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An Air Stable Moisture Resistant Titanium Triflate Complex as a Lewis Acid Catalyst for C–C Bond Forming Reactions

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Dedicated to the 150th anniversary of Japan-UK diplomatic relations

Abstract: An air and moisture stable C_3 -symmetric titanium(IV) triflate, supported by a tripodal amine-(tris-phenolate) ligand, has been synthesized and characterized by X-ray crystallography and shown to be a good Lewis acid catalyst for a range of *aza*-Diels–Alder, Diels–Alder, *syn* aldol, allylation, and alkylation reactions.

Introduction

Titanium(IV) compounds, derived from halide, alkoxide, phenolate, or triflate ligands have been widely employed as catalysts for organic synthesis.^[1] Although these salts (or their precursors) are often cheap and commercially available, these air and moisture sensitive liquids require storage and manipulation under inert conditions. In significant quantities, they represent a considerable caustic and corrosive hazard that can cause problems on scale-up,^[2] often affording decomposition products on aqueous work-up that are difficult to remove. Many of these titanium catalysts are generated in situ by mixing precursor titanium complexes with ligands which can lead to the formation of rapidly interconverting mixtures of undefined multimeric species with different catalytic properties.^[1] The development of well defined air stable titanium reagents that are easy to prepare and convenient to use, but retain good catalytic activity, is potentially of great importance to the synthetic community.^[3]

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Multidentate ligands have often been used to prepare highly stable metal complexes as low loading recyclable catalysts for organic synthesis,^[4] because their coordination chemistry results in the ligand binding to multiple sites on the metal center, which reduces the chances that multimeric catalytic species are formed. The selective formation of single catalytically active species is highly desirable because this simplifies any mechanistic studies required to optimize catalyst performance.^[5] Consequently, there has recently been much interest in using readily available amine-(trisphenolate) ligands^[6] for the preparation of main group complexes (P^{V,[7]} Si^{IV[8]}) and metal complexes (including Ti^{IV,[9]} Zr^{IV} ^[9i,10] In^{III},^[11] Ga^{III},^[11] Ta^V,^[9g,12] V^{III},^[13] V^V,^[13,14] Nb^V,^[9g] Fe^{III} , [15] Al^{III} , [16] Ni^{II} , [17] Sn^{II} , [10] and $Ge^{IV[18]}$). Many of these complexes are monomeric five-coordinate trigonal bipyramidal complexes that arise from coordination of the three aryloxide and tertiary amine groups of this class of tetradentate ligand to their metal centers. The electronic and steric properties of the metal centers of these complexes may be easily tuned by varying the aryl substituents of their ligand frameworks.^[19] It has been widely reported that these types of tripodal metal complexes may be used as highly efficient catalysts for stereoselective polymerization reactions,^[20] however, their potential as versatile catalysts for organic synthesis is less well explored.^[21] We previously communicated preliminary results that a crystalline titanium amine-tris(phenolate) triflate complex $6^{[22]}$ could be used as a catalyst for aza-Diels-Alder reactions,^[23] and now describe our full investigations into its use as an air stable and moisture insensitive Lewis acid catalyst for organic synthesis.^[24]



Results and Discussion

Prior to the commencement of our studies, Kol and coworkers had reported that treatment of $Ti(OiPr)_4$ with amine-(tris-phenolate) ligands **1a,b** resulted in formation of stable mononuclear C_3 -symmetric titanium alkoxides **2a,b** whose aryl rings exhibited propeller chirality with high barriers to inversion (Scheme 1).^[9a] Given the widespread use



Scheme 1. Synthesis of titanium isopropoxide 2a.

of titanium complexes as catalysts for organic synthesis,^[1] we were interested in the potential activity of these titanium complexes as catalysts for a range of C–C bond-forming reactions.^[23] Therefore, the parent amine-(tris-phenol) ligand **1a** was first prepared in 80% yield through a one-pot variant of the Mannich reaction involving refluxing hexamethy-lenetetramine with 2,4-dimethylphenol and paraformalde-hyde in water for 3 days.^[25,26] Subsequent refluxing of ligand **1a** with Ti(O*i*Pr)₄ in toluene gave the known amine-(tris-phenolate) titanium isopropoxide **2a**^[9a] as a yellow air-stable crystalline solid in 88% yield (Scheme 1), whose structural identity was confirmed using single crystal X-ray analysis (Figure 1).^[22] This revealed a monomeric C₃-symmetric complex whose approximately trigonal bipyramidal Ti center lay slightly above the plane of the three equatorial phenolate

oxygen atoms [distance of Ti atom above the plane of the three phenolate oxygen atoms (Å):0.251(1)/0.2457(1)], whilst its axial sites were occupied by the neutral nitrogen atom of the ligand [Ti–N bond length = 2.303(2) Å] and the monodentate isopropoxide anion [Ti– OiPr bond length = 1.774(2) Å]. The complex **2a**, although gen-



Figure 1. X-ray crystal structure of titanium isopropoxide 2a (only one of two similar molecules found within the asymmetric unit shown and hydrogen atoms omitted for clarity). Selected bond lengths (Å): Ti(1)–O(1) 1.862(2), Ti(1)–O(2) 1.845(2), Ti(1)–O(3) 1.851(2), Ti(1)–O(4) 1.774(2), Ti(1)–N(1) 2.305(2); Bond angles (°): N(1)-Ti(1)-O(4) 179.70(8), Ti(1)-O(1)-C(11) 141.71(15), Ti(1)-O(2)-C(21) 143.19(15), Ti(1)-O(3)-C(31) 141.87(14), Ti(1)-O(4)-C(41) 161.56(18).

erated from an achiral ligand is racemic, since complexation of ligand **1a** to the titanium metal center results in formation of two enantiomers with 'propeller' chirality.^[27] This was clear from the presence of both (*P*) and (*M*) enantiomers in the crystallographic asymmetric unit, whilst two well resolved AX resonances were observed at $\delta = 2.75$ and 3.90 ppm (*J*=10.6 Hz) in its ¹H NMR spectrum that were assigned to the diastereotopic benzylic methylene protons of the tripodal ligand fragment. The structural parameters of titanium isopropoxide **2a** were very similar to those reported previously for the related titanium isopropoxide **2b** which is derived from the *tert*-butyl substituted amine-(tris-phenolate) ligand **1b**.^[9a]

Titanium isopropoxide **2a** proved to be a relatively poor Lewis acid catalyst for a range of synthetic transformations for which other types of titanium alkoxides/phenolates had been used previously.^[1] **2a** was screened as a catalyst for the formal *aza*-Diels–Alder reaction between imine **3a** and Danishefsky's diene **4** in CH₂Cl₂ (Scheme 3),^[28] since this reaction had been reported to occur in the absence of a strong Lewis acid under these conditions.^[29] In this case, it was found that using a stoichiometric amount of **2a** afforded dihydropyridone **5a** in 62% conversion (40% yield of isolated



Scheme 2. Synthesis of amine-tris(phenolate) titanium triflate (rac)-6.

at $\delta = 3.80$ ppm (Figure 3 a). Conversely, the enantiomers of (rac)-titanium triflate 6 were

at

and

product) after 2 h (Table 1, Entry 1), whist 10 mol % of catalyst afforded only 30% conversion (12% yield of isolated product) after 48 h (Table 1, Entry 2). Since ¹H NMR specstudies revealed that rapid racemization of (rac)-titanium triflate 6 occurred at 50 °C (Figure 4) with its two diastereotopic benzylic resonances coalescing to exhibit a broad peak

Entry	Catalyst	Equivalents of imine 3a	Equivalents of diene 4	t	Conversion [%]
1	100 mol % 2a	1 (0.03 м)	1	2 h	62
2	10 mol % 2a	1 (0.03 м)	1	48 h	30
3	100 mol % 6	1 (0.03 м)	1	<5 min	>95
4	50 mol % 6	1 (0.03 м)	1	15 min	>95
5	10 mol % 6	1 (0.03 м)	1	70 min	>95
6	10 mol % 6	3 (1.2м)	1	45 min	>95
7	10 mol % 6	1 (0.4 м)	3	45 min	>95
8	3 mol % 6	3 (1.2 м)	1	4 h	>95



Scheme 3. Aza-Diels-Alder reaction of imine 3a with Danishefsky's diene 4 to afford dihydropyridone 5a.

troscopic analysis of crude reaction products revealed that 2a was stable under these conditions, it was reasoned that its lack of catalytic activity might arise from stabilization of its metal center arising from apical nitrogen lone-pair donation and that an alternative complex containing a more weakly coordinating apical triflate ligand might enhance catalyst reactivity. Reaction of 2a with Me₃SiOTf in toluene at reflux gave amine-(tris-phenolate) titanium triflate 6 as a red crystalline solid in 98% yield (Scheme 2), the structure of which was confirmed by X-ray crystallographic analysis (Figure 2).^[22] As expected, the triflate bond to Ti in 6 was significantly longer than the equivalent parameter in 2a [Ti-O distances: 1.774(2)/1.776(2) Å for alkoxide 2a vs 2.002(2)/2.017(2) Å for triflate 6] suggesting weaker metalligand coordination. There was a concomitant shortening (and implied strengthening) of the Ti-N bond in triflate 6 [Ti-N distances: 2.303(2)/2.295(2) Å for **2a** and 2.216(2)/ 2.213(2) Å for 6, respectively]; a slight shortening of the Ti-O(phenolate) distances [average Ti-O(phenolate) distance: 1.850 Å for 2a and 1.797 Å for 6]; whilst the Ti atom sits further into the 'pocket' of the ligand for 6 [distance of Ti atom above the plane of the three phenolate O atoms: 0.251(1)/0.247(1) Å for **2a** and 0.188(1)/0.178(1) Å for **6**]. There was little variation in the tilt of the propeller between the two complexes (average angle between aryl planes and Ti-N bond vector: 15.2° for 2a and 13.0° for 6). Analysis of the ¹H NMR spectra of 6 revealed that the resonances corresponding to its benzylic protons at $\delta = 3.09$ and 4.04 ppm had broadened at room temperature, implying that the presence of the weakly coordinating triflate ligand results in slow interconversion of its (P) and (M) enantiomers (Figure 3). Variable temperature ¹H NMR spectroscopic

configurationally stable -50 °C as shown by the presence of two well defined AX doublets at $\delta = 3.57$ 4.35 ppm in its ¹H NMR spectrum (Figure 3). Complex 6 was then screened

as a catalyst for the aza-Diels-Alder reaction of imine 3a and Danishefsky's diene 4

(Scheme 3) with the aim of identifying optimal conditions for this transformation. We first varied the amount of 6 used



Figure 2. X-ray crystal structure of titanium triflate 6 (only one of two molecules found within the asymmetric unit shown and hydrogen atoms omitted for clarity). Selected bond lengths (Å): Ti(1)-O(1) 1.793(2), Ti(1)-O(2) 1.799(2), Ti(1)-O(3) 1.808(2), Ti(1)-O(4A) 2.002(2), Ti(1)-N(1) 2.216(2); Bond angles (°): N(1)-Ti(1)-O(4A) 177.25(8), Ti(1)-O(1)-C(11) 141.94(17), Ti(1)-O(2)-C(21) 143.15(16), Ti(1)-O(3)-C(31) 142.62(16), Ti(1)-O(4A)-S(1) 158.14(12).



4.40 4.20 4.00 3.80 3.60 3.40 3.20

Figure 3. Expansion of variable temperature ¹H NMR spectra showing benzylic methylene resonances of titanium triflate (rac)-6.



Figure 4. Rapid racemisation of titanium triflate (*rac*)-6 occurs through inversion of propeller chirality at 50 °C.

to catalyze reaction of a 1:1 ratio of imine 3a and diene 4, with 100 mol% of catalyst 6 affording >95% conversion in <5 min (Table 1, Entry 3), with 50 mol% catalyst 6 resulting in >95% conversion after 15 min (Table 1, Entry 4), and 10 mol% catalyst **6** affording >95% conversion in 70 min (Table 1, Entry 5). These initial screening reactions were carried out at a relatively low concentration of reactants (0.03 M), so we increased the concentration of the reaction, as well as increasing the ratio of imine 3a (1.2 M) to diene 4 to 3:1. This resulted in 10 mol% of catalyst 6 catalyzing >95% conversion in 45 min (Table 1, Entry 6), whilst similar rates of reactivity could be obtained using one equivalent of imine 3a and three equivalents of diene 4 (1.2 M) (Table 1, Entry 7). Using <10 mol% of the catalyst resulted in longer reaction times, with 3 mol% of triflate 6 requiring 4 h for the aza-Diels-Alder reaction to proceed to completion (Table 1, Entry 8).

These optimal *aza*-Diels–Alder conditions (Table 1, Entry 7) were then applied for the synthesis of a small series of six dihydropyridones **5a–f** in good yield.^[28,29] Therefore, one equivalent of imines **3a–f** were reacted with three equivalents of Danishefsky's diene **4** at high concentration (1.2 m in diene **4**) to afford their corresponding dihydropyridones **5a–f** in good yield (56–73 %), with reaction times of <1.5 h in all cases (Scheme 4, Table 2).^[30]



Scheme 4. Titanium triflate 6 as a catalyst for the synthesis of *N*-alkyl-dihydropyridones **5a-f**.

We then demonstrated that **6** could be used as a catalyst to facilitate the one-pot three-component *aza*-Diels–Alder reaction^[29] of one equivalent of benzaldehyde **7** with one equivalent of benzylamine **8** and three equivalents of Danishefsky's diene **4**, to give *N*-benzyl-dihydropyridone **5a** (> 95% conversion) in 69% yield of isolated product (Scheme 5).

Having demonstrated that **6** could facilitate *aza*-Diels– Alder reactions^[31] in good yield, we used this complex as a Lewis acid catalyst in conventional Diels–Alder reactions. It was found that treatment of 2,3-dimethyl-1,3-butadiene **9** and *N*-phenyl-maleimide **10** with 20 mol% **6** in CH₂Cl₂ resulted in >95% conversion after 4 h to afford 3,4,7,8-tetrahydro-5,6-dimethyl-2-phenyl-2H-isoindole-1,3-dione **11** in 96% yield of isolated product (Scheme 6).^[32] Similarly, reaction of 2,3-dimethyl-1,3-butadiene **9** with α , β -unsaturated *N*-acyl-oxazolidin-2-ones **12a** (20 mol% **6**, 0.5 h) and **12b** (100 mol% **6**, 3 h) gave their corresponding cycloadducts **13a** and **13b** in 72% and 68% yield, respectively (Scheme 6).^[33]

We then investigated the Diels–Alder reactions of α,β -unsaturated N-acyl-oxazolidin-2-ones 12a-c with cyclopentadiene in order to determine whether the C_3 -symmetric properties of catalyst 6 might affect the endo/exo facial selectivities of its cycloaddition reactions (Scheme 7). Firstly, it was found that the Diels-Alder reaction of the highly reactive N-acryloyl-oxazolidin-2-one 12a with cyclopentadiene 14 using 5 mol% 6, gave 3-(bicyclo[2.2.1]hept-2-enecarbonyl)oxazolidin-2-one 15a (81% yield, 30 min) with an excellent endo/exo selectivity ratio of 97:3. The corresponding reaction of (E)-N-but-2-enoyloxazolidin-2-one **12b** with cyclopentadiene 14 required a catalyst loading of 20 mol% to proceed to completion in 3 h, affording an endo/exo ratio of 87:13, with the endo-cycloadduct 15b obtained in 83% yield of isolated product. In comparison, the least reactive dienophile N-((E)-3-phenyl-acryloyl)oxazolidin-2-one **12c** required 100 mol% of catalyst to proceed to 100% conversion over a period of 6 h in an endo/exo ratio of 84:16 affording endo-cycloadduct 15c in 74% yield (Table 3. The excellent endo/exo ratios observed in these Diels-Alder reactions compare favourably with the diastereoselectivities normally observed using other types of titanium complexes as catalysts, which typically afford endo/exo ratios of 82:18 to 96:4 in favour of their *endo*-isomers **15a–c**.^[34]

Following the good endo selectivities obtained in these Diels-Alder reactions, we then investigated the corresponding reaction of a chiral α,β -unsaturated-N-acyl-oxazolidin-2one (S)-17 in order to determine whether high levels of diastereoselectivity would be observed (Scheme 8, Table 4).^[35] It was found that treatment of (S)-4-benzyl-N-butenoyloxazolidin-2-one 17 with cyclopentadiene 14 in the presence of 20 mol% of 6 resulted in 100% conversion after 3 h to afford a mixture of diastereoisomeric products endo-18/ endo-19/exo-isomer in an excellent ratio of 88:1:11. This compares favourably with the diastereoselectivity observed for this Diels-Alder reaction using 20 mol% of (iPrO)₃TiCl as catalyst which resulted in formation of endo-18/endo-19/ exo-isomer in a ratio of 77:2:21, whilst use of 20 mol% of (2,4-dimethylphenoxy)₃TiCl^[36] gave all four possible diastereoisomers endo-18/endo-19/exo-major isomer/exo-minor isomer in a ratio of 70:2:16:12. Therefore, it is proposed that the improved diasteroselectivity observed for formation of endo-18 using 6 as catalyst may be a result of improved stereoselective interactions between its rigid propeller-like scaffold and the diene/dienophile substrates within the coordination sphere of the catalytically active titanium center.

We then demonstrated that 6 could be used as an air and moisture stable catalyst in three other types of C–C bond-



hyde that had been catalyzed previously using other titanium reagents. Firstly, in a variation of Evans syn-aldol protocol,^[37] the titanium enolate of N-acyloxazolidin-2-one (S)-20 was prepared by treatment with a stoichiometric amount of 6 and *N*,*N*,-diisopropylethylamine in CH₂Cl₂ at 0°C for 1 h. The resultant titanium enolate was then reacted with benzaldehyde at 0°C to afford a syn-aldol (S,S,S)-21 in 73% yield (85%) conversion) and >95% de after 48 h (Scheme 9).

We then showed that 6 could be used as a catalyst in alkylation/allylation addition reactions of benzaldehyde that had been catalyzed previously in a stereoselective manner using chiral titanium-BINOL complexes (Scheme 10). Firstly, it was shown that treatment of benzaldehyde and allyltributyltin with 5 mol % of 6 in CH_2Cl_2 resulted in formation of 1-phenylbut-3-en-1-ol 22 (>95% conversion) in 64 % yield of isolated product after 4 h.[38] Alternatively, addition of 20 mol% of 6 to a solution of three equivalents of Et₂Zn in CH₂Cl₂ at room temperature, before cooling to 0°C, and addition of one equivalent of benzaldehyde gave 1-phenyl-propan-1-ol 23 (>95% conversion) in 77% yield after 6 h.[39]

In conclusion, we have described the use of C_3 -symmetric amine-(tris-phenolate) titanium triflate 6 as a Lewis acid catalyst for a range of synthetically useful C-C bond-forming reactions. The observed catalytic activity of titanium triflate 6 under ambient conditions is noteworthy in itself, however, importantly, and most in marked contrast to many other titanium-based reagents in common usage, it is an air and moisture stable crystalline solid that is simple to prepare and

Scheme 5. Titanium triflate 6 catalyzed one-pot three-component synthesis of dihydropyridone 5a.

3 Equivalents

69%



13a, R =H, 20 mol% **6**, 30 min, 72% **13b**, R = Me,100 mol% **6**, 3 h, 68%

Scheme 6. Titanium triflate 6 catalyzed Diels–Alder reactions.



Scheme 7. Titanium triflate 6 catalyzed Diels-Alder reactions of α,β -unsaturated-*N*-acyl-oxazolidin-2-ones 12a-c with cyclopentadiene 14.

Table 3. Titanium triflate 6 catalyzed Diels-Alder reactions of α,β -unsaturated-N-acyl-oxazolidin-2-ones **12a- c** with cyclopentadiene **14**.

Entry	Substrate	Catalyst loading	<i>t</i> [h]	Endo/exo ratio	Yield [%]
1	12a (R=H)	5 mol% triflate 6	0.5	97:3 (15a/16a)	92 (15a)
2	12b (R = Me)	20 mol % triflate 6	3	87:13 (15b/16b)	81 (15b)
3	12c (R = Ph)	100 mol % triflate 6	6	84:16 (15c/16c)	74 (15c)



Scheme 8. Titanium triflate 6 catalyzed Diels–Alder reaction of (S)-4-benzyl-N-but-2-enoyloxazolidin-2-one 17 with cyclopentadiene 14.

isolate on a large scale. In the course of this investigation we routinely used a single batch of this catalyst on the bench over a period of three months with no noticeable loss in catalytic activity,^[40] which we believe makes this reagent a white solid (23.41 g, 55.8 mmol, 80%): \vec{v}_{max} =858, 1156, 1484, 1608, 2874, 3369 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ =2.20 (9H, s, ArCH₃), 2.21 (9H, s, ArCH₃)), 3.63 (6H, s, NCH₂), 4.54 (3H, brs, ArOH), 6.72 (3H, m, ArH), 6.85 ppm (3H, m, ArH); ¹³C NMR (75 MHz, CDCl₃): δ =16.3 (CH₃), 20.8 (CH₃), 56.8 (CH₂), 122.1, 125.0, 129.3, 129.5, 131.7, 151.5 ppm

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very attractive Lewis acid catalyst for use in synthetic laboratories.

Spectroscopic characterization for compounds **5a-f**, **11**, **13a-b**, **15a-c**, **18**, **21**, **22**, and **23** is available in the Supporting Information.

Experimental Section

General

All reactions were carried out under nitrogen or argon using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen, whilst CH_2Cl_2 was distilled from CaH_2 under nitrogen. Chromatography was performed on silica gel (Kieselgel 60). TLC was performed on Merck aluminium sheets coated with 0.2 mm silica gel 60 F254. Plates were visualized either by UV light (254 nm), iodine, ammonium molybdate (7% solution in ethanol), or potassium permanganate (1% in 2% aqueous acetic acid, containing 7% potassium carbonate).

Infra red spectra were recorded as thin films or KBr discs using a Perkin-Elmer PARAGON 1000 FT-IR spectrometer, with selected peaks reported in cm⁻¹. ¹H and ¹³C NMR spectra were recorded on a Bruker AM-300 spectrometer with chemical shifts reported in parts per million (ppm) and referenced to the residual solvent peak, with coupling constants (J) measured in Hertz. Accurate mass measurements were recorded on a Finnigan MAT 900 XLT instrument. Melting points were recorded on a Büchi 535 melting point apparatus and are uncorrected. Elemental analyses were performed using an Exeter Analytical Inc CE-440 Elemental analyzer. Single crystal X-ray diffraction data for 2a and 6 were collected on a Nonius Kappa CCD machine. Structural determination and refinement were achieved using the SHELX suite of programs^[41] with drawings being produced using ORTEX.^[42] Imines 3a- $\mathbf{f}^{[28a]}$ and *N*-acyl-oxazolidin-2-ones 12a-c, 17, 20^[35,43] were prepared according to published literature procedures or variants thereof. All other chemicals were used as purchased from Aldrich.

Synthesis

Tris(2-hydroxy-3,5-dimethylbenzyl)

amine $1a^{[9a]}$: Hexamethylenetetraamine (2.45 g, 17.5 mmol) and paraformaldehyde (3.15 g, 105 mmol) were added to 2,4-dimethylphenol (25.0 mL, 210 mmol) in water (3 mL). The reaction mixture was stirred at reflux for 64 h, after which the resultant yellow precipitate was filtered and washed with cold hexane to afford the title compound as an off-

Table 4. Titanium triflate 6 catalyzed Diels-Alder reaction of (S)-4-benzyl-N-but-2-enoyloxazolidin-2-one 17 with cyclopentadiene 14.

Entry	Catalyst	<i>t</i> [h]	Endo-18/endo-19/ exo-major/exo-minor	Yield [%]
1	Titanium triflate 6	3	88:1:11:0	82
2	TiCl(OiPr)3	24	77:2:21:0	69
3	2,4-(dimethylphenoxy) ₃ TiCl	2	70:2:16:12	58



Scheme 9. Titanium triflate 6 mediated *syn*-aldol reaction of *N*-acyl-oxa-zolidin-2-one (*S*)-21.



Scheme 10. Titanium triflate $\mathbf{6}$ catalyzed allylation and alkylation reactions of benzaldehyde.

(ArCOH); MS (ES⁺) m/z calcd for C₂₇H₃₃NO₃ $[M-H]^+$, 420.2533; found: 420.2531.

Amine-(tris-phenolate) titanium iso-propoxide 2a^[22]: Titanium tetra isopropoxide (6.2 mL, 20 mmol) was added to a suspension of amine-(trisphenol) 1a (8.4 g, 20 mmol) in toluene (50 mL) under a nitrogen atmosphere. The resulting yellow solution was heated to reflux and concentrated under vacuum to afford the title compound as a yellow powder (9.2 g, 17.6 mmol, 88%): m.p.: 193–196°C (from hexane); $\tilde{\nu}_{max} = 862$, 1160, 1362, 1379, 1476, 1607, 2853 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): $\delta = 1.45$ (6H, d, J=6.0 Hz, OCH(CH₃)2), 2.14 (9H, s, ArCH₃), 2.17 (9H, s, ArCH₃), 2.75 (3 H, J = 10.6 Hz, CH_AH_B) 3.90 (3 H, J = 10.6 Hz, CH_AH_B), 5.13 (1 H, hept, J=6.0 Hz, OCH(CH₃)₂), 6.62 (3H, s, ArH), 6.78 ppm (3H, s, ArH); ¹³C NMR (100 MHz, CDCl₃): $\delta = 16.4$ (ArCH₃), 20.7 (ArCH₃), 25.7 (CH-(CH₃)₂), 58.6 (CH₂) 79.8 (CH(CH₃)₂), 123.5, 124.1, 127.3, 129.1, 130.5, 159.4 ppm (ArCO); MS (FAB): m/z 523.5 [M^+], elemental analysis: calcd (%) for C₃₀H₃₇NO₄Ti: C 68.5, H 7.1, N 2.6; found: C 68.8, H 7.1, N 2.7. Crystal data for $C_{30}H_{37}N_1O_4Ti_1$, M = 523.51, yellow blocks, crystal size 0.25×0.22×0.17 mm, triclinic, P-1, a=13.0760(1), b=14.2000(2), c= 16.4720(3) Å, $\alpha = 82.170(1), \quad \beta = 88.758(1), \quad \gamma = 62.785(1)^{\circ},$ V =2691.70(7) Å³, Z=4, $\rho_{cald} = 1.292 \text{ g cm}^{-3}$, T=150(2) K, 52968 reflections measured, 12285 unique reflections ($2\theta = 27.51^\circ$, $R_{int} = 0.0556$) against 666 parameters gave $R_1 = 0.0500$ and $wR_2 = 0.1181 [I > 2\sigma(I)] (R_1 = 0.0803$ and $wR_2 = 0.1306$ for all data). CCDC 209584 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

Amine-(tris-phenolate) titanium triflate $6^{[22]}$. Amine-(tris-phenolate) titanium *iso*-propoxide **2a** (5.23 g, 10 mmol) in toluene was treated with trimethylsilyl triflate (1.8 mL, 10 mmol), under a nitrogen atmosphere. The resulting red suspension was heated to reflux for six hours and concentrated under vacuum which gave a red/orange solid that was suspended in hexane and filtered. The residue was washed with hexane and dried

under vacuum to afford the title compound as a red/orange powder (6.05 g, 9.8 mmol, 98%); m.p.: (dec.) 285– 287 °C (from hexane); \tilde{v}_{max} =640, 860, 1029, 1160, 1243, 1416, 1477, 1685, 2922 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, -50 °C): δ =2.14 (9H, s, ArCH₃), 2.18 (9H, s, ArCH₃), 3.09 (3H, *J*=10.6 Hz, CH_AH_B), 4.04 (3H, *J*=10.6 Hz, CH_AH_B), 6.70 (3H, s, ArH), 6.82 ppm (3H, s, ArH); ¹³C NMR (75 MHz,

CDCl₃): $\delta = 16.1$ (*C*H₃), 21.1 (*C*H₃), 59.3 (*C*H₂), 123.4, 124.6, 128.9, 132.1, 133.1, 160.9 ppm (ArCO); ¹⁹F NMR (376 MHz): $\delta = 78.15$ ppm; MS (FAB): *m*/z 613.5 [*M*⁺]; elemental analysis: calcd (%) for C₂₈H₃₀F₃NO₆STi: C 54.8, H 5.0, N 2.3; found: C 54.8; H 4.9; N 2.3; C_{59.5}H₆₄F₆N₂O₃S₂Ti₂, *M*=1273.04, red blocks, crystal size 0.20×0.22× 0.15 mm, triclinic, *P*-1, *a*=10.1340(2), *b*=16.8420(3), *c*=18.2010(4) Å, *a*=101.613(1), *β*=93.762(1), *γ*=95.259(1)°, *V*=3018.8(1) Å³, *Z*=2, $\rho_{\rm cald}$ =1.401 gcm⁻³, *T*=150(2) K, 41484 reflections measured, 10600 unique reflections (2 θ =25.03°, *R*_{int}=0.0420 against 786 parameters gave *R*₁=0.0436 and *wR*₂=0.1056 [*I*>2 σ (*I*)] (*R*₁=0.0630 and *wR*₂=0.1159 for all data). CCDC 209585 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

General Procedure for Aza-Diels–Alder Reactions Catalyzed by Titanium Triflate **6**

Titanium triflate catalyst 6 (0.042 mmol) was added to a solution of Danishefsky's diene 4 (1.26 mmol) and the corresponding imine 3a–f (0.42 mmol) in CH₂Cl₂ (1 mL) at room temperature. The mixture was then stirred for 2 h before addition of silica (0.50 g) and removal of solvent under vacuum. The crude reaction mixture was then purified using column chromatography to afford the desired dihydropyridones 5a–f.

General Procedure for Diels-Alder Reactions Catalyzed by Titanium Triflate 6

The relevant dienophile (0.5 mmol) and titanium triflate **6** (0.05 mmol) were stirred together in CH_2Cl_2 (2 mL) at room temperature for 15 min. The diene (1.5 mmol) was then added using a syringe and the reaction mixture stirred at room temperature until no dienophile remained. The reaction mixture was then filtered through a small plug of silica which was washed with CH_2Cl_2 (2 mL), before the combined organic solvent and excess diene were removed under vacuum to afford a crude product that was purified by chromatography to afford the title compounds **11**, **13a–b**, **15 a–c**, **19**.

Titanium Triflate 6 Mediated syn-Aldol Reaction

(S)-4-Benzyl-3-propionyloxazolidin-2-one **20** (0.117 g, 0.5 mmol) and diisopropylethylamine (0.9 mL, 0.53 mmol) were added to a solution of (*rac*)-titanium triflate **6** (0.307 g, 0.5 mmol) in CH₂Cl₂ (3 mL) at 0 °C, and the reaction stirred at 0 °C for one hour before benzaldehyde (0.5 mL, 0.5 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 48 h, before being filtered. The organic solvent was removed to afford a crude product that was purified by chromatography resulting in (*S*,*S*,*S*)-4-benzyl-3-(3-hydroxy-2-methyl-3-phenylpropanoyl)oxazolidin-2-one **21** (0.125 g, 0.36 mmol, 74 % yield, 85 % conversion, $|a|_{25}^{25} = +54$ (*c*=1.3, CHCl₃)) as a colourless oil.

Titanium Triflate 6 Catalyzed Allylation Reaction

Benzaldehyde (0.1 mL, 1 mmol) and allyltributyltin (0.34 mL, 1.1 mmol) were added to a solution of titanium triflate **6** (0.026 g, 0.05 mmol) in CH₂Cl₂ (2 mL) at room temperature and the resultant solution stirred for 4 h before being quenched by addition of 1.0 N HCl (4 mL). The organic layer was washed with water before being dried over MgSO₄ and the solvent removed under vacuum to afford a crude product that was purified by chromatography to afford 1-phenylbut-3-en-1-ol **22** (0.094 g, 0.64 mmol, 64%) as a yellow oil.

Titanium Triflate 6 Catalyzed Alkylation Reaction

Benzaldehyde (0.1 mL, 1 mmol) was added to a solution of diethyl zinc (3 mL, 1.0 μ in hexane, 3 mmol) and titanium triflate **6** (0.105 g, 0.2 mmol) in CH₂Cl₂ (2 mL) at 0°C, and the reaction mixture was stirred for 6 h before being quenched by addition of 1.0 μ HCl (4 mL). The organic layer was washed with water before being dried over MgSO₄ and the solvent removed under vacuum to afford a crude product that was purified by chromatography resulting in 1-phenyl-propanol **23** (0.104 g, 0.77 mmol, 77%) as a yellow oil.

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