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Trifluoroacetic acid-promoted intramolecular hydroamination of unfunctionalized olefins bearing electron-rich amino groups

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ABSTRACT

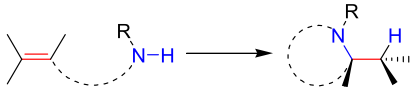
Trifluoroacetic acid was found to be effective in intramolecular hydroamination of unfunctionalized olefins bearing electron-rich amino groups, and the corresponding *N*-heterocycles were obtained in good isolated yields. The scope of the substrates was investigated, and a possible reaction mechanism was proposed. Substituents on C=C double bonds and amino groups of the substrates showed drastic effects on the course of the reactions.

1. Introduction

Nitrogen-containing organic compounds constitute the most important part of privileged structures and have played vital roles in medicinal chemistry.[1] To this end, continuous efforts have been devoted towards the formation of C–N bonds and the construction of nitrogen-containing heterocyclic skeletons.[2] For example, electrophile-induced cyclization of *N*-protected pent-4-en-1-amines or pent-4-en-1-imines with bromine[3] or PhSeBr[4] produced the bromo- or functionalized heterocycles, and $LiAlH_4$[3] or tributylstannane[5] reduction of these compounds gave 2-methylpyrrolidines in good yields. In such a way, a variety of substituted pyrrolidines and piperidines could be obtained via ring expansion of substituted aziridines[6] or azetidines.[7]

In addition to these traditional methods, hydroamination, direct addition of an N–H bond to unsaturated carbon–carbon bonds (Scheme 1), has been proved to be a waste-free and highly atom-economical method for the construction of C–N bonds and nitrogen-containing heterocycles.

In the absence of a catalyst, hydroamination of unfunctionalized olefins is generally difficult to occur due to a high activation barrier caused by electrostatic repulsion between the lone pair of the amine nitrogen and the electron-rich C=C double bond, although the direct addition of amines to alkenes is thermodynamically feasible ($\Delta G \approx 14.7$ kJ/mol for the addition of ammonia to ethylene).[8] Moreover, the negative reaction entropy feature impedes the use of elevated temperatures to overcome the activation barrier. Therefore, a catalyst was generally required to promote the hydroamination of unfunctionalized olefins.



Scheme 1. Schematic presentation of hydroamination of unactivated olefins.

Over the past decades, huge efforts have been made towards transition metal-catalyzed hydroamination and a variety of efficient catalysts have been developed as a result.[9] These catalysts include organolanthanides and related compounds,[9f,g] group IV compounds,[9e,10] noble metal compounds from palladium,[11] platinum,[12] silver,[13] gold,[14] rhodium,[15] iridium,[16] and ruthenium[17] as well as some first row transition metal compounds.[18]

In contrast, Brønsted acid-promoted hydroamination of unfunctionalized olefins bearing electron-rich amino groups is still at the primitive stage mainly due to the buffering effect of the amino group.[11b,19] For Brønsted acid-mediated hydroamination, it is essential to form a carbenium ion intermediate via protonation of

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C=C double bond, and the hydroamination product will be produced by trapping the thus formed carbenium ion with nucleophilic amines. However, in the presence of more basic amino groups, amines would be much easy to get protonated, and alkenes are usually not protonated to give the carbenium ion intermediate. Protonation of amines would in turn decrease the nucleophilicity of the amino groups, rendering the reaction difficult to take place.

In order to achieve sufficient degree of alkene protonation, less basic amino groups, such as arylamine[19,20] or sulfonamides[21] have frequently been used for Brønsted acid-catalyzed hydroamination of alkenes. The rate determining step for these reactions was the formation of a carbenium ion via proton transfer to the C=C double bond. Trapping of the carbenium ion with sulfonamide nitrogen furnished the hydroamination product. Successful examples for hydroamination of unfunctionalized olefins bearing electron rich nitrogen sources were very rare. Ackermann et al. showed that in the presence of 10–20 mol % of BINOL-derived phosphoric acids, intramolecular hydroamination of several *N*-alkyl-pent-4-en-1-amine substrates produced the corresponding 2-methylpyrrolidine products in good yields after 20–24 h of reaction at 130 °C. Some extent of enantioselectivity was also observed when optically pure chiral phosphoric acid was used as the catalyst.[22] The same group also showed that intramolecular hydroamination could be realized using amine salts as acid surrogates.[23] Toste et al. showed that 3,3'-disubstituted BINOL-derived dithiophosphoric acid was effective for intramolecular asymmetric hydroamination of both 1,2- and 1,3-dienes bearing sulfonamides.[21a] The successfulness of this work relied on the high reactivity of the sulfur-containing organocatalyst as well as the high reactivity of both allene and 1,3-diene substrates. These current results indicate that it is essential to fully understand the effects of acidity of the organocatalysts on the course of the organocatalytic hydroamination reactions. In this paper, we wish to report our recent results on CF_3COOH-catalyzed intramolecular hydroamination of *N*-electron-rich unfunctionalized olefins.

2. Results and discussion

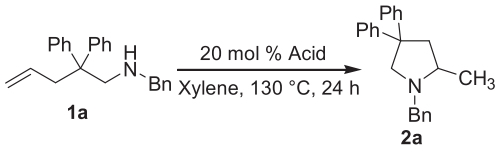
Recently we have shown that zinc salts were able to promote intermolecular and intramolecular hydroamination of *N*-electron-rich unfunctionalized olefins, and ZnI_2 was found to be more suitable than $ZnBr_2$, $ZnCl_2$ or $Zn(OTf)_2$ in intramolecular hydroamination reaction.[24] These preliminary results indicated that in order for a meaningful hydroamination to take place, the catalyst should bear balanced Lewis acidity, i.e., the Lewis acidity of the catalyst should be strong enough so that it could efficiently activate the substrate C=C double bond, but would not over-coordinate with amino group to diminish the nucleophilicity of the latter. It was believed that during ZnI_2-catalyzed hydroamination reactions, the C=C double bond was activated upon zinc coordination, and intramolecular hydroamination was made possible as a result of nucleophilic attack of amino groups on the activated C=C double bond.

Studies also indicated that in addition to zinc halides, such as zinc iodide, the corresponding hydrogen halides were also able to promote the hydroamination of electron-rich amine substrates although in a less effective manner. Encouraged by these preliminary results, we carried out a thorough study on Brønsted acid-catalyzed intramolecular hydroamination of *N*-electron-rich unfunctionalized olefins, and found that 3-hydroxy-2-naphthoic acid was also able to promote the intramolecular hydroamination of *N*-benzyl 4-penten-1-amines and 5-hexen-1-amines.[25]

Study showed that the acidity of the catalyst was very crucial for successful intramolecular hydroamination of 4-penten-1-amines and 5-hexen-1-amines bearing electron-rich amino groups. The use of a weak Brønsted acid allows the preservation of some free acid as well as free amino group in the reaction system, while the use of a strong Brønsted acid would force the equilibrium towards the deprotonated acids and the ammonium.

Based on our understanding of Lewis and Brønsted acid-catalyzed hydroamination of electron-rich amine substrates, we assumed that hydroamination of *N*-electron rich aminoalkenes should be possible using mono-functional Brønsted acid as catalyst. To test this assumption, *N*-benzyl-2,2-diphenylpent-4-en-1-amine (**1a**) was subjected to intramolecular hydroamination in the presence of different inexpensive and easily available Brønsted acids. Compound **1a** was chosen as model substrate due to its ease of preparation and its UV absorption property, which made it easy to monitor the reaction.[24] Further, substrates bearing 2,2-geminal substituents would be cyclized more easily as a result of Thorpe–Ingold effect.[26] Xylene was first chosen as the reaction medium based on previous studies, and the results were summarized in Table 1.

Table 1
Hydroamination of **1a** using different acids[a]



Entry	Acid	**1a**:**2a**[b]	
1	None	100	0
2	TsOH	93	7
3	CSA	89	11
4	TfOH	61	39
5	CH_3SO_3H	54	46
6	**TFA**	<1	**>99**
7	AcOH	86	14
8	Citric acid	68	32
9	Fumaric acid	88	12
10	L-Tartaric acid	73	27
11	Formic acid	>95	<5
12	Malonic acid	82	18
13	Oxalic acid	71	29
14	HCl	>95	<5
15	H_2SO_4	76	24
16	HNO_3	>95	<5
17	H_3PO_4	68	32

The bold signifies the best result in entry 6.
[a] The reactions were carried out with 0.5 mmol of **1a**, 2 mL of xylene, and 0.1 mmol (20 mol %) of acids. Sealed tube was used in the reaction to avoid the evaporation of solvents. Care must be taken when opening the sealed tube.
[b] Based on ^1H NMR analysis of the reaction mixtures.

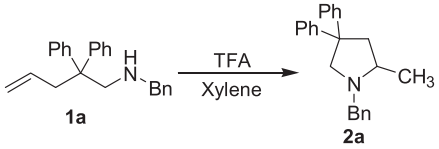
As shown in Table 1, no desired product was observed in the absence of acid (Table 1, entry 1), indicating the important role played by Brønsted acid. Sulfonic acids could promote the reaction but gave product below moderate yields (Table 1, entries 2–5). Complete conversion of **1a** was observed when trifluoroacetic acid was employed (Table 1, entry 6). However, treatment of **1a** with AcOH gave a rather low yield of 14% (Table 1, entry 7), indicating that the Brønsted acid must have enough acidity to promote the reaction. This observation was in good agreement with previous reactions catalyzed by Lewis acids in such a way that the catalyst should bear balanced Lewis acidity to ensure the activation of C=C double bond in one aspect, and to maintain the reactivity of amino groups on the other. Other common organic acids were also investigated, but failed to give satisfactory yields (Table 1, entries 8–13). Inorganic acids generally gave poor results, possibly due to the presence of large amount of water, and the strong Brønsted acid nature of these compounds (Table 1, entries 14–17). These preliminary results indicated that in order for a meaningful

hydroamination to occur, the acid catalyst should have balanced acidity, and preferably without the involvement of water. It was noteworthy that 24% of **2a** could be obtained when concd H_2SO_4 was used as catalyst, which was in disagreement with the observations made by Hartwig that the intramolecular addition of amines without an electron-withdrawing group did not occur when concentrated sulfuric acid was used.[21c] This may be attributed to the use of different substrates. While substrate without geminal-dialkyl groups was used in Hartwig's study, Thorpe–Ingold substrate **1a** was used in the current study. Cyclization of the latter was easier than the former due to the Thorpe–Ingold effect. Other strong inorganic acids gave conversions less than sulfuric acid, possibly due to the large amount of water presented in these acids.

After the finding of a suitable acid for hydroamination reaction, the effects of temperature and catalyst loading on the course of the reaction were studied and the results were summarized in Table 2. As these results indicated, reducing the reaction time led to poor conversions (Table 2, entry 1 vs entry 2). Lowering the amount of catalyst to 10 mol % led to the drop of conversion (Table 2, entry 3), but this could be overcome by elongating the reaction time to 36 h (Table 2, entry 4). Temperature also showed drastic effect on the course of the reaction, and only half of the substrate was converted when the reaction was carried out at 110 °C (Table 2, entry 5).

In order to find a more suitable reaction condition, the reaction carried out in different solvents was examined and the results were listed in Table 3. As these results indicated, high boiling point solvents were superior to low boiling point ones (entries 8–11 vs entries 1–7), and toluene or 1,4-dioxane was more suitable for the reaction. 1,4-Dioxane was finally chosen as the solvent for further study due to its good performance as well as its relatively low toxicity and its ease of removal. Some strong acids were checked in this solvent and showed no improvements (entries 14–17).[27] Reaction in xylene was not further pursued due to the issue of solvent removal.

Table 2
Hydroamination of **1a** under different conditions[a]



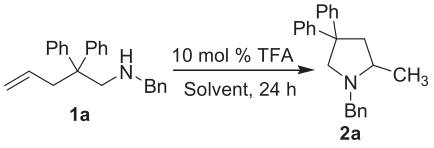
Entry	TFA (mol %)	Temp/time	**1a**:**2a**[b]	
1	20	130 °C, 24 h	<1	>99
2	20	130 °C, 12 h	39	61
3	10	130 °C, 24 h	24	76
4	10	130 °C, 36 h	<1	>99
5	10	110 °C, 48 h	48	52

[a] The reactions were carried out with 0.5 mmol of **1a** and 2 mL of xylene. Sealed tube was used in the reaction to avoid the evaporation of solvents. Care must be taken when opening the sealed tube.
[b] Based on ^{1}H NMR analysis of the reaction mixtures.

With the optimized reaction conditions in hand, the scope of the substrates was studied by varying the substituents on both nitrogen atom and the main chain, and the results were presented in Table 4.

As shown in Table 4, intramolecular hydroamination of *N*-electron-rich olefins proceeded readily, giving the corresponding pyrrolidine products in good to excellent isolated yields. Substrates bearing different *N*-substituents did not significantly influence the reaction outcomes (Table 4, entries 1–14). Notably, methyl, isopropyl, methoxy, fluoro, chloro, bromo, nitro, cyano or ester on the

Table 3
Hydroamination of **1a** in different solvents[a]



Entry	Solvent	*T* (°C)	**1a**:**2a**[b]	
1	THF	80	89	11
2	CH_3CN	80	91	9
3	DCE	80	92	8
4	Hexane	80	>95	<5
5	Acetone	80	>95	<5
6	MeOH	80	>95	<5
7	Benzene	80	87	13
8	Toluene	110	53	47
9	1,4-Dioxane	110	50	50
10	DMF	110	73	27
11	NMP	110	70	30
12[c]	Toluene	110	26	74
13[c]	**1,4-Dioxane**	**110**	4	**96**
14[d]	1,4-Dioxane	110	90	10
15[e]	1,4-Dioxane	110	93	7
16[f]	1,4-Dioxane	110	91	9
17[g]	1,4-Dioxane	110	93	7

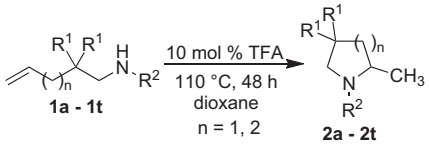
The bold signifies the best result in entry 13.
[a] The reactions were carried out with 0.5 mmol of **1a**, 2 mL of solvent, and 0.05 mmol (10 mol %) of TFA. Sealed tube was used in the reaction to avoid the evaporation of solvents. Care must be taken when opening the sealed tube.
[b] Based on ^{1}H NMR analysis of the reaction mixtures.
[c] Reaction time=48 h.
[d] 10 mol % of TfOH was used.
[e] 10 mol % of CH_3SO_3H was used.
[f] 10 mol % of citric acid was used.
[g] 10 mol % of H_3PO_4 was used.

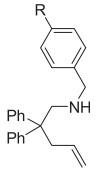
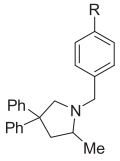
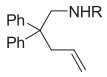
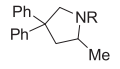
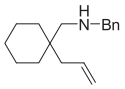
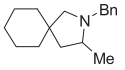
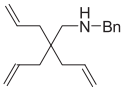
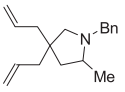
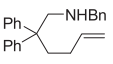
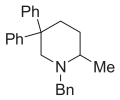
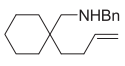
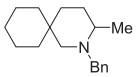
aromatic rings were tolerated, and the electronic effect of the benzylamines had little impact on the course of the reaction (Table 4, entries 1–10). Alkyl substituents, such as isopropyl, isobutyl at the nitrogen atom also showed little effect on the course of the reaction (Table 4, entries 11 and 12). Furthermore, the heteroatom-containing substrates also underwent the cyclization efficiently under the optimal conditions (Table 4, entries 13 and 14). Thorpe–Ingold effect[28] was observed in the reaction, and changing the *gem*-diphenyl groups to other small *gem*-dialkyl groups on the main chain resulted in a drop of yields (Table 4, entries 1–14 vs entries 15–17). Linear aminoalkene lacking of *gem*-substituents (**1r**) failed to react possibly due to lack of Thorpe–Ingold effect (Table 4, entry 18). 5-Hexen-1-amines generally gave poor results possibly due to the unfavorable entropy feature of the reaction (Table 4, entries 19 and 20).[29]

Based on the above observations and previous literature reports,[21c,30] a tentative reaction mechanism was proposed in Scheme 2. Firstly, amino group is protonated by TFA (step 1), and high temperature is needed to generate the free amine and the acid. The second step is the rate limiting step in which the proton is transferred to C=C double bond to give a carbenium ion (step 2).[21c] The thus formed carbenium ion is trapped by amino group, leading to the formation of hydroamination product (step 3). This mechanism indicates that in the proton transfer step, the amino group should be brought close to C=C double bond in space.[31] Therefore, dialkyl substitution at main chain is essential, and this also accounts for the fact that substrates bearing small substituents (Table 4, entries 16 and 17) or lacking of substituents on the main chain (entry 18) show poor reactivity.

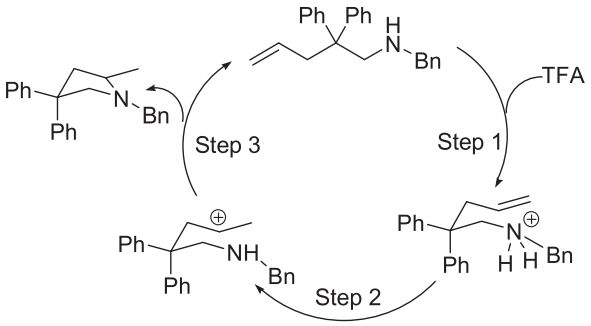
To further test the influence of steric effect of the reaction, di- and trisubstituted aminoalkenes **1u** and **1v** were synthesized and subjected to hydroamination reaction under the standard conditions. As can be predicted, only trace amount of cyclization

Table 4
Intramolecular hydroamination of unactivated alkenes[a]



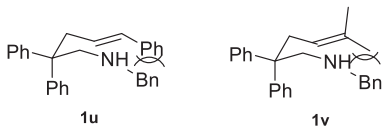
Entry	Substrates		Product		Isolated yield
1		R=H (**1a**)		R=H (**2a**)	93%
2		R=Me (**1b**)		R=Me (**2b**)	93%
3		R=OMe (**1c**)		R=OMe (**2c**)	94%
4		R=*i*-Pr (**1d**)		R=*i*-Pr (**2d**)	90%
5		R=F (**1e**)		R=F (**2e**)	90%
6		R=Cl (**1f**)		R=Cl (**2f**)	88%
7		R=Br (**1g**)		R=Br (**2g**)	83%
8		R=NO_2 (**1h**)		R=NO_2 (**2h**)	86%
9		R=CN (**1i**)		R=CN (**2i**)	86%
10		R=CO_2Me (**1j**)		R=CO_2Me (**2j**)	90%
11		R=*i*-Pr (**1k**)		R=*i*-Pr (**2k**)	82%
12		R=*i*-Bu (**1l**)		R=*i*-Bu (**2l**)	88%
13		2-Furanyl (**1m**)		2-Furanyl (**2m**)	87%
14		2-Pyridyl (**1n**)		2-Pyridyl (**2n**)	80%
15		(**1o**)		(**2o**)	65%
16		(**1p**)		(**2p**)	46%
17		(**1q**)		(**2q**)	16%
18		(**1r**)		(**2r**)	No reaction
19		(**1s**)		(**2s**)	43%
20		(**1t**)		(**2t**)	36%

[a] The reactions were carried out with 0.5 mmol of substrate, 2 mL of dioxane, and 0.05 mmol (10 mol %) of TFA. Sealed tube was used in the reaction to avoid the evaporation of solvents. Care must be taken when opening the sealed tube.



Scheme 2. Proposed reaction mechanism.

products were detected for both substrates. This may be attributed to the steric hindrance of these substrates, which pushed the amino groups away from the reaction center, and rendering the reactions difficult to proceed.



3. Conclusions

In summary, the acidity of a Brønsted acid was essential for promoting the intramolecular hydroamination of unfunctionalized olefins bearing electron rich nitrogen sources. Trifluoroacetic acid showed the highest activity among commonly available inorganic and organic acids tested. In the presence of 10 mol % trifluoroacetic acid, *N*-alkyl-pent-4-en-1-amines were converted to the corresponding 2-methylpyrrolidines in good isolated yields. Thorpe–Ingold effect was observed during the reaction. The amino group and the C=C double must close to each other in order for a meaningful hydroamination to take place. The current work would shed light on the understanding of Brønsted acid-catalyzed intramolecular cyclization of unfunctionalized olefins.

4. Experimental section

4.1. General information

All starting materials were purchased from commercial sources and were used as received. All solvents used in the reactions were dried and distilled from appropriate drying agents prior to use. A sealed tube was used in the reaction to avoid the evaporation of the solvent, but this is not a must. Reactions were monitored by thin layer chromatography using silica gel GF_{254} plates. Flash column chromatography was performed using silica gel (200–300 meshes). Petroleum ether used had a boiling point range of 60–90 °C. ^1H and ^{13}C NMR (400 and 100 MHz, respectively) spectra were recorded with Bruker Avance DRX-400 NMR Spectrometer in $CDCl_3$. ^1H NMR chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants (Hertz) and integration. ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS). High resolution mass spectrometry (HRMS) analyses were carried out on IonSpec 7.0T FTICR HR-ESI-MS.

4.2. General procedure for TFA-catalyzed intramolecular hydroamination

A sealed tube was charged with dry 1,4-dixoane (2 mL), aminoalkene (0.5 mmol), and trifluoroacetic acid (0.05 mmol, 10 mol %). The tube was then sealed and was heated in an oil bath (110 °C). The reaction mixture was stirred at this temperature for 48 h and was cooled to room temperature. The sealed tube was opened with care, and 30 mL of CH_2Cl_2 was added. The mixture was washed with aqueous Na_2CO_3, dried ($MgSO_4$), and concentrated to give an oil, which was purified by flash column chromatography to give the corresponding products.

*4.2.1. 1-Benzyl-2-methyl-4,4-diphenylpyrrolidine (**2a**).* Compound **2a** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=20:1) in 93% yield as a white solid. Mp 67–68 °C. ^1H NMR (400 MHz, $CDCl_3$) δ=7.45–6.93 (m, 15H), 3.99 (d, *J*=13.2 Hz, 1H), 3.55 (d, *J*=9.9 Hz, 1H), 3.14 (d, *J*=13.2 Hz, 1H), 2.82 (dd, *J*=12.7, 7.7 Hz, 1H), 2.77–2.72 (m, 1H), 2.68 (d, *J*=9.9 Hz, 1H), 2.11 (dd, *J*=12.7, 7.7 Hz, 1H), 1.07 (d, *J*=6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=149.57, 147.64, 139.01, 127.52, 127.14, 127.07, 126.75, 126.36, 126.17, 125.71, 124.73, 124.33, 65.38, 58.59, 56.94, 51.44, 46.93, 18.46. ^1H NMR and ^{13}C NMR data agreed with those reported previously.[32]

*4.2.2. 2-Methyl-1-(4-methylbenzyl)-4,4-diphenylpyrrolidine (**2b**).* Compound **2b** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=25:1) in a 93% yield as a white solid. Mp 74–75 °C. ^1H NMR (400 MHz, $CDCl_3$) δ=7.41–7.01 (m, 14H), 4.08 (d, *J*=13.1 Hz, 1H), 3.65 (d, *J*=9.9 Hz, 1H), 3.23 (d, *J*=13.1 Hz, 1H), 2.94 (dd, *J*=12.8, 7.7 Hz, 1H), 2.87–2.82 (m, 1H), 2.78 (d, *J*=9.9 Hz, 1H), 2.37 (s, 3H), 2.22 (dd, *J*=12.8, 7.7 Hz, 1H), 1.19 (d, *J*=6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=150.82, 148.89, 137.07, 136.38, 129.03, 128.67, 128.25, 127.94, 127.57, 127.39, 125.90, 125.50, 66.51, 59.73, 57.82, 52.60, 48.15, 21.27, 19.65. HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{25}H_{27}N$, 342.2216; found: 342.2221.

*4.2.3. 1-(4-Methoxybenzyl)-2-methyl-4,4-diphenylpyrrolidine (**2c**).* Compound **2c** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=20:1) in 94% yield as a white solid. Mp 86 °C. ^1H NMR (400 MHz, $CDCl_3$) δ=7.36–7.10 (m, 12H), 6.91 (d, *J*=8.5 Hz, 2H), 4.07 (d, *J*=13.0 Hz, 1H), 3.85 (s, 3H), 3.67 (d, *J*=9.9 Hz, 1H), 3.23 (d, *J*=13.0 Hz, 1H), 2.96 (dd, *J*=12.8, 7.8 Hz, 1H), 2.90–2.81 (m, 1H), 2.80 (d, *J*=9.9 Hz, 1H), 2.24 (dd, *J*=12.8, 7.8 Hz, 1H), 1.20 (d, *J*=6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=158.53, 150.70, 148.82, 132.11, 129.72, 128.15, 127.84, 127.47, 127.28, 125.80, 125.40, 113.60, 66.35, 59.57, 57.31, 55.29, 52.46, 48.07, 19.54. ^1H NMR and ^{13}C NMR data agreed with those reported previously.[32]

*4.2.4. 1-(4-Isopropylbenzyl)-2-methyl-4,4-diphenylpyrrolidine (**2d**).* Compound **2d** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=20:1) in 90% yield as oil. ^1H NMR (400 MHz, $CDCl_3$) δ=7.44–7.16 (m, 14H), 4.19 (d, *J*=13.3 Hz, 1H), 3.79 (d, *J*=9.9 Hz, 1H), 3.35 (d, *J*=13.3 Hz, 1H), 3.09–2.99 (m, 2H), 2.98–2.94 (m, 1H), 2.92 (d, *J*=9.7 Hz, 1H), 2.33 (dd, *J*=12.6, 7.8 Hz, 1H), 1.39 (d, *J*=7.0 Hz, 6H), 1.29 (d, *J*=6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=149.02, 150.86, 148.86, 147.42, 137.44, 128.59, 128.23, 127.92, 127.59, 127.40, 126.35, 125.89, 125.50, 66.58, 59.68, 57.62, 52.56, 48.16, 34.08, 24.25, 24.20, 19.53. HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{27}H_{31}N$, 370.2529; found: 370.2532.

*4.2.5. 1-(4-Fluorobenzyl)-2-methyl-4,4-diphenylpyrrolidine (**2e**).* Compound **2e** was purified by flash chromatography on silica

gel (petroleum ether/ethyl acetate=20:1) in 90% yield as a white solid. Mp 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.48–7.01 (m, 14H), 4.06 (d, J=13.2 Hz, 1H), 3.64 (d, J=9.8 Hz, 1H), 3.26 (d, J=13.2 Hz, 1H), 2.96 (dd, J=12.6, 7.8 Hz, 1H), 2.91–2.83 (m, 1H), 2.80 (d, J=9.8 Hz, 1H), 2.25 (dd, J=12.6, 7.8 Hz, 1H), 1.19 (d, J=5.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=161.87 (d, J_{C-F}=244 Hz), 150.53, 148.67, 135.80, 129.99 (d, J_{C-F}=7.8 Hz), 128.18, 127.87, 127.42, 127.21, 125.67 (d, J_{C-F}=38.7 Hz), 115.09, 114.88, 66.37, 59.61, 57.21, 52.52, 47.97, 19.53. ^{19}F NMR (376 MHz, $CDCl_3$) δ=−116.39. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR data agreed with those reported previously.[32]

*4.2.6. 1-(4-Chlorobenzyl)-2-methyl-4,4-diphenylpyrrolidine (**2f**).* Compound **2f** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=20:1) in 88% yield as a white solid. Mp 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.35–6.93 (m, 14H), 3.94 (d, J=13.4 Hz, 1H), 3.51 (d, J=9.8 Hz, 1H), 3.13 (d, J=13.4 Hz, 1H), 2.83 (dd, J=12.7, 7.8 Hz, 1H), 2.75 (dt, J=13.5, 6.6 Hz, 1H), 2.67 (d, J=9.8 Hz, 1H), 2.13 (dd, J=12.7, 7.7 Hz, 1H), 1.07 (d, J=5.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=149.39, 147.54, 137.63, 131.34, 128.80, 127.29, 127.12, 126.82, 126.33, 126.12, 124.81, 124.44, 65.32, 58.58, 56.21, 51.48, 46.84, 18.46. ^{1}H NMR and ^{13}C NMR data agreed with those reported previously.[33]

*4.2.7. 1-(4-Bromobenzyl)-2-methyl-4,4-diphenylpyrrolidine (**2g**).* Compound **2g** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=50:1) in 83% yield as a white solid. Mp 93–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.52 (d, J=8.1 Hz, 2H), 7.35–7.22 (m, 12H), 4.09 (d, J=13.4 Hz, 1H), 3.69 (d, J=9.8 Hz, 1H), 3.29 (d, J=13.4 Hz, 1H), 3.00 (dd, J=12.6, 7.8 Hz, 1H), 2.95–2.88 (m, 1H), 2.85 (d, J=9.8 Hz, 1H), 2.31 (dd, J=12.6, 7.8 Hz, 1H), 1.24 (d, J=5.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=150.44, 148.60, 139.24, 131.39, 130.26, 129.23, 128.19, 127.82, 127.40, 127.18, 125.94, 125.42, 66.39, 59.66, 57.33, 52.57, 47.89, 19.53. ^{1}H NMR and ^{13}C NMR data agreed with those reported previously.[34]

*4.2.8. 2-Methyl-1-(4-nitrobenzyl)-4,4-diphenylpyrrolidine (**2h**).* Compound **2h** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=15:1) in 86% yield as a white solid. Mp 123–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.22 (d, J=8.4 Hz, 2H), 7.56 (d, J=8.4 Hz, 2H), 7.44–7.15 (m, 10H), 4.16 (d, J=14.3 Hz, 1H), 3.64 (d, J=9.7 Hz, 1H), 3.46 (d, J=14.3 Hz, 1H), 3.01–2.92 (m, 2H), 2.88 (d, J=9.7 Hz, 1H), 2.33 (dd, J=12.6, 7.8 Hz, 1H), 1.23 (d, J=5.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=149.02, 147.27, 147.21, 145.95, 127.95, 127.19, 126.91, 126.25, 126.00, 125.01, 124.61, 122.49, 65.41, 58.67, 56.27, 51.67, 46.57, 18.45. ^{1}H NMR and ^{13}C NMR data agreed with those reported previously.[12b]

*4.2.9. 4-((2-Methyl-4,4-diphenylpyrrolidin-1-yl)methyl)benzonitrile (**2i**).* Compound **2i** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=40:1) in 86% yield as a white solid. Mp 102–104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.65 (d, J=8.1 Hz, 2H), 7.51 (d, J=8.1 Hz, 2H), 7.45–7.07 (m, 10H), 4.14 (d, J=14.1 Hz, 1H), 3.64 (d, J=9.7 Hz, 1H), 3.40 (d, J=14.2 Hz, 1H), 3.06–2.90 (m, 2H), 2.88 (d, J=9.7 Hz, 1H), 2.32 (dd, J=11.5, 6.4 Hz, 1H), 1.22 (d, J=5.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=150.18, 148.40, 146.14, 132.16, 129.07, 128.28, 127.98, 127.36, 127.11, 126.01, 125.68, 119.13, 110.65, 66.50, 59.72, 57.63, 52.75, 47.72, 19.56. ^{1}H NMR and ^{13}C NMR data agreed with those reported previously.[18d]

*4.2.10. Methyl 4-((2-methyl-4,4-diphenylpyrrolidin-1-yl)methyl) benzoate (**2j**).* Compound **2j** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=40:1) in 90% yield as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.91 (d, J=8.1 Hz, 2H), 7.35 (d, J=8.1 Hz, 2H), 7.27–6.97 (m, 10H), 4.02 (d, J=13.8 Hz, 1H), 3.83 (s, 3H), 3.52 (d, J=9.8 Hz, 1H), 3.24 (d, J=13.8 Hz, 1H), 2.81 (ddd, J=26.0, 12.9, 7.4 Hz, 2H), 2.71 (d, J=9.8 Hz, 1H), 2.15 (dd, J=12.3, 7.3 Hz, 1H), 1.08 (d, J=5.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=167.15, 150.37, 148.57, 145.78, 129.61, 128.78, 128.44, 128.19, 127.89, 127.38, 127.16, 125.88, 125.52, 66.50, 59.77, 57.77, 52.64, 52.02, 47.86, 19.52. ^{1}H NMR and ^{13}C NMR data agreed with those reported previously.[18d]

*4.2.11. 1-Isopropyl-2-methyl-4,4-diphenylpyrrolidine (**2k**).* Compound **2k** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=5:1) in 82% yield as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.56–6.98 (m, 10H), 3.82 (d, J=9.6 Hz, 1H), 3.13–3.00 (m, 3H), 2.90 (dd, J=12.7, 8.0 Hz, 1H), 2.19 (dd, J=12.7, 7.8 Hz, 1H), 1.23 (d, J=6.7 Hz, 3H), 1.03 (d, J=6.2 Hz, 3H), 1.00 (d, J=6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=150.11, 149.02, 128.19, 127.92, 127.41, 127.28, 125.78, 125.41, 59.32, 55.39, 52.22, 48.84, 47.20, 22.66, 20.61, 15.64. HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{20}H_{25}N$, 280.2060; found: 280.2064.

*4.2.12. 1-Isobutyl-2-methyl-4,4-diphenylpyrrolidine (**2l**).* Compound **2l** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=30:1) in 88% yield as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.63–6.98 (m, 10H), 3.93 (d, J=9.6 Hz, 1H), 2.94 (dd, J=12.8, 7.6 Hz, 1H), 2.87 (d, J=9.6 Hz, 1H), 2.78–2.67 (m, 1H), 2.54–2.47 (m, 1H), 2.28–2.10 (m, 2H), 1.95–1.83 (m, 1H), 1.18 (d, J=6.0 Hz, 3H), 1.09 (d, J=6.6 Hz, 3H), 1.01 (d, J=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=151.38, 148.96, 128.21, 127.88, 127.68, 127.38, 125.88, 125.48, 67.52, 62.72, 60.36, 52.80, 48.15, 27.85, 21.49, 21.00, 19.69. ^{1}H NMR and ^{13}C NMR data agreed with those reported previously.[35]

*4.2.13. 1-(Furan-2-ylmethyl)-2-methyl-4,4-diphenylpyrrolidine (**2m**).* Compound **2m** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=50:1) in 87% yield as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.30–7.03 (m, 11H), 6.26 (s, 1H), 6.11 (s, 1H), 3.88 (d, J=14.3 Hz, 1H), 3.67 (d, J=9.8 Hz, 1H), 3.43 (d, J=14.3 Hz, 1H), 2.93 (d, J=9.9 Hz, 1H), 2.84–2.65 (m, 2H), 2.12 (dd, J=11.4, 7.4 Hz, 1H), 1.07 (d, J=5.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=153.05, 150.35, 148.68, 141.79, 128.18, 127.98, 127.41, 127.18, 125.83, 125.49, 110.11, 107.83, 66.13, 58.80, 52.48, 49.29, 47.91, 19.20. ^{1}H NMR and ^{13}C NMR data agreed with those reported previously.[18b]

*4.2.14. 2-((2-Methyl-4,4-diphenylpyrrolidin-1-yl)methyl)pyridine (**2n**).* Compound **2n** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=10:1) in 80% yield as a white solid. Mp 83–85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.46 (d, J=4.4 Hz, 1H), 7.56 (td, J=7.7, 1.4 Hz, 1H), 7.37 (d, J=7.7 Hz, 1H), 7.24–7.01 (m, 11H), 4.09 (d, J=14.4 Hz, 1H), 3.60 (d, J=9.9 Hz, 1H), 3.50 (d, J=14.4 Hz, 1H), 2.93 (d, J=9.8 Hz, 1H), 2.83 (ddd, J=19.7, 12.6, 7.1 Hz, 2H), 2.21 (dd, J=12.1, 7.6 Hz, 1H), 1.10 (d, J=5.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=159.43, 149.38, 147.87, 147.48, 135.37, 127.13, 126.86, 126.41, 126.14, 124.82, 124.48, 121.74, 120.77, 65.51, 58.64, 58.61, 51.83, 46.76, 18.42. ^{1}H NMR and ^{13}C NMR data agreed with those reported previously.[18b]

*4.2.15. 2-Benzyl-3-methyl-2-azaspiro[4.5]decane (**2o**).* Compound **2o** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=20:1) in 65% yield as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.44–7.25 (m, 5H), 4.09 (d, J=13.2 Hz, 1H), 3.16 (d, J=13.2 Hz, 1H), 2.85 (d, J=9.3 Hz, 1H), 2.66–2.49 (m, 1H), 1.94 (d, J=9.3 Hz, 1H), 1.82 (dd, J=12.4, 7.0 Hz, 1H), 1.56–1.30 (m, 11H), 1.22 (d, J=5.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=140.04, 128.70, 128.12, 126.56, 66.85, 59.06, 58.12, 47.20, 39.60, 38.70, 26.24, 23.71, 23.54, 19.09. ^{1}H NMR and ^{13}C NMR data agreed with those reported previously.[12b]

*4.2.16. 4,4-Diallyl-1-benzyl-2-methylpyrrolidine (**2p**).* Compound **2p** was purified by flash chromatography on silica gel (petroleum

ether/ethyl acetate=60:1) in 46% yield as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.49–7.03 (m, 5H), 5.96–5.44 (m, 2H), 5.17–4.79 (m, 4H), 3.94 (d, J=13.3 Hz, 1H), 2.99 (d, J=13.3 Hz, 1H), 2.63 (d, J=9.5 Hz, 1H), 2.54–2.34 (m, 1H), 2.12–2.07 (m, 2H), 1.98 (d, J=5.2 Hz, 2H), 1.88 (d, J=9.5 Hz, 1H), 1.69 (dd, J=12.7, 7.2 Hz, 1H), 1.29 (dd, J=12.7, 9.2 Hz, 1H), 1.06 (d, J=6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=140.11, 135.80, 135.42, 128.50, 128.06, 126.57, 117.15, 116.99, 64.54, 59.42, 57.74, 44.81, 44.45, 43.45, 41.64, 19.21. HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{26}N$, 256.2065; found: 256.2063.

*4.2.17. 1-Benzyl-2,4,4-trimethylpyrrolidine (**2q**).* Compound **2q** was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=30:1) in 16% yield as oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.42–7.24 (m, 5H), 4.06 (d, J=13.2 Hz, 1H), 3.15 (d, J=13.2 Hz, 1H), 2.68 (d, J=9.1 Hz, 1H), 2.65–2.54 (m, 1H), 1.99 (d, J=9.1 Hz, 1H), 1.77 (dd, J=12.4, 7.3 Hz, 1H), 1.42–1.30 (m, 1H), 1.20 (d, J=6.0 Hz, 3H), 1.12 (s, 3H), 1.02 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ=140.10, 128.72, 128.08, 126.59, 68.41, 59.80, 58.06, 49.14, 35.39, 30.65, 29.28, 19.49. ^{1}H NMR and ^{13}C NMR data agreed with those reported previously.[12b]

*4.2.18. 1-Benzyl-2-methyl-5,5-diphenylpiperidine (**2s**).* Compound **2s** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=50:1) in 43% yield as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.32–6.90 (m, 15H), 3.96 (d, J=13.3 Hz, 1H), 3.27 (d, J=12.3 Hz, 1H), 3.05 (d, J=13.3 Hz, 1H), 2.35 (dt, J=21.9, 6.1 Hz, 3H), 2.14–2.03 (m, 1H), 1.59–1.49 (m, 1H), 1.35–1.23 (m, 1H), 1.05 (d, J=6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=148.64, 146.80, 139.51, 129.54, 128.52, 128.06, 127.99, 127.67, 127.10, 126.93, 125.70, 125.35, 61.03, 58.97, 56.17, 46.61, 34.30, 31.05, 18.70. ^{1}H NMR and ^{13}C NMR data agreed with those reported previously.[36]

*4.2.19. 2-Benzyl-3-methyl-2-azaspiro[5.5]undecane (**2t**).* Compound **2t** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=50:1) in 36% yield as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.34–7.27 (m, 4H), 7.23–7.19 (m, 1H), 3.99 (d, J=14.0 Hz, 1H), 3.05 (d, J=14.0 Hz, 1H), 2.52 (d, J=11.6 Hz, 1H), 2.27–2.22 (m, 1H), 1.62 (d, J=11.2 Hz, 1H), 1.54–1.28 (m, 10H), 1.17–1.03 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ=140.7, 128.5, 128.0, 126.4, 61.6, 58.3, 57.2, 37.9, 34.8, 33.2, 30.8, 26.9, 21.6, 19.1. ^{1}H NMR and ^{13}C NMR data agreed with those reported previously.[36]

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Supplementary data

Supplementary data include Table 1 with pK_a values of the acids and copies of NMR spectra of the products. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.06.061.

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