Gem-Difluoroallylation of Aldehydes and Ketones as a Convenient Route to α,α-Difluorohomoallylic Alcohols

Zhen-Yu Yang and Donald J. Burton*

Department of Chemistry, The University of Iowa, Iowa City, Iowa 52242

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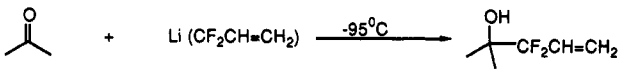
In the presence of zinc, 3-bromo-3,3-difluoropropene or 3-iodo-1,1-difluoropropene reacted with carbonyl compounds to give the corresponding α,α-difluorohomoallylic alcohols in good yields at 0 °C to room temperature. The reaction is applicable to aliphatic and aromatic aldehydes, dialkyl ketones, and alkyl aryl ketones. Reaction with α,β-unsaturated aldehydes and ketones yielded 1,2-adducts exclusively. However, the reaction could not be extended to esters and acyl chlorides. Other metals such as cadmium and tin could also be used to mediate gem-difluoroallylation. The regiochemistry of this reaction could be rationalized in terms of the more nucleophilic α-carbon of the *gem*-difluoroallyl intermediate.

Introduction

Profound changes in the biological effects of organic compounds are observed when the hydrogen atoms are replaced by fluorine.[1] In recent years, the introduction of the difluoromethylene functionality into organic compounds has proved attractive, due to the production of a molecule that may inhibit one or more enzymes or be partially metabolized into a more active substance.[2] It has been argued that the difluoromethylene group could be regarded as an isopolar–isosteric replacement for oxygen.[3] In addition, since such difluoromethylene-containing compounds exhibit biological stability,[4] the difluoromethylene functionality may prove particularly significant as a replacement for oxygen at a biochemically labile position.

The most widely used method for the introduction of this functionality has been the Reformatsky reaction employing halodifluoroacetates,[2,4,5] chlorodifluoromethyl ketones,[5g,6] and (bromodifluoromethyl)acetylene.[7] More recently, difluoroketene silyl acetals[8] and [(alkoxycarbonyl)difluoromethyl]copper[9] have also been utilized for the preparation of difluoromethylene-functionalized compounds. The gem-difluoroallylation of carbonyl compounds is analogous to these reactions, since the resulting gem-difluorohomoallylic alcohol can be readily converted to the aldol. Further, the allylation has significant advantages over Reformatsky type reactions, since the alkene may be oxidized to either an aldehyde[10] or an epoxide[11] or converted to a δ-lactone via hydroformylation.[12]

Allylation of carbonyl compounds has been extensively investigated with nonfluorinated precursors. It was reported that a variety of metals, such as lithium,[13] mangnesium,[13] cerium,[14] lead,[15] bismuth,[16] indium,[17] zinc,[18] tin,[19] cadmium,[20] and manganese,[21] mediated reactions of allyl halides with ketones and aldehydes. These reactions occurred under mild conditions and gave homoallyl alcohols in excellent yields; some of the allylations could proceed even in aqueous solution.[18b] In contrast to nonfluorinated allylation, there exist few reports of gem-difluoroallylation. Seyferth generated (*gem*-difluoroallyl)lithium by either lithium–halogen exchange[22] of 3-bromo-3,3-difluoropropene or metal exchange[23] of tributyl(difluoroallyl)tin with butyllithium at low temperature (−95 °C). Although this procedure gave reasonable yields with dialkyl ketones, aryl alkyl ketones, and aliphatic aldehydes, low yields of gem-difluorohomoallylic alcohols were obtained with aromatic aldehydes and α,β-unsaturated aldehydes, due to the competitive reaction of butyllithium with these carbonyl compounds. Hiyama obtained somewhat better results



by generation of the gem-difluoroallylic anion via reaction of (α,α-difluoroallyl)silane[24] or (γ,γ-difluoroallyl)silane[25]

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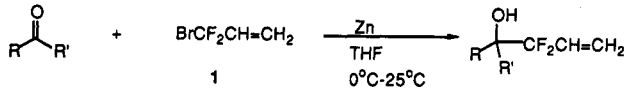
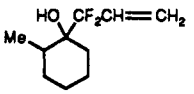
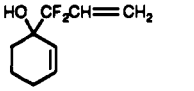
Table I. Gem-Difluoroallylation of Aldehydes and Ketones



no.	R	R′	product	yield,[a] %
3	C_6H_5	H	$C_6H_5CH(OH)CF_2$-CH=CH_2	67
4	n-C_6H_{13}	H	n-$C_6H_{13}CH(OH)$-CF_2CH=CH_2	53
5	n-C_5H_{11}	H	n-$C_5H_{11}CH(OH)$-CF_2CH=CH_2	47
6	C_6H_5CHMe	H	$C_6H_5CHMeCH(OH)$-CF_2CH=CH_2	47
7	i-Bu	Me	i-BuC(OH)(Me)-CF_2CH=CH_2	55
8	C_6H_5	Me	$C_6H_5C(OH)(Me)$-CF_2CH=CH_2	45
9	C_6H_5	CF_3	$C_6H_5C(OH)(CF_3)CF_2$-CH=CH_2	73
10	p-MeC_6H_4	CF_3	p-$MeC_6H_4C(OH)(CF_3)$-CF_2CH=CH_2	69
11	$-(CH_2)_5-$		c-$C_6H_{10}(OH)CF_2$-CH=CH_2	67
12	$-(CH_2)_4CH(Me)-$			41
13	Me_2C=$CH(CH_2)_2$	CH_3	Me_2C=$CHCH_2$-$CH_2C(OH)(Me)CF_2$-CH=CH_2	54
14	$-(CH_2)_3CH$=$CH-$			46(44)[b]
15	C_6H_5CH=CH	H	C_6H_5CH=$CHCH(OH)$-CF_2CH=CH_2	75

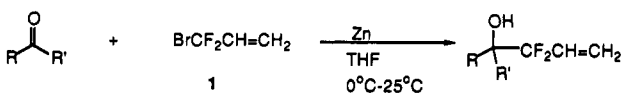
[a] Isolated yields are based on aldehydes or ketones. [b] Reaction was carried out in the presence of cuprous iodide.

with fluoride or *tert*-butoxide ion in the presence of carbonyl substrates. However, this method necessitated the prior preparation of the requisite (difluoroallyl)silanes.

In a preliminary communication[26] we briefly described a direct gem-difluoroallylation of aldehydes and ketones via the in situ reaction of 3-bromo-3,3-difluoropropene with acid-washed zinc powder. This methodology avoids the utilization of the thermally unstable lithium intermediate, the problem of the competitive reaction of carbonyl substrates with butyllithium, and the prior preparation of (difluoroallyl)silanes. We now report in detail results of the synthesis of various gem-difluorohomoallylic alcohols.

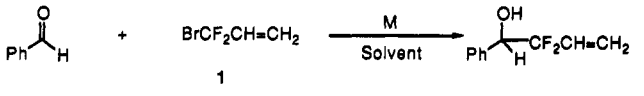
Results and Discussion

The most convenient allylation of aldehydes and ketones with nonfluorinated allyl halides was mediated by zinc.[18] Accordingly, we found that gem-difluoroallylation of a variety of aldehydes with 3-bromo-3,3-difluoropropene (1) in the presence of zinc gave the corresponding α,α-difluorohomoallylic alcohols in good yields. The results of these reactions are summarized in Table I.



Spectroscopic analysis of the products indicated that only the CF_2 terminus of 1 attacked the carbon of the carbonyl group. Attack at the CF_2 terminus and/or CH_2 terminus of 1 are easily distinguished by virtue of the differences in the IR and ^{19}F NMR spectra. For example, upon reaction of 1 with benzaldehyde and zinc in THF, one signal in the FT-IR spectrum appears as a weak CH=CH_2 absorption at 1653 cm^{-1}, indicating CF_2-terminus attack. Conversely, in the CH_2-terminus-attacked product a typical fluorinated alkenyl (C=CF_2) strong absorption should be observed at 1750 cm^{-1}. Also, the ^{19}F NMR spectrum of the CF_2-terminus-attacked product exhibits a characteristic AB doublet of triplets at −107.3 and −110.7 ppm ($^2J_{F,F}$ = 249 Hz, $^3J_{F,H}$ = 10 Hz). The appearance of this AB pattern is due to attachment of the difluoromethylene moiety to a chiral center.

Table II. Reaction of 1 with Benzaldehyde and Metals



entry	M	solvent	T, °C	t, h	yield,[a] %
1	Zn	THF	0–25	10	67[b]
2	Sn	THF	25	15	67[b]
3	10 mol % of $SnCl_2$ + Al	EtOH/AcOH/H_2O	60	20	56
4	Cd	THF	25	15	0
5	Cd	THF	67	30	30
6	Cd	DMF	25	4	75[b]
7	Mn	THF	25	20	0
8	Mn	DMF	25–70	20	0

[a] ^{19}F NMR yields vs $CF_3C_6H_5$. [b] Isolated yields.

Ketones also proved to be efficacious reaction substrates. Little or no qualitative difference was observed among the reactions of 1 with aldehydes and ketones; compare entries 3, 7, and 8 (Table I). Ketones containing electron-withdrawing groups (entries 9 and 10) gave higher yields of the difluorohomoallyl alcohols, presumably due to enhanced electrophilicity of the carbonyl carbon.

Zinc-mediated addition of 1 to α,β-unsaturated aldehydes and ketones gave exclusive formation of the 1,2-addition product; no 1,4-addition product was observed. For example, when 2-cyclohexenone was treated with 1, 46% of the 1,2-addition product was isolated, even when cuprous iodide was used as a catalyst. The structural assignment for the product was based on ^1H NMR and FT-IR. The ^1H NMR spectrum showed signals ranging from 6.01 to 5.45 ppm which integrated for five vinyl protons. FT-IR spectroscopy exhibited the OH group at 3611 cm^{-1} and two sets of double-bond absorptions at 1690 and 1653 cm^{-1}, respectively. Similarly, the reaction with cinnamaldehyde afforded the corresponding alcohol in 75% yield.

Other carbonyl substrates such as methyl benzoate or benzoyl chloride failed to give α,α-difluorohomoallylated products under the same conditions.

As illustrated in Table II, cadmium and tin also could be used to effect difluoroallylation of carbonyl substrates with 1. Upon reaction with benzaldehyde in the presence of cadmium in DMF at room temperature, 75% of 3 was obtained. A similar reaction with cadmium in THF indicated that a low yield of 3 was formed. The tin metal mediated reaction of benzaldehyde with 1 gave a 67% yield of alcohol 3 in THF. Interestingly, in the presence of aluminum and catalytic amounts of tin dichloride, which has been reported to generate tin metal in situ,[27] the reaction could be carried out in protic solvents. For example, when 1 reacted with benzaldehyde in the presence of tin

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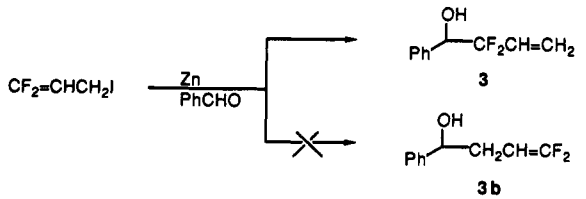
dichloride and aluminum in water, ethanol, and acetic acid in a 1:1:2 ratio at 60 °C, **3** was formed in 56% yield. In either THF or DMF at room temperature to 70 °C, manganese failed to react with **1**.

In other work, it has been clearly demonstrated that (γ,γ-difluoroallyl)tributyltin gave α,α-difluorohomoallyl alcohols when treated with butyllithium at −95 °C in the presence of carbonyl substrates.[23] No other regioisomer was observed. Similarly, the reaction of (γ,γ-difluoroallyl)silane with aldehydes or ketones and fluoride ion yielded exclusively α,α-difluorohomoallyl alcohols.[25] Thus, the same intermediate is produced from either the (α,α- or γ,γ-difluoroallyl)silane.[24,25] It remained to be determined whether or not the same intermediate would be similarly produced from the 1,1-difluoro-3-iodopropene and **1** with carbonyl substrates in the presence of zinc.

Halogen exchange between alkyl bromides and sodium iodide in acetone is well documented in the literature. Recently, Fried reported that 1-bromo-1,1-difluoro-2-alkynes reacted with sodium iodide to give 1-iodo-1,1-difluoro-2-alkynes in good yields.[28] Similarly, we found that when **1** was treated with sodium iodide in acetone, it afforded the S_N2' product, 1,1-difluoro-3-iodopropene (**2**) as the major product and 3,3-difluoro-3-iodopropene (**2b**) as the minor product (**2**:**2b** = 23:1). When the crude product mixture was distilled, isomerization was not observed. On the other hand, 1,1-difluoro-3-bromopropene has been reported to undergo isomerization to form **1** upon slow distillation.[22]

$$\underset{\mathbf{1}}{BrCF_2CH{=}CH_2} + NaI \rightarrow \underset{\mathbf{2}}{CF_2{=}CHCH_2I} + \underset{\mathbf{2b}}{ICF_2CH{=}CH_2}$$

Upon reaction of a mixture of **2** and **2b** with benzaldehyde and zinc in THF at room temperature for 2 h, only one regioisomeric product, **3**, was obtained, in 61% yield. No **3b** was either observed in the reaction mixture by ^{19}F NMR spectroscopic analysis or detected in the isolated product. This result demonstrated the formation of the same active intermediate in gem-difluoroallylation with **1** and **2**.



In all products formed in the reaction of **1** and **2** with carbonyl compounds in the presence of zinc, it was found that the CF_2 terminus attacks the carbon of the carbonyl group exclusively. This result is similar to the results reported by Seyferth[22,23] and Hiyama.[24,25] In order to explain the regioselectivity in the reaction of (*gem*-difluoroallyl)lithium with carbonyl compounds, Seyferth proposed that the lithium ion would coordinate to the CH_2 terminus where the negative charge would be the greatest, and would block the CH_2 terminus from attack by an electrophile relative to the "free" CF_2 terminus. Although Seyferth's hypothesis could explain the regioselectivity of the (*gem*-difluoroallyl)lithium reaction, this rationalization cannot be applied to either Hiyama's work[24,25] or our work. Based on Seyferth's proposal, reaction of a lithium-free difluoroallylic intermediate with carbonyl substrates would give the γ,γ-difluorohomoallyl alcohol due to the greater negative charge of the CH_2 terminus of the *gem*-difluoroallyl species without the lithium block. The opposite results, however, have been described by Hiyama,[24,25] who generated, in situ, the "free" gem-difluoroallylic anion from the reaction of (α,α- or γ,γ-difluoroallyl)silane with a catalytic amount of KO^{t}Bu or TASF. This gem-difluoroallylic anion gave α,α-difluorohomoallylic alcohols exclusively with aldehydes and ketones. Similarly, from either **1** or **2** only the CF_2-terminus-attacked products are obtained, suggesting that the capture of the CF_2 terminus of the difluoroallylic anion also occurs in the zinc-mediated reactions of **1** or **2**.

In related work with (*gem*-dichloroallyl)lithium and carbonyl substrates, Seyferth invoked the HSAB theory to explain the regioselectivity observed with various ketones.[29] For example, with hard electrophiles, such as trifluoroacetophenone, the carbon of the carbonyl group was attacked by only the CH_2 terminus of the *gem*-dichloroallyl species due to its greater electron density compared to the CCl_2 terminus. On the other hand, upon reaction with softer electrophiles, such as dialkyl ketones, the CCl_2 terminus attacked the carbon atom of the carbonyl exclusively. It might be expected then that the two termini of the *gem*-difluoroallyl intermediate would exhibit similar discrimination with hard electrophiles. However, with both trifluoroacetophenone and *p*-tolyl trifluoromethyl ketone (entries 9 and 10 in Table I), **1** and zinc gave exclusively α,α-difluorohomoallyl alcohols. Thus, in all cases only capture of the CF_2 terminus of **1** is observed.

Our experimental results are in agreement with Tonachini's recent theoretical description,[30] in which the electron distribution and HOMO polarization induced the reaction of both (*gem*-difluoroallyl)lithium and the free gem-difluoroallylic anion with both hard and soft electrophiles to give α-selective products (CF_2-terminus capture). The α-selectivity is due to the pyramidal structure of the *gem*-difluoroallyl intermediate, which is more stable than the planar structure. The negative charge in the intermediate resides at the α-carbon (CF_2 site). Thus, the regiochemistry of gem-difluoroallylation can be rationalized in terms of attack of the more nucleophilic α-carbon of the *gem*-difluoroallyl intermediate.

In conclusion, we present a convenient and practical regiospecific synthesis of a variety of α,α-difluorohomoallylic alcohols. This reaction offers a new method for the introduction of the difluoromethylene functionality into organic compounds under mild conditions, and it is proposed that the greater nucleophilicity of the CF_2 terminus of the *gem*-difluoroallyl intermediate renders it more susceptible to electrophilic attack.

Experimental Section

General. All the reactions were performed in an oven-dried apparatus that consisted of a two- or three-necked flask equipped with an addition funnel, a Teflon-coated magnetic stir bar, and a reflux condenser connected to a nitrogen source and mineral oil bubbler. All boiling points were determined during fractional distillation using a partial immersion thermometer and are uncorrected. ^{19}F NMR and ^1H NMR spectra were recorded on a 90-MHz multinuclear spectrometer. All chemical shifts are reported in parts per million downfield (positive) of the standard. ^{19}F NMR spectra are referenced against internal $CFCl_3$ and ^1H NMR spectra against internal tetramethylsilane. FT-IR spectra and IR spectra were recorded as CCl_4 solutions using a solution cell with a 0.1-cm path length. GC–MS spectra were obtained

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at 70 eV, in the electron-impact mode. GLPC analyses were performed on a 5% OV-101 column with thermal conductivity detector.

Materials. Tetrahydrofuran (THF) was purified by distillation from sodium benzophenone ketyl. Dimethylformamide (DMF) was distilled at reduced pressure from calcium hydride. Zinc (325 mesh), cadmium (100 mesh), and tin (100 mesh) were obtained from Aldrich Chemical Co., activated by washing with dilute hydrochloric acid, and dried in vacuo at room temperature. Tin dichloride, sodium iodide, and aluminum were obtained from Aldrich Chemical Co. and used without purification. All carbonyl compounds were distilled prior to use. 3-Bromo-3,3-difluoropropene was obtained from Japan Halon Co.

Representative General Procedure for the Preparation of α,α-Difluorohomoallylic Alcohol. Preparation of 2,2-Difluoro-1-phenyl-3-buten-1-ol (3). A heterogeneous solution of 2.6 g (40 mmol) of acid-washed zinc powder, 2.1 g (20 mmol) of benzaldehyde, and 20 mL of THF was cooled to 0 °C in an ice water bath, and a mixture of 3.3 g (21 mmol) of 3-bromo-3,3-difluoropropene (1) and 10 mL of THF was slowly added via an additional funnel. After the addition was completed, the reaction mixture was warmed with stirring to room temperature and then stirred at room temperature overnight. Then, 30 mL of 5% aqueous hydrochloric acid was added to the reaction mixture, which was stirred for 5 min. Excess zinc was removed by suction filtration and washed with 30 mL of ether. The organic layer was separated. The aqueous layer was extracted with ether (2 × 50 mL), and the ether extracts were combined with the organic layer, which was washed with saturated sodium bicarbonate solution (50 mL) and water (2 × 50 mL), and then dried over $MgSO_4$. After evaporation of the solvents, the residue (3.4 g) was distilled to give 2.5 g (67%) of **3**,[22b,25b] bp 56–57 °C/0.5 mmHg, 99% GLPC purity. ^{19}F NMR ($CDCl_3$): −107.3 (dt, $^2J_{F,F}$ = 249 Hz, $^3J_{F,H}$ = 10 Hz, 1 F), −110.7 (dt, $^2J_{F,F}$ = 249 Hz, $^3J_{F,H}$ = 10 Hz, 1 F). ^1H NMR ($CDCl_3$): 7.34 (s, 5 H), 5.82–5.33 (m, 3 H), 4.83 (t, $^3J_{F,H}$ = 10 Hz, 1 H), 2.84 (br, 1 H). FT-IR (CCl_4): 3619 (s), 3033 (s), 1653 (w), 1150 (s), 1060 (s), 997 (s), 983 (s). MS: 184 (M^+, 0.3), 108 (7.5), 107 (100), 79 (67.3), 77 (47.2), 51 (11.9).

Preparation of 3,3-Difluoro-1-decen-4-ol (4). Similarly, **4** was prepared from 2.6 g (40 mmol) of zinc, 2.3 g (20 mmol) of heptanal, and 3.3 g (21 mmol) of 1 in 30 mL of THF. Usual workup of the reaction mixture gave a residue, which was distilled to give 2.0 g (53%) of **4**, bp 92–95 °C/5 mmHg, and 2.1 g of a mixture of higher boiling, non-fluorine-containing materials. ^{19}F NMR ($CDCl_3$): −108.6 (dt, $^2J_{F,F}$ = 249 Hz, $^3J_{F,H}$ = 10 Hz, 1 F), −113.2 (dt, $^2J_{F,F}$ = 249 Hz, $^3J_{F,H}$ = 10 Hz, 1 F). ^1H NMR ($CDCl_3$): 6.18–5.45 (m, 3 H), 3.73 (m, 1 H), 2.20 (s, 1 H), 1.50–1.31 (m, 10 H), 0.89 (m, 3 H). IR (CCl_4): 3580 (s), 2900 (s), 1700 (m), 1170 (s), 1060 (s), 985 (s). MS: 149 ($M^+ - C_3H_7$, 0.2), 115 (19.4), 97 (74.2), 77 (14.0), 69 (21.4), 57 (9.6), 55 (100), 43 (21.1), 41 (15.5).

Preparation of 3,3-Difluoro-1-nonen-4-ol (5). Similarly, **5** was prepared from 4.6 g (70 mmol) of zinc, 3.0 g (30 mmol) of hexanal, and 5.5 g (35 mmol) of 1. Usual workup of the reaction mixture gave a residue, which was distilled to give 2.5 g (47%) of **5**, bp 62–64 °C/2 mmHg, and 3.4 g of a mixture of higher boiling, non-fluorine-containing materials. ^{19}F NMR ($CDCl_3$): −108.5 (dt, $^2J_{F,F}$ = 249 Hz, $^3J_{F,H}$ = 10 Hz, 1 F), −133.1 (dt, $^2J_{F,F}$ = 249 Hz, $^3J_{F,H}$ = 10 Hz, 1 F). ^1H NMR ($CDCl_3$): 5.97–5.46 (m, 3 H), 3.71 (m, 1 H), 2.30 (s, 1 H), 1.47–1.31 (m, 8 H), 0.90 (t, $^3J_{H,H}$ = 6 Hz, 3 H). FT-IR (CCl_4): 3619 (s), 2957 (s), 1660 (w), 1121 (s), 1079 (s), 987 (s). MS: 101 ($M^+ - CF_2CH{=}CH_2$, 33.0), 84 (7.7), 83 (96.8), 77 (17.6), 59 (9.3), 57 (14.4), 51 (8.3), 55 (100), 43 (14.0), 41 (24.0).

Preparation of 4,4-Difluoro-2-phenyl-5-hexen-3-ol (6). Similarly, **6** was prepared from 2.6 g (40 mmol) of zinc, 2.7 g (20 mmol) of 2-phenylpropanal, and 3.3 g (21 mmol) of 1. Usual workup gave a residue, which was distilled to give 2.0 g (47%) of **6**, bp 92–96 °C/2 mmHg. ^{19}F NMR ($CDCl_3$): −105.8 (dt, $^2J_{F,F}$ = 251 Hz, $^3J_{F,H}$ = 10 Hz, 1 F), −109.5 (dt, $^2J_{F,F}$ = 251 Hz, $^3J_{F,H}$ = 10 Hz, 1 F). ^1H NMR ($CDCl_3$): 7.23 (s, 5 H), 6.07–5.34 (m, 3 H), 3.88 (td, $^3J_{F,H}$ = 10 Hz, $^3J_{H,H}$ = 6 Hz, 1 H), 3.05 (m, 1 H), 2.41 (s, 1 H), 1.33 (d, $^3J_{H,H}$ = 7 Hz, 3 H). FT-IR (CCl_4): 3620 (s), 3031 (m), 1653 (m), 1420 (s), 1063 (s), 984 (s). MS: 212 (M^+, 1.5), 135 (28.6), 105 (100), 77 (28.6), 43 (18.2).

Preparation of 3,3-Difluoro-4,6-dimethyl-1-hepten-4-ol (7). Similarly, **7** was prepared from 2.6 g (40 mmol) of zinc, 2.0 g (20 mmol) of 4-methyl-2-pentanone, and 3.3 g (21 mmol) of 1. Usual workup gave a residue, which was distilled to give 2.0 g (55%) of **7**, bp 64–66 °C/8 mmHg. ^{19}F NMR ($CDCl_3$): −114.7 (d, $^3J_{F,H}$ = 10 Hz). ^1H NMR ($CDCl_3$): 6.04–5.46 (m, 3 H), 2.16–1.77 (m, 1 H), 1.80 (s, 1 H), 1.46 (d, $^3J_{H,H}$ = 7 Hz, 2 H), 1.28 (s, 3 H), 1.01 (d, $^3J_{H,H}$ = 6 Hz, 3 H), 0.97 (d, $^3J_{H,H}$ = 6 Hz, 3 H). IR (CCl_4): 3580 (s), 2930 (s), 1220 (s), 1165 (s), 1050 (s), 990 (s). MS: 177 ($M^+ - 1$, 0.3), 121 (9.3), 102 (9.1), 101 (100), 83 (13.7), 77 (26.0), 73 (14.0), 59 (39.0), 57 (38.3), 51 (11.8), 43 (38.0), 41 (16.7).

Preparation of 3,3-Difluoro-2-phenyl-4-penten-2-ol (8). Similarly, **8** was prepared from 3.3 g (50 mmol) of zinc, 2.4 g (20 mmol) of phenyl methyl ketone, and 3.9 g (25 mmol) of 1 at room temperature. Usual workup gave a residue, which was distilled to give 1.8 g (45%) of **8**,[22b] bp 88–90 °C/2 mmHg. ^{19}F NMR ($CDCl_3$): −109.6 (dd, $^2J_{F,F}$ = 244 Hz, $^3J_{F,H}$ = 10 Hz, 1 F), −113.3 (dd, $^2J_{F,F}$ = 244 Hz, $^3J_{F,H}$ = 10 Hz, 1 F). ^1H NMR ($CDCl_3$): 7.30 (s, 5 H), 5.90–5.30 (m, 3 H), 2.36 (s, 1 H), 1.65 (s, 3 H). FT-IR (CCl_4): 3614 (s), 3064 (w), 1228 (s), 1142 (s), 1099 (s), 1044 (s), 999 (s). MS: 122 ($M^+ + 1 - CF_2CH{=}CH_2$, 8.8), 121 (100), 105 (8.2), 77 (27.2), 51 (13.0), 43 (82.5).

Preparation of 1,1,1,3,3-Pentafluoro-2-phenyl-4-penten-2-ol (9). Similarly, **9** was prepared by the general procedure from 4.6 g (70 mmol) of zinc, 5.2 g (30 mmol) of trifluoroacetophenone, and 5.5 g (35 mmol) of 1. Usual workup gave a residue, which was distilled to give 5.5 g (73%) of **9**, bp 87–89 °C/6 mmHg. ^{19}F NMR ($CDCl_3$): −73.9 (t, $^4J_{F,F}$ = 12 Hz, 3 F), −109.3 (m, 2 F). ^1H NMR ($CDCl_3$): 7.63 (s, 2 H), 7.39 (m, 3 H), 5.78–5.32 (m, 3 H), 3.33 (s, 1 H). IR (CCl_4): 3575 (s), 3020 (m), 1670 (w), 1550 (m), 1270–1160 (vs), 980 (s). MS: 252 (M^+, 0.6), 176 (8.4), 175 (95.2), 127 (17.5), 106 (8.1), 105 (100), 77 (31.6), 69 (7.5), 51 (8.1).

Preparation of 1,1,1,3,3-Pentafluoro-2-(4-methylphenyl)-4-penten-2-ol (10). Similarly, **10** was prepared from 4.6 g (70 mmol) of zinc, 5.6 g (30 mmol) of *p*-tolyl trifluoromethyl ketone, and 5.5 g (35 mmol) of 1. Usual workup gave a residue, which was distilled to give 5.4 g (69%) of **10**, bp 80–84 °C/2 mmHg. ^{19}F NMR ($CDCl_3$): −73.8 (t, $^4J_{F,F}$ = 12 Hz, 3 F), −109.3 (m, 2 F). ^1H NMR ($CDCl_3$): 7.55 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 7.20 (d, $^3J_{H,H}$ = 8 Hz, 2 H), 5.79–5.38 (m, 3 H), 3.22 (s, 1 H), 2.36 (s, 3 H). IR (CCl_4): 3570 (s), 3000 (m), 2920 (m), 1520 (m), 1270–1160 (s), 1095 (s). MS: 266 (M^+, 0.5), 190 (8.8), 189 (84.3), 141 (7.6), 120 (9.5), 119 (100), 91 (32.1), 77 (11.9), 65 (7.6).

Preparation of 1-(1,1-Difluoro-2-propenyl)cyclohexanol (11). Similarly, **11** was prepared by the general procedure from 22.7 g (350 mmol) of zinc, 19.6 g (200 mmol) of cyclohexanone, and 36.0 g (210 mmol) of 1. Usual workup gave a residue, which was distilled to give 23.6 g (67%) of **11**,[22b] bp 62–62 °C/2 mmHg. ^{19}F NMR ($CDCl_3$): −116.2 (d, $^3J_{F,H}$ = 12 Hz). ^1H NMR ($CDCl_3$): 6.02–5.44 (m, 3 H), 1.91 (s, 1 H), 1.90–1.56 (m, 10 H). FT-IR (CCl_4): 3604 (s), 2941 (s), 1224 (s), 1094 (s), 996 (s). MS: 176 (M^+, 2.8), 175 (27.3), 99 (2.1), 81 (7.9), 77 (100), 55 (21.3).

Preparation of 1-(1,1-Difluoro-2-propenyl)-2-methylcyclohexanol (12). Similarly, **12** was prepared from 2.6 g (40 mmol) of zinc, 2.2 g (20 mmol) of 2-methylcyclohexanone, and 3.3 g (21 mmol) of 1. Usual workup gave a residue, which was distilled to give 1.5 g (41%) of **12**, bp 65–67 °C/1.5 mmHg. ^{19}F NMR ($CDCl_3$): −108.0 (dd, $^2J_{F,F}$ = 244 Hz, $^3J_{F,H}$ = 10 Hz, 1 F), −111.5 (dd, $^2J_{F,F}$ = 244 Hz, $^3J_{F,H}$ = 10 Hz, 1 F). ^1H NMR ($CDCl_3$): 6.12–5.41 (m, 3 H), 2.20–1.46 (m, 10 H), 0.95 (d, $^3J_{H,H}$ = 6 Hz, 3 H). FT-IR (CCl_4): 3609 (s), 2941 (s), 1217 (s), 1152 (s), 1091 (s). MS: 175 ($M^+ - CH_3$, 0.1), 114 (8.0), 113 (100), 95 (78.6), 77 (16.2), 69 (15.8), 67 (14.6), 55 (11.6), 43 (9.4), 41 (9.0).

Preparation of 3,3-Difluoro-4,8-dimethyl-1,7-nonadien-4-ol (13). Similarly, **13** was prepared from 2.6 g (40 mmol) of zinc, 2.5 g (20 mmol) of 6-methyl-5-hepten-2-one, and 3.3 g (21 mmol) of 1. Usual workup gave a residue, which was distilled to give 2.2 g (54%) of **13**, bp 76–77 °C/2 mmHg. ^{19}F NMR ($CDCl_3$): −113.4 (d, $^3J_{F,H}$ = 10 Hz). ^1H NMR ($CDCl_3$): 5.99–5.40 (m, 3 H), 2.16–1.89 (m, 5 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.26 (s, 3 H). IR (CCl_4): 3585 (s), 2925 (s), 1680 (w), 1550 (m), 1200 (s), 1100 (s), 1060 (s). MS: 204 (M^+, 0.3), 186 (4.7), 110 (0.5), 109 (100), 77 (12.5), 69 (75.3), 67 (20.5), 55 (14.7), 43 (32.6), 41 (26.9).

Preparation of 1-(1,1-Difluoro-2-propenyl)-2-cyclohexen-1-ol (14). Similarly, **14** was prepared from 4.5 g (70 mmol) of zinc, 2.9 g (30 mmol) of 2-cyclohexenone, and 5.5 g (35 mmol) of 1. Usual workup gave a residue, which was distilled to give 2.4 g (46%) of **14**, bp 65–67 °C/2 mmHg. ^{19}F NMR ($CDCl_3$): −112.5

(dd, $^2J_{F,F}$ = 247 Hz, $^3J_{F,H}$ = 10 Hz, 1 F), -116.6 (dd, $^2J_{F,F}$ = 247 Hz, $^3J_{F,H}$ = 10 Hz, 1 F). ^{1}H NMR ($CDCl_3$): 6.01-5.42 (m, 5 H), 2.13 (s, 1 H), 2.03-1.05 (m, 6 H). FT-IR (CCl_4): 3611 (s), 2946 (s), 1689 (m), 1653 (w), 1169 (s), 1072 (s). MS: 156 ($M^+ - H_2O$, 0.1), 97 (100), 79 (17.7), 77 (16.8), 67 (9.4).

Reaction of 1 with 2-Cyclohexenone and Zinc in the Presence of Cuprous Iodide. Similarly, reaction of 5.5 g (35 mmol) of 1, 2.9 g (30 mmol) of 2-cyclohexenone, 4.5 g (70 mmol) of zinc, and 0.7 g (3.5 mmol) of cuprous iodide in 30 mL of THF at room temperature for 4.5 h gave a residue, which was distilled to give 2.3 g (44%) of **14**.

Preparation of 4,4-Difluoro-1-phenyl-1,5-hexadien-3-ol (15). Similarly, **15** was prepared from 3.6 g (55 mmol) of zinc, 4.0 g (30 mmol) of cinnamaldehyde, and 5.5 g (35 mmol) of 1. Usual workup gave a residue, which was purified by column chromatography (silica gel, 200-425 mesh; hexane/ethyl acetate, 8:2) to afford 4.7 g (75%) of **15**.[25b] ^{19}F NMR ($CDCl_3$): -107.7 (dt, $^2J_{F,F}$ = 247 Hz, $^3J_{F,H}$ = 10 Hz, 1 F), -111.5 (dt, $^2J_{F,F}$ = 249 Hz, $^3J_{F,H}$ = 10 Hz, 1 F). ^{1}H NMR ($CDCl_3$): 7.28 (s, 5 H), 6.85-5.45 (m, 5 H), 4.44 (m, 1 H), 2.69 (s, 1 H). IR (CCl_4): 3580 (s), 3030 (m), 1650 (w), 1550 (s), 1165 (s), 1080 (s). MS: 211 (M^+ + 1, 0.3), 210 (M^+, 1.6), 133 (100), 115 (34.7), 105 (8.5), 103 (11.8), 77 (20.3), 55 (13.4), 51 (7.8).

Reaction of 1 with Benzaldehyde and Cadmium or Tin. Similarly, reaction of 3.1 g (20 mmol) of 1 with 4.2 g (40 mmol) of benzaldehyde and 4.4 g (40 mmol) of cadmium (**CAUTION: Toxic!**) in 30 mL of DMF at room temperature overnight gave a residue, which was distilled to give 2.7 g (75%) of **3**.

Similarly, reaction of 3.1 g (20 mmol) of 1, 4.2 g (40 mmol) of benzaldehyde, and 4.7 g (40 mmol) of tin in 20 mL of THF at room temperature gave 2.5 g (67%) of **3**.

Reaction of 1 with Benzaldehyde and Tin Dichloride in the Presence of Aluminum. A flask fitted with a stir bar and a nitrogen inlet was charged with 0.57 g (3 mmol) of tin dichloride, 0.87 g (30 mmol) of aluminum, 0.5 mL of acetic acid, 2.5 mL of water, and 5 mL of ethanol. The reaction mixture was stirred for 10 min, and then 1.6 g (15 mmol) of benzaldehyde and 4.7 g (30 mmol) of 1 were added via syringe. The resultant mixture was stirred at room temperature for 20 h. ^{19}F NMR (vs $PhCF_3$) indicated the formation of **3** in 56% yield.

Preparation of 1,1-Difluoro-3-iodopropene (2). A flask fitted with a stir bar and an isopropyl alcohol condenser with nitrogen inlet was charged with 11.3 g (75 mmol) of sodium iodide and 25 mL of acetone. After a Neslab Cryocool 100 was used to cool the isopropyl alcohol to -40 °C, 7.8 g (50 mmol) of 1 was added via a syringe and the mixture was stirred at room temperature for 2 days. The reaction mixture was then poured into a beaker with water, and the organic lower layer was separated, washed with saturated sodium sulfite solution and water, and dried over molecular sieves. Distillation of the crude material gave 7.7 g (75%) of a mixture of **2** and **2b**, bp 93 °C. ^{19}F NMR and GLPC analysis of the product showed it to be a 23:1 mixture of 3-iodo-1,1-difluoropropene (**2**) and 3-iodo-3,3-difluoropropene (**2b**). ^{19}F NMR ($CDCl_3$) **2**: -84.1 (d, $^2J_{F,F}$ = 27 Hz, 1 F), -85.3 (dd, $^2J_{F,F}$ = 27 Hz, $^3J_{F,H\text{-trans}}$ = 23 Hz, 1 F). ^{19}F NMR ($CDCl_3$) **2b**: -41.9 (d, $^3J_{F,H}$ = 12 Hz). ^{1}H NMR ($CDCl_3$) **2**: 4.69 (dt, $^3J_{F,H\text{-trans}}$ = 23 Hz, $^3J_{H,H}$ = 12 Hz, 1 H), 3.81 (d, $^3J_{H,H}$ = 12 Hz, 2 H). FT-IR (CCl_4): 3103 (w), 1733 (s), 1335 (s), 1244 (s), 1161 (s). MS: 204 (M^+, 5.2), 127 (16.0), 77 (100), 75 (9.4), 51 (20).

Preparation of 3 from 2 and 2b. A mixture of 2.2 g (10 mmol) of **2** and **2b**, 1.1 g (10 mmol) of benzaldehyde, and 1.3 g (20 mmol) of zinc in 20 mL of THF was reacted at 0 °C for 2 h. Usual workup gave 1.1 g (61% isolated yield) of **3**.

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Supplementary Material Available: ^{19}F and/or ^{1}H NMR spectra for compounds **2-15** (29 pages). Ordering information is given on any current masthead page.

Micellar Catalysis of Organic Reactions. 29.[1] S_NAr Reactions with Neutral Nucleophiles

Trevor J. Broxton* and Victor Marcou

Department of Chemistry, La Trobe University, Bundoora, Victoria, Australia 3083

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The reaction of a number of nitroactivated halobenzoates (**1-4**) with some primary and tertiary amines has been studied in the presence of micelles of cetyltrimethylammonium bromide (CTAB) and in water. With primary amines aminodehalogenation was observed, and it was found that if the reaction center of the aromatic substrate was located at the micelle water interface (compounds **1** and **2**) the reaction was catalyzed by CTAB, but if the reaction center was more deeply buried into the micellar interior the reaction with aniline was inhibited by micelles of CTAB (compounds **3** and **4**), while CTAB had little effect on the reaction of *n*-propylamine with compound **4**. With the more sterically bulky tertiary amines, hydroxydehalogenation was observed rather than aminodehalogenation, and the reactions were all catalyzed by CTAB, but for the substrate with a more deeply buried reaction center (compound **4**), the catalysis was stronger than for that with a reaction center at or near the interface (compound **2**). The mechanism of hydroxydehalogenation was found to be specific base catalysis by the tertiary amine. Thus the observation of micellar catalysis or inhibition of these reactions depends on the orientation of the organic substrate within the micellar aggregate and the reaction product, amine or phenol, depends on the steric bulk of the amine at least for the compounds investigated here which contain two substitutents ortho to the reaction center.

Introduction

Previous studies of the effects of substrate orientation in micelles on the magnitude of catalysis[2a,b] have been hampered by the small catalysis observed for the selected reactions. In most cases substrates containing charged substituents (e.g. carboxylate groups) have been used because the orientation of these compounds in micelles is known from NMR studies of chemical shift changes of the aromatic protons on transfer from water to micelles of cetyltrimethylammonium bromide (CTAB). The presence of the charged substituent serves two purposes. Firstly it provides sufficient water solubility to obtain an NMR

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