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Brine-Stabilized 2,2,2-Trifluorodiazoethane and Its Application in the Synthesis of CF_3−Substituted Cyclopropane α-Amino Acids

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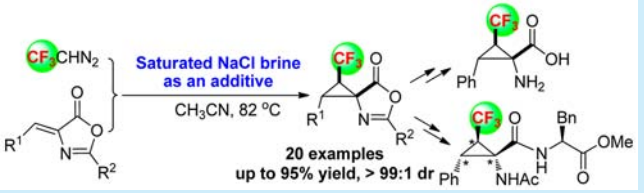
Supporting Information

ABSTRACT: A facile thermodynamic cyclopropanation of trisubstituted olefinic azlactones with a stock solution of CF_3CHN_2 in CH_3CN is realized. This method shows excellent generality, affording a wide range of trifluoromethyl-substituted cyclopropanes bearing azlactone rings in good to high yields and diastereoselectivities. With the products in hand, the trifluoromethyl-substituted cyclopropane α-amino acids and relative peptide derivatives could be readily obtained.



Artificial CF_3-substituted amino acids have emerged as powerful labels for the ^{19}F NMR analysis of peptides and proteins because most of the natural biomolecules contain no fluorine. These amio acids possess a 100% abundant spin-$^1/_2$ nucleus with intrinsic sensitivity, spectral simplicity, and a large chemical shift range.[1] In this context, the incorporation of the ^{19}F reporter group into a well-defined position relative to the peptide and protein backbone has led to a demand for the synthesis of conformationally rigid CF_3-substituted amino acids.[2] Several elegant reports have addressed the preparation and use of structurally relevant trifluoromethylated analogues of bulky aliphatic amino acids (**I**), proline (**II**), serine/threonine (**III**), α-aminoisobutyric acid (**IV**), and aromatic phenylalanine (**V** and **VI**) (Figure 1).[3] In contrast, α-aminocyclopropane-

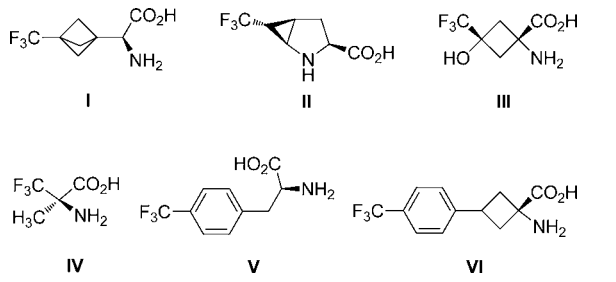


Figure 1. CF_3-substituted amnio acids for the ^{19}F NMR analysis of peptides and proteins.

carboxylic acids (ACCs), as conformationally constrained analogues of proteinogenic amino acids, have served as a valuable tool for the characterization and mechanistic studies of peptides and proteins.[4] However, to the best of our knowledge, the construction of CF_3-substituted α-aminocyclopropane-carboxylic acids having an aliphatic or aromatic side chain has not been reported to date.[5] Such a challenge is mainly due to the lack of applicable synthetic approaches toward this promising skeleton.

One of the most direct and convenient methods for the construction of CF_3-substituted cyclopropane moieties is the reaction of 2,2,2-trifluorodiazoethane (CF_3CHN_2) with alkenes.[6] Earlier studies focused on the carbene-cyclopropanation by the photolysis of 2,2,2-trifluorodiazoethane,[6c−f] whereas recent research has paid more attention to transition metal-catalyzed carbenoid-cyclopropanation reactions.[6g−o] However, a severe limitation of these methods is that the reactions only worked with mono and disubstituted alkenes, but it was not known whether these strategies were applicable to more sterically hindered polysubstituted olefins. Very recently, the Mykhailiuk and Xiao groups described the sequential [3 + 2] cycloaddition/ring contraction reactions of alkenes with 2,2,2-trifluorodiazoethane, and an extra heating step is required for denitrogenation to obtain the desired cyclopropane products.[6p,q] Encouraged by these results, and also an extension of our recent interest in the utilities of CF_3CHN_2,[7] we have conceived that a novel thermodynamic cyclopropanation reaction could be developed by using trisubstituted olefinic azlactones **1** and 2,2,2-trifluorodiazoethane (Figure 2). Considering that CF_3CHN_2 is gaseous under ambient conditions and easily decomposed under harsh conditions, an appropriate balance between maximizing olefin reactivity and minimizing diazo decomposition would be very important for the thermodynamic cyclopropanation of polysubstituted olefins.[8] Herein we report the successful implementation of this strategy to provide CF_3-substituted cyclopropane α-amino acids and relative peptide derivatives. We demonstrate that the cyclopropanation of trisubstituted olefinic azlactones with a stock solution of CF_3CHN_2 could proceed smoothly in the presence of saturated NaCl brine under reflux conditions. This approach not only obviates the utility of toxic and/or expensive metal reagents, but also helps solve the longstanding problem

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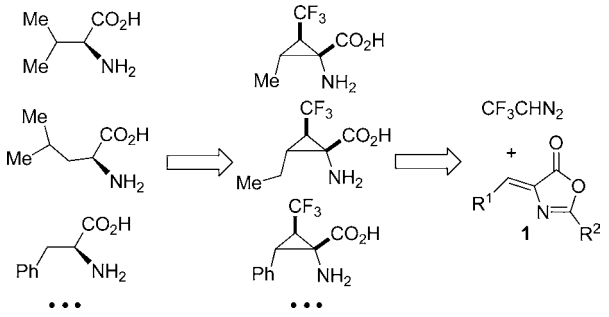


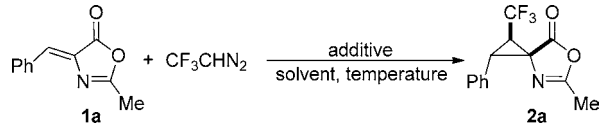
Figure 2. Design of novel conformationally constrained CF_3-substituted cyclopropane α-amino acids.

of the thermodynamic instability of CF_3CHN_2 and enhance the application of these cyclopropane-forming reactions.

To establish the cyclopropanation conditions, we started our research with the model reaction between benzylidene azlactone **1a** and 2,2,2-trifluorodiazoethane. Four of the most extensively used metal complexes for olefin cyclopropanation were examined at room temperature, including $Cu(OTf)_2$, [Fe(TPP)Cl] (TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine), [Co(TPP)], and $[Rh_2(esp)_2]$ [esp =3,3′-(1,3-phenylene)bis(2,2-dimethylpropanoate)]. Unfortunately, no desired product was obtained, whereas CF_3CHN_2 was completely decomposed and **1a** was fully recovered. We assumed that the lack of reaction could be due to steric hindrance and low reactivity of olefin. In this sense, the logical follow-up consideration was the increase of reaction temperature (Table 1: entries 1−3). To our delight, when the reaction was conducted in acetonitrile at 80 °C without the need of any transition metal complexes, the cyclopropanation product **2a** was formed in 27% yield with excellent diastereoselectivity. We hypothesized that, if CF_3CHN_2 could be stabilized at the reflux temperature, the chemical yield should be improved. Subsequently, the addition of water or sodium chloride as additives provided a moderate yield of product **2a** (entries 4 and 5). These interesting results prompted us to examine the effect of various aqueous solutions of common inorganic salts (entries 6−16). After careful experimentation, it was found that the utility of saturated NaCl brine delivered the cyclopropanation product **2a** in good yield (entry 8), whereas all the other additives tested resulted in moderate yields (entries 7−13). Finally, the choice of organic solvent is also critical: the utility of THF, DMF, toluene, and benzene leads to a significantly lower yield (<15%) (entries 17−20). In addition, the use of the in situ generated CF_3CHN_2 in this cyclopropanation reaction could not deliver any desired product.

With the optimized conditions in hand, we then studied the substrate scope of this thermodynamic cyclopropanation reaction of 2,2,2-trifluorodiazoethane with a variety of trisubstituted olefinic azlactones **1**, and the results are summarized in Scheme 1. Treatment of 2,2,2-trifluorodiazoethane with a series of phenyl-substituted olefinic azlactones furnished the corresponding products **2a**−**l** in moderate to good yields with nearly perfect diastereoselectivities. Both electron-donating and electron-withdrawing groups on the phenyl ring were effective, although a slightly lower yield was observed when the substituents were *p*-MeO, *o*-Br, and *p*-NO_2. 2-Naphthyl- and 3-pyridyl-substituted olefinic azlactones were also found to be good substrates, thus delivering the products **2m** and **2n** in 51−79% yields with excellent diastereoselectivities. To further define the scope of our methodology, the

Table 1. Optimization of the Reaction Conditions[a]



entry	additive	solvent	temp (°C)	yield (%)[b]	dr[c]
1		CH_3CN	40	0	
2		CH_3CN	60	14	>99:1
3		CH_3CN	80	27	>99:1
4	H_2O (1 equiv)	CH_3CN	80	41	>99:1
5	NaCl (1 equiv)	CH_3CN	80	34	>99:1
6	saturated brine (3 μL)	CH_3CN	80	54	>99:1
7	saturated brine (6 μL)	CH_3CN	80	67	>99:1
8	saturated brine (9 μL)	CH_3CN	80	72	>99:1
9	saturated brine (12 μL)	CH_3CN	80	70	>99:1
10[d]	NaF aqueous (9 μL)	CH_3CN	80	55	>99:1
11[d]	NaBr aqueous (9 μL)	CH_3CN	80	54	>99:1
12[d]	NaI aqueous (9 μL)	CH_3CN	80	36	>99:1
13[d]	LiCl aqueous (9 μL)	CH_3CN	80	58	>99:1
14[d]	KCl aqueous (9 μL)	CH_3CN	80	49	>99:1
15[d]	$CaCl_2$ aqueous (9 μL)	CH_3CN	80	54	>99:1
16[d]	$MgCl_2$ aqueous (9 μL)	CH_3CN	80	55	>99:1
17[e]	saturated brine (9 μL)	THF	80	14	>99:1
18[e]	saturated brine (9 μL)	DMF	80		
19[e]	saturated brine (9 μL)	toluene	110	8	>99:1
20[e]	saturated brine (9 μL)	C_6H_6	80	10	>99:1

[a]A mixture of **1a** (0.1 mmol), a stock solution of CF_3CHN_2 (4 mL), and additive was sealed in a 10 mL Schlenk tube at the stated temperature for 48 h. The concentration of the CF_3CHN_2 solution in different solvents: 0.11 M in acetonitrile (MeCN), 0.1 M in tetrahydrofuran (THF), 0.1 M in toluene, 0.2 M in dimethylformamide (DMF), and 0.1 M in benzene (C_6H_6). [b]Isolated yield was obtained from an average of two runs unless other notice is given. [c]Diastereomeric ratio (dr) values were determined by ^{19}F NMR spectroscopy of the crude product with $PhCF_3$ as an internal standard. [d]Based on the amount of 9 μL saturated brine, other aqueous solutions are 0.55 equiv inorganic salt in 9 μL water. [e]Determined by ^{19}F NMR spectroscopy using (trifluoromethyl)-benzene as an internal standard.

reactions of alkyl-substituted olefinic azlactones with 2,2,2-trifluorodiazoethane were tested. The cyclopropanations of these substrates all proceeded efficiently to give the products **2o**−**t** in 87−95% yields with good to high diastereoselectivities.

The presence of an azlactone group in the cyclopropanation products offers a potential opportunity for further synthetic transformation. As demonstrated in Scheme 2, direct hydrolysis of **2a** under acidic conditions could proceed smoothly to afford CF_3-substituted cyclopropane α-amino acid hydrochloride **3**, whereas an neutral condition gave rise to the corresponding 1-acetamido-3-(trifluoromethyl)cyclopropanecarb-oxylic acid **4** in high yield. These hydrolysis products might be able to serve as the key labels for the ^{19}F NMR analysis and characterization of relative enzymes and proteins.[4] Also, treatment of **2a** with N-

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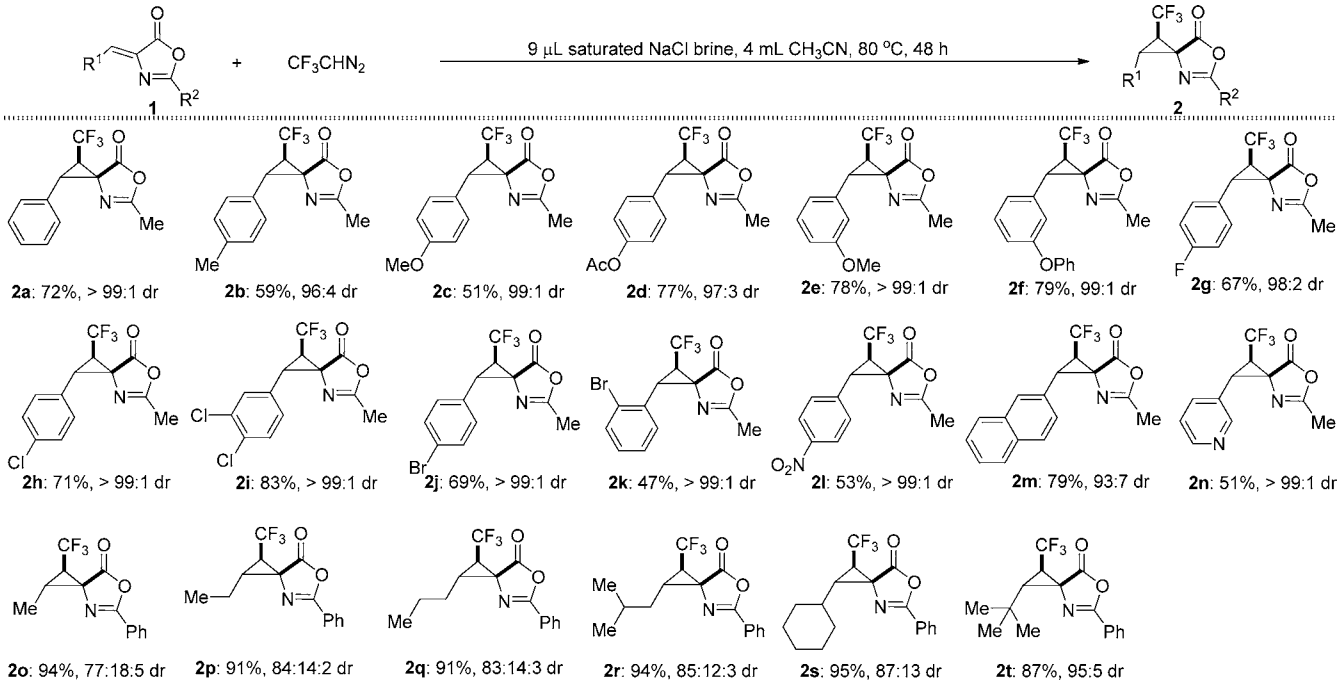
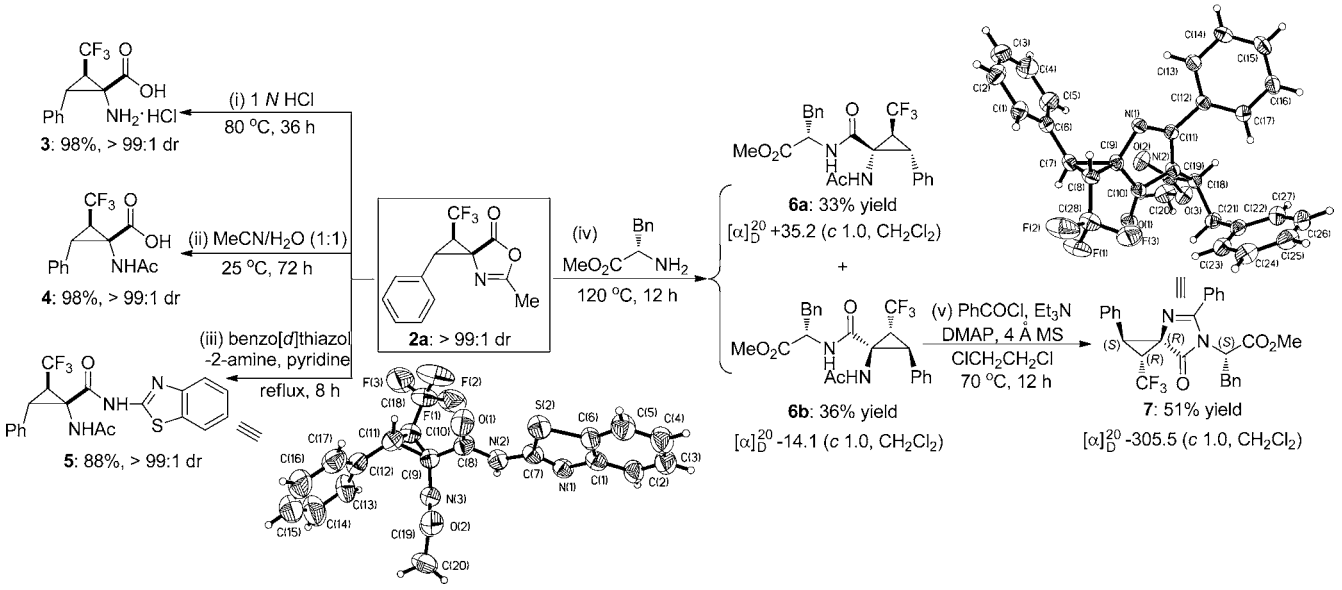
Scheme 1. Scope of Cyclopropanation of Olefinic Azlactones 1 with 2,2,2-Trifluorodiazoethane (CF_3CHN_2)[a]



[a]Yields shown are of isolated products from an average of two runs. The dr values are determined by ^{19}F NMR spectroscopy of the crude product.

Scheme 2. Synthetic Utilities of the Cyclopropanation Products[a]



[a]ORTEP representation with 50% probability thermal ellipsoids of the crystal structures of **5** and **7**.

nucleophilic reagents, such as benzo[*d*]thiazol-2-amine and methyl (*S*)-2-amino-3-phenyl-propanoate, furnished 1-acetamido carboxamide **5** and dipeptide **6** in one single step. The relative structure of compound **5** was further confirmed by means of X-ray crystallographic analysis.[9] The two diastereoisomers (**6a** and **6b**) of dipeptide were successfully separated in enantiomerically pure form by column chromatography, and the absolute configuration of **6b** was allowed to be determined by X-ray crystallographic analysis of its derivative **7**.[9] These promising results indicate that the present protocol provides a reliable and convenient approach for the synthesis of conformationally constrained CF_3-substituted cyclopropane α-amino acids and relative peptide derivatives.

In conclusion, we have successfully demonstrated that the thermodynamic cyclopropanation reaction of trisubstituted olefinic azlactones with a stock solution of CF_3CHN_2 in CH_3CN could proceed smoothly in the presence of saturated NaCl brine under reflux conditions. This method shows excellent generality, affording a wide range of trifluoromethyl-substituted cyclopropanes bearing azlactone rings in good to high yields and diastereoselectivities. Convenient synthetic transformation allows for efficient access to highly function-

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alized trifluoromethyl-substituted α-cyclopropane amino acids and relative dipeptide derivatives. Further construction of CF_3-labeling polypeptides and proteins for the solid-state ^{19}F NMR analysis as well as mechanistic studies are ongoing in our laboratories, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral data of all the new compounds, and the CIF information on **5** and **7**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01450.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(8) **Caution**: Normally, diazo compounds are potentially explosive. Although no relevant safety study has been carried out on CF_3CHN_2 solution, such liquid must be handled carefully. We strongly recommend all operations involving CF_3CHN_2 solution should carry out in a well-ventilated hood behind a blast shield. In addition, the utility of ground glass joints and any glass equipment with sharp edges should be avoided. For additional information on hazards of CF_3CHN_2 see: Fields, R.; Tomlinson, J. P. *J. Fluorine Chem.* **1979**, *13*, 147.

(9) The X-ray crystallographic structures for **5** and **7** have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 972764, and 972765. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk/data_request/cif.

■ NOTE ADDED AFTER ASAP PUBLICATION

A new reference 8, describing a safety caution, was added on July 8, 2015.

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