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Full Paper

A Fortuitous, Mild Catalytic Carbon–Carbon Bond Hydrogenolysis by a Phosphine-Free Catalyst

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The putative catalyst *trans*-[Ru((*S*,*S*)-skewphos)$(H)_2$((*R*,*R*)-dpen)] (skewphos = 2,4-bis(diphenylphosphino)pentane; dpen = 1,2-diphenylethylenediamine) transforms the trifluoroacetyl amide 2,2,2-trifluoro-1-(piperidin-1-yl)ethanone under mild conditions (4 atm H_2, room temperature, 4–24 h, 1 mol-% Ru, 15 mol-% KO^{t}Bu in tetrahydrofuran) to generate the formylated amine 1-formylpiperidine and fluoroform via C–C bond hydrogenolysis. Catalysts are also prepared by reacting *cis*-[Ru(η^3-C_3H_5)$(MeCN)_2(COD)$]BF_4 (COD = 1,5-cyclooctadiene) with diamine ligands in situ. Low-temperature NMR studies provided insight into this reaction.

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Introduction

We report the unexpected hydrogenolysis of an sp^3–sp^2 C–C bond with homogeneous catalysis under mild conditions. Homogeneous catalytic C–C bond functionalization is an efficient strategy to modify the skeletal structures of organic molecules. Tangible progress has been reported on such catalytic systems,[1] but further developments are required to broaden the net applicability of this methodology. The intrinsic difficulty is to devise a catalyst that overcomes the inherent kinetic inertness and thermodynamic stability of a specific C–C bond, while accommodating the presence of spectator functional groups. We recently reported the catalytic hydrogenation of amides with the bifunctional catalyst precursors [Ru$(Ph_2PCH_2CH_2NH_2)_2$(η^3-C_3H_5)]$^+$(BF_4^-) (for hydrogenations under basic conditions)[2] and *trans*-Ru$(Ph_2PCH_2CH_2NH_2)_2(H)(BH_4)$ (for hydrogenations under neutral conditions).[3] These hydrogenations occur with cleavage of the amide C–N bond to generate the corresponding amine and primary alcohol products. The reactions proceed with high turnover numbers (up to 6700) under moderate conditions (100°C, 50 atm reaction pressure), and they tolerate a propitious variety of functional groups. We now report the fortuitous discovery of a catalytic C–C hydrogenolysis that selectively converts a trifluoroacetyl amide into the corresponding formylated amine.

Formylated amines are used as solvents and they are intermediates in syntheses of pharmaceuticals.[4,5] They are typically prepared from the parent amine using formic acid or its derivatives as the formylating reagent.[5] There are several reports of Ru complexes that catalyze the formylation of amines using CO,[6] methanol,[7] and quite recently, CO_2/H_2[8] as the source of the formyl group.

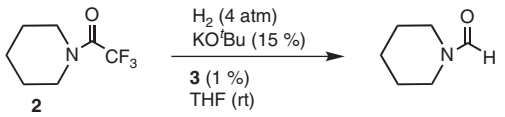
Results and Discussion

We showed previously that Ru-dihydride catalysts of the type *trans*-Ru(P–P)$(H)_2$(N–N) and related complexes are prepared by reaction of *cis*-[Ru(η^3-C_3H_5)$(MeCN)_2(COD)$]BF_4 (**1**; COD is 1,5-cyclooctadiene) with P–P and N–N ligands.[2,9] Typically, **1** and 1 equivalent of the P–P and N–N ligands are allowed to react for 30 min at 60°C to displace MeCN and COD. The resulting allylic-Ru complexes are then mixed with KO^{t}Bu and the amide and placed under H_2. The putative Ru-dihydride catalyst is formed in situ for hydrogenation to proceed. For this study, we chose Bosnich's ligand (*S*,*S*)-2,4-bis(diphenylphosphino)pentane ((*S*,*S*)-skewphos)[10] as the diphosphine and (*R*,*R*)-1,2-diphenylethylenediamine ((*R*,*R*)-dpen) as the diamine.

We found that the catalytic reaction between the trifluoroacetyl amide 2,2,2-trifluoro-1-(piperidin-1-yl)ethanone (**2**) and 1 mol-% of *trans*-Ru((*S*,*S*)-skewphos)$(H)_2$((*R*,*R*)-dpen) (**3**) proceeded in 100 % yield after 4 h under mild conditions (15 mol-% KO^{t}Bu, 4 atm H_2, THF, room temperature (rt)). To our surprise, rather than the expected amide hydrogenation products, 1-formylpiperidine was the sole detectable (NMR) product of the reaction (Scheme 1).

The related acyclic amide 2,2,2-trifluoro-1-(diethylaminyl) ethanone formed diethylformamide as sole detectable product in 68.7 % conversion.

Assuming the putative catalyst in this reaction is *trans*-Ru ((*S*,*S*)-skewphos)$(H)_2$((*R*,*R*)-dpen) (**3**), we prepared the stable dichloride *trans*-Ru((*S*,*S*)-skewphos)$(Cl)_2$((*R*,*R*)-dpen) (**4**) as a structural model for the catalyst. Fig. 1 shows the solid-state structure of **4** as determined by X-ray diffraction. The backbone of (*S*,*S*)-skewphos is in the chair conformation with one methyl group in the axial orientation and the other group in the



Scheme 1.

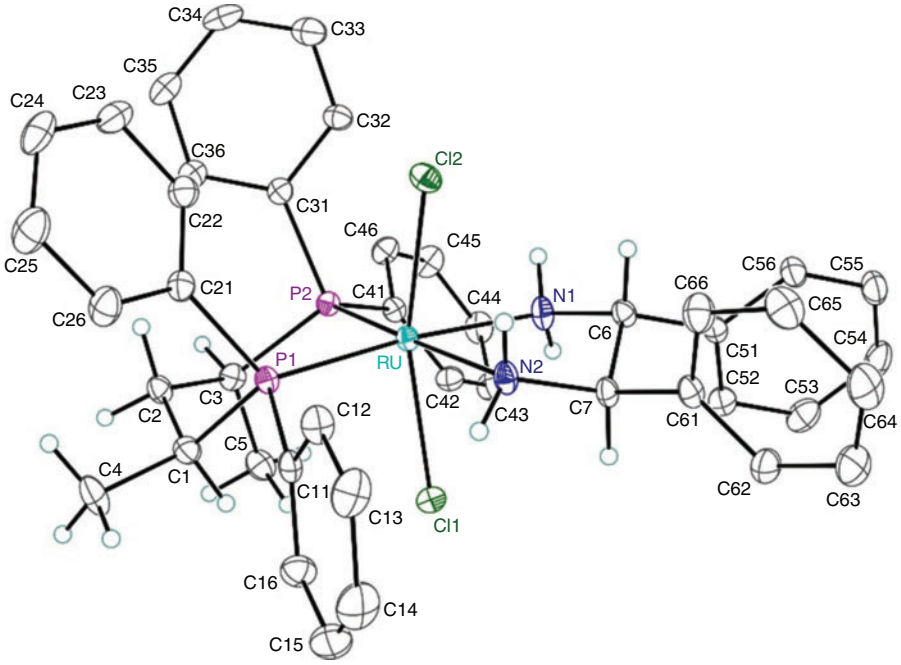


Fig. 1. Solid-state structure of *trans*-Ru((*S*,*S*)-skewphos)$(Cl)_2$((*R*,*R*)-dpen) (**4**) as determined by X-ray diffraction. The positions of the hydrogen atoms are based upon idealized geometries.

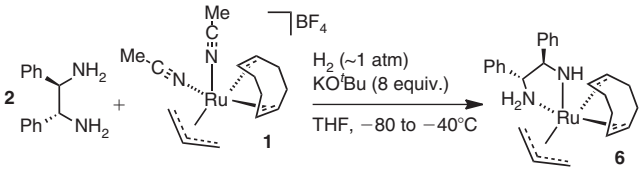
equatorial orientation. This conformation holds the phenyl rings on phosphorus in a pseudo achiral spatial array. Perhaps the exigencies of crystal packing prevented the ligand from adopting the more stable δ-skew conformation which would place both methyl groups in the equatorial position and the phenyl rings in a chiral disposition.[10] As expected, the backbone of (*R*,*R*)-dpen is puckered in the λ-conformation with both phenyl rings equatorially disposed.

Remarkably, (*S*,*S*)-skewphos could be omitted, and another equivalent of (*R*,*R*)-dpen was used during the reaction with **1** to generate the phosphine-free catalyst **5**; the latter also catalyzed the conversion of **2** into the formyl amine in 100 % yield after 23 h under the same mild conditions. The corresponding ethylenediamine catalyst, made by reacting **1** with 2 equivalents of ethylenediamine, was also active, however, with only 11 % conversion after 15 h.

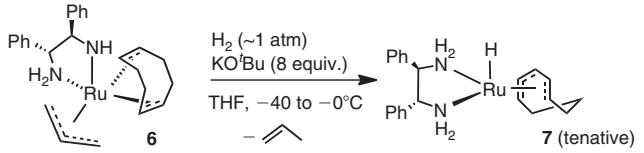
The reaction between the bis(acetonitrile) precursor **1** with 2 equivalents of (*R*,*R*)-dpen and 8 equivalents of KO^{t}Bu under ~1 atm H_2 in [D8]THF at −78°C was monitored by NMR spectroscopy to investigate the reaction. At −78°C, the MeCN ligands were displaced by 1 equivalent of (*R*,*R*)-dpen to form the η^3-C_3H_5-amido complex **6**, with one NH_2 group in (*R*,*R*)-dpen deprotonated by the excess KO^{t}Bu (Scheme 2). The compound was fully characterized in solution by ^{1}H NMR, ^{1}H–^{1}H gCOSY, ^{1}H–^{13}C gHSQC, ^{1}H–^{15}N gHSQC and TOSCY, and ROESY NMR experiments.

Notably, the ^{1}H NMR chemical shift for the amido N–*H* group was −1.37 ppm. The shifts for the N*H*$_2$ protons were 4.87 and 5.13 ppm. Compound **6** loses propylene upon slow warming to approximately −20°C. We tentatively propose that the transition metal product is the hydride **7**, with the C_8 ring bonded to Ru through an olefin and a η^3-allyl group (Scheme 3).[9]

Overlap of peaks prevented conclusive identification of compound **7**. The proposed structure would result from allylic activation of the 1,5-cyclooctadiene ring in **6**, followed by elimination of propylene. Further warming to room temperature



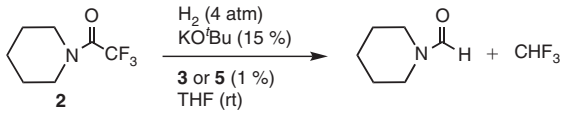
Scheme 2.



Scheme 3.

resulted in the hydrogenation of propylene to propane, the hydrogenation of the acetonitrile to ethylamine, and the formation of unidentified ruthenium-containing products. All attempts to identify the ruthenium-containing products formed by warming the mixture of **7** and (*R*,*R*)-dpen failed. Addition of the trifluoroacetyl amide **2** to this mixture, however, resulted in the formation of fluoroform, CHF_3, as the major fluoride-containing product (identified by ^{19}F NMR and by a headspace analysis by gas chromatography mass spectrometry). Thus, the net catalytic reaction between 2,2,2-trifluoro-1-(piperidin-1-yl) ethanone (**2**) and the catalysts **3** and **5** is the hydrogenolysis of the C–C bond to form 1-formylpiperidine and CHF_3 (Scheme 4).

While investigating the nature of **5**, we found that elemental mercury (200 equiv.) did not inhibit the hydrogenolysis catalyzed by **5**, and the activity of reduced Ru black was minimal (~1 % conversion) under these conditions. Taken together, these results suggest that **5** is a homogeneous Ru-H-dpen compound.



Scheme 4.

Conclusion

To our knowledge, the catalytic transformation of **2** into 1-formylpiperidine and fluoroform is the first catalytic hydrogenolysis of the sp^3–sp^2 C–C bond in a trifluoro amide. The mild conditions, along with the absence of phosphine ligands are attractive features of this novel transformation. Efforts are underway in our laboratories to investigate the scope, the identity of the catalysts, and the mechanism of this reaction.

Experimental

General Information

Deuterated solvents were obtained from Aldrich and Cambridge Isotope Laboratories. Both [D8]THF and THF were dried using Na/benzophenone just before each experiment. All pressurized reactions were carried out in a steel pressure reactor equipped with a magnetic stir bar. Potassium *tert*-butoxide was sublimed before use.

Piperidine, potassium *tert*-butoxide, and trifluoroacetic anhydride were obtained from Aldrich and (1*R*, 2*R*)-1,2-diphenylethylenediamine was obtained from Alfa Aesar. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded using 400 and 600 MHz Varian Inova, and 500 and 700 MHz Varian DirectDrive spectrometers. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) relative to TMS with the deuterated solvent as the internal reference. ^{19}F chemical shifts are reported in parts per million relative to $CFCl_3$ as the external reference. NMR peak assignments were made using ^{1}H NMR, ^{1}H–^{1}H gCOSY, ^{1}H–^{13}C gHSQC, ^{1}H–^{15}N gHSQC and TOSCY, and ROESY NMR experiments. Gas chromatography mass spectrometry analysis was performed by using a Hewlett Packard 5890 chromatograph equipped with a 5970B mass-selective detector and Supelco Beta DEX 225 capillary column (30 m × 0.25 mm × 0.25 µm film thickness). Elemental analysis data were obtained using a Carlo Erba CHNS-O EA1108 elemental analyzer.

Hydrogenation Procedure

Cis-[Ru(η^3-C_3H_5)(COD)$(MeCN)_2$]BF_4 (**1**; 0.025 mmol, 10.5 mg), 2 equiv. (*R*,*R*)-dpen (0.05 mmol, 11.0 mg) (or 1 equiv. (*R*,*R*)-dpen and 1 equiv. of (*S*,*S*)-skewphos), and KO^{t}Bu (0.375 mmol, 42.1 mg) were weighed out into three NMR tubes in a glove box. Freshly distilled THF (0.8 mL) was then added by cannula under argon pressure into the tube containing (*R*,*R*)-dpen. The resultant solution was then cannulated into the NMR tube containing **1** under argon. It was then heated at 60°C for 30 min with occasional shaking (pale brown, clear liquid). Meanwhile, 100 equiv. substrate (2.5 mmol, 453 mg) was dissolved in THF (1.0 mL) in a NMR tube, and the resultant solution was then cannulated into a stainless steel autoclave under H_2 pressure and purged with hydrogen for 20 min. After 30 min, KO^{t}Bu in THF (0.7 mL) was added to the pre-heated NMR tube. The resultant orange-red solution was transferred to the autoclave under hydrogen pressure followed by washing with THF (2.5 mL). The autoclave was then pressurized to 4 atm H_2 and stirred at room temperature for 4–24 h. The reaction was stopped by slowly de-pressurizing the autoclave and opening it to the atmosphere. The percentage conversions were determined by ^{1}H NMR spectroscopy. The catalyst was removed by passing the solution through a Florisil plug using CH_2Cl_2 as the rinsing solvent. The solvent was then removed under reduced pressure using a rotary evaporator, and the NMR spectra were recorded using $CDCl_3$.

NMR Study of the Reaction between **1**, ((R,R)-dpen), KO^{t}Bu, H_2, and **2**

Cis-[Ru(η^3-C_3H_5)(COD)$(MeCN)_2$]BF_4 (**1**) (0.03 mmol, 12.6 mg), (*R*,*R*)-dpen (0.06 mmol, 12.7 mg), and KO^{t}Bu (0.24 mmol, 26.9 mg) were weighed into three separate NMR tubes inside the glove box. Distilled [D8]THF (0.5 mL) was added to (*R*,*R*)-dpen by cannula under argon, and the ^{1}H NMR spectrum was recorded. Then, the solution was transferred to the NMR tube containing **1** under argon. The resulting solution was then heated at 60°C for 30 min with occasional shaking. After 30 min, the ^{1}H and ^{19}F NMR spectra were recorded. Then, the solution temperature was decreased to −80°C by immersing the NMR tube in dry ice/acetone mixture. The base in [D8]THF (0.2 mL) was added to Ru-dpen mixture under hydrogen at −80°C. The product was characterized using ^{1}H, ^{19}F, ^{1}H–^{15}N HSQC, gTOCSY, gCOSY, and gROESY NMR experiments in [D8]THF at variable temperatures (−80°C to room temperature). The *cis*-[Ru(η^3-C_3H_5)(COD)$(MeCN)_2$]BF_4/(*R*,*R*)-dpen/ KO^{t}Bu precatalyst was prepared again at −80°C as described above and 10 equiv. 2,2,2-trifluoro-1-(piperidin-1-yl)ethanone (**2**) were added at −60°C. The reaction was monitored from −60°C to room temperature.

Supplementary Material

Additional experimental and spectroscopic details, as well as structural data and parameters from the X-ray crystallography study are available on the Journal's website.

Acknowledgements

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