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Synthesis, structure and catalytic activity of an air-stable titanium triflate, supported by an amine tris(phenolate) ligand†

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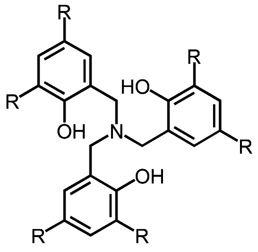
An air- and moisture-stable titanium(IV) triflate, 3, supported by a C_3-symmetric amine tris(phenolate) ligand has been synthesised, characterised by X-ray crystallography and demonstrated to be an excellent catalyst for formal aza-Diels–Alder reactions.

Titanium(IV) compounds, which are usually derived from halide, alkoxide, phenolate or triflate ligands, are amongst the most widely used catalysts in organic synthesis.[1] Although these salts (or their precursors) are often cheap and commercially available, they have the disadvantage of being air- and moisture-sensitive liquids requiring storage and manipulation under inert conditions. Furthermore, in significant quantities, they can present a considerable caustic and corrosive hazard.[2] Therefore, the design of new titanium-based reagents that are convenient to use yet retain high catalytic activity is of considerable importance to the synthetic community. In this communication we describe the development of air-stable titanium complexes of an easily prepared amine tris(phenolate) ligand and report the remarkable reactivity of the air-stable triflate salt **3** as a catalyst for formal aza-Diels–Alder reactions.[3]

In common with a wide range of other tripodal ligands, there has been much recent interest in main group and transition metal coordination chemistry of amine tris(phenolate) ligands derived from **1a–c** (where R = Me, **1a**; ^{t}Bu, **1b**; H, **1c**).[4,5] Given the ease of preparation of these ligands *via* a one-pot variant of the Mannich reaction, its unusual yet simple coordination chemistry, and the reported activity of similar titanium complexes as polymerisation catalysts,[5] we considered that titanium complexes of **1a–c** might be versatile catalysts in organic synthesis.

The amine tris(phenolate) titanium isopropoxide **2a** was prepared in high yield from **1a** using a modification of the procedure reported by Kol *et al.*[5c] Its identity was established spectroscopically,† and was confirmed by a single crystal X-ray structure ‡ (Fig. 1) which revealed a monomeric, C_3-symmetric complex as expected. The approximately trigonal bipyramidal Ti centre lies slightly above the plane of the three equatorial phenolate oxygen atoms whilst the axial sites are occupied by the neutral nitrogen atom of the ligand, and the monodentate isopropoxide anion. The complex **2a**, although generated from an achiral ligand is racemic, since complexation to the metal centre results in the formation of two enantiomers with 'propeller' chirality. This was evidenced by the presence of both *P* and *M* enantiomers in the crystallographic asymmetric unit, whilst two resonances at δ 2.75 and 3.89, (J = 10.6 Hz) were observed in the ^{1}H NMR spectrum of **2a** that were ascribed to the diastereotopic *N*–CH$_2$ protons of the tripodal ligand fragment. The structural parameters of **2a** are very similar to those reported previously for the related amine tris(phenolate) titanium isopropoxide **2b** derived from **1b**.[5c]



1a-c

1a R=Me; **1b** R=^{t}Bu; **1c** R=H

In preliminary screening experiments for catalytic activity, we found complex **2a** to be a poor Lewis acid catalyst for a range of synthetic transformations for which Lewis acidic titanium alkoxides and phenolates have been used previously. We reasoned that this lack of reactivity was in part due to stabilisation of the metal centre arising from apical *N* donation from the amine tris(phenolate) ligand, and that an alternative complex containing a more weakly coordinating apical ligand would enhance catalyst reactivity.

Reaction of **2a** with Me$_3$SiOTf yielded complex **3** in high yield† whose structure was determined by X-ray crystallography (Fig. 2).‡ As expected, the triflate bond to Ti in **3** was significantly longer than the equivalent parameter in the alkoxide **2a** [Ti–O distances: 1.774(2)/1.776(2) Å for alkoxide **2a** *vs.* 2.002(2)/2.017(2) Å for triflate **3**] suggesting weaker metal–ligand coordination. There is a concomitant shortening

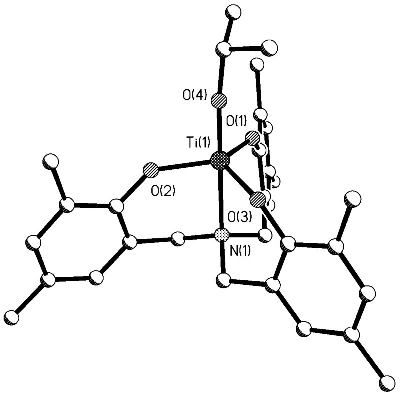


Fig. 1 Molecular structure of **2a** (only one of two similar molecules found within the asymmetric unit shown and hydrogen atoms omitted for clarity). Selected bond lengths (Å): Ti(1)–O(1) 1.862(2), Ti(1)–O(2) 1.845(2), Ti(1)–O(3) 1.851(2), Ti(1)–O(4) 1.774(2), Ti(1)–N(1) 2.305(2); Bond angles (°): 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).

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† Electronic supplementary information (ESI) available: characterisation data and experimental procedures for the synthesis of **2a** and **3** and experimental details of aza-Diels–Alder reactions using **3** as a catalyst. See http://www.rsc.org/suppdata/cc/b3/b304704k/

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(and implied strengthening) of the Ti–N bond in triflate **3** [Ti–N distances: 2.303(2)/2.295(2) Å for **2a** and 2.216(2)/2.213(2) Å for **3**, respectively]; a slight shortening of the Ti–O(phenolate) distances [average Ti–O(phenolate) distance: 1.850 for **2a** and 1.797 Å for **3**]; whilst the Ti atom sits further into the 'pocket' of the ligand for **2a** [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 **3**]. There is 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 **3**).

In catalytic screening triflate **3** demonstrated significantly enhanced activity relative to the isopropoxide complex **2a**.[6] We chose to optimise the use of **3** as a catalyst for the formal aza-Diels–Alder reaction between imine **4a** and Danishefsky's diene **5** (Scheme 1), since this reaction was known not to occur in CH_2Cl_2 in the absence of a strong Lewis acid.[7] Our results demonstrate that triflate **3** is competitive with the best-known catalysts available for this reaction.[8] For example, 10 mol% of catalyst **3** resulted in 100% conversion of imine **4a** and diene **5** to *N*-benzyl-2,3-dihydro-2-phenyl-1*H*-pyridin-4-one **6a** (73% isolated yield) at room temperature in 45 minutes. Subsequent use of 10 mol% of triflate **3** as a catalyst for a representative range of *N*-benzyl-imines **4b–f** with diene **5** afforded the corresponding 2,3-dihydropyridin-4-ones **6b–f** in good yield (56–73%),[9] with reaction times of < 1.5 h in all cases (Scheme 1, Table 1).

The observed catalytic activity of triflate **3** is notable in itself, however most importantly, and in marked contrast to other titanium-based reagents in common usage, **3** is an air- and moisture-stable crystalline solid that is simple to prepare and isolate on a reasonable scale. For example, in the course of this work we have used one batch of **3** on the bench over a period of three months with no noticeable loss in activity or degradation.

In summary, we have described the use of C_3-symmetric titanium triphenolate **3** as a catalyst for formal aza-Diels–Alder reactions. In addition to being a cheap and readily prepared complex, **3** is an air-stable crystalline solid making it a very attractive reagent for use as a Lewis acid catalyst in synthetic laboratories. We are currently investigating further the range of synthetic transformations in which triflates **3** can function as an effective catalyst.

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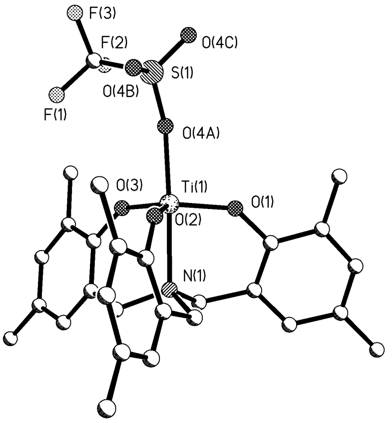
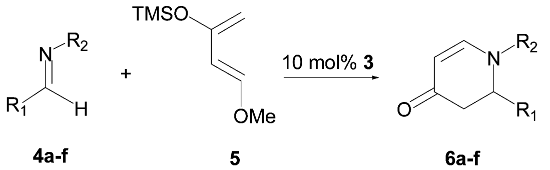


Fig. 2 Molecular structure of **3** (only one of two similar molecules found within the asymmetric unit shown and hydrogen atoms omitted for clarity). Selected bond lengths (Å): Ti(1)–O(1) 1.793(2), Ti(1)–O(2) 1.799(2), Ti(1)–O(3) 1.808(2), Ti(1)–O(4A) 2.002(2), Ti(1)–N(1) 2.216(2); Bond angles (°): 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).



Scheme 1

Table 1 Yield of dihydropyridin-4-ones **6a–f**

Entry	R_1	R_2	Time/min	Yield[a] (%)
a	Ph	Bn	45	73
b	2-Npth	Bn	40	71
c	3,5-$(MeO)_2$Ph	Bn	70	60
d	Cyc	Bn	45	56
e	Ph	^{i}Pr	60	72
f	Ph	3,4-$(MeO)_2$Bn	80	62

[a] All yields for chromatographically pure compounds. ^{1}H NMR spectroscopic analysis of crude reaction products revealed that **6a–f** were formed in 100% conversion as the only products.

Notes and references

‡ *Crystallography*. Data were collected on a Nonius KappaCCD area detector diffractometer using Mo-Kα radiation (λ = 0.71073 Å), and all structures were solved by direct methods and refined on all F^2 data using the SHELX-97 suite of programs.[10]

Crystal data for **2a**: $C_{30}H_{37}N_1O_4Ti_1$, $\underline{M}$ = 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, α = 82.170(1), β = 88.758(1), γ = 62.785(1)°, V = 2691.70(7) Å^3, Z = 4, D_c = 1.292 g cm^{-3}, T = 150(2) K, 52968 reflections measured, 12285 unique reflections (2θ = 27.51°, 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 $wR2$ = 0.1306 for all data). CCDC 209584.

For **3**: $C_{59.5}H_{64}F_6N_2O_3S_2Ti_2$, $\underline{M}$ = 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, α = 101.613(1), β = 93.762(1), γ = 95.259(1)°, V = 3018.8(1) Å^3, Z = 2, D_c = 1.401 g cm^{-3}, T = 150(2) K, 41484 reflections measured, 10600 unique reflections (2θ = 25.03°, R_{int} = 0.0420) against 786 parameters gave R_1 = 0.0436 and $wR2$ = 0.1056 [$I > 2\sigma(I)$] (R_1 = 0.0630 and $wR2$ = 0.1159 for all data). CCDC 209585. See http://www.rsc.org/suppdata/cc/b3/b304704k/ for crystallographic data in CIF or other electronic format.

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