



Oxidative carbonylation of benzotrifluoride to form trifluoromethylbenzoic acid

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ABSTRACT

The oxidative carbonylation of benzotrifluoride to form trifluoromethylbenzoic acid (TFMBA) has been catalyzed using either Rh(III) or a Pd(II) cation in combination with a carboxylic acid and its anhydride, ammonium metavanadate, CO, and O₂. The influence of metal cation and vanadate concentrations, temperature, time, acid composition, and gas pressures, were explored. The accumulated data suggest that oxidative carbonylation of benzotrifluoride proceeds via an electrophilic mechanism. Rh-catalyzed reactions exhibited higher activity (~70 turnovers in 4 h at 353 K) and trifluoromethylbenzoic acid selectivity (~92–95%) than Pd-catalyzed reactions (~6 turnovers in 4 h at 353 K and a trifluoromethylbenzoic acid selectivity of 80%). Formation of the principle reaction byproducts, benzoyl fluoride and benzoic acid, was highly dependant on the V(V) concentration and the acid composition. Reactions conducted in the presence of CF₃COOH yielded the highest catalytic activity, but reactions conducted in CCl₃COOH resulted in the highest trifluoromethylbenzoic acid selectivity. A possible mechanism for the reaction has been proposed.

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1. Introduction

Trifluoromethylbenzoic acid has attracted considerable interest as a precursor for a wide range of pharmaceuticals [1]. For example, it can be used as a synthon for products that act as an inhibitor of interleukin-1 β , which plays a pathogenic role in atherosclerosis, sepsis syndrome, inflammatory bowel syndrome, and periodontal disease [2]. Trifluoromethylbenzoic acid can also be used as an analogue of α -galactosylceramide and other derivatives, which possess anti-tumor activity [3,4], and as a precursor to Luotonin A derivatives, which serve as anti-leukemia agents [5]. Trifluoromethylbenzoic acid has been demonstrated to be effective in drugs for the treatment of strokes [6], whereas the coupling of trifluoromethylbenzoic acid with amino acids and peptides [7,8], or its electrophilic aromatic arylation [9], can be used to produce products that are useful as antibiotics or precursors to anti-malarial drugs [9]. Finally, trifluoromethylbenzoic acid can be converted to oxazoles [10] and 2-hydroxy-4-trifluoromethylbenzoic acid (HTB) [11], which can be used as an anti-inflammatory drug.

A number of approaches have been investigated for synthesizing trifluoromethylbenzoic acid from benzotrifluoride or related compounds. These included lithiation of the benzene ring of benzotrifluoride and subsequent reaction of the lithium with CO₂ and HCl [12]. Alternatively, trifluoromethylbenzoic acid can be formed

by reacting (trifluoromethyl)phenyl iodide with CO in the presence of Pd and aqueous sodium or potassium hydroxide [13]. The oxidation of compounds, such as trifluoromethylbenzaldehyde [14,15] or the corresponding alcohol [16], and the saponification and hydrolysis of the methyl and ethyl esters of trifluoromethylbenzoic acid [17,18] have also been shown to be effective routes to trifluoromethylbenzoic acid. The decarboxylation of mandelic acid derivatives represents yet another approach for the synthesis of trifluoromethylbenzoic acid [19–21]. Recently, it has been shown that the carboxylation of alkenylboronic esters can be used to synthesize trifluoromethylbenzoic acid, a process which proceeds with high yields [22]. Since most of the previously mentioned methods involve multiple steps or the utilization of compounds inherently more complex than trifluoromethylbenzoic acid, the development of a direct method for converting benzotrifluoride to trifluoromethylbenzoic acid would be attractive.

The aim of the present work is to show that trifluoromethylbenzoic acid can be synthesized by the oxidative carbonylation of benzotrifluoride. This effort is based on recent studies of the oxidative carbonylation of aromatic hydrocarbons to form aromatic acids using a Rh(III) or Pd(II) precursor in combination with a mixture of trifluoroacetic acid, its anhydride [23–27], and ammonium metavanadate [26,27]. Our work suggests that in a low dielectric medium such as toluene, the metal cations form cation–anion pairs with trifluoroacetate anions serving as the ligands [27]. During the course of the reaction, the metal cations undergo a two-electron reduction and are re-oxidized by the metavanadate cations present in solution. The reduced metavanadate cations are then re-oxidized by molecular oxygen.

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2. Results and discussion

Table 1 summarizes the results of scoping experiments in which some components of the reaction mixture were omitted in order to determine their importance. Entries 1 and 2 show standard reaction conditions for Rh- and Pd-catalyzed reactions, respectively. The observed products in all cases were 4-trifluoromethyl benzoic acid (4-TFMBA), 3-trifluoromethylbenzoic acid (3-TFMBA), 2-trifluoromethylbenzoic acid (2-TFMBA), benzoyl fluoride (BF) and benzoic acid (BA). The Rh-catalyzed reaction (entry 1) produces roughly equal quantities (~0.14 mmol) of trifluoromethylbenzoic acid, benzoyl fluoride, and benzoic acid, whereas the Pd-catalyzed reaction (entry 2) produces much more benzoyl fluoride and benzoic acid (~0.2 mmol) relative to trifluoromethylbenzoic acid (~0.05 mmol). 2-Trifluoromethylbenzoic acid was not formed using the Rh complex (entry 1) most likely as a consequence of steric inhibition by the CF₃ group on the benzene ring interacting with the bulky Rh complex. A small quantity of the 2-trifluoromethylbenzoic acid was observed using the Pd complex, with a typical 4/2 isomer ratio of approximately 3. In general, for all the reactions, the ratio of 4-trifluoromethylbenzoic acid to 3-trifluoromethylbenzoic acid was approximately 0.25 for the Rh-catalyzed system and 0.3 for the Pd-catalyzed system. Entries 3, 4, and 5 show the results of reactions carried out without CO. In each case, only benzoyl fluoride and benzoic acid were observed as products. Less benzoyl fluoride and benzoic acid were produced using the Rh complex (entry 3) than the Pd complex (entry 4). The absence of Rh or Pd (entry 5) resulted in the highest yields of benzoyl fluoride and benzoic acid. Further removal of the vanadate species (entry 6) resulted in only a small amount of benzoyl fluoride and benzoic acid and no trifluoromethylbenzoic acid. Entries 7 and 8 show the results of reactions without an oxidant present but in the presence of either the Rh or Pd complex. For these cases, a small amount of trifluoromethylbenzoic acid was observed, and the yields of benzoyl fluoride and benzoic acid were reduced significantly compared to what was observed under standard reaction conditions (entries 1 and 2). Substitution of NH₄VO₃ (entry 5) with VO(acac)₂ (entry 9) resulted in a significantly reduced yield of benzoyl fluoride and benzoic acid. Omission of the anhydride (entry 10) resulted in significantly reduced quantities of all products, and no products were observed when both the anhydride and acid were omitted (entries 11 and 12). These results indicate that the acid plays two roles. The first is as the source of ligands that coordinate with the Rh or Pd cations present in solution. These ligands withdraw electron density from the metal thereby enhancing the ability of the metal to coordinate benzotrifluoride and facilitate the abstraction of a proton from the coordinated molecule the C–H bond activation step [27]. The second role of the acid is to hydrogen bond with the fluorine atoms on the methyl group of the arene, a process that is unique to fluorine [28]. The interaction of the proton with the fluorine atoms facilitates the replacement of fluorine by oxygen from the vanadate species, leading to the formation of benzoyl fluoride.

Taken together, the results presented in Table 1 indicate that the catalyst (either Rh or Pd), carbon monoxide, and trifluoroacetic acid are indispensable for the oxidative carbonylation of benzotrifluoride to form trifluoromethylbenzoic acid. The presence of the anhydride is necessary to obtain high yields of product by maintaining an optimal water content as also observed during toluene oxidative carbonylation [27]. The product distribution, both of the desired trifluoromethylbenzoic acid isomers and the undesired benzoyl fluoride and benzoic acid, is influenced by whether Rh(III) or Pd(II) cations are used. The presence of an oxidant is important in the formation of the benzoyl fluoride and benzoic acid, although small quantities of these products are observed without the oxidant present. The observation of significantly more benzoyl fluoride and benzoic acid with vanadium in the 5+ oxidation state than the 4+

Table 1
Scoping experiments. Reaction conditions: benzotrifluoride (37.5 mmol); T = 353 K, t = 4 h.

	CF ₃ COOH (mmol)	(CF ₃ CO) ₂ O (mmol)	Rh(acac) ₃ (μmol)	Pd(CF ₃ COO) ₂ (μmol)	NH ₄ VO ₃ (mmol)	VO(acac) ₂ (mmol)	O ₂ (MPa)	CO (MPa)	4-TFMBA (mmol)	3-TFMBA (mmol)	2-TFMBA (mmol)	BF (mmol)	BA (mmol)
1	13.0	3.8	10	0	0.516	0.000	0.35	0.35	0.034	0.101	0.000	0.111	0.146
2	13.0	3.8	0	5	0.516	0.000	0.35	0.35	0.016	0.040	0.010	0.254	0.216
3	13.0	3.8	10	0	0.516	0.000	0.35	0.00	0.000	0.000	0.000	0.084	0.070
4	13.0	3.8	0	5	0.516	0.000	0.35	0.00	0.000	0.000	0.000	0.205	0.179
5	13.0	3.8	0	0	0.516	0.000	0.35	0.00	0.000	0.000	0.000	0.287	0.224
6	13.0	3.8	0	0	0.000	0.000	0.35	0.00	0.000	0.000	0.000	0.002	0.002
7	13.0	3.8	10	0	0.000	0.000	0.00	0.35	0.004	0.015	0.000	0.000	0.022
8	13.0	3.8	0	5	0.000	0.000	0.00	0.35	0.003	0.004	0.001	0.003	0.007
9	13.0	3.8	0	0	0.000	0.516	0.00	0.35	0.000	0.000	0.000	0.007	0.001
10	13.0	0.0	10	0	0.516	0.000	0.35	0.35	0.003	0.009	0.000	0.000	0.011
11	0.0	0.0	10	0	0.516	0.000	0.35	0.35	0.000	0.000	0.000	0.000	0.000
12	0.0	0.0	0	5	0.516	0.000	0.35	0.35	0.000	0.000	0.000	0.000	0.000

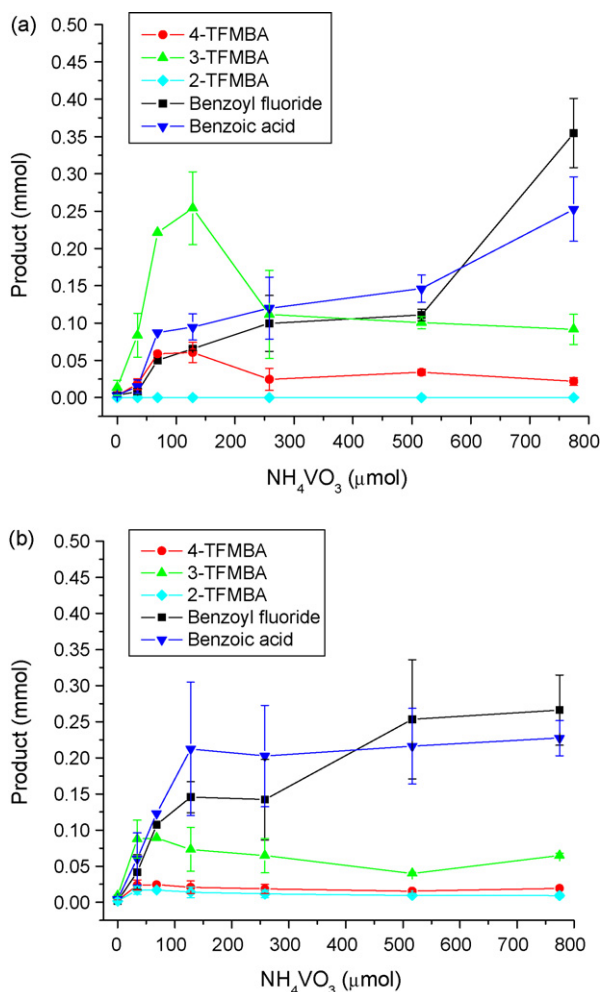


Fig. 1. (a) Product formation versus vanadium loading with Rh as the catalyst. Reaction conditions: benzotrifluoride (37.5 mmol), CF_3COOH (13.0 mmol), $(\text{CF}_3\text{CO})_2\text{O}$ (3.8 mmol), $\text{Rh}(\text{acac})_3$ (10 μmol), O_2 (0.35 MPa), CO (0.35 MPa), $T = 353 \text{ K}$, $t = 4 \text{ h}$. (b) Product formation versus vanadium loading with Pd as the catalyst. Reaction conditions: benzotrifluoride (37.5 mmol), CF_3COOH (13.0 mmol), $(\text{CF}_3\text{CO})_2\text{O}$ (3.8 mmol), $\text{Pd}(\text{CF}_3\text{COO})_2$ (5 μmol), O_2 (0.35 MPa), CO (0.35 MPa), $T = 353 \text{ K}$, $t = 4 \text{ h}$.

oxidation state indicates that the more highly oxidized form of V is responsible for the formation of benzoyl fluoride and benzoic acid.

Fig. 1a and b indicates the product distribution versus vanadium loading for Rh- and Pd-catalyzed reactions, respectively. The trifluoromethylbenzoic acid isomer product distribution was independent of vanadium loading with a 4/3 isomer ratio of approximately 0.3 for Pd and 0.25 for Rh. The ratio of trifluoromethylbenzoic acid isomers to benzoyl fluoride and benzoic acid decreased from approximately 2.6 at zero vanadium concentration to 0.19 at high vanadium concentrations for both the Rh- and Pd-catalyzed reactions over the range of vanadium concentrations investigated, with the decrease occurring more rapidly for Pd than for Rh. For Rh-catalyzed reactions, an optimum in trifluoromethylbenzoic acid yield was observed at 128 mmol NH_4VO_3 , whereas an optimum was observed at 64 mmol NH_4VO_3 for Pd. This optimum reflects the two separate roles of vanadium. The first is to re-oxidize $\text{Rh}(\text{I})$ to $\text{Rh}(\text{III})$ or $\text{Pd}(\text{0})$ to $\text{Pd}(\text{II})$ so that the metal in the higher oxidation state can participate in the oxidative carbonylation of benzotrifluoride to form trifluoromethylbenzoic acid. This interpretation is based on the assumption that the oxidative carbonylation of benzotrifluoride occurs in a manner similar to that for the oxidative carbonylation of toluene [26,27]. The second role of the vanadate cations is to assist in the hydrolysis of benzotriflu-

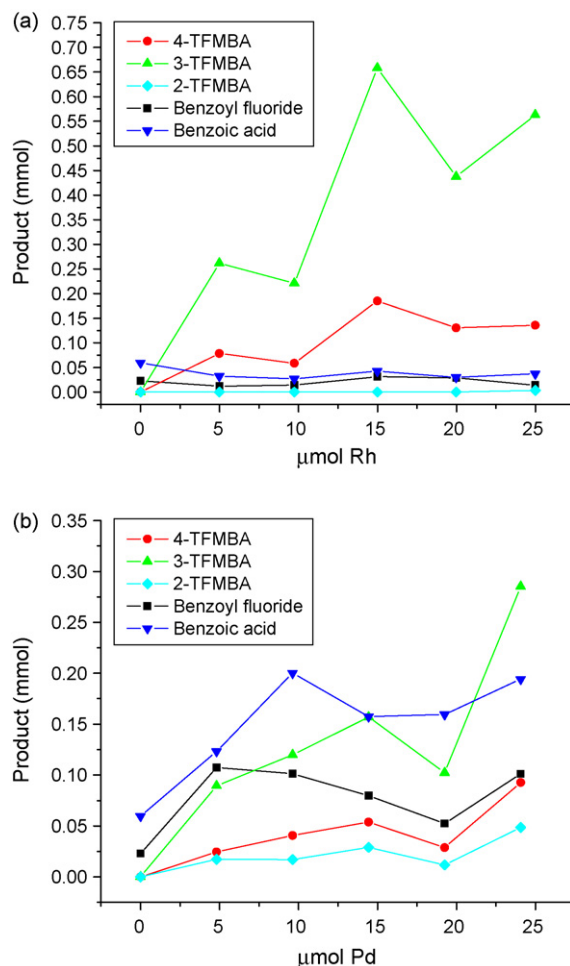


Fig. 2. (a) Product formation versus Rh concentration. (b) Product formation versus Pd concentration. Reaction conditions: benzotrifluoride (37.5 mmol), CF_3COOH (13.0 mmol), $(\text{CF}_3\text{CO})_2\text{O}$ (3.8 mmol), NH_4VO_3 (68 μmol), O_2 (0.35 MPa), CO (0.35 MPa), $T = 353 \text{ K}$, $t = 4 \text{ h}$.

oride to benzoyl fluoride, which can react further to form benzoic acid. A high ratio of the concentrations of vanadium relative to Rh or Pd favors the second process, and the yields of benzoyl fluoride and benzoic acid then exceeds the yield of trifluoromethylbenzoic acid produced. On the other hand, with no vanadium or at extremely low vanadium concentrations, the reduced Rh or Pd cations cannot be re-oxidized sufficiently rapidly, resulting in limited formation of trifluoromethylbenzoic acid. The optimum is, thus, a balance between having sufficient oxidizing potential to re-oxidize the catalyst and not having too high an oxidizing potential that would favor the formation of benzoyl fluoride and benzoic acid.

Fig. 2a and b indicates the influence of Rh and Pd loading on product formation. In accordance with the scoping experiments, trifluoromethylbenzoic acid was not formed in the absence of Pd or Rh, but benzoyl fluoride and benzoic acid were observed. Addition of 5 μmol Rh resulted in the formation of trifluoromethylbenzoic acid and a slight decrease in the formation of benzoyl fluoride and benzoic acid. Increasing the Rh concentrations tended to increase the formation of trifluoromethylbenzoic acid, although this increase was irregular. Additional Rh did not appear to influence the production of benzoyl fluoride or benzoic acid. For the Pd-catalyzed system, an increase in all products was observed with the addition of 5 μmol Pd relative to 0 μmol Pd. As with the Rh system, the formation of trifluoromethylbenzoic acid isomers tended to increase with increasing Pd loading, with the exception of the data for $\sim 20 \mu\text{mol}$ Pd. The quantity of benzoic acid formed did

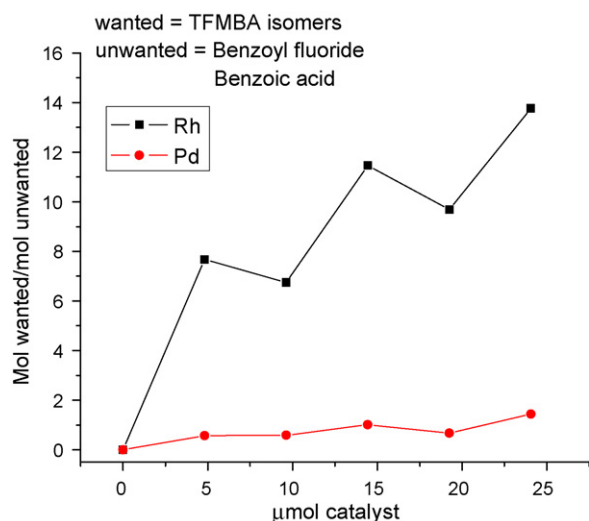


Fig. 3. Ratio of trifluoromethylbenzoic acid isomers to benzoyl fluoride and benzoic acid versus catalyst concentration. Reaction conditions: benzotrifluoride (37.5 mmol), CF_3COOH (13.0 mmol), $(\text{CF}_3\text{CO})_2\text{O}$ (3.8 mmol), NH_4VO_3 (68 μmol), O_2 (0.35 MPa), CO (0.35 MPa), $T=353\text{ K}$, $t=4\text{ h}$.

not increase significantly with increasing Pd concentration. Similarly, the quantity of benzoyl fluoride produced appeared roughly constant. Nevertheless, as indicated in Fig. 3, the ratio of desired products (trifluoromethylbenzoic acid isomers) to undesired product (benzoyl fluoride and benzoic acid), tended to increase with increasing catalyst concentration, and the magnitude of the change is higher for the Rh-catalyzed system compared to the Pd-catalyzed system. The change in selectivity is attributed to a shift in the fraction of the vanadium present as V(IV) versus V(V). At the beginning of the reaction, all of the vanadium is present as V(V). As the Rh- or Pd-catalyzed carbonylation of benzotrifluoride proceeds, Rh(III) is reduced to Rh(I) or Pd(II) is reduced to Pd(0). The V(V) species oxidize Rh(I) to Rh(III) or Pd(0) to Pd(II), resulting in the formation of V(IV). Molecular oxygen restores the V(IV) back to V(V). As noted above, V(V) species facilitate the formation of benzoyl fluoride and benzoic acid, whereas V(IV) species do not. The difference between Rh and Pd (see Fig. 3) arises because the reduced form of the Rh remains in solution where it can readily undergo oxidation, whereas the reduced Pd deposits on the autoclave walls, where the V(V) species are less able to re-oxidize it. As a consequence the concentration of V(V) species tends to be higher for the Pd system than for the Rh system for comparable reaction conditions. The higher V(V) concentration for the Pd system relative to the Rh system contributes to the increased formation of benzoic acid and benzoyl fluoride seen when Pd is used as the catalyst. The distribution of trifluoromethylbenzoic acid isomers was independent of catalyst concentration with a typical 4/3 ratio of 0.25 for Rh and 0.3 for Pd.

As noted earlier, the scoping experiments demonstrated the importance of the acid and its anhydride on the formation of both the trifluoromethylbenzoic acid isomers and benzoyl fluoride and benzoic acid. To explore the effects of acid strength, the composition of the acid was modified. The results of these experiments are presented in Fig. 4a and b. The optimum catalytic activity for the formation of trifluoromethylbenzoic acid was observed with trifluoroacetic acid ($\text{pK}_a \sim 0$), and the activity decreased when the pK_a was either increased or decreased. For both Rh and Pd, the use of methanesulfonic acid ($\text{pK}_a = -2$) resulted in extensive benzoyl fluoride and benzoic acid formation, but trifluoromethylbenzoic acid formation was not observed. The reaction solution turned a dark brown color when methanesulfonic acid was used as the acid, but no additional products were observed by gas chromatography.

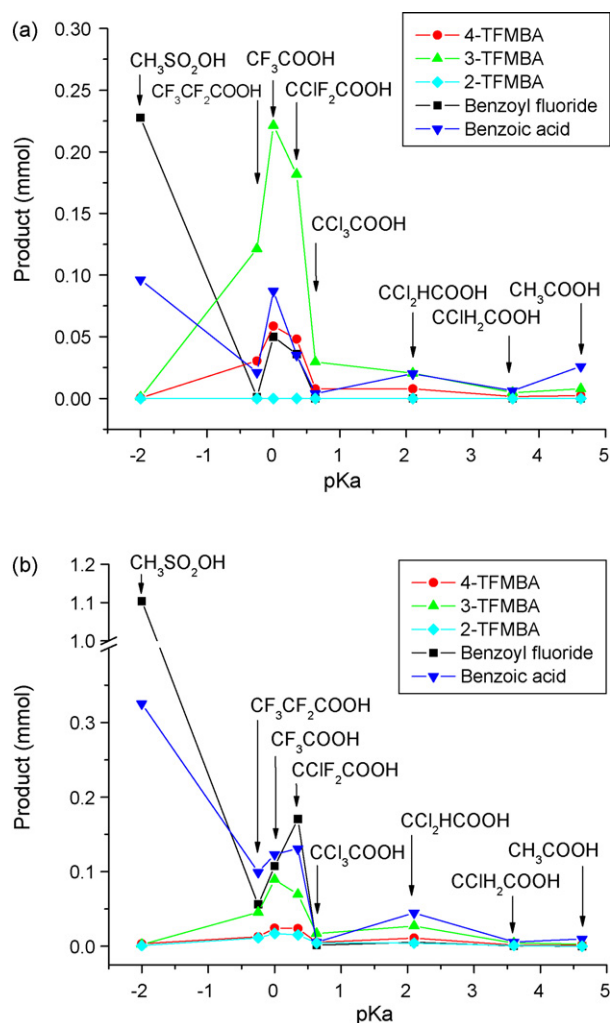


Fig. 4. (a) Product formation versus pK_a of corresponding acid with Rh catalyst. Reaction conditions: benzotrifluoride (37.5 mmol), acid (13.0 mmol), corresponding anhydride (3.8 mmol), $\text{Rh}(\text{acac})_3$ (10 μmol), NH_4VO_3 (68 μmol), O_2 (0.35 MPa), CO (0.35 MPa), $T=353\text{ K}$, $t=4\text{ h}$. (b) Product formation versus pK_a of corresponding acid with Pd catalyst. Reaction conditions: benzotrifluoride (37.5 mmol), acid (13.0 mmol), corresponding anhydride (3.8 mmol), $\text{Pd}(\text{CF}_3\text{COO})_3$ (5 μmol), NH_4VO_3 (68 μmol), O_2 (0.35 MPa), CO (0.35 MPa), $T=353\text{ K}$, $t=4\text{ h}$.

Although trifluoroacetic acid yielded the highest catalytic activity, trichloroacetic acid resulted in the highest ratio of trifluoromethylbenzoic acid isomers to benzoyl fluoride and benzoic acid for both Pd and Rh (see Fig. 5). Since trichloroacetic acid is a weaker acid than trifluoroacetic acid, the trichloroacetic acid is less effective in protonating the fluorine of the benzotrifluoride, an essential first step enabling the reaction protonated CF_3 group to react with the vanadate cations to form HF and benzoyl fluoride. Acids weaker than trichloroacetic acid, such as acetic acid or chloroacetic acid, however, significantly reduced the formation of trifluoromethylbenzoic acid.

The role of acid pK_a on the activity of Rh and Pd, and on the ratio of desired to undesired products, is complex and results from the effects of the anionic ligand associated with the metal cation on both the coordination of the arene and the activation of one of the C–H bonds in arene ring. With increasing pK_a the anion associated with the acid becomes more Brønsted basic and, hence, less electron withdrawing when present as a ligand associated with Rh(III) or Pd(II). As a consequence, the electrophilicity of the Rh(III) or Pd(II) cation decreases with increasing pK_a , resulting in weaker coordination of benzotrifluoride. On the other hand increasing the

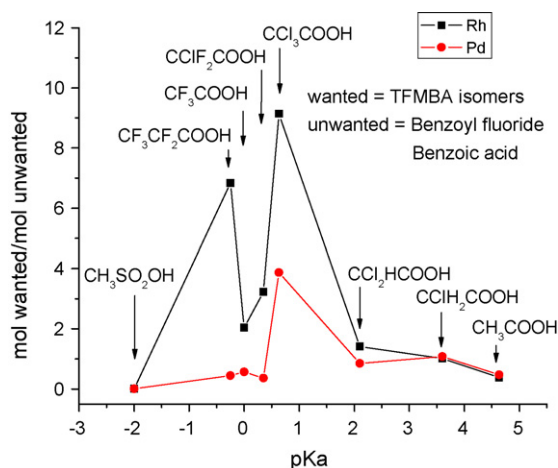


Fig. 5. Ratio of trifluoromethylbenzoic acid isomers to benzoyl fluoride and benzoic acid versus acid pK_a . Reaction conditions: benzotrifluoride (37.5 mmol), acid (13.0 mmol), corresponding anhydride (3.8 mmol), $Rh(acac)_3$ (10 μ mol) or $Pd(CF_3COO)_2$ (5 μ mol), NH_4VO_3 (68 μ mol), O_2 (0.35 MPa), CO (0.35 MPa), $T = 353$ K, $t = 4$ h.

basicity of the anion increases its ability to accept a proton from the coordinated benzotrifluoride. These two effects of anion basicity work in opposite directions with the net effect that the activity of the catalyst rises moving as the composition of the methyl group on the acetate anion shifts from CH_3- to CF_3- . Lower acid pK_a 's were achieved by shifting from an acetate to sulfonate anion. In doing so, the binding energy for the substrate decreases due to steric hindrance resulting from the additional O atom (viz, $R-SO_3^-$ versus $R-CO_2^-$) [29]. The net effect is that even though the pK_a of the methanesulfonic is lower than those of trifluoroacetic acid, the catalytic activity of Rh(III) and Pd(II) cations coordinated with S-containing anions is lower than that when these cations are coordinated with CF_3COO^- anions.

The pK_a of the acid also affects the reaction of benzotrifluoride to benzoyl fluoride and benzoic acid. The stronger the acid, i.e., the lower its pK_a , the more effective it will be in promoting the reactivity of the CF_3 group in benzotrifluoride. Thus, the effects of acid pK_a work in different directions on the ratio of desired to undesired products, leading to the observed maximum for CCl_3COOH and CF_3CF_2COOH seen in Fig. 5.

The effects of reaction time on product formation are depicted in Fig. 6a for the Rh system. CCl_3COOH was used as the acid because it reduces the formation of unwanted products formed relative to other acids, as mentioned above. After a small decline, the concentrations of 3-trifluoromethylbenzoic acid and 4-trifluoromethylbenzoic acid increased monotonically with reaction time. Very little additional benzoyl fluoride was observed even after 24 h, and the concentration of benzoic acid increased only slightly from that formed initially. By contrast, the data for the Pd-catalyzed system, depicted in Fig. 6b, exhibited an increase in the concentration of benzoyl fluoride with time, while the concentrations of trifluoromethylbenzoic acid isomers and benzoic acid did not change significantly after the first hour of reaction. Consistent with these trends, the selectivity to trifluoromethylbenzoic acid isomers for the Rh system increased with increasing reaction time, whereas it decreased with increasing reaction time for Pd (see Fig. 7). The increase in trifluoromethylbenzoic acid selectivity with time for the Rh system is attributed to changes in the distribution of vanadium oxidation states with time. Initially, the vanadium was present as V(V), which, as discussed above, participates in the reaction of benzotrifluoride to the benzoyl fluoride and benzoic acid. As the formation of trifluoromethylbenzoic acid proceeds, more and more of the V(V) is reduced to V(IV) as a consequence of its oxi-

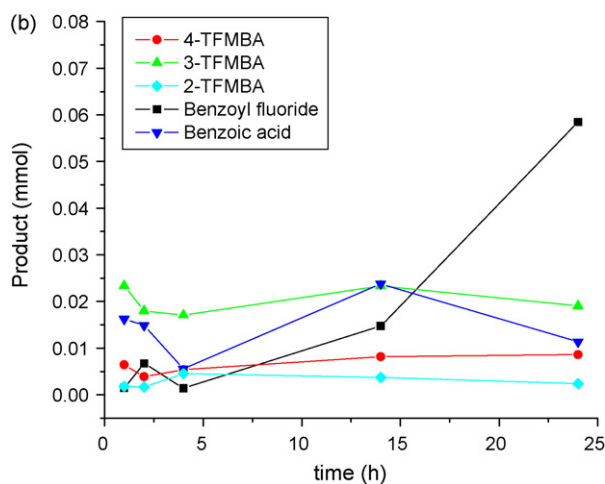
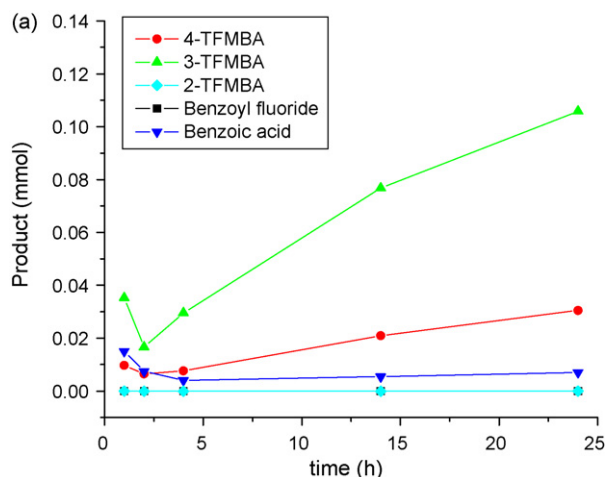


Fig. 6. (a) Product formation versus time. Reaction conditions: benzotrifluoride (37.5 mmol), CCl_3COOH (13.0 mmol), $(CCl_3CO)_2O$ (3.8 mmol), $Rh(acac)_3$ (10 μ mol), NH_4VO_3 (68 μ mol), O_2 (0.35 MPa), CO (0.35 MPa), $T = 353$ K. (b) Product formation versus time with Pd as catalyst. Reaction conditions: benzotrifluoride (37.5 mmol), CCl_3COOH (13.0 mmol), $(CCl_3CO)_2O$ (3.8 mmol), $Pd(CF_3COO)_2$ (5 μ mol), NH_4VO_3 (68 μ mol), O_2 (0.35 MPa), CO (0.35 MPa), $T = 353$ K.

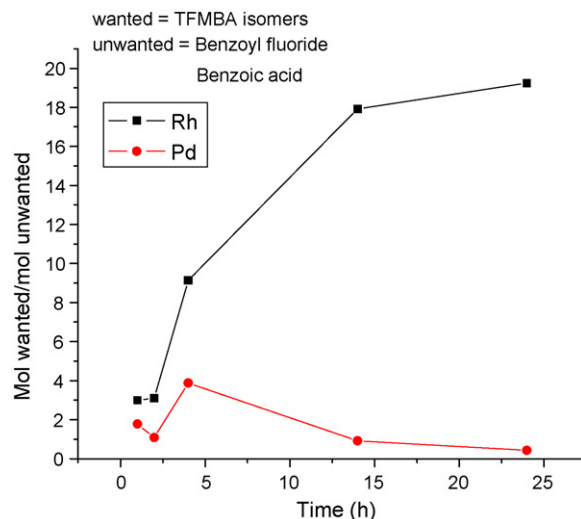


Fig. 7. Ratio of trifluoromethylbenzoic acid isomers to benzoyl fluoride and benzoic acid versus time. Reaction conditions: benzotrifluoride (37.5 mmol), CCl_3COOH (13.0 mmol), $(CCl_3CO)_2O$ (3.8 mmol), $Rh(acac)_3$ (10 μ mol) or $Pd(CF_3COO)_2$ (5 μ mol), NH_4VO_3 (68 μ mol), O_2 (0.35 MPa), CO (0.35 MPa), $T = 353$ K.

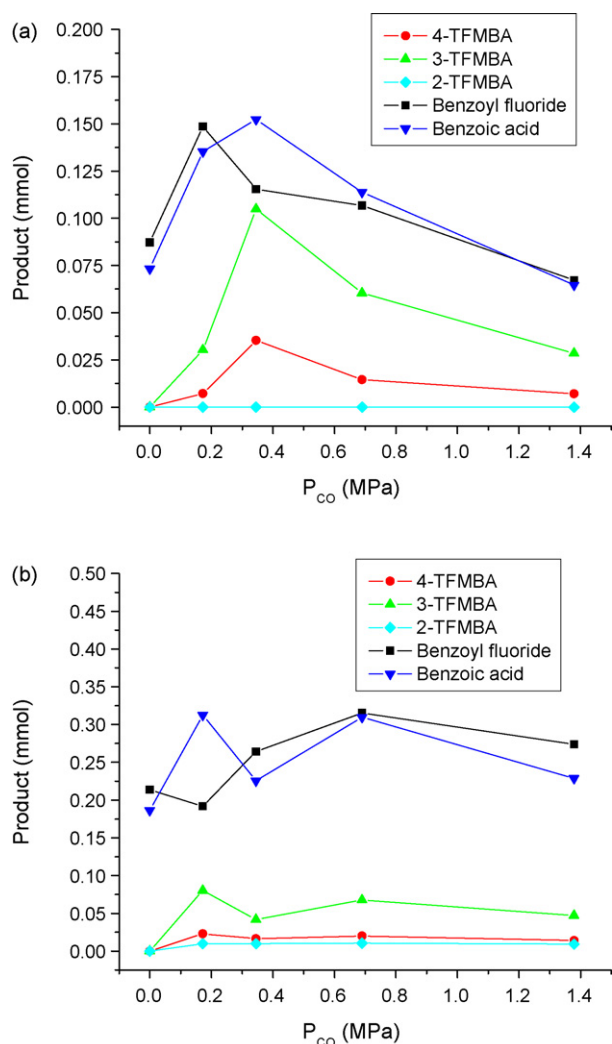


Fig. 8. (a) Product formation versus CO pressure with Rh catalyst. Reaction conditions: benzotrifluoride (37.5 mmol), CF₃COOH (13.0 mmol), (CF₃CO)₂O (3.8 mmol), Rh(acac)₃ (10 μmol), NH₄VO₃ (0.516 mmol), O₂ (0.35 MPa), T = 353 K, t = 4 h. (b) Product formation versus CO pressure with Pd catalyst. Reaction conditions: benzotrifluoride (37.5 mmol), CF₃COOH (13.0 mmol), (CF₃CO)₂O (3.8 mmol), Pd(CF₃COO)₂ (5 μmol), NH₄VO₃ (0.516 mmol), O₂ (0.35 MPa), T = 353 K, t = 4 h.

duction of Rh(I) to Rh(III) or Pd(0) to Pd(II). For the Rh system, the V(V) concentration tends to decrease with time as the re-oxidation of V(IV) to V(V) by O₂ is relatively slow [27]. Decreasing the V(V) concentration reduces the formation of benzoyl fluoride and benzoic acid. For the Pd system, V(V) species were not very effective in oxidizing the Pd(0) deposited on the reactor walls and, hence, the concentration of V(V) species did not decrease to as great an extent with time as in the case of the Rh system. The net consequence of the higher concentration of V(V) species was a higher rate of benzotrifluoride reaction to benzoyl fluoride and benzoic acid.

The influence of carbon monoxide pressure on product formation for Rh is shown in Fig. 8a. Trifluoromethylbenzoic acid was not observed in the absence of CO. For Rh, an optimum in catalytic activity occurred at 0.345 MPa CO. At CO partial pressures below this level, the formation of trifluoromethylbenzoic acid rises with increasing CO partial pressure as a consequence of the increasing concentration of CO in the liquid phase. At CO pressures above 0.345 MPa, the formation of all products, including benzoyl fluoride and benzoic acid, decreased. This decrease in formation of trifluoromethylbenzoic acid is attributed to the reduction of Rh(III) to Rh(I) [27]. A similar reduction of V(V) to V(IV) reduces the oxidizing

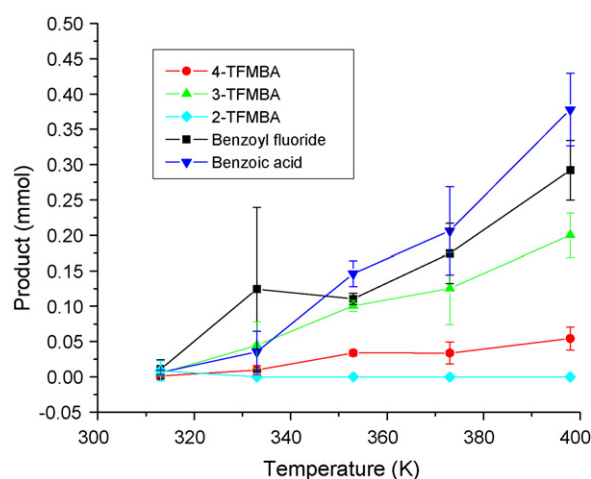


Fig. 9. Product formation versus temperature with Rh catalyst and CF₃COOH. Reaction conditions: benzotrifluoride (37.5 mmol), CF₃COOH (13.0 mmol), (CF₃CO)₂O (3.8 mmol), Rh(acac)₃ (10 μmol), NH₄VO₃ (0.516 mmol), O₂ (0.35 MPa), CO (0.35 MPa), t = 4 h.

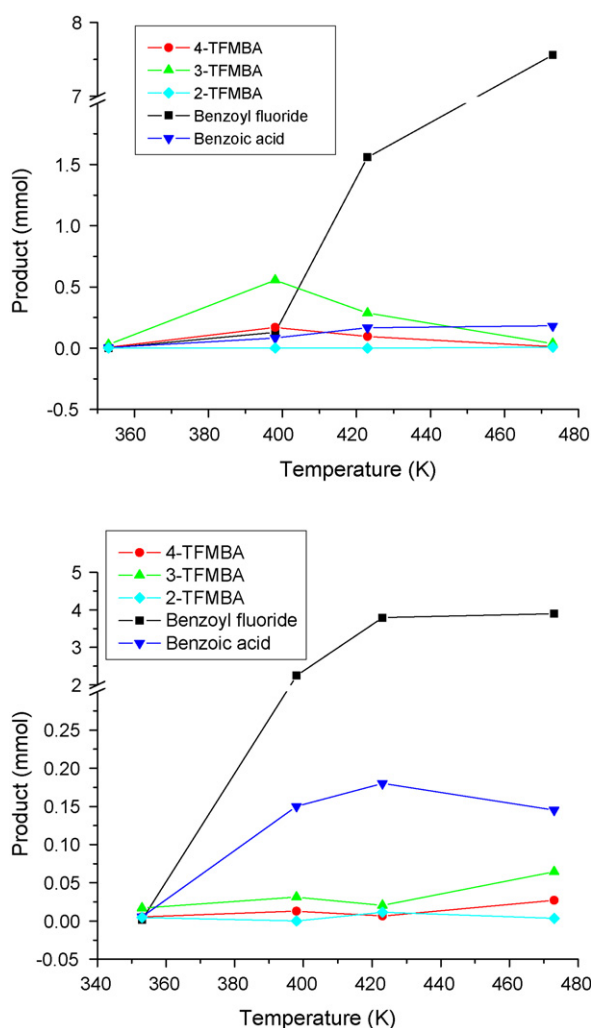


Fig. 10. (a) Product formation versus temperature with Rh catalyst and CCl₃COOH. Reaction conditions: benzotrifluoride (37.5 mmol), CCl₃COOH (13.0 mmol), (CCl₃CO)₂O (3.8 mmol), Rh(acac)₃ (10 μmol), NH₄VO₃ (68 μmol), O₂ (0.35 MPa), CO (0.35 MPa), t = 4 h. (b) Product formation versus temperature with Pd catalyst and CCl₃COOH. Reaction conditions: benzotrifluoride (37.5 mmol), CCl₃COOH (13.0 mmol), (CCl₃CO)₂O (3.8 mmol), Pd(CF₃COO)₂ (5 μmol), NH₄VO₃ (68 μmol), O₂ (0.35 MPa), CO (0.35 MPa), t = 4 h.

potential in the autoclave, which in turn reduces the formation of benzoyl fluoride and benzoic acid. The influence of CO pressure on the Pd-catalyzed reaction is presented in Fig. 8b. Here again, trifluoromethylbenzoic acid was not observed in the absence of CO, and an optimum in trifluoromethylbenzoic acid formation occurred at 0.17 MPa CO. The slight variations between the quantity of benzoyl fluoride and benzoic acid produced are attributed to hydrolysis of benzoyl fluoride to benzoic acid [28]. In contrast to the Rh system, the Pd system exhibited only a weak dependence on CO pressure, with only a slight decrease in catalytic activity for all products at higher CO pressures. The 4/3 trifluoromethylbenzoic acid isomer ratio appeared independent of CO pressure, and the ratio of trifluoromethylbenzoic acid isomers to benzoyl fluoride exhibited a maximum at 0.35 MPa for Rh and 0.17 MPa for Pd.

The influence of temperature on product formation for Rh in CF_3COOH is depicted in Fig. 9. The production of all products increases monotonically with temperature. Both the distribution of trifluoromethylbenzoic acid isomers and the ratio of trifluoromethylbenzoic acid to benzoyl fluoride and benzoic acid remained approximately constant for the temperature range investigated. No 2-trifluoromethylbenzoic acid was observed for the Rh-catalyzed reactions even at high temperatures. A similar increase in product formation with temperature was observed with the Pd-catalyzed system. Because of the superior ratio of trifluoromethylbenzoic acid isomers to benzoyl fluoride and benzoic acid exhibited when the CCl_3COOH and $\text{CF}_3\text{CF}_2\text{COOH}$ were used, the influence of temperature for these systems was investigated. The results of the CCl_3COOH system for Rh are depicted in Fig. 10a. Increasing the temperature from 353 K to 473 K resulted in a dramatic increase in benzoyl fluoride formation, and the ratio of trifluoromethylbenzoic acid isomers decreased from approximately 9 at 353 K to 0.02 at 473 K. A large quantity of CO_2 was also formed at 473 K from decomposition of the CCl_3COOH , and the autoclave pressure doubled by the end of the reaction. The results for the Pd-catalyzed reaction are depicted in Fig. 10b. Trifluoromethylbenzoic acid production appeared independent of temperature over the range of temperatures investigated. The quantity of benzoyl fluoride and benzoic acid increased significantly from 353 K to 398 K, but

additional temperature increases beyond 398 K failed to increase the formation of these products. The influence of temperature on the system containing $\text{CF}_3\text{CF}_2\text{COOH}$ is similar to that for the system containing CF_3COOH in that the formation of all products appeared to increase with temperature. For the Rh system, the ratio of trifluoromethylbenzoic acid isomers to benzoyl fluoride and benzoic acid decreased from approximately 6.8 at 353 K to 1.8 at 473 K; a similar decrease was observed with the Pd system, with the ratio decreasing from 0.44 to 0.04. No CO_2 was observed in the headspace of the autoclave at the conclusion of the reaction at 473 K in contrast to the CCl_3COOH system. Under optimal conditions, approximately 70 turnovers of Rh were observed in 4 h with ~90% selectivity using trifluoroacetic acid. Higher selectivity (~95%) was observed using CCl_3COOH , but fewer turnovers were observed (~4). The Pd system under optimal conditions yielded reduced activity and selectivity compared to Rh, with only approximately 22 turnovers in 4 h and 31% selectivity using trifluoroacetic acid. As with Rh, higher selectivity was observed using trichloroacetic acid (66%), but the Pd activity was reduced to approximately 4 turnovers in 4 h.

A proposed catalytic cycle for the Rh system is illustrated in Fig. 11. The individual steps appearing in this cycle are suggested by the experiments described above and are identical to the scheme proposed for the oxidative carbonylation of toluene, which proceeds through an electrophilic mechanism [23–27]. The oxidative carbonylation of benzotrifluoride is also consistent with an electrophilic mechanism based on the reduced reactivity relative to other aromatic hydrocarbons caused by the electron-withdrawing CF_3 group. Indeed, the relative activity of benzotrifluoride oxidative carbonylation lies on a Hammett plot for other substituted benzene compounds ($\rho = -1.86$), indicating that the carbonylation of this compound proceeds via a mechanism that is slightly favored by electron-donating substituents [30,31] (see Fig. 12). Similar results were also observed for the Pd-catalyzed systems ($\rho = -1.86$). The formation of trifluoromethylbenzoic acid is initiated by the coordination of benzotrifluoride to $\text{Rh}(\text{CO})_2(\text{CF}_3\text{COO})_3$ followed by activation of a C–H bond in the benzene ring to form a Rh-aryl complex. The preference of Rh to coordinate in the three-position suggests that this step proceeds through an

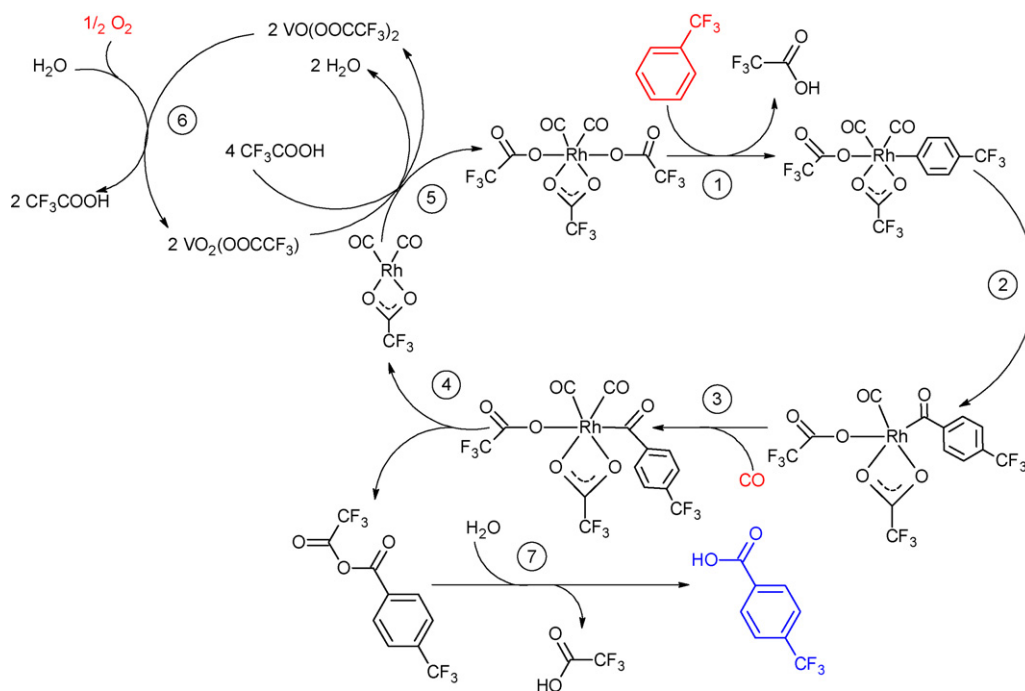


Fig. 11. Proposed mechanism.

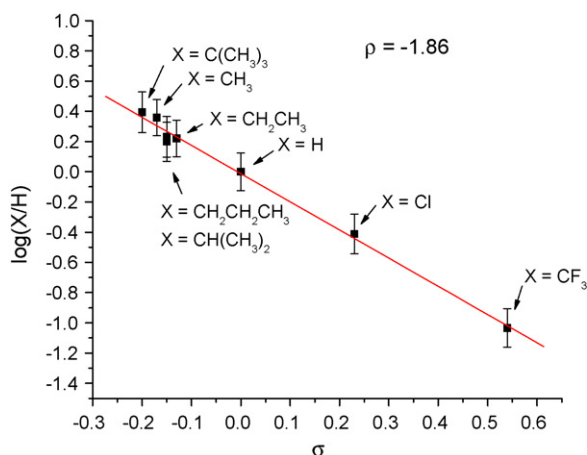


Fig. 12. Hammett plot for Rh-catalyzed aromatic oxidative carbonylation. Reaction conditions: C₆H₅X (37.5 mmol), CF₃COOH (12.9 mmol), (CF₃CO)₂O (3.8 mmol), Rh(acac)₃ (10 μmol), NH₄VO₃ (516 μmol), O₂ (0.35 MPa), CO (0.35 MPa), T = 353 K, t = 4 h.

electrophilic mechanism since CF₃ substituents are known to direct to the three-position [32]. In the case of toluene, which contains an electron-donating substituent, the carbonylation at the four-position is favored as expected for electrophilic mechanisms. The next step involves a migratory insertion of a carbonyl ligand associated with the Rh complex into the metal–arene bond to form a 16-electron Rh complex. Uptake of CO restores the complex to a stable 18-electron system, which then facilitates the reductive elimination of (CO)(C₆H₄CF₃) and CF₃COO to form a mixed anhydride. This product then readily hydrolyses to form the desired trifluoromethylbenzoic acid product. In the process, the Rh(III) species is reduced to Rh(CO)₂(CF₃COO). This species is then re-oxidized from Rh(I) to Rh(III) by the reduction of VO₂(CF₃COO) to VO(CF₃COO)₂, which closes the catalytic cycle. Molecular oxygen then restores the VO(CF₃COO)₂ to VO₂(CF₃COO), thereby closing the oxidation cycle. An analogous cycle is proposed for the Pd system, with the exception that the cycle is initiated by the binding of benzotrifluoride with the 16-electron square-planar Pd(CO)₂(CF₃COO)₂. The reduced steric bulk of the square-planar complex relative to the bulky pseudo-octahedral Rh system accounts for the formation of a small quantity of the 2-trifluoromethylbenzoic acid isomer with Pd, whereas the two-isomer is not observed with Rh. During the course of the reaction, the Pd(II) reduces to Pd(0), which often deposits on the walls of the autoclave. As with the Rh systems, VO₂(CF₃COO) serves to re-oxidize Pd(CO)₂ to Pd(CO)₂(CF₃COO)₂.

3. Conclusions

This study has shown that trifluoromethylbenzoic acid isomers can be formed by the oxidative carbonylation of benzotrifluoride. The reaction proceeds through an electrophilic mechanism that can be catalyzed by either Rh(III) or Pd(II) cations in the presence of a halogenated acetic acid and its anhydride, carbon monoxide, oxygen, and vanadate cations. The Rh system exhibits higher activity and trifluoromethylbenzoic acid selectivity compared to the Pd system. Balancing the concentration of vanadium co-catalyst in this reaction is critical. If the vanadium concentration is too low, then the rate of reoxidation of Rh(I) or Pd(0), formed at the end of the synthesis cycle, will be insufficient to restore the catalyst to its initial oxidation state—Rh(III) or Pd(II). However, an excessive concentration of V(V) leads to the reaction of benzotrifluoride to benzoyl fluoride and benzoic acid. The selectivity to trifluoromethylbenzoic acid improves with reaction time because the ratio of the concentration of V(V) to V(IV) species decreases with time. Similarly,

increasing the catalyst loading improves the selectivity as more of the vanadium is kept in the lower oxidation state (as V(IV)). Altering the composition of the acetate or sulfonate anion influences both the activity and trifluoromethylbenzoic acid selectivity. The highest activity is achieved using CF₃COOH, whereas the highest trifluoromethylbenzoic acid selectivity is achieved using CCl₃COOH.

4. Experimental

Reactions were conducted in stirred, 50 mL Parr autoclaves made of Hastelloy C. Between runs, the reactors were washed thoroughly with acetone and then dried in a vacuum oven. The reaction temperature was monitored using a thermocouple located inside a Hastelloy C thermowell. During a typical reaction, benzotrifluoride (5.48 g, 37.5 mmol), either CF₃COOH (1.48 g, 13 mmol), CF₂ClCOOH (1.69 g, 13 mmol), CF₃CF₂COOH (2.13 g, 13 mmol), CCl₃COOH (2.12 g, 13 mmol), CCl₂HCOOH (1.67 g, 13 mmol), CClH₂COOH (1.23 g, 13 mmol), CH₃COOH (0.78 g, 13 mmol), or CH₃SO₃H (1.24 g, 13 mmol), (CF₃CO)₂O (0.8 g, 3.8 mmol), (CF₂ClCO)₂O (0.93 g, 3.8 mmol), (CF₃CF₂CO)₂O (1.18 g, 3.38 mmol), (CCl₃CO)₂O (1.23 g, 3.8 mmol), (CCl₂HCO)₂O (0.92 g, 3.8 mmol), (CClH₂CO)₂O (0.66 g, 3.8 mmol), (CH₃CO)₂O (0.39 g, 3.8 mmol), or (CH₃SO₂)₂O (0.66 g, 3.8 mmol), either Rh(acac)₃ (0.0039 g, 10 μmol) or Pd(CF₃COO)₂ (0.0016 g, 5 μmol), and NH₄VO₃ (0.008 g, 68 μmol) were placed into the autoclave, which was then sealed and purged four times with helium. After purging, the reactor was pressurized at 293 K with O₂ (0.35 MPa) and CO (0.35 MPa). The reactor was then heated to 353 K in approximately 10 min and then held at this temperature for 4 h. Upon the completion of the reaction, the reactor was quenched with ice water to 308 K and vented.

After reaction, the contents of the autoclave were transferred to a glass scintillation vial and weighed. Typically, deionized water (12 g) was then added to the contents of the vial to extract the metals and halogenated acetic acid from the organic phase. The solution was centrifuged and decanted, and the organic phase was analyzed by gas chromatography. The aqueous phase was analyzed by ¹H and ¹⁹F NMR. The concentration of trifluoromethylbenzoic acid, benzoic acid, and benzoyl fluoride was determined by gas chromatography using an Agilent Technologies 6890N gas chromatograph equipped with a DB-WAX capillary column and an FID detector. Occasionally, the reaction solution was analyzed by gas chromatography before aqueous work-up. No discrepancies were observed in the product peaks observed before or after aqueous-phase work-up, indicating that products were not lost during the work-up process. This conclusion was confirmed by NMR analysis of the aqueous phase. The identity of gas chromatographic peaks were confirmed using standards and by GC/MS. A sample of the head-space gas was collected and analyzed for O₂, CO, and CO₂ by gas chromatography. An Alltech Hayesep DB 100/120 column was used to separate the gaseous products, which were detected by a TCD.

Acknowledgement

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