C–H Activation

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Iridium-Catalyzed Reactions of Trifluoromethylated Compounds with Alkenes: A C_{sp^3}–H Bond Activation α to the Trifluoromethyl Group**

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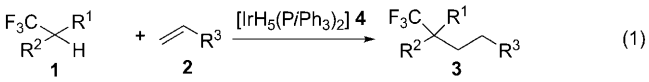
Trifluoromethylated compounds play an important role in medicinal,[1] agrochemical,[2] and material science;[3] therefore, exploitation of a general method for the synthesis of these compounds is highly desirable. Introduction of an α-trifluoromethyl group into the target molecule relies on either trifluoromethyl reagents or trifluoromethylated synthetic building blocks.[4] It has been difficult to achieve carbon–carbon bond formation via α-trifluoromethyl carbanions because these carbanions and related organometallic species spontaneously release fluoride species to produce 1,1-difluoroolefins.[4–5] This notorious decomposition of α-trifluoromethyl carbanions has hindered the development of this species for use in organic synthesis.[6] Only few methods on the synthetic use of α-trifluoromethyl carbanions, under specific reaction conditions, have been reported.[6–7]

Our research group has developed the transition-metal-catalyzed C_{sp^3}–H functionalization reaction stemming from the α heteroatom effect.[8] In light of the potent ability of the transition-metalated carbon nucleophiles to promote carbon–carbon bond forming reactions under neutral reaction conditions, we examined the activation of a C_{sp^3}–H bond α to a trifluoromethyl group. Herein, we report the iridium- or ruthenium-catalyzed reactions of trifluoromethylated compounds with alkenes to afford alkylated products in an atom-economic and selective manner under neutral reaction conditions without the formation of any defluorinated by-product.

We found that $[IrH_5(PiPr_3)_2]$ acts as an efficient catalyst for the reaction of trifluoromethyl compounds (**1**) with alkenes (**2**) at room temperature or at higher temperatures [Eq. (1)]. To our knowledge, no example of C–H bond activation α to a trifluoromethyl group with transition metal catalysts has been reported. Although recent progress on the transition-metal-catalyzed activation of carbon–fluorine bonds is striking.[9]

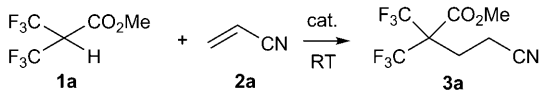
Initially, we examined the reaction of methyl 1,1-trifluoromethyl acetate (**1a**) with acrylonitrile (**2a**) at room temperature and found that the low valent hydride complexes of



(1)

iridium and ruthenium catalyzed the reaction highly efficiently (Table 1). $[IrH_5(PiPr_3)_2]$ (**4**) proved to be the best catalyst among those examined. In the presence of 1 mol% of

Table 1: The reaction of methyl 1,1-bis(trifluoromethyl) acetate (**1a**) with acrylonitrile (**2a**) in the presence of Ru/Ir catalysts or conventional bases.[a]



Entry[a]	Catalyst	Mol [%]	Solvent	*t* [h]	Conv. [%]	Yield [%][b]
1	$[IrH_5(PiPr_3)_2]$	1	toluene	22	99	92 (89)
2	$[IrH_5(PiPr_3)_2]$	5	toluene	3	100	97 (94)
3	$[Cp^*Ru(PPh_3)_2]$	1	toluene	24	94	94
4	$[CpRuH(PPh_3)_2]$	1	toluene	24	38	84
5	$[RuH_2(PPh_3)_4]$	1	toluene	24	18	78
6	$[RuH_2(CO)(PPh_3)_3]$	1	toluene	24	0	0
7	$PiPr_3$	10	toluene	3	16	19
8	PPh_3	100	THF	24	11	0
9	DBU	100	toluene	16	40	10
10	*t*BuOK	100	THF	16	50	0
11	MeONa	100	MeOH	16	50	0
12	Et_3N	100	MeCN	64	100	27
13	$BnNMe_3^+OH^-$[c]	100	MeOH	16	100	0

[a] Unless specified, the reaction was carried out with **1a** (0.2 mmol, 0.5 M in toluene) and acrylonitrile **2a** (0.6 mmol, 3 equiv) in the presence of a catalyst at room temperature. [b] Yield determined by ^{19}F NMR spectroscopy using 1,3-bis(trifluoromethyl)benzene as an internal standard. Yield of the isolated product is shown in parenthesis. [c] 40% methanol solution. Bn = benzyl, Cp = cyclopentadienyl, Cp* = pentamethylcyclopentadienyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

the catalyst **4** in toluene, the reaction gave methyl 4-cyano-2,2-bis(trifluoromethyl)butyrate (**3a**) in 92% yield and with 99% conversion of **1a** (Table 1, entry 1). $[Cp^*RuH(PPh_3)_2]$ was also useful as a catalyst (Table 1, entry 3). Notably, the desired product **3a** was not obtained by the reaction of **1a** in the presence of conventional bases such as DBU, *t*BuOK, MeONa, Et_3N, or $BnNMe_3^+OH^-$ (Table 1, entries 9–13). Phosphines such as $PiPr_3$ and PPh_3 were not effective (Table 1, entries 7 and 8). Changing the solvent effect had a dramatic effect. The best yield was obtained in a nonpolar solvent such as toluene. The reactions of **1a** in DME (1,2-dimethoxyethane) and THF (tetrahydrofuran) gave **3a** in

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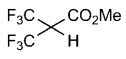
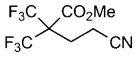
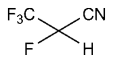
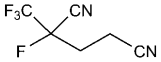
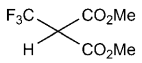
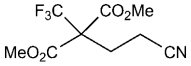
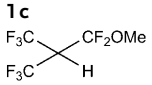
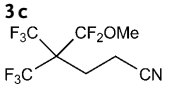
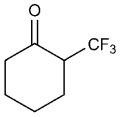
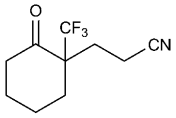
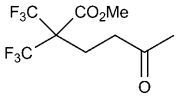
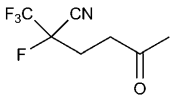
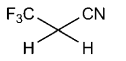
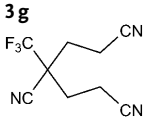
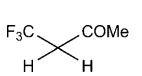
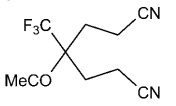
92% and 88% yield, respectively. Meanwhile, the same reaction in acetonitrile resulted in 5% yield.

The representative results of the iridium-catalyzed reaction of trifluoromethylated compounds with alkenes are shown in Table 2. The substrates bearing nitrile (**1b**) and ester (**1c**) functionalities were converted into the corresponding products in excellent yields (Table 2, entries 1–3). Notably, reactions that involved a substrate bearing an electron-donating substituent, such as a methoxy group, occurred readily. Thus, the iridium-catalyzed reaction of 1,1,1,3,3-pentafluoro-2-(trifluoromethyl)-3-methoxypropane (**1d**) gave the product **3d** in 56% yield (Table 2, entry 4).

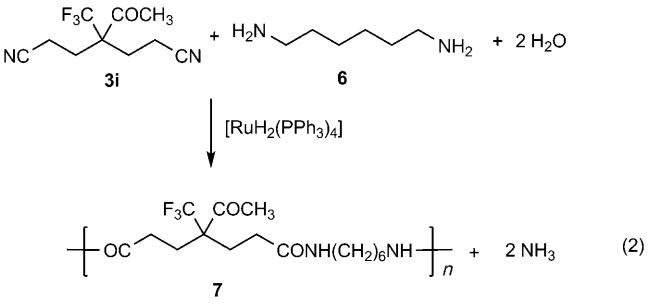
The reaction of 2-(trifluoromethyl)cyclohexanone (**1e**) with acrylonitrile gave the product (**3e**) in 65% yield (Table 2, entry 5). The reactions of trifluoromethylated compounds **1** with methyl vinyl ketone (**2b**) also proceeded but required a higher reaction temperature in comparison to the reaction with acrylonitrile (Table 2, entries 6 and 7). Thus, the reactions of **1a** and **1b** with **2b** at 110°C gave the corresponding compounds **3f** and **3g** in 82% and 61% yields, respectively. The reaction of trifluoromethyl compounds bearing two C–H bonds α to the trifluoromethyl group gave the double alkylation products exclusively. Thus, the reaction of 3,3,3-trifluoropropionitrile (**1f**) with **2a** gave 4-cyano-4-(trifluoromethyl)-heptane-1,7-dinitrile (**3h**) in 77% yield (Table 2, entry 8), and the reaction of 4,4,4-trufluoro-2-butanone (**1g**) with **2a** gave 4-acetyl-4-trifluoromethylheptane-1,7-dinitrile (**3i**) in good yield (Table 2, entry 9).

Table 2: Iridium-catalyzed reaction of α-trifluoromethylated compounds (**1**) with alkenes (**2**).[a]

Entry	Substrate **1**	Alkene **2**	Product **3**	*T* [°C]	*t* [h]	Yield [%][b]
1				25	3	97
	1a	**2a**	**3a**			(94)
2		**2a**		50	1	(91)
	1b		**3b**			
3		**2a**		25	5	(93)
	1c		**3c**			
4		**2a**		25	40	81
	1d		**3d**			(56)
5[c]		**2a**		50	40	76
	1e		**3e**			(65)
6				110	18	(82)
	1a	**2b**	**3f**			
7		**2b**		110	16	(61)
	1b		**3g**			
8		**2a**		110	7	(77)
	1f		**3h**			
9		**2a**		50	5	(70)
	1g		**3i**			

[a] The reaction was carried out with **1** (0.2 mmol) and **2** (0.3 mmol) in the presence of $[IrH_5(PiPr_3)_2]$ (5 mol%) in toluene (0.5 mL) under argon or in a sealed tube. [b] Yield determined by ^{19}F NMR spectroscopy using 1,3-bis(trifluoromethyl)benzene as an internal standard. Yield of the isolated product is shown in parenthesis. [c] The ratio of **1e**/**2a** is 1.5:1 and the conversion was 86%.

The products obtained are highly useful intermediates for the synthesis of industrially important trifluoromethylated compounds.[9] Next, we demonstrated the catalytic production of polyamides bearing trifluoromethyl groups (which are useful for material science) by using our unique environmentally benign ruthenium-catalyzed method.[10] The polycondensation of the dinitrile compound bearing a trifluoromethyl group **3i** with 1,6-hexanediamine (**6**) in the presence of $[RuH_2(PPh_3)_4]$ catalyst (3 mol%) and two equivalents of water in DMF at 160°C gave the trifluoromethylated polyamide **7** in 96% yield along with ammonia as shown in Equation (2). The GPC analysis of **7** showed $Mn = 2592\ g\,mol^{-1}$ and $Mw = 10878\ g\,mol^{-1}$, as well as PDI = 4.20.



(2)

The present iridium-catalyzed reaction can be rationalized by assuming that the C_{sp^3}–H bond α to the trifluoromethyl group is activated with low valent iridium or ruthenium species,[7] and subsequent insertion to alkenes and reductive elimination gives the product. It is oteworthy that the reaction occurs under heating conditions without the formation of defluorinated by-products. The lack of by-products may result from the stability of the fluoromethyl–iridium complex against decomposition that involves β-fluoro elimination, particularly under neutral reaction conditions.[11]

In conclusion, we have found a novel and efficient iridium- or ruthenium-catalyzed reactions of trifluoromethylated compounds with alkenes without the formation of defluorinated by-products. The reaction is highly useful and will provide scope for finding other new types of catalytic reactions in fluorine chemistry.

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