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

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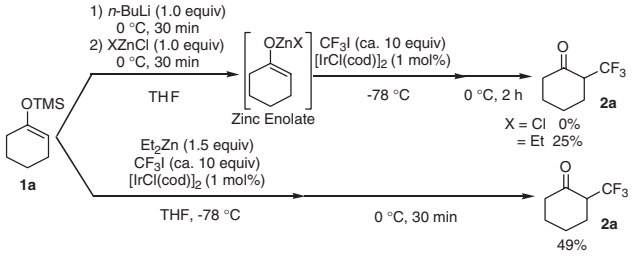
Trifluoromethylation of ketone silyl enol ethers is found to be significantly accelerated by late-transition-metal catalysts and dialkylzincs to give α-trifluoromethyl ketones in good yields. Addition of dialkylzinc is the key to the high yielding α-trifluoromethylation of carbonyl compounds.

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.

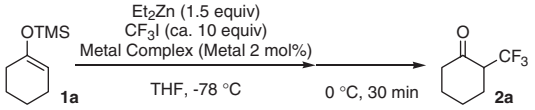
Several group VIII transition metal complexes including Ir, Rh, Pd, Ni, and Ru were thus screened (Table 1). Without group VIII transition metal, α-trifluromethyl ketone **2a** was obtained only in 12% yield (Entry 1). In the presence of late-transition-metal complexes, **2a** was obtained in up to 69%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

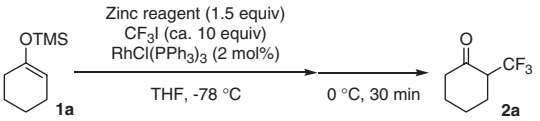
Table 1. Group VIII transition metal catalyses



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

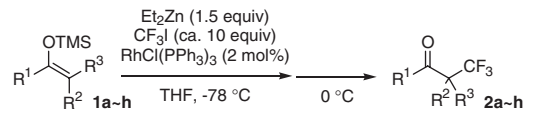


1a **2a**

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. α-Trifluoromethylation of ketone silyl enol ethers



1a~h **2a~h**

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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