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Zn-mediated rhodium-catalyzed α-trifluoromethylation of ketones via silyl enol ethers

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Abstract

The treatment of silyl enol ethers of ketones with CF_3–I and Et_2Zn in the presence of $RhCl(PPh_3)_3$ in DME gave α-trifluoromethyl ketones in good yields. The reaction can be widely applicable to silyl enol ethers derived from aliphatic or aromatic ketones. In the absence of the rhodium catalyst, the reaction was very slow and the yields were quite poor.

Keywords: Fluorine; Trifluoromethyl; Rhodium; Silyl enol ether; α-Position

In the field of organofluorine chemistry, trifluoromethylation is one of the most fascinating reactions and it has been reported by many authors.[1] For example, Kobayashi–Kumadaki's trifluoromethylation,[2] which uses CF_3Cu derived from CF_3–X, and Burton's trifluoromethylation,[3] which uses CF_2X_2/Zn or Cd were applied to various halides to give coupling products. CF_3–TMS reacts with carbonyl compounds in the presence of fluoride ion[4] or CF_3–I treated with tetrakis(dimethylamino)ethylene (TDAE)[5] to afford trifluoromethylated carbinols. In addition, a CF_3 radical derived from CF_3–I with SmI_2 or Et_3B was added to olefins.[6]

Although there are a number of methods for introducing a CF_3 unit into an organic molecule, it is difficult to introduce a CF_3 group at the α-position of ketones. This might be due to the fact that the polarization of $CF_3^{\delta-}$–$I^{\delta+}$ is opposite to that of $CH_3^{\delta+}$–$I^{\delta-}$, which makes it difficult to introduce CF_3^+ unit to enolates.[7] Therefore, there are very few reports for introducing the CF_3 group at the α-position of ketones. One of the most simple methods is the use of electrophilic trifluoromethylating reagents such as trifluoromethyl chalcogenium salts,[8] but their insolubility in most organic solvents inhibits their common use in organic synthesis. Another method is the use of radical trifluoromethylation protocols, but these methods lead to low yields and require special equipment or techniques in some cases.[9–11]

Recently, Mikami and co-workers reported radical α-trifluoromethylation of ketones using Li, Ti or Si enolates assisted by Et_3B/O_2.[12] Their reaction is very simple and easily gives the α-CF_3 ketones, but they have applied the reaction only to aliphatic ketones. More recently, Cahard et al. reported a radical α-trifluoromethylation of ammonium enolates of 1,3-dicarbonyl compounds using $Na_2S_2O_4$,[13] and Togni et al. reported an electrophilic trifluoromethylation using a hypervalent iodine(III)–CF_3 reagent.[14] However, they did not apply their reaction to simple ketones.

On the other hand, we recently reported a novel trifluoromethylation at the α-position of α,β-unsaturated ketones (**2**) by treating it with CF_3–I (**1**) and Et_2Zn in the presence of Wilkinson's catalyst.[15] This reaction proceeded smoothly, and it could be applied to other halofluoroalkyl compounds (R_f-X) in place of **1** to give α-R_f ketones.[16]

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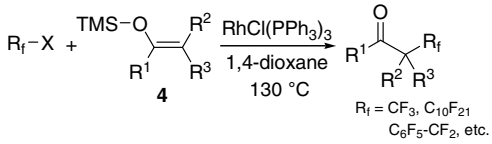
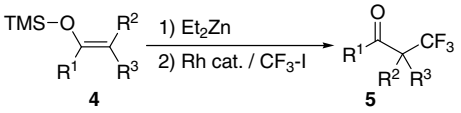


Scheme 1. Rh-catalyzed α-fluoroalkylation via silyl enol ethers.

Furthermore, we recently reported a rhodium-catalyzed α-fluoroalkylation of silyl enol ethers of ketones (**4**) as an expansion of this reaction (Scheme 1).[17]

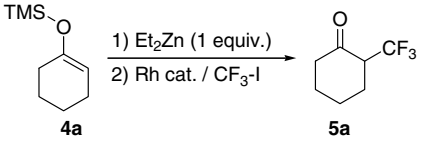
In that work,[17] we obtained the α-R_f ketones with large R_f groups in moderate yields. However, the reaction of the low-boiling R_f-X such as CF_3–I or C_4F_9–I resulted in very low yields, because the reaction only proceeded at 130 °C. Herein, we would like to report that this Rh-catalyzed α-trifluoromethylation of silyl enol ethers of ketones is accelerated tremendously by Et_2Zn.

Thus, to solve this problem, we examined various reaction conditions for α-trifluoromethylation, and found that the addition of Et_2Zn into the reaction mixture allowed the reaction to proceed at or below room temperature and improved the yields of α-CF_3 ketones (**5**) tremendously (Scheme 2). Then, we optimized the reaction conditions extensively using 1-(trimethylsiloxy)cyclohexene (**4a**) as the substrate (Table 1).[18,19]



Scheme 2. Zn-mediated Rh-catalyzed α-trifluoromethylation using **4**.

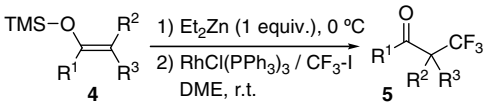
Table 1
Optimization of reaction conditions

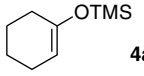
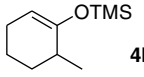
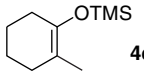
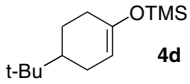
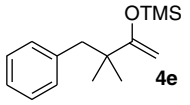
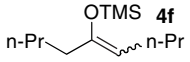
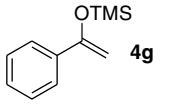
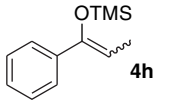
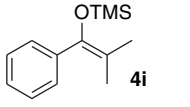


Entry	Rh cat. (mol %)	Solv.	Time (h)	Yield[a] (%)
1	$RhCl(PPh_3)_3$ (4)	Toluene	1	17
2	$RhCl(PPh_3)_3$ (4)	CH_2Cl_2	2	59
3	$RhCl(PPh_3)_3$ (4)	Et_2O	1	63
4	$RhCl(PPh_3)_3$ (4)	THF	0.5	62
5	$RhCl(PPh_3)_3$ (4)	DME	0.5	77
6	$RhCl(PPh_3)_3$ (4)	CH_3CN	2	6
7	$RhCl(PPh_3)_3$ (2)	DME	0.5	81
8	$RhCl(PPh_3)_3$ (1)	DME	1	72
9	None	DME	24	16
10	$[Rh(dppb)(cod)]BF_4$ (2)	DME	1	76
11	$Rh(acac)(CO)_2$ (2)	DME	0.5	70
12	$[RhCl(cod)]_2$ (1)	DME	0.5	73
13	$Rh_4(CO)_{12}$ (0.5)	DME	0.5	70

[a] ^{19}F NMR yield calculated from benzotrifluroide (BTF).

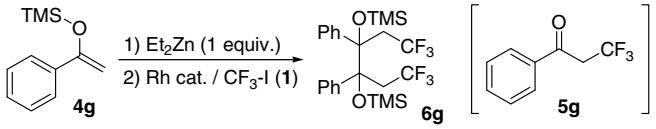
Table 2
α-Trifluoromethylation of various silyl enol ethers of ketones



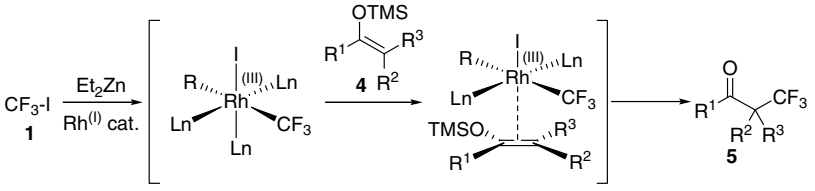
Entry	4	Time (h)	Yield[a] (%)	Ratio[b]
1	 **4a**	0.5	74 (81)[c]	
2	 **4b**	0.5	— (62)[c,d,e]	[1:1]
3	 **4c**	0.5	— (37)[c]	
4	 **4d**	0.5	68[d] (70)[c]	[3:2]
5	 **4e**	0.5	84	
6	 **4f**	0.5	50	
7	 **4g**	0.5	— (84)[f]	[1:1][g]
8	 **4h**	0.5	53	
9	 **4i**	0.5	23	

[a] Isolated yield.
[b] Diastereomeric ratio was calculated from ^{19}F NMR.
[c] ^{19}F NMR yield calculated from benzotrifluoride (BTF).
[d] Total yield of diastereomeric mixture.
[e] **5c** was obtained in 15% as a by-product.
[f] The dimer (**6g**) was isolated in the yield in parentheses as the diastereomeric mixture.
[g] Diastereomeric ratio of **6g** was calculated from ^{19}F NMR.

In entries 1–8, the reaction proceeded smoothly to give the desired α-CF_3 ketone (**5a**) in good yields in ethereal



Scheme 3. Generation of the dimerization product (**6g**).



Scheme 4. Proposed reaction mechanism of α-trifluoromethylation.

solvents, especially, in DME. Furthermore, although other Rh catalysts allowed the reaction to proceed in good yields (entries 10–13), $RhCl(PPh_3)_3$ gave the best result as shown in entry 7. On the other hand, without a rhodium catalyst, the reaction gave the product in a very low yield as shown in entry 9. It is clear that the Rh catalyst played an important role in this reaction.

Next, we applied the reaction to the various substrates (**4**) using the conditions of entry 7 in Table 1 and the results are shown in Table 2.

As shown in entries 1–6, the reaction with aliphatic silyl enol ethers proceeded smoothly to give the α-CF_3 ketones (**5a**–**f**) in moderate to good yields regardless of whether cyclic or acyclic compounds were used. Furthermore, the reaction could be applied to the silyl enol ethers derived from aromatic ketones to give the desired products (**5h** and **5i**) (entries 8 and 9). The bulkier the substrates were, the lower the yield became (compare entries 1 with 3, or 8 with 9). In our previous work using α,β-unsaturated ketones,[15] a product with a CF_3-attached quaternary carbon was not obtained. This reaction overcame this problem, although the yields of products (**5c** and **5i**) were not so high (entries 3 and 9). On the other hand, the silyl enol ether of acetophenone (**4g**) did not give product (**5g**), but gave the dimerization product (**6g**) in a good yield as shown in entry 7, although we do not know the reason at this moment (Scheme 3).

We have not clarified the mechanism of the α-trifluoromethylation reaction yet, but we found that the formation of Zn enolate from **4** and Et_2Zn has not been formed in this α-trifluoromethylation. Because, when the reaction was quenched by NaCl aq before the addition of $RhCl(PPh_3)_3$ and CF_3–I (**1**), the TMS enol ether (**4a**) was detected on GLC. In addition, Mikami et al. reported that a zinc enolate could not be observed upon the addition of Me_2Zn to a TMS enol ether by TLC or NMR analysis, and they have explained the complexation of Me_2Zn with the TMS enol ether as d–π^* complex or Lewis acid/base complex.[12d] It might mean that a Rh enolate by transmetalation does not concern in this reaction as we proposed before.[17] Furthermore, the formation of CF_3 radical by Rh catalyst or Et_2Zn also would not be a reasonable mechanism because of the generation of **5c** from **4b** as the by-product. This result might suggests that the coordination of Rh complex to π-bond of **4b** leads the isomerization to thermodynamically more stable **4c** to give **5c**.

In our case, the addition of Et_2Zn improved the yield and the reaction rate tremendously. So, it is clear that Et_2Zn played an important role, and we suggest that the coordination of Rh complex to the silyl enol ether (**4**) gives the α-CF_3 ketones (Scheme 4).

In conclusion, we have developed a Zn-mediated rhodium-catalyzed α-trifluoromethylation reaction of ketones by using silyl enol ethers. The reaction could be widely applicable to silyl enol ethers of ketones, regardless of aliphatic or aromatic ketones. Furthermore, we could obtain the products with a CF_3-attached quaternary carbon easily. Unfortunately, the reaction mechanism has not fully been clarified. We are now carrying on a detailed examination of the mechanism.

Acknowledgment

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References and notes

1. (a) *Fluorine-Containing Synthons*; Soloshonok, V. A. Ed.; ACS Publications Division and Oxford University Press: Washington, DC, 2005; (b) Uneyama, K *Organofluorine Chemistry*; Blackwell: Oxford, 2006; (c) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975–996.
2. (a) Kobayashi, Y.; Kumadaki, I. *Tetrahedron Lett.* **1969**, *10*, 4095–4096; (b) Kobayashi, Y.; Yamamoto, K.; Kumadaki, I. *Tetrahedron Lett.* **1979**, *20*, 4071–4072.
3. Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014–5015.
4. For the nucleophilic trifluoromethylation by using CF_3–TMS: (a) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393–395; (b) Krishnamurti, R.; Bellew, D. R.; Prakash, G. K. S. *J. Org. Chem.* **1991**, *56*, 984–989; (c) Ramaiah, P.; Krishnamurti, R.; Prakash, G. K. S. *Org. Synth.* **1995**, *72*, 232–240; (d) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613–7632; (e) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123–131.
5. For the nucleophilic trifluoromethylation by using CF_3–I with tetrakis(dimethylamino)ethylene (TDAE): (a) Aiet-Mohand, S.; Takechi, N.; Medebielle, M.; Dolbier, W. R., Jr. *Org. Lett.* **2001**, *3*, 4271–4273; (b) Petrov, V. A. *Tetrahedron Lett.* **2001**, *42*, 3267–3269; (c) Xu, W.; Dolbier, W. R., Jr. *J. Org. Chem.* **2005**, *70*, 4741–4745; (d) Pooput, C.; Dolbier, W. R., Jr.; Medebielle, M. *J. Org. Chem.* **2006**, *71*, 3564–3568.
6. (a) Lu, X.; Ma, S.; Zhu, J. *Tetrahedron Lett.* **1988**, *29*, 5129–5130; (b) Takeyama, Y.; Ichinose, Y.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 3159–3162; (c) Yajima, T.; Nagano, H.; Saito, C. *Tetrahedron Lett.* **2003**, *44*, 7027–7029.
7. (a) Huheey, J. E. *J. Phys. Chem.* **1965**, *69*, 3284–3291; (b) Yoshida, M.; Kamigata, N. *J. Fluorine Chem.* **1990**, *49*, 1–20.
8. (a) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156–2164; (b) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757–1777 and references cited therein; (c) Ma, J.-A.; Cahard, D. *J. Org. Chem.* **2003**, *68*, 8726–8729.

9. For the trifluoromethylation of silyl and germyl enolates of esters and ketones: (a) Miura, K.; Taniguchi, M.; Nozaki, K.; Oshima, K.; Utimto, K. *Tetrahedron Lett.* **1990**, *31*, 6391–6394; (b) Miura, K.; Takeyama, Y.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542–1553.
10. For the trifluoromethylation of lithium enolate of imides: (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169–2170; (b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961–974.
11. For the trifluoromethylation of enamines: (a) Cantacuzène, D.; Dorme, R. *Tetrahedron Lett.* **1975**, *25*, 2031–2034; (b) Cantacuzène, D.; Wakselman, C.; Dorme, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1365–1371; (c) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186–5191; (d) Semisch, C.; Margaretha, P. *J. Fluorine Chem.* **1986**, *30*, 471–475.
12. (a) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 649–651; (b) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 4883–4885; (c) Itoh, Y.; Mikami, K. *Tetrahedron* **2006**, *62*, 7199–7203; (d) Mikami, K.; Tomita, Y.; Ichikawa, Y.; Amikura, K.; Itoh, Y. *Org. Lett.* **2006**, *8*, 4671–4673; (e) Itoh, Y.; Houk, K. N.; Mikami, K. *J. Org. Chem.* **2006**, *71*, 8918–8925.
13. Petrik, V.; Cahard, D. *Tetrahedron Lett.* **2007**, *48*, 3327–3330.
14. (a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, *12*, 2579–2586; (b) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754–757.
15. (a) Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *Org. Lett.* **2004**, *6*, 4359–4361; (b) Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *Org. Synth.* **2006**, *83*, 177–183.
16. Sato, K.; Ishida, Y.; Murata, E.; Oida, Y.; Mori, Y.; Okawa, M.; Iwase, K.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Tetrahedron* **2007**, *63*, 12735–12739.
17. Sato, K.; Higashinagata, M.; Yuki, T.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *J. Fluorine Chem.* **2008**, *129*, 51–55.
18. *Typical procedure for 2-(trifluoromethyl)cyclohexanone* (**5a**): To a solution of 1-(trimethylsiloxy)cyclohexene (**4a**, 0.195 mL, 1 mmol) in DME (3 mL) was added 1.0 M Et_2Zn in hexane (1 mL, 1 mmol) gradually at 0 °C and stirred for 1 h at this temperature. After the reaction mixture was cooled to −30 °C, CF_3–I (**1**, ca. 1 mL at −78 °C) was introduced through a gas inlet tube, then the solution of $RhCl(PPh_3)_3$ (18.5 mg, 2 mol %) in DME (2 mL) was added. The reaction mixture was allowed to warm up to room temperature and stirred for 0.5 h. The resulting mixture was quenched with 10% HCl and extracted with Et_2O. The Et_2O layer was washed with sat. NaCl and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was purified by column chromatography (SiO_2, Et_2O–hexane = 10:90) to give 2-(trifluoromethyl)cyclohexanone (**5a**, 123.7 mg, 74.5%).
19. *Spectroscopic data of* **5a**: A colorless oil; ^1H NMR ($CDCl_3$) δ: 1.66-1.88 (3H, m), 1.96–2.15 (2H, m), 2.30–2.40 (2H, m), 2.46–2.54 (1H, m), 3.02–3.14 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.80, 27.14, 27.59 (q, $J = 2.5$ Hz), 42.25 (q, $J = 1.7$ Hz), 53.66 (q, $J = 25.4$ Hz), 124.58 (q, $J = 278.7$ Hz), 202.88–202.95 (m); ^{19}F NMR (90 MHz, $CDCl_3$) δ: −6.01 (3F, d, $J = 8.3$ Hz); MS m/z: 166 (M^+); HRMS calcd for $C_7H_9F_3O$: 166.061 (M^+), found: 166.060; IR (neat) cm^{-1}: 2952, 2880, 1726, 1270, 1172, 1134.