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Amide-Group-Directed Protonolysis of Cyclopropane: An Approach to 2,2-Disubstituted Pyrrolidines

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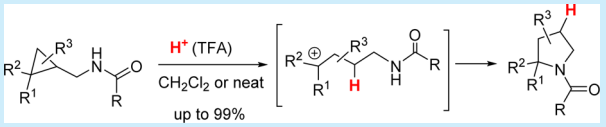
Supporting Information

ABSTRACT: Regioselective protonolytic C−C bond cleavage of acylated aminomethyl cyclopropanes can be achieved using trifluoroacetic acid. The intermediate tertiary carbenium ion undergoes an intramolecular amination to give 2,2-substituted pyrrolidines. The strength of the acid and the amine substituent are important factors to achieve high regioselectivity, suggesting intramolecular proton transfer from the protonated amide function. Preliminary mechanistic studies revealed that cyclopropane cleavage proceeds with retention of configuration at the carbon to which the proton is attached. This observation is consistent with the "edge" protonation trajectory of the C−C bond.



Because of the ring strain, the cyclopropane C−C bonds exhibit increased reactivity compared with those of larger cycles or acyclic systems.[1] Introduction of a donor and/or acceptor group on the cyclopropane enables ring opening under relatively mild conditions with predictable regioselectivity.[2] However, unactivated cyclopropanes **1** also can undergo C−C bond cleavage leading to functionalized products **2** when exposed to strong electrophilic reagents[1b,3] such as Brønsted acids,[4] Br_2,[5] diborane,[6] and acetyl chloride/$AlCl_3$[7] as well as Hg(II),[8] Pd(II),[9] Pt(II),[10] Tl(III),[11] and Ti(IV)[12] salts (Figure 1).

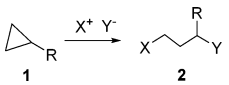


Figure 1. Electrophilic cleavage of cyclopropanes **1**.

Certain electrophiles induce high levels of regioselectivity by attacking the cyclopropane at the least-substituted carbon. This approach was recently demonstrated by the groups of Hennecke and Yeung, who exploited the regioselective halogenation of cyclopropane for the synthesis of lactones,[13,14] tetrahydrofurans,[13] pyrrolidines,[13] and oxazolines.[15]

The regioselectivity of the cyclopropane protonolysis tends to follow the modified Markownikoff's rule,[4j,16] which predicts the preferential ring opening to occur between the carbons bearing the largest and smallest numbers of substituents.[4a,b,h,e,k] However, typically the selectivity is modest, as demonstrated by the systematic studies of Wiberg and Kass[4k] for toluenesulfonic acid-catalyzed acetolysis of cyclopropanes with different substitution patterns (Figure 2, using cyclopropane **3** as a representative example).

We have investigated whether intramolecular proton delivery from the protonated amide function in cyclopropanes **4** (Figure 1) can direct regioselective protonolysis of the cyclopropane C−C bond. For this purpose, carbamate-

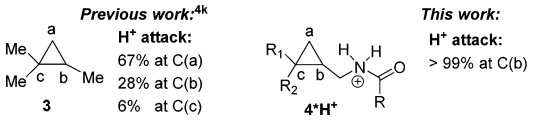
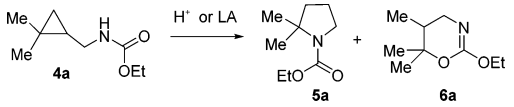


Figure 2. Regioselectivity of protonolysis of cyclopropanes **3** and **4**.

containing substrate **4a** was subjected to a range of Brønsted and Lewis acids (Table 1).

Table 1. Acid-Promoted Cleavage of Cyclopropane 4a[a]



entry	acid/solvent	product (% yield)[b]
1	TFA (neat)	**5a** (98)
2	MsOH (1 vol %)/CH_2Cl_2	**5a** (70), **6a** (17)
3	TfOH (1 vol %)/CH_2Cl_2	**5a** (47), **6a** (25)
4	$Fe(OTf)_3$ (1.0 equiv)/CH_2Cl_2	**5a** (61), **6a** (17)
5	$BF_3{\cdot}OEt_2$ (1.0 equiv)/CH_2Cl_2	no reaction
6	$(CuOTf)_2{\cdot}C_6H_6$ (1.0 equiv)/CH_2Cl_2	no reaction

[a]Reactions were performed on a 0.1 mmol scale at rt for 24 h. [b]NMR yields using 1,4-bis(trichloromethyl)benzene as an internal standard.

According to these studies, trifluoroacetic acid (TFA) was superior for selective and high-yielding formation of pyrrolidine **5a** (Table 1, entry 1). This product obviously results from selective proton attack at C(b) of cyclopropane **4a** (Figure 2) and subsequent cyclization of the intermediate carbenium ion. Stronger acids such as MsOH or TfOH proved to be less selective, providing considerable amounts of oxazine **6a** (Table 1, entries 2 and 3). The formation of oxazine **6a** could be explained by proton attack at C(a) of the

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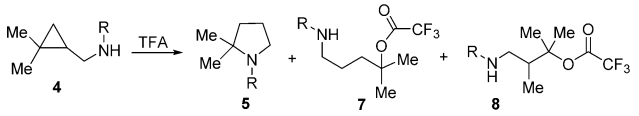
cyclopropane (Figure 2) followed by trapping of the carbenium ion with the amide oxygen. On the basis of these results, it can be proposed that TFA can induce cyclopropane C−C bond cleavage via amide protonation and intramolecular proton transfer, while in the case of stronger acids intermolecular proton transfer is a competing process. Several Lewis acids were also screened (Table 1, entries 4−6). Only $Fe(OTf)_3$ induced the cleavage of cyclopropane **4a** but did so in an unselective manner, providing both products **5a** and **6a**. Weaker Lewis acids such as $BF_3{\cdot}Et_2O$ and $(CuOTf)_2{\cdot}C_6H_6$ were unreactive.

Next, the impact of the nitrogen substituent was investigated (Table 2). In addition to ethoxycarbonyl

Table 2. Scope of the Cyclopropane N Substituent[a]



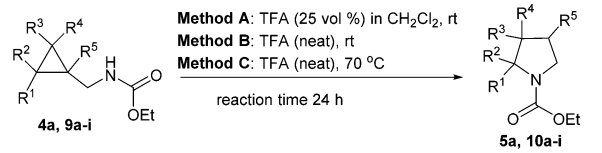
entry	4, R	product (% yield)
1	**4a**, EtOCO	**5a** (92)
2	**4b**, PhNHCO	**5b** (99)
3	**4c**, PhCO	**5c** (99)
4	**4d**, MeCO	**5d** (74)[b,c]
5	**4e**,$ClCH_2CO$	**5e** (99)[b]
6	**4f**, Cl_3CCO	**5f**:**7f**, 1:1 ratio (97)[d,e]
7	**4g**, MeCS	**5g** (17)[e] and unidentified byproducts
8	**4h**, 4-$NO_2C_6H_4$	no conversion of **4h**[a,d]
9	**4i**, CF_3CO	mixture of **5i**, **7i**, and **8i**
10	**4j**, $PhSO_2$	mixture of **5j**, **8j**, and $PhSO_2NH_2$

[a]Reaction conditions: a solution of **4** (c = 0.1 M) in TFA (25 vol %) in CH_2Cl_2, rt, 24 h, unless otherwise stated (see Table S2 for the impact of the TFA concentration). Isolated yields are given. [b]TFA (50 vol %) in CH_2Cl_2, rt. [c]Volatile compound. [d]TFA (neat). [e]NMR yield using 1,4-bis(trichloromethyl)benzene as an internal standard.

derivative **4a** (entry 1), also urea **4b** (entry 2) and several carboxamides **4c−e** (entries 3−5) proved to be suitable substrates for the formation of pyrrolidine derivatives **5a−e** in good to excellent yields. Trichloroacetamide **4f** gave a mixture of pyrrolidine **5f** and the ring-opening product **7f** (entry 6), which could be explained by the reduced nucleophilicity of **4f**. Thioamide **4g** was reactive under the protonolytic conditions but formed a mixture of products with a low content of the expected pyrrolidine **5g** (entry 7). Aniline derivative **4h** was unreactive even in neat TFA (entry 8). In the case of trifluoroacetamide **4i** (entry 9) and sulfonamide **4j** (entry 10), considerable amounts of products **8i** and **8j**, respectively, resulting from unselective proton attack at the less-substituted carbon of cyclopropane were formed. In these substrates, protonation of the carboxamide/sulfonamide function is minimized, which could prevent it from acting as a directing group for intermolecular proton delivery.

A range of substituted *N*-ethoxycarbonyl aminomethyl cyclopropanes **4a** and **9a−i** were investigated as substrates for the synthesis of pyrrolidines **5a** and **10a−i** (Table 3). Differences in reactivity were observed for diastereomeric amides *cis*- and *trans*-**9a** bearing a phenyl group. Surprisingly, while *trans*-**9a** smoothly gave the product **10a**, the conversion of *cis*-**9a** required neat TFA as a reaction medium. The formation of spirocyclic pyrrolidine **10b** from cyclopropane derivative **9b** was achieved efficiently with diluted TFA.

Table 3. Substrate Scope for the Synthesis of Pyrrolidines[a]



entry	substrate	product, method (yield %)
1	**4a**	**5a**, **A** (92)
2	*cis*-**9a** *trans*-**9a**	**10a**, **B** (92 from *cis*-**9a**) **A** (99 from *trans*-**9a**)
3	**9b**	**10b**, **A** (97)
4	**9c**	**10c**, **C** (77)
5	*cis*-**9d** *trans*-**9d**	**10d**, **B** (95 from *cis*-**9d**) **A** (92 from *trans*-**9d**)
6	**9e**	**10e**, **A** (97)
7	**9f**	**10f** (17) **10f′** (79) **A** (total 96)[b]
8	**9g**	**10g**, **A** (97)
9	**9h**	**10h**, **B** (0)[c]
10	*cis*-**9i** *trans*-**9i**	**10i**, **B** (0)[c]

[a]Reactions were performed on a 0.07−0.8 mmol scale, c = 0.1 M. Isolated yields are given. [b]**10f**/**10f′** = 1:4, as determined by GC−MS. [c]No reaction at rt in neat TFA; mixture of products at higher temperature.

However, to achieve the ring cleavage in oxygen analogue **9c**, harsher reaction conditions were required, leading to pyrrolidine **10c** in good yield.

2,2,3-Trisubstituted pyrrolidine **10d** was prepared from both diastereomers *cis*- and *trans*-**9d**. Again a notable difference in reactivity was observed for the isomers: harsher conditions were required to achieve the cleavage of substrate

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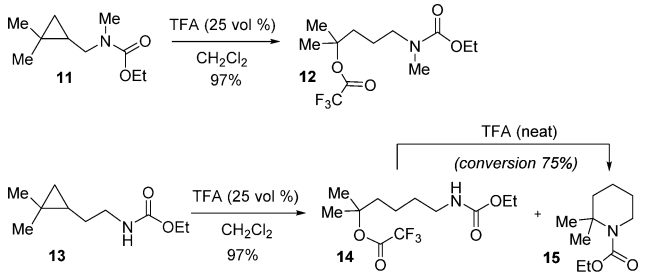
cis-**9d**. 2,2,3,3-Tetrasubstituted pyrrolidine **10e** was formed in high yield from the corresponding substrate **9e**.

The cleavage of the similar substrate **9f** bearing two nonequal quaternary centers provided a mixture of isomeric pyrrolidines **10f** and **10f′** with a preference for product **10f′** formation. 2,2,3,4-Tetrasubstituted pyrrolidine **10g** was obtained as a single *cis* diastereomer starting from stereodefined substrate **9g** (vide infra). Diphenyl- and hexyl-substituted cyclopropanes **9h** and **9i** failed to give the expected products **10h** and **10i**. The low reactivity of substrate **9h** implies that the stability of the intermediate carbenium ion is not the only factor that enables the protonolysis of the cyclopropane C−C bond, as in this case a very stable diphenyl carbenium ion should form. Apparently the electron density in the scissile C−C bond may also play an important role.

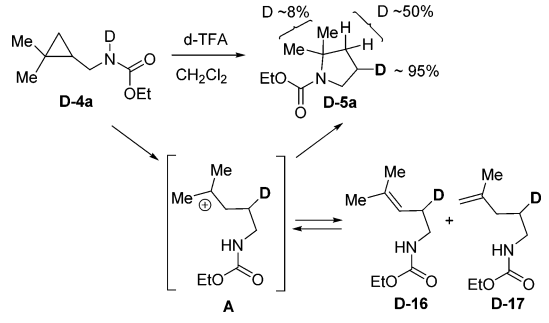
N-Methyl substrate **11** was also subjected to the protonolytic cleavage conditions using diluted TFA (Scheme 1). The reaction efficiently provided the corresponding trifluoroacetate **12**, indicating that N substitution does not prevent the regioselective proton attack on the cyclopropane.

Scheme 1. Protonolytic Cleavage of Cyclopropane 11 Bearing N-Substituted Carbamate and Homologous Substrate 13



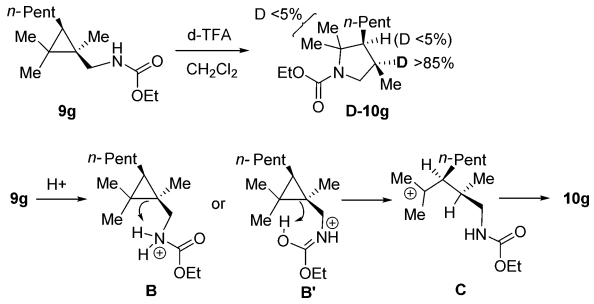
Substrate **13** with the two-carbon chain between the cyclopropane and carbamate could also be regioselectively cleaved. However, in this case a mixture of trifluoroacetatate **14** and piperidine **15** was formed. Trifluoracetate **14** could be transformed to piperidine **15** with good conversion using neat TFA as the reaction medium. To gain insight into the mechanistic details for the protonolytic cleavage of cyclopropanes **4**, deuterium-labeled substrate **D-4a** was subjected to deuterated TFA (Scheme 2). The analysis of the reaction product **D-5a** revealed almost complete deuterium incorporation at the 3-CH position of pyrrolidine, as expected for the proton attack at C(b) of cyclopropane (Figure 2). Deuterium

Scheme 2. Mechanism of Cyclopropane D-4a Protonolysis Based on Deuterium Incorporation into the Product D-5a



incorporation was also observed in the methyl groups and at the 2-CH_2 position of product **D-5a**. This indicates that a certain portion of intermediate carbenium ion **A** undergoes equilibration with alkenes **D-16** and **D-17** via deprotonation/protonation. In contrast, when substrate **9g** was subjected to deuterated TFA, a relatively small amount of deuterium incorporation was observed in the methyl groups and at the 2-CH position of product **D-10g** (Scheme 3). This confirms

Scheme 3. Deuterium Incorporation into the Product D-10g and Stereochemistry of Proton Transfer in Cyclopropane 9g[a]

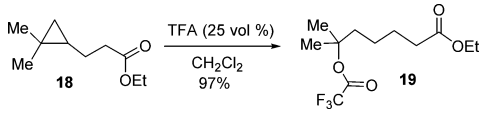


[a]See the Supporting Information for the X-ray structure determination of **9g** and NOESY structure determination of **10g**.

the high degree of stereointegrity at the chiral center of carbenium ion **C**, which allows the determination of the stereoselectivity of C−C bond protonolyis. The *cis* configuration of the starting material **9g** and the *cis* configuration of the product **10g** are consistent with the "edge" trajectory of the proton transfer from protonated amide **B** or imine tautomer **B′**.[17]

The protonolytic cleavage of ester **18** was also performed in order to investigate the role of nitrogen in amides **4** and **9** for the selective proton delivery (Scheme 4). Selective formation

Scheme 4. Regioselective Protonolytic Cleavage of Ester 18



of trifluoroacetate **19** was observed. This result together with the unselective cleavage of substrates **4i** and **4j** and the low reactivity of substrate **4h** indicates that oxygen rather than nitrogen in the amide function is involved in the intramolecular proton transfer to cyclopropane (tautomer **B′** in Scheme 3).

In summary, we have shown that the regioselective protonolytic C−C bond cleavage of acylated aminomethyl cyclopropanes can be achieved. The intermediate tertiary carbenium ion undergoes intramolecular amination to give 2,2-substituted pyrrolidines. The strength of the acid and the amine substituent are important factors to achieve high regioselectivity, suggesting intramolecular proton transfer from the protonated amide function. Preliminary mechanistic studies revealed that cyclopropane cleavage proceeds with retention of configuration at the carbon to which the proton is attached. This observation is consistent with the "edge" protonation trajectory of the C−C bond.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00584.

Detailed experimental procedures and characterization data for new compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(16) An exception to the modified Markownikoff's rule is the protonolysis of tricyclo[3.2.1.$0^{2,4}$]octane[4i] and tricyclo [3.2.2.$0^{2,4}$] nonane[4l] systems, in which the proton addition preferentially takes place at the most-substituted carbon of the cyclopropane.

(17) "Edge"[4l] and "corner"[4d,i,l] protonated cyclopropane transition states have been postulated to explain the retention or inversion of stereochemistry of the carbon attacked by the proton. Other hypotheses propose an "edge" trajectory of the protonation as the transition to the corner-protonated intermediate.[4c,f,g]

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