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Highly Chemoselective Rhodium-Catalyzed Methylenation of Fluorine-Containing Ketones

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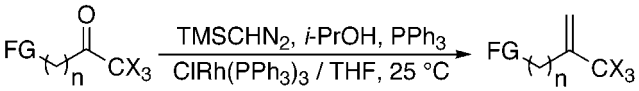
ABSTRACT



The rhodium(I)-catalyzed methylenation of functionalized fluorinated ketones using trimethylsilyldiazomethane proceeds to give the corresponding fluoromethylalkenes in good yields (61−90%). Remarkable chemoselectivity was observed for the synthesis of keto-substituted organofluorine alkenes.

Organofluorine compounds have attracted considerable attention in various fields, notably in medicinal chemistry, as a result of their unique physiological and physical properties.[1] As a result, numerous methodologies for the selective introduction of fluoro substituents, such as CF_3, into organic molecules have been reported.[2] The reactivity of fluorinated molecules is also quite different from that of the related hydrocarbons, mainly because of the strong electronic effect of the fluorine atom.[3] For instance, fluoromethylalkenes were much more reactive than normal alkenes in a variety of cyclization reactions.[4] Functionalized *gem*-difluoroalkenes are important synthetic intermediates displaying unique properties and have been used extensively in the synthesis of fluorine-containing molecules.[5] Different strategies have been used for the preparation of fluoromethylalkenes, including the palladium-catalyzed cross-coupling reaction of 2-bromo-3,3,3-trifluoropropene and the Barbier-type reaction.[6] The methylenation of trifluoromethylketones has also been reported for the preparation of trifluoromethylalkenes.[7] However, to the best of our knowledge, such a strategy has never been applied to the synthesis of mono- or difluoro-

(1) (a) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (b) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. (b) Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II: A Critical Review*. ACS Monograph Series 187; American Chemical Society: Washington, DC, 1995. (c) Baasner, B.; Hagemann, H.; Tatlow, J. C. *Organo-Fluorine Compounds*; Houben-Weyl: Thieme, 1999; Vols. 1−5. (d) Schofield, H. *J. Fluorine Chem.* **1999**, *100*, 7−11. (e) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431−12477.

(2) (a) *Synthetic Fluorine Chemistry*; Olah, G. A., Prakash, G. K. S., Chambers, R. D., Eds.; Wiley: New York, 1992. (b) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555−6666. (c) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757−786. (d) Fei, X. S.; Tian, W. S.; Chen, Q. Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1139−1142. (e) Sanin, A. V.; Nenajdenko, V. G.; Smolko, K. I.; Denisenko, D. I.; Balenkova, E. S. *Synthesis* **1998**, 842−846. (f) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613−7632. (g) Billard, T.; Bruns, S.; Langlois, B. R. *Org. Lett.* **2000**, *2*, 2101−2103. (h) Singh, R. P.; Shreeve, J. M. *J. Org. Chem.* **2000**, *65*, 3241−3243. (i) Singh, R. P.; Leitch, J. M.; Twamley, B.; Shreeve, J. M. *J. Org. Chem.* **2001**, *66*, 1436−1440.

(3) (a) Chambers, R. D.; Vaughan, J. F. S. *Top. Curr. Chem.* **1997**, *192*, 1−38. (b) Percy, J. M. *Top. Curr. Chem.* **1997**, *193*, 131−195. (c) Lin, P.; Jiang, J. L. *Tetrahedron* **2000**, *56*, 3635−3671.

(4) For selected examples, see: (a) Hanzawa, Y.; Suzuki, M.; Kobayashi, Y.; Taguchi, T. *J. Org. Chem.* **1991**, *56*, 1718−1725. (b) De Clercq, P. J.; Zhu, G. D.; Vanlancker, B.; Vanhaver, D.; Declercq, P. J. *Bull. Soc. Chim. Belg.* **1994**, *103*, 263−271. (c) Nemoto, H.; Satoh, A.; Fukumoto, K.; Kabuto, C. *J. Org. Chem.* **1995**, *60*, 594−600. (d) Nemoto, H.; Satoh, A.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 10159−10174. (e) Ichikawa, J.; Fujiwara, M.; Okauchi, T.; Minami, T. *Synlett* **1998**, 927−929. (f) Komatsu, Y.; Sakamoto, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 8369−8374.

(5) (a) Begue, J. P.; Bonnetdelpon, D.; Rock, M. H. *Synlett* **1995**, *6*, 659−660. (b) Begue, J. P.; Bonnetdelpon, D.; Rock, M. H. *Tetrahedron Lett.* **1995**, *36*, 5003−5006. (c) Begue, J. P.; Bonnetdelpon, D.; Bouvet, D.; Rock, M. H. *J. Org. Chem.* **1996**, *61*, 9111−9114. (d) Begue, J. P.; Bonnetdelpon, D.; Rock, M. H. *J. Chem. Soc., Perkin Trans.* **1996**, *21*, 1409−1413.

(6) For selected examples, see: (a) Jiang, B. A.; Xu, Y. Y. *Tetrahedron Lett.* **1992**, *33*, 511−514. (b) Iseki, K.; Kuroki, Y.; Nagai, T.; Kobayashi, Y. *J. Fluorine Chem.* **1994**, *69*, 5−6. (c) Nader, B. S.; Cordova, J. A.; Reese, K. E.; Powell, C. L. *J. Org. Chem.* **1994**, *59*, 2898−2901. (d) Peng, S.; Qing, F. L.; Guo, Y. L. *Synlett* **1998**, 859−860.

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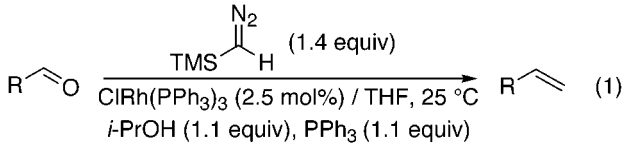
methylalkenes. We have recently reported a new method for the methylenation of aldehydes based on the in situ generation of methylenetriphenylphosphorane from the rhodium-(I)-catalyzed decomposition of trimethylsilyldiazomethane in the presence of triphenylphosphine and 2-propanol (eq 1).[8] In this communication, we now present the methylenation of fluoromethylketones, leading to a new synthesis of fluoromethylalkenes. The chemoselectivity of this reaction toward other keto functionalities will also be discussed.

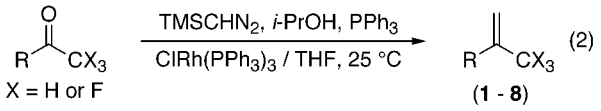


(1)

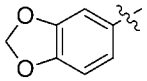
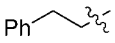
Our interest in de novo synthesis of alkenes prompted us to develop a new rhodium-catalyzed olefination reaction of carbonyl derivatives using readily available reagents.[8] The reaction conditions do not require the use of a base and are mild enough to be compatible with sensitive and enolizable substrates, thereby allowing the synthesis of a variety of functionalized alkenes in excellent yields. This method constitutes a powerful means to access terminal olefins, which are potent precursors for a variety of reactions, including the ring-closing metathesis reaction.[9] Moreover, the chemoselectivity of the methylenation reaction is excellent, and keto aldehydes react selectively to produce exclusively the aldehyde methylenation product. To pursue our work on rhodium-catalyzed methylenation reactions, we have screened various ketones (Table 1). When aryl- or alkyl-methylketones were reacted with trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol in THF using 2.5 mol % of Wilkinson's catalyst ($ClRh(PPh_3)_3$), the corresponding alkene derivatives were produced, albeit in low yields (entries 1 and 5). The major products observed in these cases were the corresponding silyl enol ethers. The substitution of one hydrogen by one fluorine atom on the ketone proved to have a beneficial effect in improving the ketone reactivity. Indeed, the methylenation of monofluoromethylketones under similar reaction conditions proceeded extremely well, leading to the formation of monofluoromethylalkenes with good yields (entries 2 and 6).

The methylenation of difluoro- and trifluoromethylketones was also successful, providing the corresponding alkenes with 73−81% yield (entries 3 and 4, 7 and 8). Activation by the fluorine atom is quite remarkable, as all the reactions with fluorine substrates presented in Table 1 were completed in less than 2 h.

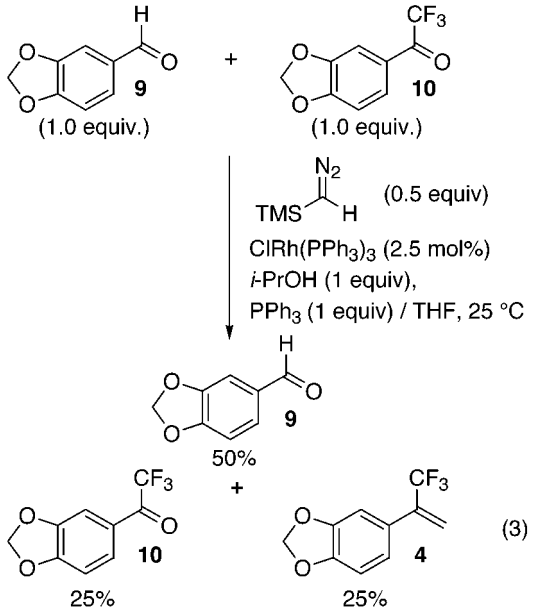
Table 1. Rhodium-Catalyzed Methylenation of Fluoromethylketones[a]



(2)

Entry	R	CX_3	Yield[b]
1		CH_3 (**1**)	25%
2		CH_2F (**2**)	73%
3		CHF_2 (**3**)	81%
4		CF_3 (**4**)	80%
5		CH_3 (**5**)	18%
6		CH_2F (**6**)	61%
7		CHF_2 (**7**)	73%
8		CF_3 (**8**)	80%

[a] Conditions: $TMSCHN_2$ (1.4 equiv), 2-propanol (1.1 equiv), triphenylphosphine (1.1 equiv), and $RhCl(PPh_3)_3$ (2.5 mol %). [b] Isolated yield.



(3)

In a competitive experiment, we have found that the rhodium-catalyzed methylenation of the aromatic trifluoromethylketone **10** was faster than with the corresponding piperonal (**9**), as only the methylenation product **4** was observed when using 0.5 equiv of trimethylsilyldiazomethane (eq 3). However, we have observed a similar rate for the methylenation of the corresponding aromatic monofluoromethylketone and piperonal, leading to a mixture both terminal olefins.

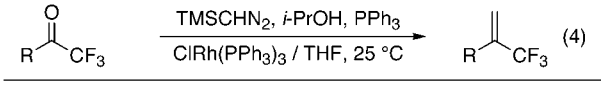
As trifluoromethylalkenes are very useful synthetic building blocks, we surveyed the methylenation of a variety of functionalized trifluoromethylketones. As outlined in Table 2, the yields are typically around 70−90%, which is

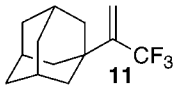
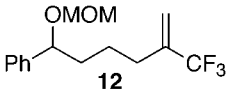
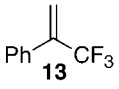
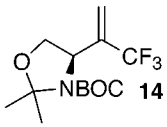
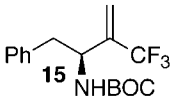
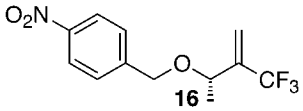
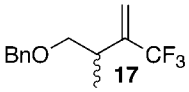
(7) (a) Nader, B. S.; Cordova, J. A.; Reese, K. E.; Powell, C. L. *J. Org. Chem.* **1994**, *59*, 2898−2901. (b) Begue, J. P.; Bonnetdelpon, D.; Kornilov, A. *Org. Synth.* **1998**, *75*, 153−160. (c) Faure, S.; Piva, O. *Synlett* **1998**, *12*, 1414−1416. (d) Yoshimatsu, M.; Sugimoto, T.; Okada, N.; Kinoshita, S. *J. Org. Chem.* **1999**, *64*, 5162−5165. (e) Shen, Y. C.; Ni, J. H.; Li, P.; Sun, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 509−512.

(8) Lebel, H.; Paquet, V.; Proulx, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2887−2890.

(9) (a) Ackermann, L.; El Tom, D.; Furstner, A. *Tetrahedron* **2000**, *56*, 2195−2202. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (c) Furstner, A. *Angew. Chem, Int. Ed.* **2000**, *39*, 3013−3043.

Table 2. Rhodium-Catalyzed Methylenation of Trifluoromethylketones



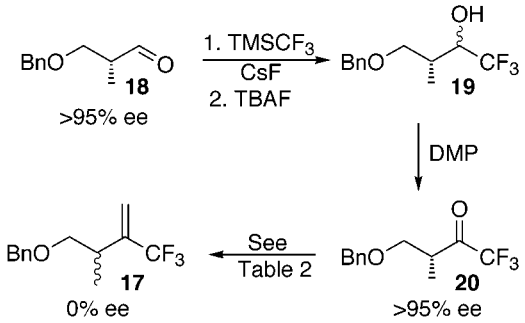
Entry	Product	Yield[a]
1	 **11**	87%[b]
2	 **12**	71%[e]
3	 **13**	71%[b,c]
4	 **14**	81%[d]
5	 **15**	69%[e]
6	 **16**	83%[e]
7	 **17**	90%[e]

[a] Isolated yield. [b] Conditions: $TMSCHN_2$ (1.4 equiv), 2-propanol (1.1 equiv), triphenylphosphine (1.1 equiv), and $RhCl(PPh_3)_3$ (2.5 mol %). [c] Alkene **13** was characterized as the corresponding diol. See Supporting Information. [d] Conditions: $TMSCHN_2$ (2.8 equiv), 2-propanol (2.1 equiv), triphenylphosphine (2.1 equiv), and $RhCl(PPh_3)_3$ (5 mol %). [e] Conditions: $TMSCHN_2$ (2.0 equiv), 2-propanol (1.5 equiv), triphenylphosphine (1.5 equiv), and $RhCl(PPh_3)_3$ (2.5 mol %).

comparable or superior to those obtained under the standard Wittig reaction conditions (Ph_3PCH_3Br and NaHMDS).

Hindered substrates such as adamantyltrifluoromethylketone (Table 2, entry 1) reacted smoothly to give the corresponding alkene (**11**) in an excellent yield. Numerous protecting groups, such as methoxymethyl ether, *tert*-butylcarbamate, acetonide, and benzyl and *p*-nitrobenzyl ethers, are compatible with the reaction conditions. The volatile trifluoromethylalkene **13** was converted to the corresponding diol for isolation purpose. As the rhodium-catalyzed methylenation reaction conditions are mild and nonbasic, we were expecting very little racemization when using chiral nonracemic fluoro substrates. Indeed, trifluoromethylalkene **14** and **15** derived from enantiomerically pure amino acids (L-serine and L-phenylalanine) have been recovered with 93% and 96% ee, respectively. In addition, trifluoromethylalkene **16** was recovered in 83% yield and 95% ee starting from the corresponding enantioenriched trifluoromethylketone derived from enantiomerically pure (*S*)-ethyl lactate. We have also synthesized trifluoromethylketone **20**, starting from enantiomerically pure 3-benzyloxy-2-methyl-propionaldehyde (**18**) (Scheme 1). The addition of

Scheme 1. Synthesis of Trifluoromethylalkene **17**



trimethylsilyltrifluoromethane catalyzed with cesium fluoride[10] produced the corresponding alcohol **19** as a mixture of two diastereoisomers. Oxidation with Dess−Martin periodinane reagent provided the desired trifluoromethylketone **20** with >95% ee.[11,12] This chiral ketone is prone to racemization upon flash chromatography and was used directly in the olefination reaction without any further purification. However, racemic trifluoromethylalkene **17** was isolated in 90% yield, indicating that the trifluoromethylketone **20** racemized under the reaction conditions.

Using chiral GC analysis of the olefination reaction mixture, we have established that the racemization of trifluoromethylketone **20** was very fast, and after only 2 min of reaction, we observed complete racemization of the starting material. Although usually we did not observe any racemization when using chiral nonracemic substrates, very sensitive substrates such as **20** cannot be converted into the corresponding terminal olefin without racemization.

The low reactivity of methylketones in the rhodium-catalyzed methylenation reaction suggested a possible use of this reaction as a chemoselective method for the methylenation of fluoromethylketones in the presence of aryl or alkyl ketones. We synthesized a number of keto fluoromethylketone substrates to test our hypothesis (Table 3).

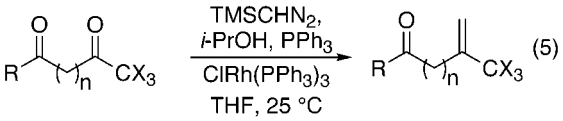
Indeed the rhodium-catalyzed methylenation reaction with trimethylsilyldiazomethane is highly chemoselective. Only traces of the diene were observed in the methylenation of the keto-monofluoromethylketone that produced mainly the desired product **21** in moderate yield (entry 1). In the case of the keto-difluoromethylketone, the methylenation favored

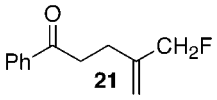
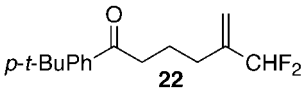
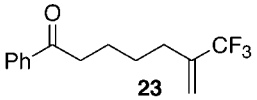
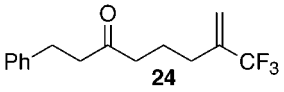
(10) (a) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393−395. (b) Singh, R. P.; Cao, G.; Kirchmeier, R.; Shreeve, J. M. *J. Org. Chem.* **1999**, *64*, 2873−2876.

(11) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (c) Linderman, R. J.; Graves, D. M. *J. Org. Chem.* **1989**, *54*, 661−668.

(12) Although there are some procedures for the direct preparation of trifluoromethylketones from carboxylic esters, those require the use of rigously anhydrous TBAF; see: Wiedemann, J.; Heiner, T.; Mloston, G.; Prakash, G. K. S.; Olah, G. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 820−821. We found it more practical to use the two-step procedure described above.

Table 3. Chemoselective Methylenation of Fluoromethylketones[a]



Entry	Product	Yield[b,c]
1	 **21**	48% (<5%)
2	 **22**	62% (8%)
3	 **23**	77% (7%)[d]
4	 **24**	63% (8%)

[a] Conditions: $TMSCHN_2$ (1.4 equiv), 2-propanol (1.1 equiv), triphenylphosphine (1.1 equiv), and $RhCl(PPh_3)_3$ (2.5 mol %). [b] Isolated yield. [c] Values in parentheses refer to the amount of diene derivatives. [d] Conditions: $TMSCHN_2$ (2.0 equiv), 2-propanol (2.0 equiv), triphenylphosphine (1.5 equiv), and $RhCl(PPh_3)_3$ (2.5 mol %).

also the difluoromethylketone, and the alkene **22** was isolated in 62% yield (entry 2). In this case, the amount of diene was slightly more important, typically between 5% and 10%. Furthermore, products **23** and **24** were isolated in 77% and 63% yield along with 7% and 8% of the corresponding diene resulting from the reaction of the two carbonyls (entries 3 and 4). In comparison, only 50% yield of the keto olefin **23** was obtained when using the standard Wittig reaction conditions (Ph_3PCH_3Br and NaHMDS). After 24 h, the reaction was not complete (25% of the starting material was recovered) and 5−10% yield of the diene was also isolated. The chemoselectivity of the rhodium-catalyzed methylenation reaction is quite remarkable since it is possible to discriminate between two ketone derivatives only on the basis of their electrophilic character. Although this concept has been widely used for other reactions, this is one of the first examples of such chemoselectivity in an olefination reaction.

In summary, we have described a versatile synthesis of useful fluoromethylalkenes that makes use of stereoelectronic effect of the fluorine atom. Fluoro-carbonyl substrates were found to be very reactive toward the rhodium-catalyzed methylenation reaction. In addition, a remarkable chemoselectivity was observed for the methylenation of keto-fluoromethylketone substrates, thus eliminating the need for protecting groups. As a result, this method provides new tools to access organofluorine derivatives that are of primary importance in medicinal chemistry

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Supporting Information Available: Experimental procedures, compound characterization data, and ^1H and ^{13}C spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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