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CO-Retentive Addition Reactions of Fluorinated Acid Chlorides to Alkynes

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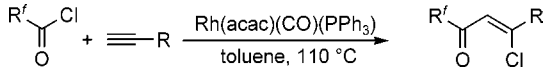
ABSTRACT



The reaction of perfluorinated acid chlorides with terminal alkynes is efficiently catalyzed by rhodium complexes and proceeds with retention of the CO moiety in the acid chloride to afford (*Z*)-1-perfluoroacyl-2-chloro-1-alkenes selectively in high yields.

Addition reactions of E−CN[1] and E−COX bonds (E = heteroatom, COX = ester or amide functionality) to unsaturated carbon linkages are currently an active area of research. So far, addition reactions of E−COX bonds made possible by us and others include rhodium- or nickel-catalyzed stannylamidation ($R_3Sn-CONR_2$),[2] rhodium-catalyzed chloroesterification (Cl−COOR),[3] and palladium-catalyzed thioesterification (RS−COOR).[4] A great feature of these reactions lies in the lack of possible decarbonylation, which is evident in, for instance, the attempted addition reactions of thioesters and selenoesters.[5] Very recently, we have found that even ethoxalyl chloride $Cl-COCOOC_2H_5$ undergoes an addition reaction with alkynes without the loss of carbon monoxide.[6] With these successful CO-retentive addition reactions in mind, we envision that the acid chlorides that are substituted by electronegative groups may undergo similar CO-retentive addition reactions. An obvious next target for extension in this context is the addition of fluorinated acid chlorides. The reaction, if it indeed proceeds, is particularly valuable since the resulting products, fluoroacylalkenes, have proved to be very versatile in synthetic applications as enones, inclusive of the synthesis of fluorinated heterocyclic compounds such as isoxazoles, pyrazoles, and thiophenes,[7] many of which are pharmacologically active.[8] However, precedents on the addition of acid chlorides to alkynes suggest that the desired reaction does not proceed readily in the desired direction. Thus, Miura, Nomura, and co-workers have reported that addition of acid chlorides to alkynes proceeds with concomitant decarbonylation although somewhat different CO-retentive reactions are also possible, depending on the structure of the alkyne.[9] To the best of our knowledge, the only CO-retentive addition of acid chlorides across alkynes reported is the reaction in the presence of $AlCl_3$ or $AgClO_4$; however, this reaction is not selective, affording (*E*)/(*Z*)

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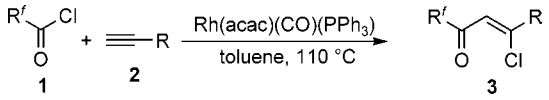
mixtures and other products, depending on the procedure.[10] However, we have found that fluorinated acid chlorides do add without decarbonylation to alkynes catalyzed by rhodium complexes to furnish (*Z*)-adducts selectively (Scheme 1).

Scheme 1



Preliminary results are disclosed in this communication.

In a representative experiment, a solution of Rh(acac)(CO)(PPh_3) (0.04 mmol), heptafluorobutyryl chloride **1a** (2.0 mmol) and 1-octyne **2a** (2.0 mmol) in toluene (2.0 mL) was heated at 110 °C for 1 h. The addition reaction proceeded smoothly and gave ethyl (*Z*)-6-chloro-1,1,1,2,2,3,3-heptafluoro-5-dodecen-4-one **3aa** in 96% GC yield. A trace of its regioisomer **3′aa** was also formed, but no other byproduct was found to be formed in the reaction mixture. Product **3aa** could be readily isolated by silica gel column chromatography followed by bulb-to-bulb distillation to allow characterization. An NOE experiment displayed 7% enhancement of the vinylic proton signal upon irradiation at the allylic proton signal (2.55 ppm), indicative of cis addition having taken place. Reduction of **3aa** with $LiAlH_4$ afforded the corresponding alcohol, which displayed a ^1H NMR spectrum consistent with the structure, supporting the regiochemistry.

Under similar reaction conditions, many other rhodium complexes also catalyze the reaction [using **1a** (2.4 mmol) and **2a** (2.0 mmol) at 110 °C for 1 h], although the performance depends on the structure. The complexes screened and the yields of **3aa** (in parentheses) were as follows: 1/2{[$RhCl(CO)_2]_2$ + $2PPh_3$} (99%) > Rh(acac)(CO)(PCy_3) (65%) > $RhCl(CO)(PPh_3)_2$ (59%) > $RhCl(CO)(PPh_2Me)_2$ (35%) > RhCl(cod)(PPh_3) (18%) > $RhCl(CO)(PCy_3)_2$ (12%) > RhCl(CO)(dppb) (9%) > $RhCl(CO)(PPhMe_2)_2$ (7%) > RhCl(CO)(dppe) (5%) > 1/2[$RhCl(CO)_2]_2$ (1%) > $RhCl(PPh_3)_3$, $RhCl(CO)(PMe_3)_2$ (<1%). The activity trends suggest that rhodium complexes ligated by only one phosphine ligand perform much better than those ligated by two phosphines or a chelating diphosphine and that more electron-donating phosphines display lower activities. GCMS analysis of the reaction mixture occasionally indicated that octyne dimers and trimers were also formed, in particular, in those reactions that did not afford **3aa** in high yields. Depending on the catalyst and the conditions, other byproducts were also formed, which will be discussed in detail for the reaction with pentafluorobenzoyl chloride.

The representative procedure could be successfully applied to the reactions of a variety of terminal alkynes with **1a** as summarized in Table 1. Besides 1-octyne, other aliphatic alkynes such as *tert*-butylacetylene and trimethylsilylacetylene reacted smoothly. 1-Ethynylcyclohexene reacted exclusively at the triple bond, suggesting the inertness of the double bond toward the reaction. Internal alkynes were totally unreactive, as suggested by both 4-octyne and **1a** being recovered unchanged even after 15 h of heating at 110 °C. Aromatic and heteroaromatic acetylenes also conform to the reaction. The electronic effect of the para substituents is not significant but is seen to indicate that electronegative *p*-fluorine substituent lowers the reactivity.

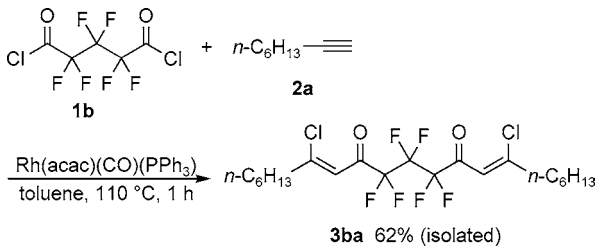
Table 1. Reactions of Heptafluorobutyryl Chloride with Terminal Alkyne

entry	product	yield (%)[a]
1	**3aa**, *n*-C_6H_{13}	96 (89)
2	**3ab**, *t*-Bu	75 (63)
3	**3ac**, $Si(CH_3)_3$	88 (12)[b]
4	**3ad**, 	92 (62)
5	**3ae**, C_6H_5	88 (46)
6	**3af**, *p*-$CH_3C_6H_4$	92 (68)
7	**3ag**, *p*-FC_6H_4	75 (66)
8	**3ah**, 	> 99 (92)

[a] Values in parentheses are isolated yields. [b] Reaction time = 6 h.

Hexafluoroglutaroyl dichloride reacted with 2 equiv of 1-octyne to afford the corresponding diketone (Scheme 2).

Scheme 2



Since Rh(acac)(CO)(PPh_3) was a catalyst of choice for aliphatic perfluoro acid chloride, we attempted to extend the

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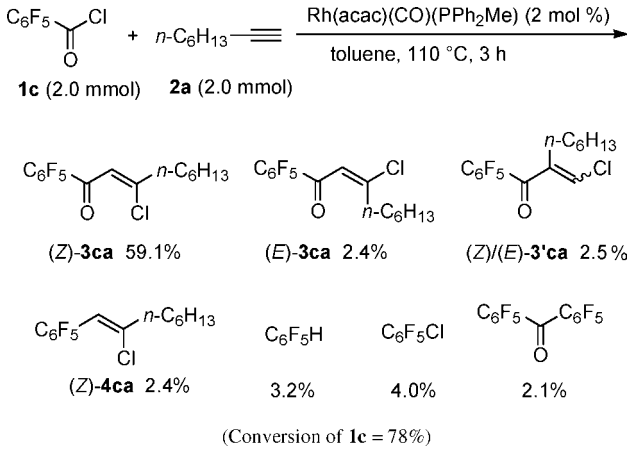
procedure to perfluorobenzoyl chloride **1c** using this catalyst. However, the reaction (under the standard conditions) with 1-octyne **2a** was slow and low yielding (27% for **3ca**). In another experiment using Rh(acac)(CO)(PPh_2Me) complex, one of the better performing catalysts, detailed GC and NMR spectroscopic analyses of the reaction mixture, with the aid of isolated products and authentic samples, revealed the formation of various products, inclusive of the other regioisomer **3′ca** and decarbonylative addition product **4ca**, derived from **1c** as shown in Scheme 3. Since the conversion of **1c**

Scheme 3

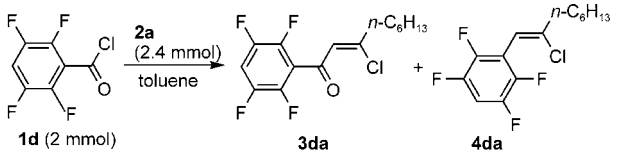


was 78%, the total yield of these products (76%) accounts for 97% of the consumption of **1c**. In addition to these, GC and GCMS analyses suggested that linear oligomers (*m*/*z* 220 and 330, corresponding to the dimer and trimer of **2a**) were also formed although not quantified. Thus, **1c** reacts much less selectively than **1a**.

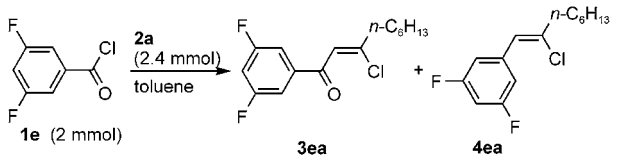
An extensive search for better catalysts for this particular reaction of **1c** has revealed that Rh(acac)(CO)(PMe_3) (generated in situ by treating Rh(acac)$(CO)_2$ with 1 equiv PMe_3) is the catalyst of choice to afford the desired (*Z*)-**3ca** in 78% GC yield (74% isolated yield). However, the addition of **1c** with phenylacetylene **3e** was slow when the same catalyst was used at 140 °C and yielded (*Z*)-**3ce** in only 39% yield after 6 h. In view of the ligand screening for the reaction of **1a** with **2a** (vide supra), the high performance of PMe_3 in the reaction of **1c** is totally unexpected.

As described above, the rhodium-catalyzed reactions of acid chlorides to alkynes usually involve decarbonylation. However, perfluorinated acid chlorides have proved to add to alkynes with retention of the CO moiety. This difference in reactivity between simple and perfluorinated acid chlorides was shown by the following experiments using partially fluorinated acid chlorides (Scheme 4). Thus, the Rh(acac)-(CO)(PPh_3)-catalyzed reaction of 2,3,5,6-tetrafluorobenzoyl chloride **1d** with 1-octyne **2a** formed (*Z*)-**3da** and (*Z*)-**4da** in 61 and 5% yield, respectively. The reaction was more selective when run in the presence of 1/2[RhCl$(CO)_2]_2$ + PPh_2Me at 80 °C, affording (*Z*)-**3da** and (*Z*)-**4da** in 92 and <1% yield, respectively, after 12 h. However, the reaction

Scheme 4



Rh(acac)(CO)(PPh_3)	110 °C, 6 h	**3da** 61%	**4da** 5%
1/2[RhCl$(CO)_2]_2$ + PPh_2Me	80 °C, 12 h	**3da** 92%	**4da** < 1%

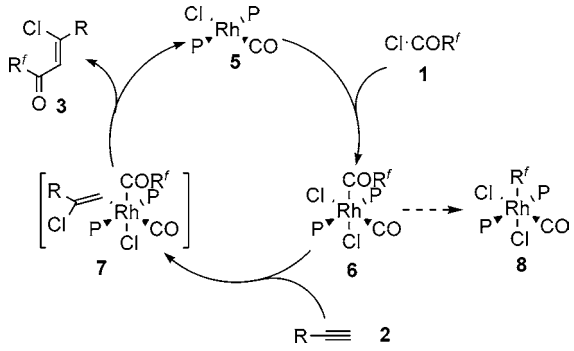


1/2[RhCl$(CO)_2]_2$ + PPh_2Me	80 °C, 6 h	**3ea** 23%	**4ea** 9%
1/2[RhCl$(CO)_2]_2$ + PPh_3	140 °C, 6 h[a]	**3ea** 2%	**4ea** 95%

of 3,5-difluorobenzoyl chloride **1e** catalyzed by the same catalyst was slower and much less selective even at 80 °C to afford (*Z*)-**3ea** and (*Z*)-**4ea** in 23 and 9% yield, respectively. Use of 1/2[RhCl$(CO)_2]_2$ + PPh_3 at 140 °C completely reversed the selectivity to lead to selective formation of (*Z*)-**4ea**. These data clearly show the necessity of an electronegative substituent for the reaction to proceed with CO retention.

A possible mechanism is outlined for the reaction using Vaska-type rhodium complexes in Scheme 5, which com-

Scheme 5



prises oxidative addition with an acid chloride, insertion of an alkyne molecule into the Rh−Cl bond, and C−C reductive elimination. The acyl-Rh intermediate **6** is envisioned to undergo decarbonylation, generating **8** to a certain extent when the acyl ligand is not electronegatively substituted.

Our attempted mechanistic study using Rh(acac)(CO)-(PPh_3) was hampered by the complex(es) generated upon treatment with **1c**, being sparingly soluble in common NMR solvents. However, the mechanistic proposal is experimentally substantiated by the following results obtained by using Vaska-type rhodium complexes **5**.

First, treatment of **1c** with $RhCl(CO)(PMe_3)_2$ **5-PMe**$_3$ (0.22 mmol each) at room temperature for 1 h in dichloromethane (3.0 mL) cleanly induced oxidative addition, and complex **6-PMe**$_3$,[11] which was stable at room temperature, was isolated in 81% yield. The structure was unequivocally characterized by X-ray diffraction (Figure 1).[11] Similar

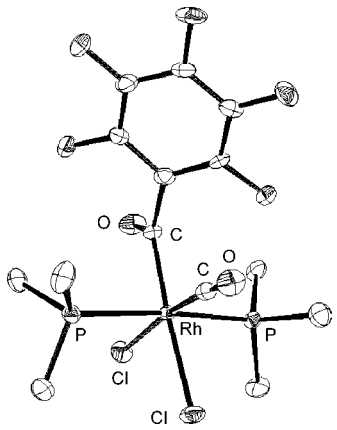


Figure 1.

oxidative addition with $RhCl(CO)(PPh_2Me)_2$ **5-PPh$_2$Me** also took place, albeit more slowly even at 80 °C. However, while the oxidative addition was still in progress, decarbonylation of the resulting acyl complex **6-PPh$_2$Me** was also in progress; for instance, after 1 h of heating of a mixture of **1c** (0.4 mmol) and **5-PPh$_2$Me** (0.04 mmol) in benzene-d_6 (0.6 mL), 52% of **5-PPh$_2$Me** was consumed, and **6-PPh$_2$Me** and **8-PPh$_2$Me** were formed both in approximately 20% yield together with $RhCl_3(CO)(PPh_2Me)_2$ (12% yield).

Second, the reaction of **6-PMe**$_3$ (110 °C for 3 h in toluene) or **6-PPh$_2$Me** (80 °C for 20 min in benzene-d_6) with **2a** (ca. 2 equiv) afforded **3ca** in 9 or 3% yield, respectively. The low yield of **3ca** in these noncatalytic reactions is due to the thermal instability of the starting complexes **6** in terms of reductive elimination, decarbonylation, and $RhCl_3(CO)L_2$-type complex formation, which indeed is evidenced by the formation of large quantities of the corresponding Vaska-type complex **5**, **8**, and $RhCl_3(CO)L_2$ (in 30, 30, and 30% yield, respectively, for the former, or in 84, 10, and 6% yield, respectively, for the latter).[12] In the former reaction of **6-PMe**$_3$, perfluorochlorobenzene and **1c** were also found and were formed in 8 and 31% yield, respectively. These experiments support the mechanism shown in Scheme 5. As for the insertion pathway, chloro-rhodation (vs acyl-rhodation) is more realistic on the basis of precedent observations, as discussed in our and Miura−Nomura's previous papers.[3,6,9]

In summary, this paper offers an efficient synthetic route to fluorinated acyl alkenes via unusual CO-retentive addition of fluorinated acid chlorides to alkynes. Detailed mechanistic study and synthetic elaboration of the products are in progress.

Supporting Information Available: Experimental procedure and specta for the new compounds (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Details of the crystal structure of the adduct and the reactivity relevant to the decarbonylation of complex **6** leading to **8** will be reported separately.

(12) Low yield may also be associated with the involvement of two phosphines, one of which is envisioned to be liberated for inserting an alkyne molecule.