

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 , $\text{Ti}(\text{O}^i\text{Pr})_4/\text{DMF}$ and $\text{Cu}(\text{OAc})_2/\text{dppp}/\text{toluene}$ conditions are described. We have successfully applied this methodology to the difluoromethylation of aldehydes using $\text{Me}_3\text{SiCF}_2\text{SePh}$, $\text{Me}_3\text{SiCF}_2\text{P}(\text{O})\text{OEt}_2$ and $\text{Me}_3\text{SiCF}_2\text{SPh}$.

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 $\text{Cu}(\text{OTf})_2$, 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), $\text{Ti}(\text{O}^i\text{Pr})_4$, 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 $\text{Ti}(\text{O}^i\text{Pr})_4$ 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

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	$\text{BF}_3/\text{Et}_2\text{O}$	24	2a	—
4	1a	TiCl_4	24	2a	—
5	1a	$\text{Cu}(\text{OTf})_2$	24	2a	2
6	1a	$\text{NiClO}_4/6\text{H}_2\text{O}$	24	2a	7
7	1a	$\text{Zn}(\text{OAc})_2$	24	2a	15
8	1a	$\text{Pd}(\text{OAc})_2$	24	2a	19
9	1a	$\text{Cu}(\text{OAc})_2$	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	$\text{Ti}(\text{O}^i\text{Pr})_4$	2	2a	96
17	1b	TiF_4	2	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	$\text{Ti}(\text{O}^i\text{Pr})_4$	2	2b	89
25	1c	$\text{Ti}(\text{O}^i\text{Pr})_4$	0.5	2c	86
26	1d	$\text{Ti}(\text{O}^i\text{Pr})_4$	4	2d	99
27	1e	$\text{Ti}(\text{O}^i\text{Pr})_4$	4	2e	84
28	1f	$\text{Ti}(\text{O}^i\text{Pr})_4$	2	2f	90
29	1g	$\text{Ti}(\text{O}^i\text{Pr})_4$	4	2g	98
30	1h	$\text{Ti}(\text{O}^i\text{Pr})_4$	6	2h	67

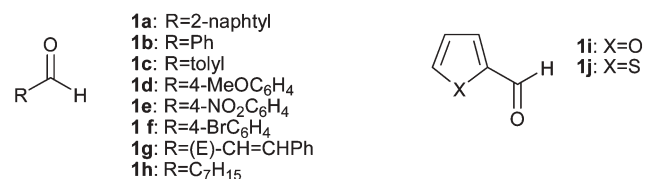


Fig. 1 Structures of the aldehydes.

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Table 2 Ligand-controlled trifluoromethylation catalyzed by Lewis acids

Entry	1	Lewis acid	Ligand	Solvent	Time/h	2	Yield (%)
1	1a	Ti(O ⁱ Pr) ₄	—	CH ₂ Cl ₂	24	2a	—
2	1a	Ti(O ⁱ Pr) ₄	—	THF	24	2a	—
3	1a	Ti(O ⁱ Pr) 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	>	2a	99
9	1a	Cu(OAc) ₂	dppe	CH ₂ Cl ₂	14	2a	71
10	1a	Cu(OAc) ₂	dppp	toluene	>	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	>	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 CH₂Cl₂, 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 PPh₃ 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 CuF₂ 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

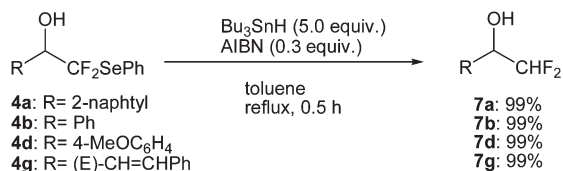
Table 3 Ligand-controlled difluoromethylation of aldehydes

Entry	1	3	Catalyst	Solvent	Time/h	4	Yield (%)
1	1a	3a ^a	Ti(O ⁱ Pr) 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 ^c	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.

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).

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 trifluoromethylation, 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, CHF₂ is considered to be an adequate substituent for CHO. 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, Me₃SiCF₂SePh (**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 TiF₄/DMF or Ti(OⁱPr)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(phenylselenenyl)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(phenylselenenyl)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 Me₃SiCF₂P(O)OEt₂^{9b–d} and Me₃SiCF₂SPh^{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 Bu₃SnH/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 Me₃SiCF₃.[‡] The conditions also provide an excellent methodology for difluoromethylation reactions, using Me₃SiCF₂X (X = SePh, P(O)OEt₂, 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(OⁱPr)₄ (5.8 μL, 0.019 mmol) in DMF (0.6 mL) was added Me₃SiCF₃ (57 μL, 0.38 mmol) at room temperature. The reaction mixture was stirred for 2 h, followed by quenching with a saturated NaHCO₃ aqueous solution (5 mL). The mixture was extracted with ethyl acetate (2 × 5 mL), the combined organic phase dried with MgSO₄ 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 Me₃SiCF₃ (57 μL, 0.38 mmol). The reaction was complete in less than 1 h, and was followed by quenching with a saturated NaHCO₃ aqueous solution (5 mL). The mixture was extracted with ethyl acetate (2 × 5 mL), the combined organic phase dried with MgSO₄ 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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