# Dialkylzinc-accelerated α-Trifluoromethylation of Carbonyl Compounds Catalyzed by Late-transition-metal Complexes

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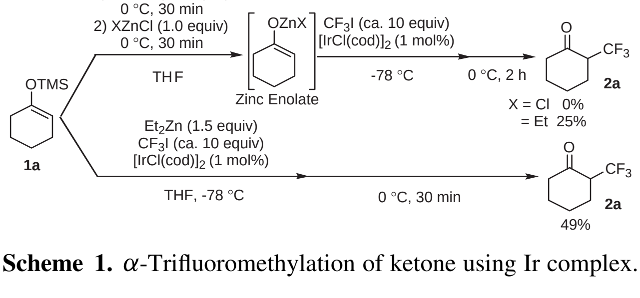
Trifluoromethylation of ketone silyl enol ethers is found to be significantly accelerated by late-transition-metal catalysts and dialkylzincs to give α-trifluoromethyl ketones in good yields. Addition of dialkylzinc is the key to the high yielding α-trifluoromethylation of carbonyl compounds.

Trifluoromethylated compounds have attracted much attention in medicinal and agrochemical science.[1] However, α-trifluoromethylation of non-fluorinated carbonyl compounds has remained difficult because of the specific physical properties of the $CF_3$ groups. The problem in the direct introduction of the $CF_3$ group to the α-position of ketones associates with the low reactivity of ketone silyl enol ethers[2] and unstable α-$CF_3$ ketonic products under basic conditions. Another problem is that the electronegativity of trifluoromethyl group is higher than that of iodine ($CF_3{}^{\delta-}$–$I^{\delta+}$),[3] which is the reason we have focused on radical methodology for α-trifluoromethylation.[4] However, the radical methodology still has problems such as difficulty in application to catalytic asymmetric reaction.[4d]

Currently, the catalytic asymmetric α-arylation of carbonyl compounds catalyzed by late-transition-metal complexes has attracted much attention.[5] Furthermore, the α-arylation of carbonyl compounds proceeds under neutral conditions using Reformatsky reagents[6,7] or silyl enol ethers in the presence of zinc salts[6,8] in good yield. Therefore, we decided to develop an efficient synthetic method for transition-metal-catalyzed α-trifluoromethylation of silyl enol ethers or metal enolates under neutral conditions.[9] This catalytic process is intriguing in terms of "Umpolung"[10] of $CF_3{}^{\delta-}$–$I^{\delta+}$ to give the formal "$CF_3{}^{+}$" for enolate alkylation by late transition metal complexes. A quite recent report[11] prompted us to report herein our own results.[9]

We first focused on an iridium-catalyzed α-trifluoromethylation of ketone enolates with $CF_3I$ (Scheme 1). Because the oxidative addition of $CF_3I$[12,13] with an iridium catalyst at low temperature has already been reported.[13a,13b] The reaction was carried out in the presence of $CF_3I$ and $[IrCl(cod)]_2$ (1 mol %) using zinc enolate of weak metal–fluoride interaction[14] to prevent defluorination of the α-$CF_3$ product. The zinc enolate prepared with $Cl_2Zn$ (X = Cl) did not give any product. The zinc enolate prepared from EtZnCl (X = Et) gave the α-trifluoromethyl ketone **2a** in 25% yield. When employing $Et_2Zn$ without using *n*-BuLi, **2a** was obtained in 49% yield.



**Scheme 1.** α-Trifluoromethylation of ketone using Ir complex.

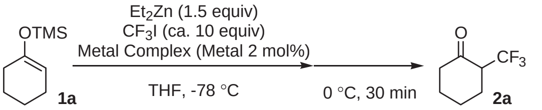
Several group VIII transition metal complexes including Ir, Rh, Pd, Ni, and Ru were thus screened (Table 1). Without group VIII transition metal, α-trifluromethyl ketone **2a** was obtained only in 12% yield (Entry 1). In the presence of late-transition-metal complexes, **2a** was obtained in up to 69% yield. Especially, the Wilkinson catalyst gave the highest yield (69% yield) (Entry 5).

Zinc reagents were also examined (Table 2). Lewis acidic zinc dihalide such as $Br_2Zn$, $F_2Zn$ did not give any product (Entries 6–9). Only dialkylzinc reagents gave **2a** in moderate to good yields (Entries 2–4). Especially, $Et_2Zn$ provides the best yield (69% yield) (Entry 3).

Finally, ketonic substrates were screened to show eventually the wide scope of this catalytic α-trifluoromethylation (Table 3).[15] Five- to seven-membered cyclic ketones gave the α-$CF_3$ products **2a**–**2f** in good yields (Entries 1–6). Starting from α-methylcyclohexanone,[16] the α-trifluoromethyl product **2f** bearing all carbon quaternary center[17] could be obtained (Entry 6).[18] Acyclic ketones also gave the products **2g** and **2h** in good yields (Entries 7 and 8).

In conclusion, we have uncovered α-trifluoromethylation of silyl enol ethers catalyzed by late-transition-metal complexes

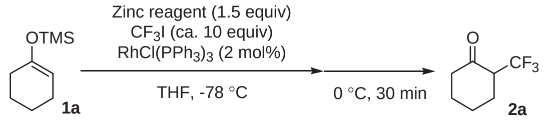
**Table 1.** Group VIII transition metal catalyses



| Entry | | Metal Complex | Yield/%[a] |
|---|---|---|---|
| 1 | | — | 12 |
| 2 | Ir | $[IrCl(cod)]_2$ | 49 |
| 3 | | $IrCl(CO)(PPh_3)_2$ | 24 |
| 4 | | IrI(CO)(dppe) | 10 |
| 5 | Rh | $RhCl(PPh_3)_3$ | 69 |
| 6 | | $[RhCl(cod)]_2$ | 54 |
| 7 | | $[Rh(OH)(cod)]_2$ | 55 |
| 8 | | $[Rh(acac)(C_2H_4)_2$ | 58 |
| 9 | | $[Rh(cod)_2](SbF_6)$ | 57 |
| 10 | Pd | $Pd(PPh_3)_4$ | 56[b] |
| 11 | | $Pd(dba)_2$ | 54[b] |
| 12 | | $Pd(OAc)_2$ | 58[b] |
| 13 | Ni | $Ni(PPh_3)_4$ | 60 |
| 14 | Ru | $RuCl_2(PPh_3)_3$ | 60 |
| 15 | | $[RuCl_2(benzene)]_2$ | 55 |

[a] Determined by $^{19}F$ NMR using BTF as an internal standard.
[b] Reaction time was 2 h.

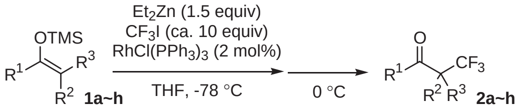
**Table 2.** Zinc reagent acceleration

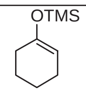
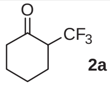
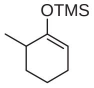
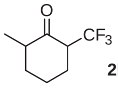
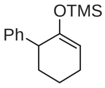
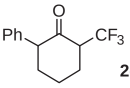
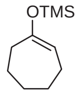
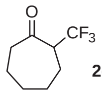
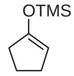
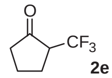
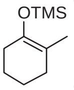
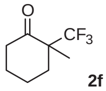
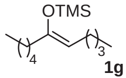
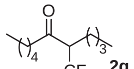
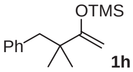
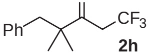


| Entry | Zinc Reagent | Yield/%[a] |
|---|---|---|
| 1 | — | 0 |
| 2 | $i$-$Pr_2Zn$ | 38 |
| 3 | $Et_2Zn$ | 69 |
| 4 | $Me_2Zn$ | 37 |
| 5 | $Ph_2Zn$ | 1 |
| 6 | $Br_2Zn$ | 0 |
| 7 | $F_2Zn$ | 0 |
| 8 | $(TfO)_2Zn$ | 0 |
| 9 | $t$-$BuO_2Zn$ | 0 |

[a]Determined by $^{19}$F NMR using BTF as an internal standard.

**Table 3.** $\alpha$-Trifluoromethylation of ketone silyl enol ethers



| Entry | *Si* Enol Ether | Product | Time/h | Yield/%[a] | dr[b] |
|---|---|---|---|---|---|
| 1 |  1a |  2a | 0.5 | 69 | — |
| 2 |  1b |  2b | 3 | 75 | 57:43 |
| 3 |  1c |  2c | 3 | 53 | 90:10 |
| 4 |  1d |  2d | 6 | 42 | — |
| 5 |  1e |  2e | 3 | 60 | — |
| 6 |  1f |  2f | 6 | 31 | — |
| 7 |  1g |  2g | 6 | 54 | — |
| 8 |  1h |  2h | 6 | 51 | — |

[a]Determined by $^{19}$F NMR using BTF as an internal standard. [b]Determined by $^{19}$F NMR.

in the absence of oxygen, which is necessary in radical trifluoromethylation. This reaction can be significantly accelerated by dialkylzincs. Studies on the reaction mechanism are currently in progress.

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