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Cobaltate Anion Couples Terminal Dienes with Trifluoroacetic Anhydride: A Direct Fluoroacylation of 1,3-Dienes

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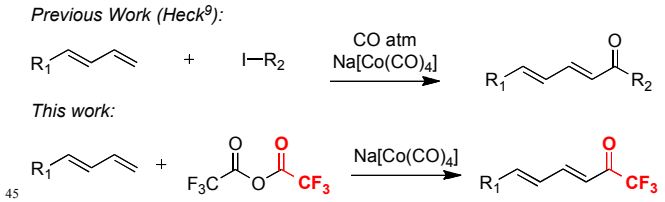
Perfluoroketones are useful products and intermediates in medicinal chemistry. Herein, cobalt-mediated fluoroacylation of 1,3-dienes is described using perfluorinated anhydrides such as TFAA. The reaction is thought to proceed through a fluoroacylcobalt reagent formed in situ. Perfluoroacylation of 1,3 dienes can also be performed to attain longer chain perfluorinated ketones.

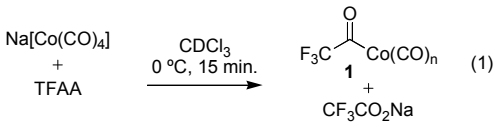
Fluorinated motifs and functionality are widely found in pharmaceutical, agrochemical, and material chemistries.[1] Not surprisingly, much attention has been devoted toward the installation of fluorine onto small molecules, either as a single fluorine atom or as a trifluoromethyl group.[2] Additional fluorinated functional groups have also gained interest. For example, perfluoromethyl ketones have been utlized as inhibitors for a variety of hydrolase targets[3] and have also been used as building blocks toward medicinal agents.[4] Herein, we describe the linearly-selective installation of a trifluoroacyl group onto dienes using readily available trifluoroacetic anhydride (TFAA).[5]

Our group has interest in studying addition processes of metals with cyclic anhydrides and the subsequent reactivity of these complexes.[6] We wished to investigate addition of metals into fluorinated anhydrides, such as TFAA. We were drawn to a report by Stone on the addition of cobaltate anions into perfluorinated acid chlorides to form a proposed fluorinated cobalt complex.[7,8] Moreover, work by Heck and Hegedus demonstrated that acylcobalt complexes undergo migratory insertion across dienes to give intermediates that are further functionalized.[9,10,11,12] Sodium cobaltate is known to perform addition reaction into activated carbonyl compounds to form acylcobalt intermediates.[13] While trifluoroacetyl chloride is a gas a room temperature, TFAA is inexpensive, readily available, and easy to handle. We theorized that a trifluoroacylcobalt intermediate may be accessed from the combination of cobaltate anion and TFAA. This cobalt complex may react in similar processes demonstrated by Heck and Hegedus to achieve fluoroacylated material.



Scheme 1 Fluoroacylation of 1,3-dienes

Upon mixing a solution of sodium cobaltate with TFAA, we observed trifluoroacetic acid (TFA) by ^{19}F NMR as well as a new fluorinated material at δ -78 ppm. This new peak is consistent with the expected resonance of a trifluoroacyl compound.[5] Thus, this material is tentatively assigned as a trifuoroacyl cobalt(I) complex **1**, which decomposes over both time and heating.



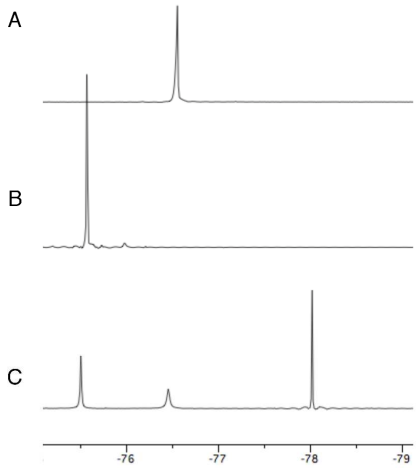
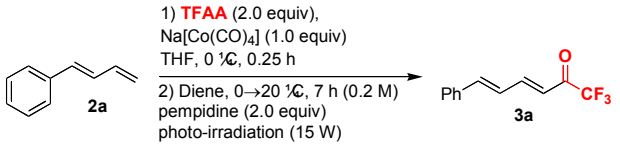


Fig. 1 ^{19}F NMR's: A) ^{19}F NMR of trifluoroacetic acid; B) ^{19}F NMR of TFAA; C) ^{19}F NMR of equation 1 after 15 min.

Upon exposure of the trifluoroacylcobalt reagent to 1,3-diene **2a** conversion to the fluoro-enone product **3a** is observed. The reaction does not proceed in the absence of

cobalt. In the absence of base, starting material **2a** is fully consumed, but product is formed in reduced yield. It is possible that hydridocobalt intermediates decompose starting material **2a** and product **3a** when no base is present.[14,15] The addition of base to the reaction may deprotonate metal-hydride complexes, thus minimizing byproduct formation. The reaction is tolerant of a variety of bases, but the strong and bulky amine base 1,2,2,6,6-pentamethylpiperidine (pempidine) gives the highest yield.[16,17] When the reaction is performed under a CO atmosphere, a lower yield of product is observed. However, under mild photo-irradiation conditions there is a small increase in product formation.[18] Finally, a decrease in yield is also observed if the reaction is allowed to proceed for longer than 7 hours.[19]

Table 1 Initial Investigation of Reaction Conditions[a]

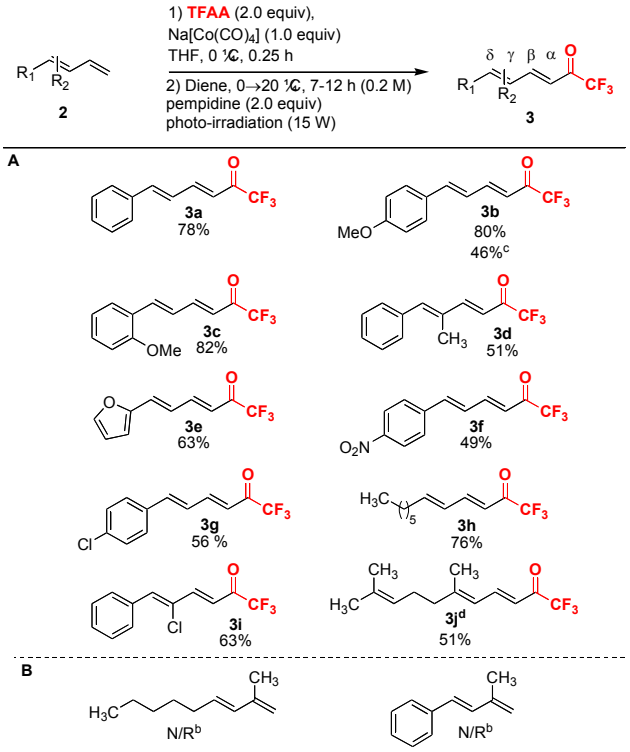


Entry	Deviation From Standard	Yield (%)[b]
1	none	78
2	no $Na[Co(CO)_4]$	0
3	no base (pempidine)	21
4	no photo-iradiation (15W white light)	48
5	Reaction performed under 1 atm CO instead of Ar	51
6	0.30 equiv of $Na[Co(CO)_4]$ under CO atm	8
7	12 h reaction time	65

[a] See supporting information for full experimental details; pempidine = 1,2,2,6,6-pentamethylpiperidine. [b]Isolated yield after column chromatography.

A variety of 1,3-dienes participate in this reaction (Table 2A) including electron-poor, electron-rich, aliphatic, and heterocyclic substrates. Migration of the olefins in aliphatic products **3h** and **3j** is not observed. Further, most products are formed with the *E*,*E* isomer as the major, with only trace *E*,*Z* isomer observed.[20] When a starting material that is a mixture of *E* and *Z* terminal dienes is subjected to the reaction conditions, only *Z* diene is recovered. This implies that the *E* diene reacts much faster than the *Z* isomer. Additional substrates that fail to react are depicted in Table 2B. Substitution in the β- and δ–positions appears to be detrimental toward reactivity and yield, most likely due to increased steric repulsion of the cobaltate in either substrate complexation or the subsequent migratory insertion. In all reactions, starting material is the only other observable compound in the reaction mixture.

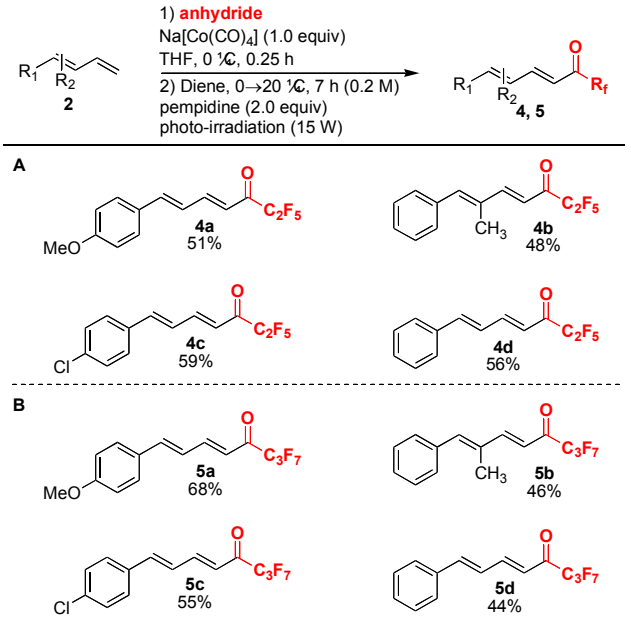
Table 2 1,3-Diene Substrate Scope[a]



[a] See footnote Table 1. [b]N/R = No reaction; only starting material was recovered. [c]A 1.7:1 mixture of *E*:*Z* starting diene **2b** was used. [d]Isolated as a 1.3:1 mixture of olefin isomers, see supporting information for details.

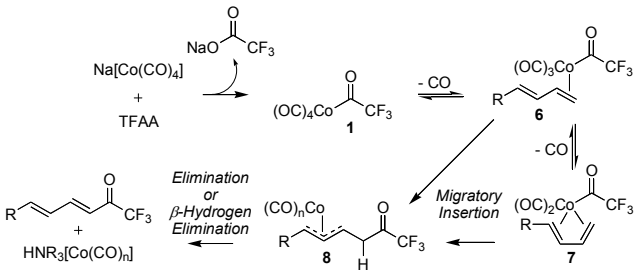
Additional fluoro-anhydrides participate in this reaction to give highly fluorinated materials (Table 3). Both pentafluoropropionic anhydride (Table 3A) and heptafluorobutyric anhydride (Table 3B) are competent in this reaction, producing highly fluorinated ketones with C_2F_5 and C_3F_7 side chains respectively.[21] Product **4d** was shown to inhibit the phospholipase GVIA $iPLA_2$.[3e]

Table 3 Perfluoro-Anhydride Scope[a]



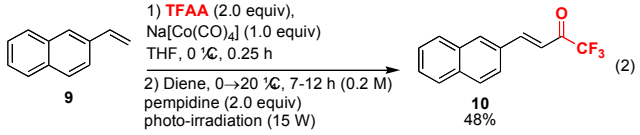
[a] See footnote Table 1.

A potential mechanism for product formation is illustrated in Scheme 2. Upon mixing the sodium cobaltate salt with TFAA, an acyl cobalt reagent **1** is formed in situ. Next, we propose that the cobaltate complex **1** loses one or more CO ligands prior to coordination of the diene. This suggestion is based on the observation that a small increase in yield is observed when the reaction is performed under photolytic conditions, whereas a decrease in yield is observed under a CO atmosphere (Table 1).[22] From either η^2- or η^4-bound complexes **6** or **7**, cobalt undergoes migratory insertion to furnish π-allylcobalt intermediate **8**. Furthermore, electron-rich dienes give product in higher yield than electron-deficient substrates, supporting ligation of the diene to cobalt is necessary for reactivity.



Scheme 2 Potential Mechanism for the Trifluoroacylation of 1,3-Dienes

Based upon this mechanistic hypothesis, we surmised that substrates that are able to form intermediates similar to **6-8** may be competent in this reaction. While simple alkenes (4-methoxystyrene, or 4-acetoxystyrene) do not give any desired product, vinyl naphthalene **9** does provide desired trifluoroacylated enone **10** (eq. 2). This supports the hypothesis that the reaction proceeds via formation of a π-allylcobalt intermediate in the reaction.[23]



We have developed a cobalt-mediated fluoroacylation reaction of 1,3-dienes that produce highly fluorinated enones under mild conditions utlizing readily availbale TFAA as the source of fluorination. Highly fluorinated small molecules can be readily accessed, and the products are potentially useful as medical targets or building blocks for more complex structures.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See

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1 M. Schlosser, *Angew. Chem. Int. Ed.*, 2006, **45**, 5432. b) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359. c) K. L. Kirk, *Org. Process Res. Dev.*, 2008, **12**, 305. d) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320. e) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881.

2 For recent reviews, see: a) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470. b) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475. c) A. Studer, *Angew. Chem., Int. Ed.*, 2012, **51**, 8950. d) Y. Ye and M. S. Sanford, *Synlett*, 2012, **23**, 2005.

3 a) M. H. Gelb, J. P. Svaren and R. H. Abeles, *Biochemistry*, 1985, **24**, 1813. b) D. W. Christianson and W. N. Lipscomb, *J. Am. Chem. Soc.*, 1986, **108**, 4998. c) M. Ilies, D. P. Dowling, P. M. Lombardi and D. W. Christianson, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5854. d) C. Baskakis, V. Magrioti, N. Cotton, D. Stephens, V. Constantinou-Kokkotou, E. A. Dennis and G. Kokotos, *J. Med. Chem.*, 2008, **51**, 8027. e) G. Kokotos, Y.-H. Hsu, J. E. Burke, C. Baskakis, C. G. Kokotos, V. Magrioti and E. A. Dennis, *J. Med. Chem.*, 2010, **53**, 3602.

4 Biologically active targets derived from fluoro-ketones: a) D. R. Fandrick, et al., *J. Org. Chem.*, 2013, **78**, 3592. b) J. T. Reeves et al., *J. Org. Chem.*, 2013, **78**, 3616.

5 For alternative methods to form α-fluorinated ketones, see: a) H. F. Bluhm, H. V. Donn and H. D. Zook, *J. Am. Chem. Soc.*, 1955, **77**, 4406. b) K. T. Dishart and R. Levine, *J. Am. Chem. Soc.*, 1956, **78**, 2268. c) J. Wiedemann, T. Heiner, G. Mloston, G. K. S. Prakash and G. A. Olah, *Angew. Chem. Int. Ed.*, 1998, **37**, 820. d) D. M. Rudzinski, C. B. Kelly and N. E. Leadbeater, *Chem, Commun.*, 2012, **48**, 9610. e) Y. Yokoyama and K. Mochida, *Synlett*, 1997, 907. f) J. Boivin, L. E. Kaim and S. Z. Zard, *Tetrahedron*, 1995, **51**, 2573. g) J. T. Reeves, F. Gallou, J. J. Song, Z. Tan, H. Lee, N. K. Yee and C. H. Senanayake, *Tetrahedron Lett.*, 2007, **48**, 189. h) L. Munoz, E. Rosa, M. P. Bosch and A. Guerrero, *Tetrahedron Lett.*, 2005, **46**, 3311. i) G. Blay, I. Fernandez, A. Marco-Aleixandre, B. Monje, J. R. Pedro and R. Ruiz, *Tetrahedron*, 2002, **58**, 8565. j) S. Kim and R. Kavali, *Tetrahedron Lett.*, 2002, **43**, 7189. k) J. T. Reeves, J. J. Song, Z. Tan, H. Lee, N. K. Yee and C. Senanayake, *J. Org. Chem.*, 2008, **73**, 9476. l) D. Yang, Y. Zhou, N. Xue and J. Qu, *J. Org. Chem.*

2013, **78**, 4171. m) C. G. Kokotos, C. Baskakis and G. Kokotos, *J. Org. Chem.* 2008, **73**, 8623.
6 a) E. A. Bercot and T. Rovis, *J. Am. Chem. Soc.*, 2002, **124**, 174. b) E. M. O'Brien, E. A. Bercot and T. Rovis, *J. Am. Chem. Soc.*, 2003, **125**, 10498. c) E. A. Bercot and T. Rovis, *J. Am. Chem. Soc.*, 2004, **126**, 10248. d) E. A. Bercot and T. Rovis, *J. Am. Chem. Soc.*, 2005, **127**, 247. e) J. B. Johnson, R. T. Yu, P. Fink, E. A. Bercot and T. Rovis, *Org. Lett.*, 2006, **8**, 4307. f) J. B. Johnson, E. A. Bercot, C. M. Williams and T. Rovis, *Angew. Chem. Int. Ed.*, 2007, **46**, 4514. g) J. B. Johnson, E. A. Bercot, J. M. Rowley, G. W. Coates and T. Rovis, *J. Am. Chem. Soc.*, 2007, **129**, 2718. h) M. J. Cook and T. Rovis, *J. Am. Chem. Soc.*, 2007, **129**, 9302. i) M. J. Cook and T. Rovis, *Synthesis*, 2009, 335. j) J. B. Johnson, M. J. Cook and T. Rovis, *Tetrahedron*, 2009, **65**, 3202.
7 a) W. R. McClellan, *J. Am. Chem. Soc.*, 1961, **83**, 1598. See also: b) B. L. Booth, R. N. Haszeldine and T. Inglis, *J. Chem. Soc. Dalt. Trans.*, 1975, 1449. c) J. B. Wilford, A. Forster and F. G. A. Stone, *J. Chem. Soc.*, 1965, 6519.
8 For references on cobaltate anions reacting with trifluoroacetic anhydride, see: a) W. Hieber and H. Duchatsch, *Chem. Ber.*, 1965, 2933. b) V. W. Hieber, W. Beck and E. Lindner, *Zeitschrift Für Naturforschung*, 1961, 229.
9 a) R. F. Heck, *J. Am. Chem. Soc.*, 1963, **85**, 3381. b) R. F. Heck, *J. Am. Chem. Soc.*, 1963, **85**, 3383. c) R. F. Heck, *J. Am. Chem. Soc.*, 1963, **85**, 3387. d) H. Alper and J. K. Currie, *Tetrahedron Lett.* 1979, **20**, 2665.
10 a) L. S. Hegedus and Y. Inoue, *J. Am. Chem. Soc.*, 1982, **104**, 4917. b) L. S. Hegedus and R. J. Perry *J. Org. Chem.*, 1984, **49**, 2570.
11 a) R. W. Bates, T. Rama-Devi and H.-H. Ko, *Tetrahedron*, 1995, **51**, 12939. b) R. W. Bates and P. Kongsaeree, *Synlett*, 1999, 1307. c) R. W. Bates V. Satchareon, *Synlett*, 2001, 532.
12 For a review on acylcobalt species, see: I. Kovács and F. Ungváry, *Coord. Chem. Rev.* 1997, **161**, 1.
13 a) M. E. Kraft J. Pankowski, *Tetrahedron Lett.*, 1990, **31**, 5139. b) M. E. Kraft and J. Pankowski, *Synlett*, 1991, 865.
14 Cobalt-hydride complexes are highly acidic, and an amine base should deprotonate any metal-hydride species that may form: E. J. Moore, J. M. Sullivan and J. R. Norton, *J. Am. Chem. Soc.*, 1986, **108**, 2257.
15 Reactivity of cobalt-hydrides with dienes: J. F. Garst, T. M. Bockman and R. Batlaw, R. *J. Am. Chem. Soc.*, 1986, **108**, 1689.
16 For evaluation of bases, see supporting information.
17 Alternatively, the amine base acting as a ligand on cobalt cannot be fully discounted, as a weak base (NaTFA) is already present in the reaction solution upon the reaction of sodium cobaltate with TFAA.
18 A 15W visible full spectrum white light was used in the reaction.
19 HPLC and ^{19}F NMR analysis of the reaction progress indicates that reaction progress stops at 7 hours followed by continued consumption of both starting material and product. See supporting information for more details and discussion of this result.
20 The *E*,*E* isomer was determined by X-Ray crystal analysis (CCDC 991428) of product **3b**; see supporting information for details. Compound **3j** is the only exception to date, formed as a 1.3:1 mixture of isomers. All other products were formed with ≤ 5% of the *E*,*Z* isomer.
21 Pentafluoropropionic anhydride (CAS: 356-42-3) and heptafluorobutyric anhydride (CAS: 336-59-4) are commercially available from several vendors, including Alfa Aesar, Acros Organics, Matrix Scientific, Oakwood Products Inc., Sigma-Aldrich, and TCI America.
22 Light has previously been used to cause metal carbonyl complexes to undergo decarbonylation: D. J. Stufkens, A. Oskam, T. Van der Graaf, H. K. Van Dijk and P. C, Servaas, P. C. *J. Inf. Rec. Mater.*, 1989, **17**, 405.
23 Examples of π–benzyl and π–naphthyl complexes, and studies on dearomatization: a) U. Nettekoven and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 1166. b) A. M. Johns, J. W. Tye, and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 16010. Theoretical studies on dearomatization: c) Y. Ren, J. Jia, W. Liu and H.-S. Wu, *Organometallics*, 2013, **32**, 52. d) H. Xie, H. Zhang, and Z. Lin, *Organometallics*, 2013, **32**, 2336.