Lewis acid-catalyzed tri- and difluoromethylation reactions of aldehydes†

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The first Lewis acid-catalyzed trifluoromethylation reactions of aldehydes with Me_3SiCF_3 under TiF_4/DMF, $Ti(O^iPr)_4$/DMF and $Cu(OAc)_2$/dppp/toluene conditions are described. We have successfully applied this methodology to the difluoromethylation of aldehydes using Me_3SiCF_2SePh, $Me_3SiCF_2P(O)OEt_2$ and Me_3SiCF_2SPh.

Lewis acid-promoted nucleophilic trifluoromethylation reactions using Ruppert's reagent, Me_3SiCF_3, have been a long-standing problem for more than 15 years in fluoroorganic chemistry, since the first report on the trifluoromethylation of aldehydes using tetrabutylammonium fluoride by Prakash *et al.*[1,2] A number of other nucleophilic catalysts,[3,4] such as cesium fluoride, alkoxides, acetates, Lewis bases and carbenes, *etc.*, have appeared to give high yields in this type of reaction. However, to our surprise, there are no reports of a successful catalytic trifluoromethylation reaction employing Lewis acids.[3n] In connection with our work on asymmetric synthesis of fluorine-containing organic compounds,[4,5] we strongly required a methodology for the Lewis acid-catalyzed trifluoromethylation reaction. It is highly likely that Ruppert's reagent would participate in a wide range of asymmetric trifluoromethylations *via* chiral a Lewis acid approach. Herein, we disclose our first step towards achieving this goal.

We began our work by examining the nucleophilic addition of Me_3SiCF_3 to 2-naphthaldehyde (**1a**) (Fig 1.), in DMF, in the presence of various Lewis acids (Table 1). The reaction using Lewis acids such as $SnCl_4$, BF_3/OEt, $TiCl_4$ and $Cu(OTf)_2$, successfully used in the conventional reaction of aldehydes with Me_3SiCN,[6] completely failed in our case, with only traces of the expected products being formed (Table 1, entries 1–5). To overcome this problem, a survey of a diverse range of Lewis acids was carried out. Among the many Lewis acids attempted (Table 1, entries 6–16), $Ti(O^iPr)_4$, TiF_4 and $MgCl_2$ proved to be very effective catalysts for the desired trifluoromethylation reaction (Table 1, entries 14–16). Since **2a**, in particular, was obtained in excellent yields within acceptable reaction times by $Ti(O^iPr)_4$ and TiF_4, we considered them to be the most suitable Lewis acids for the trifluoromethylation of various aldehydes (Table 1, entries 17–30). As can be seen from the data, the reaction was effective for a class of aldehydes. Non-enolizable aromatic aldehydes with electron-donating or electron-withdrawing groups (**1b–f**) and an enolizable aldehyde (**1h**) were trifluoromethylated smoothly to furnish the desired products in high yields. With unsaturated aldehyde **1g**, the 1,2-addition occurred exclusively to give allyl alcohol derivative **2g** in 98% yield (Table 1, entry 29).

Ligand-controlled trifluoromethylation reactions catalyzed by Lewis acids are the next point of interest. It is obvious from the general concept that the combination of a wide range of Lewis

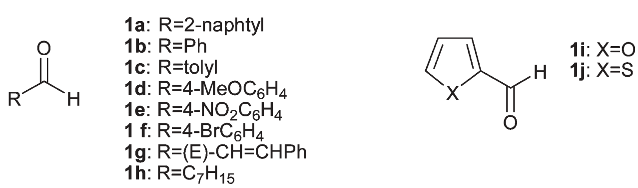

Fig. 1 Structures of the aldehydes.

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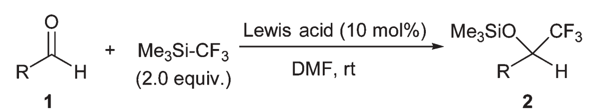
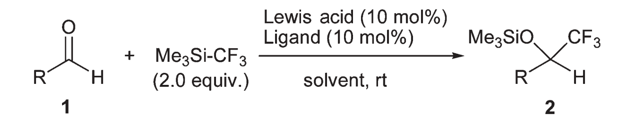
Table 1 Lewis acid-catalyzed trifluoromethylation of aldehydes



Entry	1	Lewis acid	Time/h	2	Yield (%)
1	**1a**	$SnCl_4$	24	**2a**	—
2	**1a**	$AlCl_3$	24	**2a**	—
3	**1a**	BF_3/Et_2O	24	**2a**	—
4	**1a**	$TiCl_4$	24	**2a**	—
5	**1a**	$Cu(OTf)_2$	24	**2a**	2
6	**1a**	$NiClO_4/6H_2O$	24	**2a**	7
7	**1a**	$Zn(OAc)_2$	24	**2a**	15
8	**1a**	$Pd(OAc)_2$	24	**2a**	19
9	**1a**	$Cu(OAc)_2$	24	**2a**	60
10	**1a**	AgF	24	**2a**	10
11	**1a**	ZnF_2	24	**2a**	23
12	**1a**	CuF_2	24	**2a**	33
13	**1a**	InF_3	24	**2a**	45
14	**1a**	TiF_4	4	**2a**	96
15	**1a**	$MgCl_2$	16	**2a**	91
16	**1a**	$Ti(O^iPr)_4$	2	**2a**	96
17	**1b**	TiF_4	4	**2b**	76
18	**1c**	TiF_4	4	**2c**	62
19	**1d**	TiF_4	19	**2d**	71
20	**1e**	TiF_4	19	**2e**	99
21	**1f**	TiF_4	2	**2f**	89
22	**1g**	TiF_4	4	**2g**	91
23	**1h**	TiF_4	19	**2h**	75
24	**1b**	$Ti(O^iPr)_4$	2	**2b**	89
25	**1c**	$Ti(O^iPr)_4$	0.5	**2c**	86
26	**1d**	$Ti(O^iPr)_4$	4	**2d**	99
27	**1e**	$Ti(O^iPr)_4$	4	**2e**	84
28	**1f**	$Ti(O^iPr)_4$	2	**2f**	90
29	**1g**	$Ti(O^iPr)_4$	4	**2g**	98
30	**1h**	$Ti(O^iPr)_4$	6	**2h**	67

Table 2 Ligand-controlled trifluoromethylation catalyzed by Lewis acids

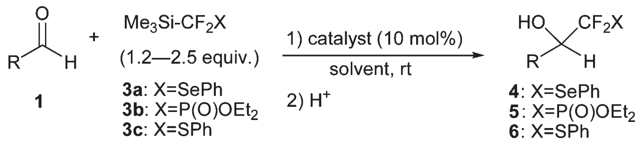


Entry	1	Lewis acid	Ligand	Solvent	Time/h	2	Yield (%)
1	**1a**	$Ti(O^iPr)_4$	—	CH_2Cl_2	24	**2a**	—
2	**1a**	$Ti(O^iPr)_4$	—	THF	24	**2a**	—
3	**1a**	$Ti(O^iPr)_4$	—	toluene	24	**2a**	—
4	**1a**	TiF_4	—	toluene	24	**2a**	—
5	**1a**	$MgCl_2$	—	toluene	24	**2a**	—
6	**1a**	CuF_2	—	toluene	24	**2a**	—
7	**1a**	$Cu(OAc)_2$	—	toluene	24	**2a**	—
8	**1a**	$Cu(OAc)_2$	dppe	toluene	1>	**2a**	99
9	**1a**	$Cu(OAc)_2$	dppe	CH_2Cl_2	14	**2a**	71
10	**1a**	$Cu(OAc)_2$	dppp	toluene	1>	**2a**	97
11	**1a**	$Cu(OAc)_2$	PPh_3	toluene	24	**2a**	—
12	**1a**	—	dppe	toluene	24	**2a**	—
13	**1a**	$Cu(OTf)_2$	dppe	toluene	24	**2a**	—
14	**1a**	$CuCl_2$	dppe	toluene	24	**2a**	—
15	**1a**	CuF_2	dppe	toluene	1>	**2a**	99
16	**1b**	$Cu(OAc)_2$	dppe	toluene	1	**2b**	96
17	**1c**	$Cu(OAc)_2$	dppe	toluene	0.5	**2c**	96
18	**1d**	$Cu(OAc)_2$	dppe	toluene	1	**2d**	93
19	**1e**	$Cu(OAc)_2$	dppe	toluene	1	**2e**	94
20	**1f**	$Cu(OAc)_2$	dppe	toluene	0.5	**2f**	92
21	**1g**	$Cu(OAc)_2$	dppe	toluene	2	**2g**	99
22	**1h**	$Cu(OAc)_2$	dppe	toluene	0.5	**2h**	95
23	**1i**	$Cu(OAc)_2$	dppe	toluene	1	**2i**	55
24	**1j**	$Cu(OAc)_2$	dppe	toluene	2	**2j**	99

acids with chiral ligands provides a very resourceful strategy for the discovery of catalytic enantioselective reactions over their non ligand-controlled counterparts.[7] In agreement with the initial report of Prakash *et al.*,[2a] we obtained identical results; *i.e.*, that Lewis acids are not effective promoters of trifluoromethylation in CH_2Cl_2, toluene and THF (Table 2, entries 1–7). These preliminary results implied that the expected ligand-controlled trifluoromethylation reaction catalyzed by a Lewis acid could be realized only in less polar solvents. We thus began to investigate whether a cocktail of a Lewis acid with a ligand could catalyze the trifluoromethylation reaction, and were pleased to find that the use of a catalytic amount of a bidentate phosphine ligand, along with $Cu(OAc)_2$, resulted in a significant promotion of the trifluoromethylation reaction (Table 2, entries 8 and 9). Namely, treatment of **1a** with 10 mol% of $Cu(OAc)_2$ in the presence of 1,2-bis(diphenylphosphino)ethane (dppe) in toluene cleanly afforded **2a** in >99% yield. Another bidentate phosphine, 1,3-bis(diphenylphosphino)propane (dppp), also gave a substantially good yield (Table 2, entry 10), whereas monodentate ligand PPh_3 did not work (Table 2, entry 11). Since dppe alone did not catalyze the reaction in toluene, even after stirring for 24 h (Table 2, entry 12), it does not compete with the Lewis base-catalyzed pathway, as described in the previous paper.[4a] Combinations of dppe and other Lewis acids were surveyed (Table 2, entries 13–15), and CuF_2 was also found to be effective in the reaction, furnishing **2a** in 99% yield (Table 2, entry 15).

To examine the efficacy of this catalyst cocktail with regards to the substrate structure, a variety of aromatic and aliphatic aldehydes were subjected to the optimized conditions; the results of which are summarized in Table 2. All reactions were completed within 2 h, and high yield conversions were achieved in both aromatic and aliphatic aldehydes including heteroaryl and unsaturated aldehydes (Table 2, entries 15–24).

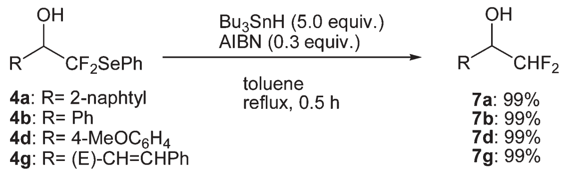
Table 3 Ligand-controlled difluoromethylation of aldehydes



Entry	1	3	Catalyst	Solvent	Time/h	4	Yield (%)
1	**1a**	**3a**[a]	$Ti(O^iPr)_4$	DMF	24	**4a**	—
2	**1a**	**3a**[a]	TiF_4	DMF	24	**4a**	—
3	**1a**	**3a**[a]	$Cu(OAc)_2$/dppe	toluene	24	**4a**	—
4	**1a**	**3a**[a]	$Cu(OAc)_2$/dppe	DMF	12	**4a**	17
5	**1a**	**3a**[b]	$Cu(OAc)_2$/dppe	DMF	20	**4a**	94
6	**1b**	**3a**[b]	$Cu(OAc)_2$/dppe	DMF	2	**4b**	99
7	**1d**	**3a**[b]	$Cu(OAc)_2$/dppe	DMF	3	**4d**	70
8	**1e**	**3a**[b]	$Cu(OAc)_2$/dppe	DMF	0.5	**4e**	94
9	**1g**	**3a**[b]	$Cu(OAc)_2$/dppe	DMF	2	**4g**	88
10	**1e**	**3b**[b]	$Cu(OAc)_2$/dppe	DMF	4	**5e**	78
11[c]	**1e**	**3c**[b]	$Cu(OAc)_2$/dppe	DMF	12	**6e**	60

[a] 1.2 equiv. of **3a** was used. [b] 2.5 equiv. of **3** was used. [c] The reaction was carried out at 85 °C.

Inspired by recent work of the Prakash[8a,b] and Uneyama[8c] groups, we finally turned our attention toward investigating the Lewis acid-catalyzed difluoromethylation reaction (Table 3). As well as trifluoromethyation, difluoromethyl substitution is another attractive tool in medicinal chemistry.[1] As the spatial size of the C–F group is larger than that of C–H and smaller than that of C–OH, CHF_2 is considered to be an adequate substituent for CHOH. Although several methodologies are available for the nucleophilic difluoromethylation reaction of aldehydes,[8,9] as far as we know, there is no precedent for a Lewis acid-catalyzed difluoromethylation reaction. Firstly, Me_3SiCF_2SePh (**3a**) was used as a difluoromethylating reagent.[9a] We were initially disappointed to find that an extension of the protocols optimized for trifluoromethylation reactions to develop difluoromethylation reactions were less successful. Reactions with **3a** (1.2 equiv.) under conditions such as TiF_4/DMF or $Ti(O^iPr)_4$/DMF did not occur at all (Table 3, entries 1 and 2). The use of a catalytic amount of $Cu(OAc)_2$ in the presence of dppe in toluene also gave no products (Table 3, entry 3). However, when $Cu(OAc)_2$/dppe was used as the catalyst in DMF, difluoro(phenylseleneny)methyl adduct **4a** was obtained in 17% yield, along with the starting **1a** (Table 3, entry 4). Since the low conversion was due to the instability of **3a**, the reaction of **1a** was next carried out using 2.5 equiv. of **3a** under $Cu(OAc)_2$/dppe/DMF conditions; the yield of **4a** dramatically increasing to 94% in the process (Table 3, entry 5). Other examples are shown in Table 3. A series of aldehydes were easily converted to the corresponding difluoro(phenylseleneny)methyl adducts **4** in high yields (Table 3, entries 5–9). It is worth noting that the described procedure can also be applied to difluoromethylation reactions with $Me_3SiCF_2P(O)OEt_2$[9b–d] and Me_3SiCF_2SPh[8b] (Table 3, entries 10 and 11), one of which leads to an example of the biologically interesting difluoromethylphosphate alcohols **5**.[10] Difluoromethylated **4** was deselenylated quantitatively to the corresponding difluoromethylated alcohol **7** under the normal radical conditions using Bu_3SnH/2,2′-azobis(isobutyronitrile) (AIBN)[9a] (Scheme 1).



Scheme 1 Radical deselenylation of **4**.

In conclusion, we have shown for the first time that Lewis acids, with or without ligands, can effectively catalyze the trifluoromethylation of various aldehydes with Me_3SiCF_3.‡ The conditions also provide an excellent methodology for difluoromethylation reactions, using Me_3SiCF_2X (X = SePh, P(O)OEt$_2$, SPh) as nucleophiles instead. The screening of chiral ligands for enantioselective fluoromethylation reactions is presently under investigation.

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‡ (a) Typical procedure for the Lewis acid-catalyzed trifluoromethylation of aldehydes: To a mixture of **1a** (30 mg, 0.19 mmol) and $Ti(O^iPr)_4$ (5.8 μL, 0.019 mmol) in DMF (0.6 mL) was added Me_3SiCF_3 (57 μL, 0.38 mmol) at room temperature. The reaction mixture was stirred for 2 h, followed by quenching with a saturated $NaHCO_3$ aqueous solution (5 mL). The mixture was extracted with ethyl acetate (2 × 5 mL), the combined organic phase dried with $MgSO_4$ and the solvent removed by evaporation. The residue was purified by silica gel column chromatography (hexane) to afford **2a** as a colorless solid (yield 96%).

(b) Typical procedure for ligand-controlled trifluoromethylation: A mixture of $Cu(OAc)_2$ (3.5 mg, 0.019 mmol), dppe (7.6 mg, 0.019 mmol) and toluene (0.6 mL) was stirred for 30 min at room temperature. To the stirred mixture was then added **1a** (30 mg, 0.19 mmol) and Me_3SiCF_3 (57 μL, 0.38 mmol). The reaction was complete in less than 1 h, and was followed by quenching with a saturated $NaHCO_3$ aqueous solution (5 mL). The mixture was extracted with ethyl acetate (2 × 5 mL), the combined organic phase dried with $MgSO_4$ and the solvent removed by evaporation. The residue was purified by silica gel column chromatography (hexane) to give **2a** (yield 99%).

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