]$_2$

\[
y = -0.5281x + 2.4251 \quad R^2 = 0.9996
\]
Iminoamination Experiments

The following reagents were measured separately by mass: (1) Ti(dpm)(NMe₂)₂ (1) (78-312 mg, 5-20 mol %), (2) dodecane (212 mg, 1.25 mmol, 0.05 M), (3) H₂NPh (465 mg-2.32 g, 5-25 mmol), (4) 'BuNC (415-830 mg, 5-10 mmol), and (5) 1-octyne (550 mg-2.75 g, 5-25 mmol). In a scintillation vial, the Ti(dpm)(NMe₂)₂ (1) was dissolved in 5 mL toluene and the dodecane and H₂NPh were added, causing the solution to change colors from bright orange to dark reddish-brown. This solution was stirred at room temperature for 5-10 min and transferred to a 25.0 mL volumetric flask. The 'BuNC and 1-octyne were added to the flask, and the solution was diluted to 25.0 mL with toluene. This solution was thoroughly mixed and transferred in 1 mL aliquots to sample tubes (generally 10-12 per entry). The tubes were sealed and transferred from the glovebox to a preheated oil bath. The elapsed time from the start of the reaction was recorded each time a sample was removed for GC analysis, ranging from 30 min to 28 h.

The samples were analyzed by GC-MS to look for reaction products and provide detection of unwanted side products. GC-FID was used to quantify the amounts of iminoamination product, hydroamination product, formamidine, and 4-component coupling product (2,3-diaminopyrrole) production in each sample based on external calibrations standardized with internal dodecane (0.05 M) from the authentic isolated products. The authentic samples had previously been obtained by separation from the organic reaction mixtures. The results of these experiments are shown in Table 1 in the manuscript.
Initial Rates of Catalysts 1 and 3

Experiments were done using 5 mol % (0.01 M) catalyst and 0.2 M 1-octyne, cyclohexylisonitrile, and aniline in toluene at 110 °C. The formation of product was followed relative to dodecane internal standard by GCFID. The initial rate vs time data are tabulated and plotted below. Reactions were followed to ~0.02 M (~10%) completion in product concentration. The fits in the plots below are forced through the origin, i.e., zero product at zero time (which was verified by examination of the reaction mixture prior to heating).

$Ti(NMe_2)_2(dpm)$ (1)

<table>
<thead>
<tr>
<th>time (min)</th>
<th>[3CC] (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.006337</td>
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<tr>
<td>10</td>
<td>0.013328</td>
</tr>
<tr>
<td>20</td>
<td>0.022899</td>
</tr>
</tbody>
</table>

$Ti(NMe_2)_2(O_2Ar-6-CH_2)$ (3)

<table>
<thead>
<tr>
<th>time (min)</th>
<th>[3CC] (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.007612</td>
</tr>
<tr>
<td>10</td>
<td>0.012406</td>
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<tr>
<td>15</td>
<td>0.016954</td>
</tr>
<tr>
<td>20</td>
<td>0.02041</td>
</tr>
</tbody>
</table>
The slopes of the lines in the two initial rates experiments above are essentially identical, 0.0012 vs 0.0012 M/min. Consequently, the two catalysts 1 and 3 are judged to have identical rates under these conditions within error of the measurement.
**LDP and \( %V_{\text{bur}} \) Measurements**

Several of the LDP values utilized for the examination of ligand effects on the equilibrium distribution of ligand exchange products have been previously published (NMe\(_2\), I, and O\(^i\)Pr).\(^3\) Other values have been re-established with improved accuracy to the NMR experiment protocol relative to the original values. The new values for these ligands are listed below. Preparation of the NCr(N\(^i\)Pr\(_2\))\(_2\)X complexes generally followed literature procedures.\(^3\)-\(^5\)

Note that the LDP values used for the various 2-\textit{tert}-butyl-4-R-phenoxide ligands are those obtained with the 4-R-phenoxide substituted derivatives on chromium. Previously, we have observed that inclusion of substitution in the 2-position of the phenoxide ligands imposes a steric interference on the LDP value obtained with the NCr(N\(^i\)Pr\(_2\))\(_2\)X system. For example, when 2,4-dimethylphenoxide is examined by LDP, the value obtained is 11.98 kcal/mol. By comparison, the values for phenoxide and 4-methylphenoxide are 11.98 and 11.82 kcal/mol, respectively. This series highlights the steric effect of raising the LDP value when a substituent, such as those in the 2 or 6 positions of a phenoxide, encroach on the first coordination sphere of the metal. Subsequently, the LDP values listed below for the 2-\textit{tert}-butyl-4-R-phenoxide ligands used with the Ti(OAr)\(_4\) complexes are those determined from the NCr(N\(^i\)Pr\(_2\))(OPh\(^{4-R}\)) complexes.\(^6\)

The \( %V_{\text{bur}} \) measurements for each ligand were determined from single crystal X-ray structures containing the ligand on 4-coordinate Ti. The exception to this was the O\(^i\)Pr ligand, for which the \( %V_{\text{bur}} \) was determined using the dimeric crystal structure of \{Ti(OArCH\(_2\)OAr)(O\(^i\)Pr)(\(\mu\)-O\(^i\)Pr)\}_2. The O\(^i\)Pr-ligands that interact with a single Ti metal were utilized for the size determination, rather than the bridging O\(^i\)Pr-ligands in this structure. The \( %V_{\text{bur}} \) determined by this method was similar to previous determinations in the chromium-based LDP system. In fact, all \( %V_{\text{bur}} \) values for the X\(^-\) ligands determined here with titanium were very similar to previous determinations in the LDP system.
Equilibrium Data Modeling with Stereoelectronics

Ligand Sets where $K_{eq} >> 2,000$  

<table>
<thead>
<tr>
<th>A</th>
<th>X</th>
<th>LDP (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMe$_2$</td>
<td>Cl</td>
<td>OPr</td>
</tr>
<tr>
<td>OPr</td>
<td>Cl</td>
<td>OMe$_2$</td>
</tr>
<tr>
<td>OCy</td>
<td>Br</td>
<td>pyrrolyl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>LDP (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>10.33</td>
</tr>
<tr>
<td>Cl</td>
<td>15.8</td>
</tr>
<tr>
<td>Cl</td>
<td>14.97</td>
</tr>
<tr>
<td>NMe$_2$</td>
<td>pyrrolyl in dpm</td>
</tr>
</tbody>
</table>

$^a$In these cases, literature reports demonstrate the formation of a single heteroleptic species from the combination of the homoleptic starting materials, TiA$_4$ and TiX$_4$. In other words, no observable disproportionation occurs. Using our model, we would estimate that $K_{eq}$ involving these ligands would be $>>K_{eq}$, the experimental limit of our $K_{eq}$ measurements. $^b$Assumed to be the same as OPr electronically. $^c$One could argue that a better estimate for the pyrrolyl in dpm would use 2-methylpyrrolyl, which has an LDP of 13.46 kcal/mol.

<table>
<thead>
<tr>
<th></th>
<th>Ti(OArCH$_2$ArO)X$_2$</th>
<th>LDP</th>
<th>$\Delta$LDP</th>
<th>$(\Delta$LDP)$^2$</th>
<th>%$V_{bur}$</th>
<th>$\Delta$%$V_{bur}$</th>
<th>$(\Delta$%$V_{bur})^2$</th>
<th>Expt. $K_{eq}$</th>
<th>Expt. Error</th>
<th>Model $K_{eq}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>NMe$_2$</td>
<td>9.34</td>
<td>-2.48</td>
<td>6.1504</td>
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<td>118</td>
<td>1136</td>
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<tr>
<td></td>
<td>OPr$^a$</td>
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<td>-1.49</td>
<td>2.2201</td>
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<td>80</td>
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<tr>
<td></td>
<td>I</td>
<td>15.8</td>
<td>3.98</td>
<td>15.8404</td>
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<td>4</td>
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<tr>
<td></td>
<td>Cl</td>
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<td>9.9225</td>
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<td>898</td>
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<td>1010</td>
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<tr>
<td>$A = 2$-tert-butyl-4-Y-phenoxide where Y is</td>
<td>$^b$Bu</td>
<td>12.01</td>
<td>0.19</td>
<td>0.0361</td>
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<td>0.04</td>
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<tr>
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<td>H</td>
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<td>0.0256</td>
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<td>Me</td>
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<td>0</td>
<td>8</td>
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<tr>
<td></td>
<td>F</td>
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<td>0.0289</td>
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<td>0.7</td>
<td>0.49</td>
<td>14</td>
<td>4</td>
<td>9</td>
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<tr>
<td></td>
<td>OMe</td>
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<td>0</td>
<td>0</td>
<td>71</td>
<td>11</td>
<td>14</td>
</tr>
</tbody>
</table>

$^a$The LDP value for OEt was used.

To perform the least squares fit to the equilibrium data with various models, the parameters and data were set up as matrices. For example, for a model using Eq. 2 reproduced below

$$K_{eq} = a + b\Delta$LDP + c$LDP^2$$

There will be a vector matrix of $K_{eq}$ values, which we will call $y$, one value for each ligand investigated. The matrix $y$ in this case is as shown below.
Corresponding to these $K_{eq}$ values, there are a series of parameters, $\Delta LD P$ and $\Delta LD P^2$. These are also used to generate a matrix. In the first column is a set of “1” values, which will generate the parameter $a$ in Eq. 2. The second column are the $\Delta LD P$ values, and in the third column is the set of $\Delta LD P^2$ values. Call this matrix $X$.

The equation to analytically determine the vector of global fitting parameters $b$ is shown below,\textsuperscript{7} which is the $1 \times 3$ vector matrix containing $a$, $b$, and $c$. The advantage of this procedure is that local minima cannot be obtained like in iterative procedures, but, generally speaking, similar values are obtained between iterative fits and this matrix operation. The matrix operations were done in Microsoft Excel.

\[
(X^T X)^{-1} X^T y = b
\]

The following combinations of variables were considered, shown as 5 trials in the table below, and the best overall fit resulted from simple electronic treatment of the $K_{eq}$ data, trial 5. Fits that included the steric parameters were generally worse and were never significantly improved over the simple fit in Trial 5. In most cases, models involving steric parameters provided unphysical negative equilibrium constants as well. Consequently, the simple fit shown in Trial 5 was used.
The fit with the coefficients calculated is shown in Eq. 3. While Eq. 3, has a linear and a squared term in LDP, an algebraic rearrangement of this quadratic equation to the vertex form of the parabolic equation gives Eq. 4. The fit shown in Figure 4 in the manuscript is from an iterative procedure done in Kaleidagraph 4.1.3, which gives very similar values to the matrix fit.
Spectral Data

$^1H$ NMR of Ti(OPh$_{2,4}$-di-butyl)$_4$ (6e) in C$_6$D$_6$
$^{13}$C NMR of Ti(O\text{Ph})$_2$-4-di-t-buty1$_4$ (6e) in C$_6$D$_6$
$^1$H NMR of $\text{Ti(OPh}_2$-butyl$)_4$ (6c) in $\text{C}_6\text{D}_6$
$^{11}$C NMR of Ti(O\textit{Ph}$_2$-$t$-\textit{butyl})$_4$ (6c) in C$_6$D$_6$
$^1$H NMR of Ti(OPh$_{2}$(2',6'-butyl-4'-methoxy)$_{4}$) (6a) in C$_6$D$_6$
$^{13}$C NMR of Ti(OPh)$_2$-t-buty1-4-methoxyl)$_4$ (6a) in C$_6$D$_6$
$^1H$ NMR of $\text{Ti(OPh}^\text{2,6-buty1-4-bromo})_4 \ (6f)$ in C$_6$D$_6$
$^{13}$C NMR of Ti(OPh$_2$-1-butyl-4-bromo)$_4$ (6f) in C$_6$D$_6$
$^1$H NMR of $\text{Ti(OPh}_2$-butyl-4-fluoro$)_4$ (6d) in $C_6D_6$
$^{13}$C NMR of Ti(OPh$_2$-t-buty1-4-fluoro)$_4$ (6d) in C$_6$D$_6$
$^{19}F$ NMR of $\text{Ti(OPh}^2\text{t-buty1-4-fluoro)}_4$ (6d) in $\text{C}_6\text{D}_6$
$^1$H NMR of $\text{Tl(OPh}^{2,6\text{-butyl-4-methyl}}\text{)}_4 \ (6b) \ in \ C_6D_6$
$^{13}$C NMR of Ti(OPh$_2$-t-butyl-4-methyl)$_4$ (6b) in CDCl$_3$
$^1H$ NMR of $Ti(O\text{Ph}^2,\text{butyl}-4-\text{CF}_3)_4$ (6g) in $C_6D_6$
$^{11}$C NMR of Ti($\text{OPh}_{2}$-t-butyl-4-CF$_3$)$_4$ (6g) in C$_6$D$_6$
$^{19}$F NMR of Ti(OPh$_2$-$t$-butyl-$t$-CF$_3$)$_4$ (6g) in C$_6$D$_6$
$^1$H NMR of Ti(OArCH$_2$ArO)(O$i$Pr)$_2$ in CDCl$_3$
$^1$H NMR of Tt(OArCH$_2$ArO)$_2$ in C$_6$D$_6$
$^1$H NMR of TiCl$_2$(OArCH$_2$ArO) in $C_6D_6$
$^{13}$C NMR of TiCl$_2$(OArCH$_2$ArO) in C$_6$D$_6$
$^1$H NMR of Ti$_2$(OArCH$_2$ArO) in CDCl$_3$
$^{13}C$ NMR of Ti$_3$(OArCH$_2$ArO) in CDCl$_3$
$^1H$ NMR of $\{\text{Ti(OArCH}_2\text{ArO)(Ntolyl)}\}_2$:HNMe$_2$ (4) in C$_6$D$_6$
$^{13}$C NMR of \{Ti(O\textit{ArCH}_2\textit{ArO})(\textit{Ntoly})\}_2\text{HNMe}_2 (4) in C_6D_6
$^1$H NMR of $\{\text{Ti(µ-Ntoly1)(dpm)}\}_2$ (2nd) in toluene-$_d_8$ room temperature

high vac grease and hexane impurities
$^1$H NMR of $\{\text{Ti(µ-Ntolyl)(dpm)}\}_2$ (2nd) in toluene-$d_8$ at −75 °C

high vac grease and hexane impurities
$^{13}$C NMR of \(\{\text{Ti}(\mu-\text{Ntolyl})(\text{dpm})\}_2\) in toluene-$d_8$ at room temperature

high vac grease and hexane impurities
\(^1\)H NMR of isomeric mixture of 3CC product from the coupling of aniline, \(\text{BuNC}\), and 1-octyne in CDCl\(_3\).
$^{13}$C NMR of isomeric mixture of iminoamination product from the coupling of aniline, $^t$BuNC, and 1-octyne in CDCl$_3$
GCMS of iminoamination product isomers A and B: fragmentation pattern for A isomer
GCMS of iminoamination product isomers A and B: fragmentation pattern for B isomer
$^1$H NMR of the 4CC product in CDCl$_3$
$^{13}$C NMR of the 4CC product in CDCl$_3$
GCMS of the 4CC product and MS fragmentation pattern
gCOSY NMR of the 4CC product in CDCl$_3$
$\text{HMBC NMR of 4CC in CDCl}_3$
$^1$H NMR of $\text{NCr(N}^\text{Pr}_2\text{)}_2(\text{OPh}^\text{methyl})$ in CDCl$_3$ at $-27$ °C
$^{13}$C NMR of $\text{NCr}(\text{NPr}_2)_2(\text{OPh}^d\text{-methyl})$ in $\text{CDCl}_3$ at $-27^\circ \text{C}$
$^1$H NMR of NCr(NiPr$_2$)$_2$(OPh$_4$-bromo) in CDCl$_3$ at –20 °C
$^{13}$C NMR of $\text{Cr(N}^\text{Pr}_2\text{)}_2(\text{OPh}_4\text{bromo}_2$) in CDCl$_3$ at $–20 \, ^\circ\text{C}$
References


