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Asymmetric 1,2-Perfluoroalkyl Migration: Easy Access to Enantioenriched α-Hydroxy-α-perfluoroalkyl Esters

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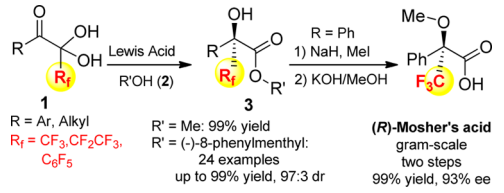
Supporting Information

ABSTRACT: This study has led to the development of a novel, highly efficient, 1,2-perfluoro-alkyl/-aryl migration process in reactions of hydrate of 1-perfluoro-alkyl/-aryl-1,2-diketones with alcohols, which are promoted by a Zn(II)/bisoxazoline and form α-perfluoro-alkyl/-aryl-substituted α-hydroxy esters. With (−)-8-phenylmenthol as the alcohol, the corresponding menthol esters are generated in high yields with excellent levels of diastereoselectivity. The mechanistic studies show that the benzilic ester-type rearrangement reaction takes place via an unusual 1,2-migration of electron-deficient trifluoromethyl group rather than the phenyl group. The overall process serves as a novel, efficient, and simple approach for the synthesis of highly enantioenriched, biologically relevant α-hydroxy-α-perfluoroalkyl carboxylic acid derivatives.

The α-hydroxy-α-trifluoromethyl carboxylic acid derivatives have received increasing attention in recent years owing to their unique pharmaceutical and agrochemical properties. To date, over 2800 bioactive compounds containing this structural unit have been prepared as part of drug development studies and have been the subjects of 330 patents (documented by Reaxys[1]).[2,3] In the past decades, an increased effort has been given to the development of concise synthesis of multifunctionalized derivatives of α-hydroxy-α-trifluoromethyl carboxylic acids.[4] For example, Jørgensen et al. recently described a strategy for facile preparation of these substances which employs Cu(II)/bisoxazoline-catalyzed Friedel−Crafts reactions of electron-rich aromatic compounds with trifluoropyruvates. This process produces α-hydroxy-α-trifluoromethyl phenylacetic esters in high yields with excellent levels of enantioselectivity.[4a,b] In addition, a method employing asymmetric nucleophilic trifluoromethylation of α-ketoesters has been shown to provide direct access to enantiomerically enriched α-hydroxy-α-trifluoromethyl carboxylates. However, the highest level of enantiomeric control was 60% ee, observed by Mukaiyama et al. using a cinchonidine derived quaternary ammonium phenoxide to catalyze the nucleophilic trifluoromethylation reaction of *tert*-butyl 2-oxo-2-phenylacetate.[4h,i] Thus, enantiocontrol of reactions that generate these targets remains as a major hurdle.

Recently, we found that hydrate of 1-trifluoromethyl-1,2-diketones[5] could undergo facile, Lewis acid promoted, benzilic ester-type rearrangement reactions involving CF_3 migration under mild conditions. The results stimulated an effort aimed at the development of a new method for the synthesis of optically active α-perfluoro-alkyl and -aryl α-hydroxy esters. Here, we report the preliminary results (Scheme 1).

Scheme 1. Asymmetric 1,2-R_f Migration



Benzilic acid (ester) rearrangement (BAR) reactions of α-diketones are atom-economic and efficient processes that are widely employed for the synthesis of tertiary α-hydroxy acids and esters.[6] We envisioned that, if successful, a rearrangement protocol of this type could be applied to 1,2-diketones **1** as part of a new strategy for the preparation of α-trifluoromethyl tertiary α-hydroxy acids. To test the validity of this proposal, we conducted a study using the hydrate of 1-phenyl-2-trifluoromethyl-1,2-diketone (**1a**) as a model substrate. In contrast to nucleophilic trifluoromethylation reactions that do not occur in solvents containing acidic protons,[3a] the trifluoromethyl migration reaction of **1a** in the presence of 50 equiv of methanol was observed to take place efficiently at 80 °C by employing 10 mol % Cu(II)/**L4a** (Scheme 1) as a catalyst.[7] Significantly, the product of this reaction, methyl α-trifluoromethyl-α-phenyl-α-hydroxy acetate (**3a**), was isolated in near quantitative yield.[8] An asymmetric version of this process using Cu(II) complexes was explored with chiral bisoxazoline (BOX) and trisoxazoline (TOX) ligands, which are efficient in asymmetric intramolecular Cannizzaro reaction.[9] However, trials on stereochemical control of this process by these chiral Lewis acid catalysts failed.[10]

Because of its potential utility in organic synthesis, we tried an alternative approach to this goal involving the use of chiral alcohols as nucleophiles. This strategy was explored in studies of reactions of **1a** with various chiral alcohols and Cu(II) complexes in DCE as the solvent. As shown in Table 1, reactions of **1a** with (*S*)-α-phenylethanol **2a**, chiral amino alcohol **2b**, and

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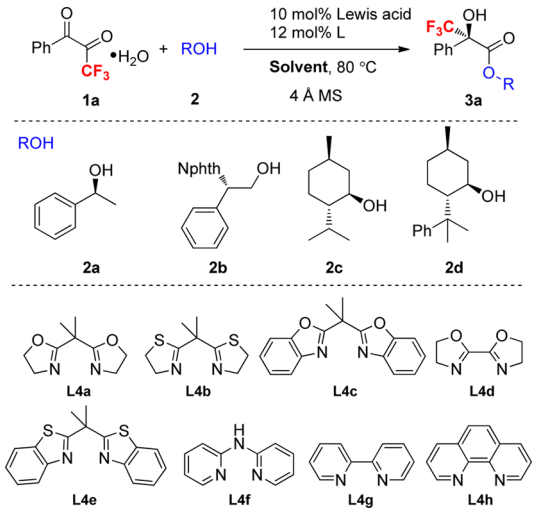
Table 1. Reaction Optimization[a]



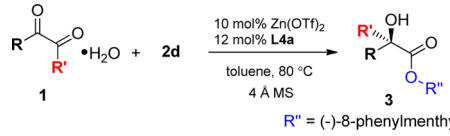
entry	Lewis acid	L	solvent	ROH	time (h)	yield (%)[b]	dr[c]
1	$Cu(OTf)_2$	**L4a**	DCE	**2a**	12	99	50/50
2	$Cu(OTf)_2$	**L4a**	DCE	**2b**	42	99[d]	55/45
3	$Cu(OTf)_2$	**L4a**	DCE	**2c**	18	80	55/45
4	$Cu(OTf)_2$	**L4a**	DCE	**2d**	41	57	94/6
5	$Zn(OTf)_2$	**L4a**	DCE	**2d**	60	61	95/5
6	$Zn(OTf)_2$	**L4a**	toluene	**2d**	48	89	96/4
7	$Zn(OTf)_2$	**L4b**	toluene	**2d**	48	85	94/6
8	$Zn(OTf)_2$	**L4c**	toluene	**2d**	48	91	89/11
9	$Zn(OTf)_2$	**L4d**	toluene	**2d**	48	44	96/4
10	$Zn(OTf)_2$	**L4e**	toluene	**2d**	48	49	92/8
11	$Zn(OTf)_2$	**L4f**	toluene	**2d**	48	32	95/5
12	$Zn(OTf)_2$	**L4g**	toluene	**2d**	48	76	96/4
13	$Zn(OTf)_2$	**L4h**	toluene	**2d**	48	61	96/4
14	$Zn(OTf)_2$	-	toluene	**2d**	48	9	95/5
15	-	-	toluene	**2d**	48	N.R.	–
16[e]	-	-	toluene	**2d**	48	N.R.	–

[a]Reaction conditions: $Zn(OTf)_2$ (0.020 mmol), **L** (0.024 mmol), **1a** (0.2 mmol), and **2** (0.4 mmol) in 2.0 mL of solvent, N_2. [b]Isolated yield. [c]The dr was determined by using ^{19}F NMR spectroscopic analysis of the crude reaction mixture. [d]Conversion of **1a**, determined by using both ^1H and ^{19}F NMR spectroscopic analysis of the crude reaction mixture. [e]20 mol % of TfOH was used.

(−)-menthol **2c** in the presence of Cu(II)/**L4a** took place efficiently, but the diastereomeric ratios (dr) were only ca. 50/50 (entries 1−3, Table 1). However, reaction of **1a** with (−)-8-phenylmenthol (**2d**) to form the corresponding ester was modestly high yielding (57%) and occurred with a much higher level of diastereoselectivity (94/6 dr, entry 4). Moreover, the process was found to be more efficient when Zn(II) rather than Cu(II) based catalysts were employed, and toluene rather than DCE was used as solvent (entries 5 and 6). An examination of the effects of ligands showed that changing from bis-oxazoline **L4a** to bis-thiazoline **L4b** led to both a lower yield and dr (entry 7). Furthermore, no improvements in yield and stereoselectivity were engendered by using other ligands (**L4c−h**, entries 8−13). In contrast, the process took place in only 9% yield when 10 mol % of $Zn(OTf)_2$ was utilized in the absence of any ligand (entry 14), and no reaction occurred in the absence of Zn(II)/L catalysts (entry 15) or when 20 mol % of triflic acid was employed as the catalyst (entry 16).

The substrate scope of the process was investigated next under the optimized conditions. As shown in Table 2, the new 1,2-CF_3

Table 2. Reaction Scope[a]



entry	R′/R (**1**)	product	time (h)	yield (%)[b]	dr[c]
1	CF_3/Ph (**1a**)	**3a**	48	89	96/4
2	CF_3/2-FC_6H_4 (**1b**)	**3b**	168	60	92/8
3	CF_3/3-FC_6H_4 (**1c**)	**3c**	47	95	96/4
4	CF_3/3-ClC_6H_4 (**1d**)	**3d**	37	99	96/4
5	CF_3/3-$CF_3C_6H_4$ (**1e**)	**3e**	33	94	97/3
6	CF_3/3-$MeOC_6H_4$ (**1f**)	**3f**	86	94	96/4
7	CF_3/4-FC_6H_4 (**1g**)	**3g**	68	94	97/3
8	CF_3/4-ClC_6H_4 (**1h**)	**3h**	87	90	96/4
9	CF_3/4-BrC_6H_4 (**1i**)	**3i**	87	86	96/4
10	CF_3/4-IC_6H_4 (**1j**)	**3j**	39	91	96/4
11	CF_3/4-$CF_3C_6H_4$ (**1k**)	**3k**	13	95	97/3
12	CF_3/4-$MeOC_6H_4$ (**1l**)	**3l**	110	86	95/5
13	CF_3/4-MeC_6H_4 (**1m**)	**3m**	137	90	95/5
14	CF_3/4-PhC_6H_4 (**1n**)	**3n**	89	84	96/4
15	CF_3/3,4-$F_2C_6H_3$ (**1o**)	**3o**	33	94	97/3
16	CF_3/3,4-$Cl_2C_6H_3$ (**1p**)	**3p**	33	95	97/3
17	CF_3/2,4-$Cl_2C_6H_3$ (**1q**)	**3q**	112	62	91/9
18	CF_3/3,4-$(MeO)_2C_6H_3$ (**1r**)	**3r**	110	89	96/4
19	CF_3/3,4-$(OCH_2O)C_6H_3$ (**1s**)	**3s**	48	92	96/4
20	CF_3/2-naphthyl (**1t**)	**3t**	86	90	95/5
21	CF_3/$CH_2CH_2C_6H_5$ (**1u**)	**3u**	6	72	93/7
22	CF_3/$CH_2CH_2C_6H_4CH_3$ (**1v**)	**3v**	4	77	92/8
23	CF_2CF_3/Ph (**1w**)	**3w**	40	95	95/5
24	C_6F_5/Ph (**1x**)	**3x**	96	86	97/3

[a]Reaction conditions: $Zn(OTf)_2$ (0.030 mmol), **L4a** (0.036 mmol), **1** (0.3 mmol), and **2d** (0.6 mmol) in 6.0 mL of toluene, N_2. [b]Isolated yield. [c]The dr was determined by using ^{19}F NMR spectroscopic analysis of the crude reaction mixture.

migration process took place smoothly with a variety of 1-aryl-2-trifluoromethyl-1,2-diketones including those that contain both electron-rich and electron-poor phenyl ring substituents (entries 1−20, Table 2). Various functional groups such as OMe, F, Cl, Br, I, and CF_3 in substrates **1a−1s** were well tolerated in reactions that form the corresponding α-hydroxy esters **3a−3s** in high to excellent yields with excellent diastereoselectivity. Compared with para- and meta-phenyl-substituted substrates, those possessing ortho-substituents reacted to give products in slightly lower yields and stereoselectivity (entries 2 and 17).

Notably, the rates of reactions of 1-aryl-2-trifluoromethyl-1,2-diketones containing electron-withdrawing phenyl ring substituents are higher than those of analogues with electron-donating phenyl substituents. This observation suggests that the migrating trifluoromethyl group in the reaction has nucleophilic character. Importantly, 1-alkyl-2-trifluoromethyl-1,2-diketones **1u** and **1v** also served as acceptable substrates for this rearrangement reaction, giving the corresponding products **3u** and **3v** in high yields and high diastereoselectivities (entries 21 and 22). Furthermore, not only trifluoromethyl diketones but also the pentafluoroethyl analogue **1w** reacted smoothly to give the migration product **3w** in 95% yield and a 95/5 diastereomeric ratio (entry 23). Likewise, the pentafluorophenyl-diketone **1x**

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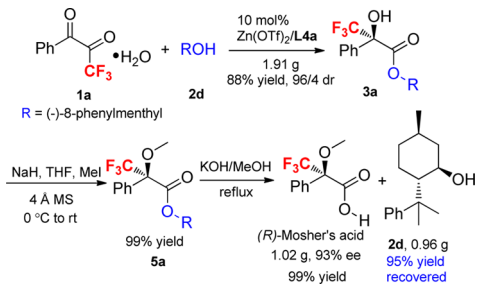
was a suitable substrate for this process, which produced the corresponding hydroxy ester **3x** in a high yield and diastereoselectivity (entry 24). The stereochemical outcome of the reaction of **1x** is highly significant because the similar steric sizes of the α-phenyl and α-pentafluorophenyl groups make it difficult to conceive of other methods to prepare substances like **3x** with high levels of diastereoselectivity.

The practical utility of the current reaction is demonstrated by its application to gram scale synthesis of (*R*)-Mosher's acid. As the results summarized in Scheme 2, ester **3a** could be readily

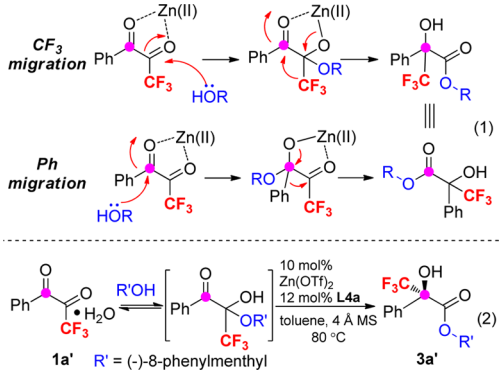
Scheme 2. Gram-Scale Synthesis of (*R*)-Mosher's Acid



transformed to highly enantioenriched (93% ee) (*R*)-α-methoxy-α-trifluoromethyl-phenyl acetic acid,[13] known as (*R*)-Mosher's acid, used as a chiral resolution reagent[11] and a key intermediate in the synthesis of hundreds of bioactive substances.[3,4,12] In addition, (−)-8-phenylmenthol could be readily recovered in 95% yield following the saponification step.

Two possible mechanistic pathways exist for this Lewis acid promoted reaction.[6c,d] Specifically, this benzylic acid rearrangement process can occur by routes involving migration of either an aryl or trifluoromethyl group following addition of the alcohol to one of the two carbonyl centers in the diketone (Scheme 3, eq 1).

Scheme 3. Isotope Labeling Study



An isotope labeling experiment was performed,[10] using 1-^{13}C-1-phenyl-2-trifluoromethyl-1,2-diketone, to distinguish between the two mechanistic routes. The results (Scheme 3, eq 2) show that the ^{13}C-labeled carbon remains connected to the phenyl group in the corresponding product formed under the optimal conditions. In addition, a crossover experiment was also carried out under the same conditions by employing the mixture of substrates **1j** and **1w**, which resulted in the corresponding mixture of **3j** and **3w** without cross over products detected.[10] These results clearly demonstrate that the reaction takes place exclusively through a unique pathway[14] in which the trifluoromethyl group migrates to the neighboring carbonyl center.

Further insight into the mechanism for this process came from the results of a preliminary kinetic experiment in which ^{19}F NMR spectroscopy was used to monitor changes in concentrations of the diketone reactant **A** (Figure 1), hemiacetal intermediate **C**,

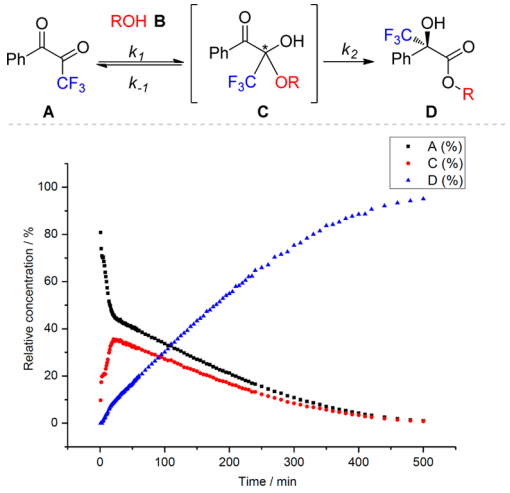


Figure 1. Monitoring reaction progress using ^{19}F NMR spectroscopy. Plot of the concentrations of substrate **A**, intermediate **C**, and product **D** function of reaction time using $PhCF_3$ as a ^{19}F NMR integration standard. Starting conditions: [**A**] (0.1 M), [**B**] (1 M), $Zn(OTf)_2$ (10 mol %), **L4a** (12 mol %) in toluene-d_8, 80 °C.

and product **D**.[10] By viewing the plot of concentrations versus time displayed in Figure 1, it can be seen that in the initial phase of this reaction, intermediate **C** formed rapidly, and then in a second stage it disappeared with simultaneous formation of product **D**. This result shows clearly that the first step of the process, interconverting **A** and **C**, is reversible and that the CF_3-migration step is rate-determining (i.e., $k_{-1} > k_2$, $k_1 \gg k_2$).[10]

In summary, a highly stereoselective Lewis acid-catalyzed 1,2-perfluoroalkyl and perfluoroaryl migration reaction of 1,2-diketones was developed. The process serves as the basis for an efficient and simple method to prepare enantioenriched α-perfluoroalkyl and α-perfluoroaryl-substituted α-hydroxy carboxylic acid derivatives, overcoming the limitations of the synthetic methods reported.[3] ^{13}C labeling study confirmed that an intramolecular trifluoromethyl migration is involved in this reaction. Importantly, as far as we are aware, this is the first example of an asymmetric intramolecular migration of a trifluoromethyl group as well as pentafluoroethyl and pentafluorophenyl groups. The newly developed method has a number of advantages, including high yield, mild reaction conditions, simple recovery, and reuse of the chiral auxiliary, ready scaling up and excellent diastereoselectivity. In particular, the broad substrate scope and fluorine-containing migration groups make this reaction useful for the synthesis of biologically active substances in medicinal chemistry studies.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) The reaction proceeded smoothly with 10 mol% $Cu(OTf)_2$/**L4a** as catalyst. When MeOH was used as nucleophile at 80 °C, the desired product can be isolated in 99% yield.

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