

Experimental realization of catalytic CH₄ hydroxylation predicted for an iridium NNC pincer complex, demonstrating thermal, protic, and oxidant stability†

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A discrete, air, protic, and thermally stable (NNC)Ir(III) pincer complex was synthesized that catalytically activates the CH bond of methane in trifluoroacetic acid; functionalization using NaIO₄ and KIO₃ gives the oxy-ester.

The most efficient methane hydroxylation catalysts utilize Pd^{II}, Pt^{II}, Hg^{II}, or Au^{I/III} cations that operate by a sequence of electrophilic CH bond activation (CHA)¹ followed by reductive oxy-functionalization (ROF).² Because of their electrophilic character, these catalysts are highly susceptible to poisoning by water or methanol, requiring strong acid solvents to minimize this inhibition. To minimize this inhibition we are modifying the highly effective Pt(bipyrimidine)Cl₂ motif^{1b,3} to reduce its electrophilicity by increasing the electron density at the metal center.

In 2003 Goddard and co-workers^{4a} used the mechanism that they had established^{4b} for the (bpym)PtCl₂ system to set up a quantum mechanical rapid prototyping (QMRP) strategy enabling 1000s of ligand–metal oxidation state and solvent conditions to be sampled rapidly. This study showed that Ir^{III} complexed to an NNC ligand motif (a simplified version of **1-TFA**) should react with methane by CHA with an activation barrier <30 kcal mol⁻¹, should not be poisoned by H₂O, and could undergo reductive functionalization through an Ir^V intermediate to generate a functionalized product.

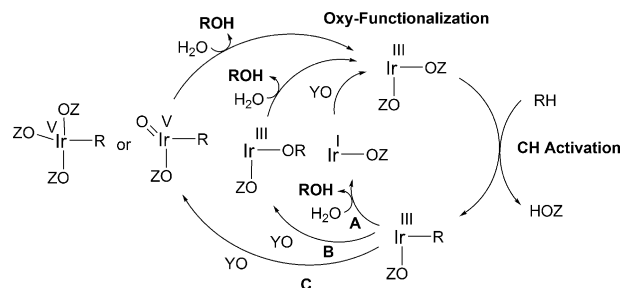
We report here the experimental realization of this predicted system. This study provides a lesson in using QM theory to examine a large number of systems to quickly narrow the candidates down to a select few, and shows the experimental processes required to develop a stable functional catalyst.

The first step was to extend the functional groups in the simplified NNC ligand to form a stable framework using donating C-ligands.^{3d} However, the key challenges are ensuring catalyst stability, maintaining efficient CHA,⁵⁻⁷ and developing compatible oxy-functionalization reactions.^{3a,8,9}

Because Ir(I) to Ir(III) conversion is likely with electron-donating ligands under protic and oxidizing conditions (e.g. Scheme 1A),⁸ we focused our efforts on catalytic systems based on CHA with Ir(III) followed by either direct O-atom insertion¹⁰ from YO and then hydrolysis (Scheme 1B) or oxidation by YO to an Ir^V–CH₃ species, followed by ROF (Scheme 1C).⁹ We observed that treatment of (NN)(NC)Ir(III)(Me)OTf (NN = κ²-4,4'-di-*tert*-butyl-2,2'-bipyridine, NC = η²-(*N*,*C*-3)-6-phenyl-2,2'-bipyridine) with PhI(TFA)₂ (PITFA)^{8c} leads to efficient ROF to generate methyl oxy-esters, presumably *via* an Ir^V–CH₃ intermediate, we designed a catalyst that would activate the methane CH bond with an Ir(III) motif and then utilize a similar ROF route.

We report an (NNC)Ir^{III} pincer complex (NNC = η³-6-phenyl-2,2'-bipyridine) that catalytically activates and functionalizes methane. Scheme 2 shows the synthetic route to the *trans*(*Et*,*TFA*)-(NNC^{*t*Bu})Ir(TFA)(C₂H₄)Et, **1-TFA** (TFA = trifluoroacetate). Treatment of 6-phenyl-4,4'-di-*tert*-butyl-2,2'-bipyridine (NNC^{*t*Bu}) with [Ir(C₂H₄)₂Cl]₂ led to the corresponding tridentate *trans*(*Cl*,*Et*)-(NNC^{*t*Bu})IrCl(C₂H₄)Et complex (**1-Cl**) in ~66% yield as an air-stable solid. **1-Cl** has been fully characterized. Treatment of **1-Cl** with AgTFA in CH₂Cl₂ replaces the Cl⁻ with the less coordinating trifluoroacetate, CF₃CO₂⁻, group to generate (NNC^{*t*Bu})Ir(Et)(TFA)(C₂H₄), **1-TFA**, which has been fully characterized. Fig. 1 shows the X-ray crystal structure. Formation of **1-TFA** is also supported by appearance of a new resonance at -78.99 ppm in the ¹⁹F spectra.

Dissolution of **1-TFA** in trifluoroacetic acid (HTFA) releases ethane with formation of (NNC^{*t*Bu})Ir(TFA)₂(C₂H₄) (**1-TFA**₂), which has been fully characterized.¹¹ Heating **1-TFA**₂ in HTFA solvent leads to loss of ethylene with formation of a solution of the solvent complex,



Scheme 1 Alternative catalytic schemes for hydrocarbon hydroxylation. Y is an O carrier.

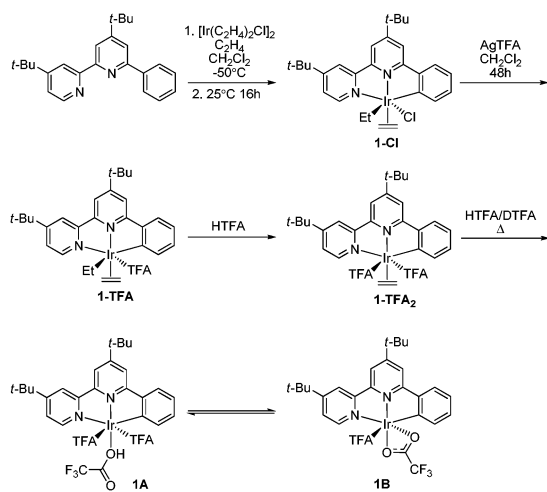
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Scheme 2

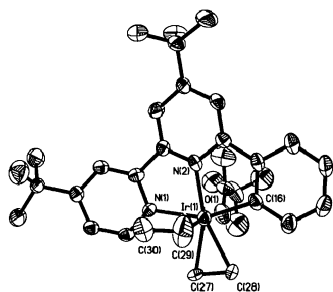


Fig. 1 Thermal ellipsoid plot of **1-TFA** with 50% probability. Hydrogens and benzene co-solvent removed for clarity. Selected bond lengths (Å): Ir(1)–N(2) 2.019(6), Ir(1)–C(16) 2.078(7), Ir(1)–C(29) 2.081(10) Ir(1)–N(1) 2.166(6), Ir(1)–O(1) 2.210(6). Selected bond angles (°): N(2)–Ir(1)–C(16) 78.8(3), N(2)–Ir(1)–C(27) 161.0(3), N(2)–Ir(1)–N(1) 76.7(2), C(16)–Ir(1)–N(1) 155.4(3), C(27)–Ir(1)–N(1) 84.3(3)C(29)–Ir(1)–O(1) 170.91(4).

(NNC^tBu) $\text{Ir}(\text{TFA})_2(\text{HTFA})$, **1A**, and the κ^2 -acetate complex, **1B**, (from NMR). These complexes could not be isolated. However, consistent with the formation of these complexes, trapping with pyridine leads to quantitative formation of the expected pyridine complex, (NNC^tBu) $\text{Ir}(\text{TFA})_2(\text{Py})$, see ESI†. *In situ* NMR analysis (see ESI†) indicates **1-TFA**₂ is thermally stable in HTFA after heating at 180 °C for 1 h.

Heating a stirred solution of DTFA–CH₄ with **1-TFA** (0.3 mol%) for 2 h at 180 °C leads to rapid and extensive methane H/D exchange. Analysis of the reaction gas phase by GC-MS indicated that ~30% of the CH₄ was converted to 21.2% CH₃D, 6.6%, CH₂D₂, 1.3% CHD₃, 0.6% CD₄, TON ≈ 153, TOF ≈ 2.12 × 10⁻² s⁻¹. Note that under identical conditions, related complexes such as (NN)(NC)Ir(III), (NNC)Pt(II), and Pt(bpy)Cl₂ show no H/D exchange.^{1b,3d,8c} The rate of methane CH activation is comparable to the Pt(bpy)Cl₂–H₂SO₄ system, the most efficient CH activation system that catalyzes methane hydroxylation.

Kinetic analysis shows that the rate of formation of the various isotopologs is consistent with a Schultz–Flory type of reaction sequence for a reaction mechanism where each encounter methane molecule with the catalyst leads to a single

H/D exchange. This contrasts with our results on (bpy)PtCl₂ where each encounter can lead to more than one exchange and simultaneous generation of all the methane isotopologs.^{1b,12} Rate data obtained between 105 °C and 135 °C give $\Delta H^\ddagger = 24 \pm 3$ kcal mol⁻¹ for H/D exchange between CH₄ and DTFA.

Analysis of the reaction mixture by ¹H NMR revealed that multiple Ir complexes were present but that the NNC-ligand remained coordinated (at least through an NN binding mode) to the Ir center. However, extensive deuterium incorporation into the phenyl ring is observed (see B3LYP calculations). At temperatures above 150 °C, slow loss of catalytic activity is observed with **1-TFA** and at 180 °C catalysis stops after ~6 h. **1A** and **1B** are still present in small amounts but the majority of the solution is composed of two new species. The catalyst is more stable at lower temperatures and at 105 °C ~62 turnovers were observed after 45 h without any loss in activity.

H/D exchange does not occur in weaker, more coordinating acids, such as acetic acid at 180 °C. Consistent with the CHA reaction proceeding *via* reversible substrate coordination, followed by CH cleavage, the addition of DMSO, a strongly coordinating ligand, leads to complete reaction inhibition. Further support for a CH activation mechanism is the observation that methane H/D exchange is also observed in non-acidic media. Thus, heating a solution of **1-TFA** in neat C₆D₆ with CH₄ (514.7 psi) at 140 °C for 6 h led to methane H/D exchange (~60 turnovers, 5.3% CH₃D, 0.7% CH₂D₂). In addition to methane, **1-TFA** also catalyzes H/D exchange with linear and cyclic alkanes such as octane, cyclohexane, and cyclooctane in trifluoroacetic acid. With octane we observed primarily C-1 and C-2 CHA on the basis of ²H and ¹³C NMR analyses.

Having established rapid H/D exchange with **1-TFA**, we examined if added oxidants would facilitate overall catalytic, selective, oxidation of methane to methyl trifluoroacetate (MeTFA). Initial attempts to form MeTFA with the hypervalent iodine oxidant, PITFA, used with the (NN)(NC)Ir(III)–CH₃ system^{8c} were unsuccessful. However, when a solution of **1-TFA** in DTFA is heated with methane (514.7 psi) at 180 °C for 3 h with NaIO₄ as the oxidant, MeTFA is produced (TON = 6.3).† There is a background reaction between NaIO₄ and CH₄ in DTFA but the rate of formation of MeTFA with **1-TFA** is faster (see ESI†). Formation of MeTFA was confirmed by ¹H, ¹³C, and ¹⁹F NMR and by GC-MS and HPLC. When the reaction was carried out with 100% ¹³CH₄, only ¹³CH₃OC(O)CF₃ was observed by ¹³C NMR and GC-MS. The catalyst activity is <6 h and the maximum yields of MeTFA based on methane, were <5%. At 160 °C the reaction is slower, and after 5 h, 2.0 turnovers of MeTFA were observed with **1-TFA**. KIO₃, a weaker oxidant, also generated MeTFA but at lower rates than KIO₄. Such oxidants as nitrous oxide, urea hydrogen peroxide, and pyridine oxide, did not generate MeTFA. Oxidants such as Na₂S₂O₈, OsO₄, or K₂Os(O)₂(OH)₄ did generate MeTFA, but with less than 1 turnover.

Several CHA mechanisms were explored using B3LYP DFT.¹³ Fig. 2 outlines the three lowest energy reaction pathways leading to methane C–H bond cleavage by a model **1-TFA** complex. We find spontaneous loss of ethane and ethylene from **1-TFA** to give an equilibrium between **1A**

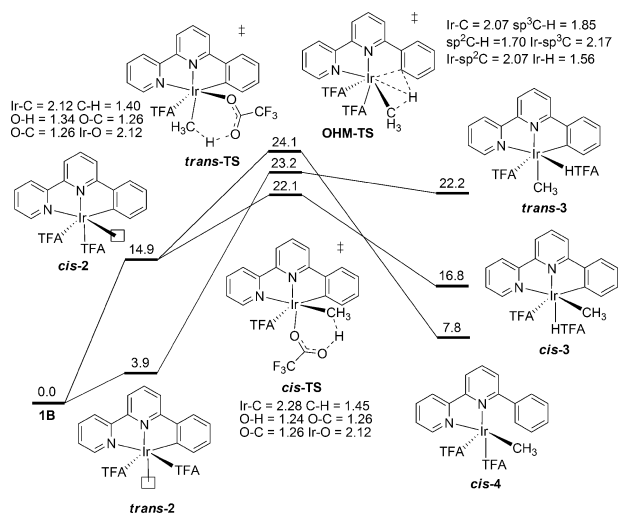


Fig. 2 B3LYP enthalpy hypersurface (453 K) including solvent corrections for HTFA. LANL effective core potential and the LACV3P++** basis set¹³ (structures optimized using the LACVP** basis set). See Scheme 2 for structure of **1B**. Note: IRCs link TSs to methane coordination structures, not *cis-2* and *trans-2*.

(3.4 kcal mol⁻¹) and **1B** (0.0 kcal mol⁻¹). From **1B**, the κ^2 -bound acetate can rearrange to either of two η^1 configurations, allowing two different methane coordination sites. Because of the σ -electron-donating capacity of the NNC ligand, breaking the Ir–O bond *trans* to this ligand, giving *trans-2*, is only 3.9 kcal mol⁻¹ above **1B**, while *cis-2* requires 14.9 kcal mol⁻¹ to generate the *cis* open coordination site. The methane complexes with *trans-2* and *cis-2* have enthalpies of 4.1 and 6.5 kcal mol⁻¹, respectively.

The lowest energy transition states for C–H bond cleavage are via a six-membered substitution mechanism, *cis*-TS with a barrier of 22.1 kcal mol⁻¹ and the *trans*-TS that is 1.1 kcal mol⁻¹ higher (see ESI† for M06 and M06-2X energies).¹⁴

In these six-membered TSs, the CF₃CO₂⁻ group assists in the cleavage of the C–H bond, simultaneously forming Ir–C and O–H bonds. Intermediate *cis-3*, generated from *cis*-TS, is endothermic by 16.8 kcal mol⁻¹ revealing why no Ir–CH₃ species was detected.

From *cis-2*, the TS for methane activation by the cyclometalated phenyl group, OHM-TS (24.1 kcal mol⁻¹), is only 2 kcal mol⁻¹ higher in energy than *cis*-TS. This oxidative hydrogen migration (OHM)¹⁵ transition state has a characteristic short Ir–H distance (1.56 Å) and no intervening iridium hydride intermediate between *cis-2* and *cis-4*. The intermediate formed from OHM-TS is *cis-4*, and is ~9 kcal mol⁻¹ more stable than *cis-3*. Therefore, deuterium incorporation into the phenyl ring may occur because of OHM-TS or *cis-3* exchanges of HTFA for DTFA followed by deuterium transfer to the cyclometalated phenyl group to give deuterated *cis-4*.

In summary, we have synthesized a discrete, air, protic, and thermally stable (NNC)Ir(III) pincer motif, **1-TFA**, that catalytically activates the CH bond of methane in trifluoroacetic acid. Functionalization of **1-TFA** using NaIO₄ and KIO₃ gives MeTFA.

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Notes and references

† Representative experimental procedure: a resealable metal reactor with a glass insert and stir bar was loaded with oxidant NaIO₄ (90 mg, 0.4207 mmol), then 10.5 mg of **1-TFA** (0.01487 mmol) in 1 mL of trifluoroacetic acid-*d*₁ was added under argon. After flushing with methane, the reactor was charged with 514.7 psi of methane while stirring. Control reactions were also prepared under identical conditions only without catalyst. The reactors were heated at 180 °C for 3 h. The reactors were then opened and 5 μ L of acetic acid were then added. Formation of MeTFA was confirmed by ¹H and ¹³C NMR analysis, GC-MS, and HPLC, by comparison with an authentic sample.

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