Tetrahedron 65 (2009) 638–643

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Solid-phase synthesis of aryl, heteroaryl, and sterically hindered alkyl amines using the Curtius rearrangement

Satoshi Sunami *, Mitsuru Ohkubo

Tsukuba Research Institute, Banyu Pharmaceutical Co. Ltd, Okubo-3, Tsukuba 300-2611, Ibaraki, Japan

ARTICLE INFO

Article history:
Received 2 October 2008
Received in revised form 5 November 2008
Accepted 6 November 2008
Available online 12 November 2008

Keywords:
Solid-phase synthesis
Curtius rearrangement
Resin-bound carbamate
Aryl and heteroaryl amines
Sterically hindered alkyl amines

ABSTRACT

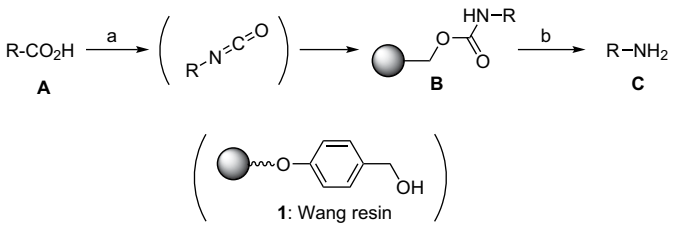
An efficient method for the solid-phase synthesis of aryl amines, heteroaryl amines, and sterically hindered alkyl amines has been developed. The key step in this process was the formation of resin-bound carbamates (**B**) by the Curtius rearrangement of aryl carboxylic acids with Wang resin providing the trapping hydroxyl group. N-Alkylation reactions of **B** gave secondary amines in good yield. Some biaryl amines, which are found widely in biologically active substances, were also prepared by the Suzuki reaction of resin-bound carbamates of 2-iodoaniline (**16**) or 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**21**). The developed methods can be applied to the preparation of libraries containing aryl, heteroaryl, and sterically hindered alkyl amine structures as the pharmacophores.

1. Introduction

Solid-phase synthetic technologies have gained increasing importance, especially in the pharmaceutical industry. Since bio logically active compounds often possess a variety of amine structures in their essential pharmacophores, the construction of such amine libraries is useful for the discovery of lead compounds for new drugs. Carbamate groups are most commonly used for N-protection of amines.[1,2] However, the direct introduction of *N*-carbamates especially to aryl or heteroaryl amines and sterically hindered alkyl amines is not an easy task. It requires long reaction times and/or high temperatures, and often times results in moderate yields, due largely to the poor nucleophilicity of the aryl amines and steric hindrance of such alkyl amines. For this reason, carbamates of such amines have usually been prepared from the corresponding carboxylic acids via the Curtius rearrangement in solution-phase, followed by trapping the isocyanate intermediate with alcohols.[3]

In solid-phase chemistry, the reaction of aryl amines with *p*-nitrophenylcarbonate resin gives carbamates in poor yield. For example, the coupling of 4,6-dimethyl-2-aminopyridine to *p*-nitrophenylcarbonate resin using potassium bis(trimethylsilyl)-amide as a base according to the previously published solution-phase method[4] resulted in a 40% yield despite the use of a threefold excess of the amine and a long reaction time (20 h). Buchstaller described the reaction of some phenylisocyanate derivatives and Wang resin to obtain the corresponding resin-bound anilines with a carbamate bond.[5] However, the number of easily available phenylisocyanate derivatives is limited. To overcome these problems, we developed the efficient synthesis of aryl and heteroaryl amines (**C**) via solid-phase Curtius rearrangement (Scheme 1).[6] The key step in this process was the formation of resin-bound aryl or heteroaryl carbamates (**B**) by the Curtius rearrangement of aryl carboxylic acids (**A**) with Wang resin (**1**) providing the trapping hydroxyl group. We believe that by this method, combinatorial libraries with more structural diversity can be prepared because many carboxylic acids, which are the starting materials for the Curtius rearrangement, can be easily obtained.

Recently, we have found that the solid-phase Curtius rearrangement could be applied to the synthesis of sterically hindered alkyl amines. To the best of our knowledge, this is the first example for the immobilization of sterically hindered alkyl amines such as primary *tert*-alkyl amines to solid-supports. Here, we report the



Scheme 1. (a) Compound **1**, diphenylphosphoryl azide, triethylamine, toluene; (b) 50% trifluoroacetic acid (TFA)/CH_2Cl_2.

* Corresponding author. Tel.: +81 29 877 2000; fax: +81 29 877 2029.
E-mail address: satoshi_sunami@merck.com (S. Sunami).

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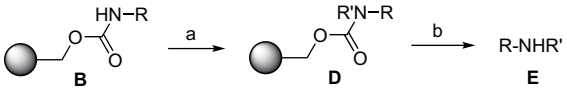
doi:10.1016/j.tet.2008.11.012

efficient synthesis of aryl, heteroaryl, and sterically hindered alkyl amines via the solid-phase Curtius rearrangement, as well as some applications of the resin-bound carbamates (**B**), including the synthesis of secondary amines (**E**) by an N-alkylation reaction of **B** (Scheme 2) and biaryl amines (**19**, **24**) by the Suzuki coupling reaction of resin-bound 2-iodoaniline (**16**) or 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**21**; Scheme 3).



Scheme 2. (a) (1) NaH or LiHMDS, DMF (2) R′-X; (b) 50% TFA/CH_2Cl_2.

2. Results and discussion

2.1. The Curtius rearrangement of aryl and heteroaryl carboxylic acids

At first, the Curtius rearrangement of a range of aryl and heteroaryl carboxylic acids was carried out in the presence of commercial polystyrene Wang resin as the trapping hydroxyl group source (Scheme 1: Wang resin (**1**)/3-fold excess of carboxylic acid (**A**)/5-fold excess of diphenylphosphoryl azide/10-fold excess of triethylamine/toluene/100 °C/16 h). The formation of resin-bound carbamate **B** was monitored by IR spectroscopy, and a strong absorbance appeared at about 1730 cm^{-1} (νC=O) as the reaction progressed (Figs. 1 and 2).

Figure 2 shows the IR spectrum of the polystyrene resin of type **B**, which was generated by the Curtius rearrangement of *p*-toluic acid (**2a**) with **1**. Compared to the IR spectrum of the starting Wang resin (Fig. 1), the appearance of the strong C=O absorbance of the carbamate bond at 1735.8 cm^{-1} was clear.

After the product was cleaved from the resin by treatment with 50% TFA in CH_2Cl_2, the desired aryl and heteroaryl amines **3a**–**3j** were afforded in good yield with good purity. The results are shown in Table 1. This procedure worked well for benzoic acids with both a strong electron-withdrawing substituent (**2b**: entry 2) and an electron-donating substituent (**2c**: entry 3) as well as *p*-toluic acid (**2a**: entry 1). The sterically hindered 2-iodobenzoic acid (**2d**) also provided the corresponding 2-iodoaniline (**3d**) in >95% yield with acceptable purity (entry 4). The reaction of pyridine carboxylic acids (**2e**–**2g**) proceeded smoothly with all regioisomers (entries 5–7). Other heteroaryl carboxylic acids, such as pyrazinyl (**2h**) and 2-thienyl carboxylic acids (**2i**, **2j**), also gave good results (entries 8–10).

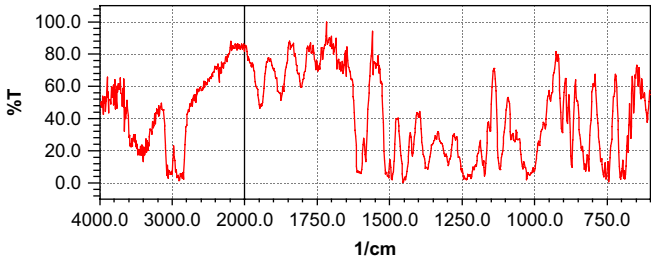


Figure 1. IR spectrum of the commercial Wang resin (Novabiochem, 100–200 mesh, 0.72 mmol/g).

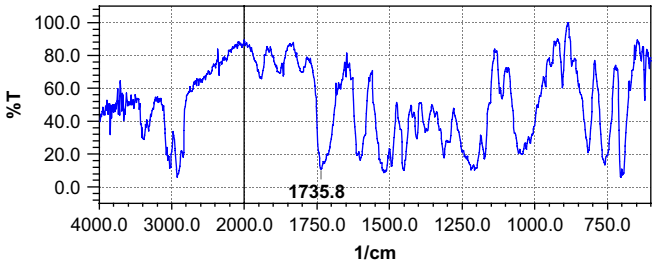
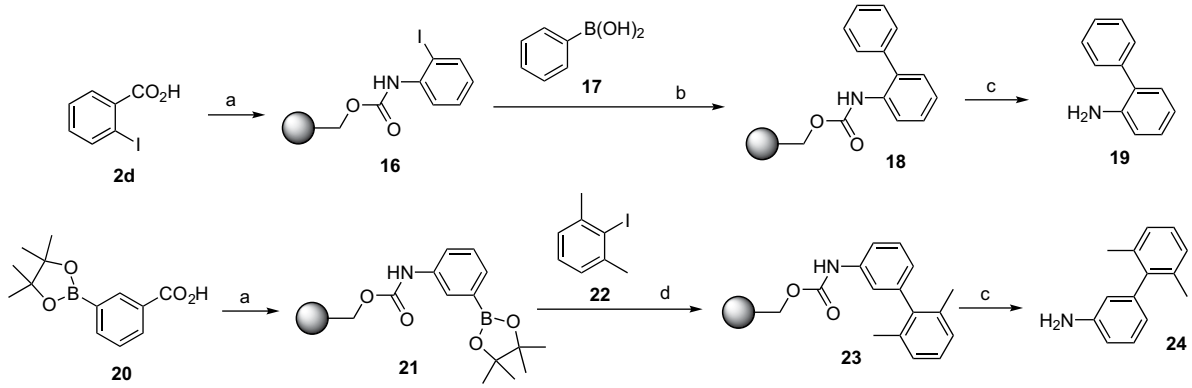


Figure 2. IR Spectrum of the resin-bound carbamate (**B**) of *p*-methylaniline.

2.2. The Curtius rearrangement of alkyl carboxylic acids

We also applied this solid-phase method to a range of sterically hindered alkyl carboxylic acids. The results are shown in Table 2. Several 1-substituted cycloalkylcarboxylic acids of three-, four-, and five-membered rings were tested (entries 1–4). This procedure worked well on 1-methyl-cyclopropylcarboxylic acid (**4a**) and 1-phenyl-cyclopropylcarboxylic acid (**4b**), as well as 1-trifluoromethylcyclobutylcarboxylic acid (**4c**) and 1-phenyl-cyclopentylcarboxylic acid (**4d**). Severely sterically hindered carboxylic acids such as 2,2-dimethylpent-4-enoic acid (**4e**) and dicyclohexylacetic acid (**4f**) also gave the corresponding amines (**5e**, **5f**) with satisfactory results (entries 5 and 6). Even carboxylic acids at sterically hindered junction positions of bridged bicyclic carbocycle systems (**4g**, **4h**) were converted to the corresponding amines (**5g**, **5h**) with excellent results (entries 7 and 8). Methyl 1-aminocyclopropanecarboxylate (**5i**) was obtained in >95% yield with good purity from easily available 1,1-cyclopropanedicarboxylic acid mono methyl ester[7] (**4i**: entry 9). Olefin (entry 5), ketone (entry 7), and methyl ester (entry 9) functional groups were all tolerated under these reaction conditions.



Scheme 3. (a) Compound **1**, diphenylphosphoryl azide, triethylamine, toluene, 100 °C; (b) **17**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, 1,2-dimethoxyethane (DME), 100 °C; (c) 50% TFA/CH_2Cl_2; (d) **22**, $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, 100 °C.

The Curtius rearrangement has been used with a variety of carboxylic acids under solution-phase conditions and we have now shown that the solid-phase Curtius rearrangement will be as widely applicable.

2.3. Application of the resin-bound carbamates

Once an efficient method for immobilization of various amines to resins was found, we then focused on some applications of the resin-bound carbamates. The N-alkylation of the resin-bound carbamates (**B**) was tested as the first example (Scheme 2).

The results are shown in Table 3. Both resin-bound carbamates of 4-methylaniline (**7**: entries 1 and 2) and 6-methyl-2-aminopyridine (**8**: entries 3 and 4), which were synthesized from **2a** and **6**, respectively, were treated with a 5-fold excess of NaH in DMF for 1.5 h at room temperature, followed by a 10-fold excess of alkylating reagents at 80 °C. Within 16 h, ethyl iodide as well as the more reactive allyl bromide reacted completely with those resins. After being cleaved from the resin, the desired secondary amines (**10**–**13**) were obtained in good yield and purity.

On the other hand, N-alkylation of the resin-bound carbamates of 1-phenylcyclopropylamine (**9**) required higher temperature and stronger base. Compound **9** was treated with a 10-fold excess of lithium hexamethyldisilazide in DMF for 1.5 h at room temperature, followed by a 10-fold excess of alkylating reagents at 120 °C. Within 16 h, ethyl iodide as well as the more reactive benzyl bromide reacted completely with those resins. After being cleaved from the resin, the desired secondary amines (**14**, **15**) were obtained with good results (entries 5 and 6).

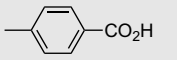
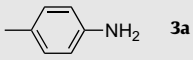
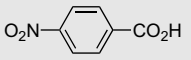
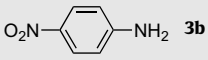
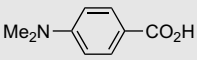
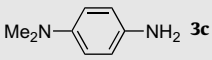
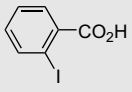
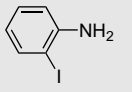
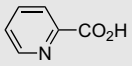
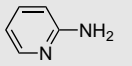
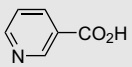
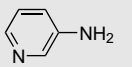
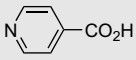
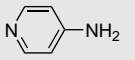
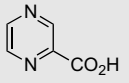
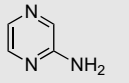
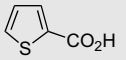
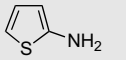
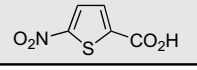
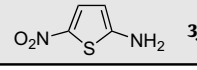
Next, we tried the Suzuki coupling reaction of resin-bound carbamates of 2-iodoaniline (**16**) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**21**) (Scheme 3).

The results are shown in Table 4. The Suzuki coupling reaction of **16** with phenylboronic acid (**17**) under typical conditions [0.05 equiv of $Pd(PPh_3)_4$, 2 M Na_2CO_3, DME, 100 °C, 16 h] followed by treatment with TFA provided the desired biphenyl-2-amine (**19**) in 85% yield with 91% purity (entry 1).

Introduction of an aniline with a boronate moiety to the solid support was successfully conducted by the solid-phase Curtius rearrangement of the commercially available 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (**20**) to give **21**. To the best of our knowledge, this is the first example of the Curtius rearrangement on a carboxylic acid containing a boronate moiety. The Suzuki coupling reaction of **21** with 2,6-dimethyliodobenzene (**22**) under the same conditions as entry 1 followed by cleavage from the resin with TFA gave the desired 3-(2,6-dimethylphenyl)aniline (**24**) in 98% yield with 90% purity (entry 2).

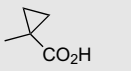
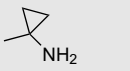
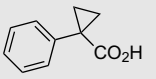
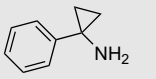
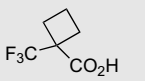
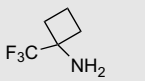
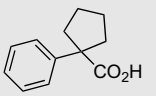
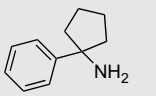
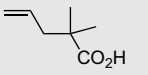
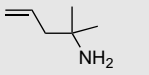
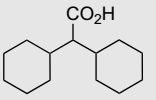
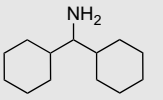
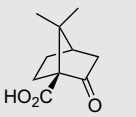
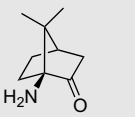
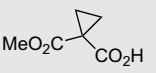
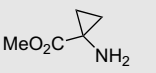
Although aryl halides are the usual immobilized coupling partners for the solid-phase Suzuki coupling reaction, immobilization of an arylboronate moiety is also profitable. Combined use of resin-bound haloanilines and anilines with boronate moieties will make it possible to prepare a variety of biaryl amines, which are found widely in biological active compounds.

Table 1
The solid-phase Curtius rearrangement of aryl and heteroaryl carboxylic acids

Entry	Starting carboxylic acid		Product amines		Yield (%)	Purity[b] (%)
1		**2a**		**3a**	>95[a]	83
2		**2b**		**3b**	>95	94
3		**2c**		**3c**	>95[a]	84
4		**2d**		**3d**	>95	82
5		**2e**		**3e**	>95[a]	91
6		**2f**		**3f**	>95[a]	82
7		**2g**		**3g**	>95[a]	83
8		**2h**		**3h**	90[a]	86
9[c]		**2i**		**3i**	>95	85
10[c]		**2j**		**3j**	>95	90

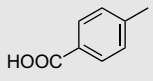
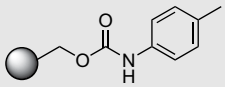
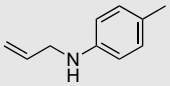
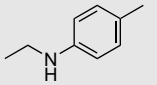
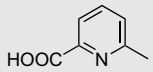
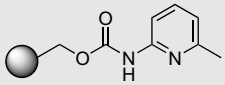
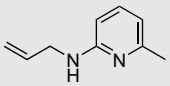
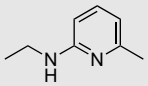
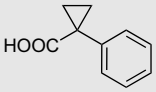
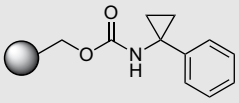
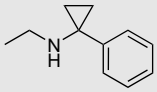
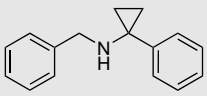
[a] Yield was based on the TFA salt.
[b] Purity was determined by HPLC and ^{1}H NMR.
[c] This reaction was carried out at 80 °C.

Table 2
The solid-phase Curtius rearrangement of sterically hindered alkyl carboxylic acids

Entry	Starting carboxylic acid		Product amines		Yield[a] (%)	Purity[b] (%)
1		**4a**		**5a**	>95	92
2		**4b**		**5b**	>95	90
3		**4c**		**5c**	>95	90
4		**4d**		**5d**	76	91
5		**4e**		**5e**	57	88
6		**4f**		**5f**	60	85
7		**4g**		**5g**	>95	92
8		**4h**		**5h**	>95	93
9		**4i**		**5i**	>95	90

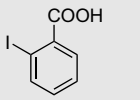
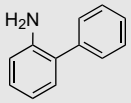
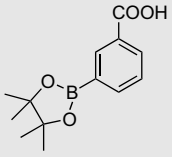
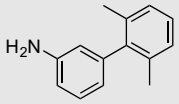
[a] Yield was based on the TFA salt relative to a theoretical loading of the resin (1.08 mmol/g).
[b] Purity was deterimined by HPLC and ^{1}H NMR.

Table 3
N-Alkylation of the resin-bound carbamates **7**–**9**

Entry	Starting carboxylic acid	Resin-bound carbamate	Product amines	Yield[a] (%)	Purity[b] (%)
1	 **2a**	 **7**	 **10**	85	91
2			 **11**	92	94
3	 **6**	 **8**	 **12**	98	93
4			 **13**	97	84
5	 **4b**	 **9**	 **14**	67	93
6			 **15**	75	94

[a] Yield was based on the TFA salt relative to a theoretical loading of the resin (1.2 mmol/g for **7**, **8** and 0.82 mmol/g for **9**).
[b] Purity was determined by HPLC and ^{1}H NMR.

Table 4
The Suzuki coupling reaction of resin-bound carbamates **16** and **21**

Entry	Starting carboxylic acid	Product amines	Yield[a] (%)	Purity[b] (%)
1	 **2d**	 **19**	85	91
2	 **20**	 **24**	98	90

[a] Yield was based on the TFA salt relative to a theoretical loading of the resin (1.2 mmol/g).
[b] Purity was determined by HPLC and ^{1}H NMR.

3. Conclusion

A useful method has been developed to provide resin-bound amine carbamates via the solid-phase Curtius rearrangement starting from carboxylic acids. This method is applicable to a variety of carboxylic acids with various substituents. Following N-alkylation, the Suzuki coupling reaction of the resultant resin-bound carbamates gives various monoalkylated aryl amines and biaryl amines in good yields.

4. Experimental section

4.1. General

Wang resin was purchased from Novabiochem. ^{1}H NMR spectra were recorded on Varian VXR-300 and Varian MERCURY 400 spectrometers with tetramethylsilane(TMS) as an internal standard. IR absorption spectra were recorded with a SHIMADZU FTIR-8900 spectrometer on KBr bed. Analytical HPLC of the products after cleavage was recorded on the HP 100 series system (pump; Binary Pump G1312A, autosampler; ALS G1329A, diode array detector; DAD G1315A) using a CAPCELLPAK ODS-UG120A (5 μm) column (gradient as follows: 5–95% acetonitrile (0.1% TFA)/water (0.1% TFA), 0.2 ml/min for 20 min), and Waters LC-MS 2690 Separations Module system (diode array detector; 996 Photodiode Array Detector, MS; micromass ZMD (ESI)) using a YMC Pack ODS AQ (5 μm) column (gradient as follows: 0–60% acetonitrile (0.1% TFA)/water (0.1% TFA), 0.2 ml/min for 20 min). Mass spectra (MS) were measured on a Waters ZQ2000 (ESI) with Binary HPLC Pump Waters 1525, and micromass Quattoro II with HP 1100 series HPLC system. HRMS were measured on a GC (Agilent 6890 series)—MS (JEOL JMS-700 V) system (EI), or LC (Waters CapLC)—MS (micromass Q-Tof-2) system (ESI).

4.2. General procedure of the solid-phase Curtius rearrangement for the synthesis of aryl and heteroaryl amines (3a–3j)

A mixture of Wang resin **1** (1.0 g, 1.2 mmol; loading 1.2 mmol/g), carboxylic acid **2a**–**2j** (3.6 mmol), diphenylphosphoryl azide (1.3 ml, 6 mmol), and triethylamine (1.67 ml, 12 mmol) in toluene (10 ml) was heated at 100 °C or 80 °C for 16 h. The resin was washed successively with DMF (4×15 ml), DMF/H_2O (1:1) (4×15 ml), MeOH (4×15 ml), and CH_2Cl_2 (4×15 ml). The product resin was shaken with 50% TFA/CH_2Cl_2 (5 ml) for 30 min, filtered, washed with CH_2Cl_2 (2 ml×2), and evaporated to dryness to leave desired amines **3a**–**3j**.

*4.2.1. 4-Methylaniline (**3a**)*[8]

Yield 237.5 mg (96%) of **3a** as a TFA salt from 489 mg of **2a**; ^{1}H NMR (300 MHz, CD_3OD) δ 2.37 (3H, s), 7.23 (2H, d, J=8.5 Hz), 7.31 (2H, d, J=8.5 Hz); MS (ESI) m/z=108 $[M+H]^+$.

*4.2.2. 4-Nitroaniline (**3b**)*[9]

Yield 151.5 mg (98%) of **2** from 601 mg of **2b**; ^{1}H NMR (300 MHz, CD_3OD) δ 6.62 (2H, d, J=8.7 Hz), 7.98 (2H, d, J=8.7 Hz); MS (ESI) m/z=139 $[M+H]^+$.

*4.2.3. 4-Dimethylaminoaniline (**3c**)*[8]

Yield 395.4 mg (97%) of **3** as two TFA salts from 594 mg of **2c**; ^{1}H NMR (300 MHz, CD_3OD) δ 3.07 (6H, s), 7.06 (2H, d, J=8.5 Hz), 7.12 (2H, d, J=8.5 Hz); MS (ESI) m/z=137 $[M+H]^+$.

*4.2.4. 4-Iodoaniline (**3d**)*[9]

Yield 268.2 mg (98%) of **3d** from 892 mg of **2d**; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.38 (1H, d, J=7.8 Hz), 6.80 (1H, t, J=7.8 Hz), 7.07 (1H, t, J=7.8 Hz), 7.54 (1H, d, J=7.8 Hz); MS (ESI) m/z=220 $[M+H]^+$.

*4.2.5. 2-Aminopyridine (**3e**)*[8]

Yield 370.9 mg (96%) of **3e** as two TFA salts from 442 mg of **2e;** ^{1}H NMR (300 MHz, CD_3OD) δ 6.85 (1H, ddd, J=1.1, 6.8, 7.4 Hz), 6.98 (1H, dd, J=1.1, 8.8 Hz), 7.79 (1H, dt, J=1.5, 6.8 Hz), 7.89 (1H, ddd, J=1.5, 7.4, 8.8 Hz); MS (ESI) m/z=95 $[M+H]^+$.

*4.2.6. 3-Aminopyridine (**3f**)*[8]

Yield 374.8 mg (97%) of **3f** as two TFA salts from 442 mg of **2f**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.65–7.66 (2H, m), 7.89 (1H, dd, J=1.1, 3.3 Hz), 7.95 (1H, d, J=1.1 Hz); MS (ESI) m/z=95 $[M+H]^+$.

*4.2.7. 4-Aminopyridine (**3g**)*[8]

Yield 370.8 mg (96%) of **3g** as two TFA salts from 44 mg of **2g**; ^{1}H NMR (300 MHz, CD_3OD) δ 6.81 (2H, d, J=7.3 Hz), 7.99 (2H, d, J=7.3 Hz); MS (ESI) m/z=95 $[M+H]^+$.

*4.2.8. Aminopyrazine (**3h**)*[8]

Yield 225.7 mg (90%) of **3h** as a TFA salt from 446 mg of **2h**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.83–7.88 (2H, m), 8.23 (1H, d, J=2.5 Hz); MS (ESI) m/z=96 $[M+H]^+$.

*4.2.9. 2-Aminothiophene (**3i**)*[9]

Yield 114.0 mg (96%) of **3i** from 457 mg of **2i**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (1H, dd, J=3.4, 1.2 Hz), 6.51 (1H, dd, J=5.4, 1.2 Hz), 6.68 (1H, dd, J=5.4, 3.4 Hz); MS (ESI) m/z=100 $[M+H]^+$.

*4.2.10. 5-Nitro-2-aminothiophene (**3j**)*

Yield 169.3 mg (98%) of **3j** from 619 mg of **2j**; ^{1}H NMR (300 MHz, CD_3OD) δ 7.71 (1H, d, J=6.5 Hz), 7.98 (1H, d, J=6.5 Hz); MS (ESI) m/z=145 $[M+H]^+$; the ^{1}H NMR data is in accordance with that of an authentic sample.[10]

4.3. General procedure of the solid-phase Curtius rearrangement for the synthesis of sterically hindered alkyl amines (5a–5i)

A mixture of **1** (100 mg, 0.108 mmol; loading 1.08 mol/g), carboxylic acids **4a–4i** (0.54 mmol), diphenylphosphoryl azide (0.116 ml, 0.54 mmol), and triethylamine (0.15 ml, 1.08 mmol) in toluene (3 ml) was heated at 110 °C for 16 h. The resin was washed successively with DMF (4×2 ml), MeOH (4×2 ml), and CH_2Cl_2 (4×2 ml). The product resin was shaken with 50% TFA/CH_2Cl_2 (2 ml) for 30 min, filtered, washed with CH_2Cl_2 (1 ml×2), and evaporated to dryness to leave desired amines **5a–5i**.

*4.3.1. 1-Methylcyclopropanamine (**5a**)*

Yield 19.4 mg (97%) of **5a** as a TFA salt from 54 mg of **4a**; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.58–0.63 (2H, m), 0.83–0.86 (2H, m), 1.33 (3H, s); MS (ESI) m/z=72 $[M+H]^+$; the ^{1}H NMR data is in accordance with that of an authentic sample.[11]

*4.3.2. 1-Phenylcyclopropanamine (**5b**)*

Yield 25.9 mg (97%) of **5b** as a TFA salt from 87 mg of **4b**; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.17–1.21 (2H, m), 1.33–1.38 (2H, m), 7.32–7.45 (5H, m); MS (ESI) m/z=134 $[M+H]^+$; the ^{1}H NMR data is in accordance with that of an authentic sample.[12]

*4.3.3. 1-(Trifluoromethyl)cyclobutanamine (**5c**)*

Yield 26.2 mg (96%) of **5c** as a TFA salt from 91 mg of **4c**; ^{1}H NMR (400 MHz, CD_3OD) δ 2.01–2.20 (2H, m), 2.40–2.50 (2H, m), 2.55–2.63 (2H, m); ESI-HRMS calcd for $C_5H_9F_3N$ $[M+H]^+$: 140.0687, found 140.0684.

*4.3.4. 1-Phenyllcyclopentanamine (**5d**)*

Yield 22.6 mg (76%) of **5d** as a TFA salt from 102 mg of **4d**; ^{1}H NMR (400 MHz, CD_3OD) δ 1.84–1.93 (4H, m), 2.23–2.33 (4H, m), 7.33–7.50 (5H, m); MS (ESI) m/z=162 $[M+H]^+$; the ^{1}H NMR data is in accordance with that of an authentic sample.[13]

*4.3.5. 2-Methylpent-4-en-2-amine (**5e**)*

Yield 8.8 mg (57%) of **5e** as a TFA salt from 69 mg of **4e**; ^{1}H NMR (400 MHz, CD_3OD) δ 1.32 (6H, s), 2.35 (2H, d, J=7.7 Hz), 5.19–5.27 (2H, m), 5.79–5.89 (1H, m); ESI-HRMS calcd for $C_6H_{14}N$ $[M+H]^+$: 100.1126, found 100.1126.

*4.3.6. 1,1-Dicyclohexylmethanamine (**5f**)*

Yield 20 mg (60%) of **5f** as a TFA salt from 121 mg of **4f**; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84–1.28, 1.52–1.77 (22H, m), 2.58–2.67 (1H, m); MS (ESI) m/z=196 $[M+H]^+$; the ^{1}H NMR data is in accordance with that of an authentic sample.[14]

*4.3.7. (1S)-1-Amino-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**5g**)*

Yield 28.3 mg (98%) of **5g** as a TFA salt from 101 mg of **4g**; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (3H, s), 1.07 (3H, s), 1.44–1.69 (2H, m), 1.99–2.18 (4H, m), 2.49–2.52 (1H, m); MS (ESI) m/z=154 $[M+H]^+$; the ^{1}H NMR data is in accordance with that of an authentic sample.[15]

*4.3.8. 4-Pentylbicyclo[2.2.2]octan-1-amine (**5h**)*

Yield 32.4 mg (97%) of **5h** as a TFA salt from 121 mg of **4h**; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.82 (3H, t, J=7.1 Hz), 1.00–1.69 (2H, m), 1.99–1.29 (8H, m), 1.35–1.46 (6H, m), 1.57–1.66 (6H, m), H; ESI-HRMS calcd for $C_{13}H_{25}N$ $[M+H]^+$: 196.2065, found 196.2066.

*4.3.9. Methyl 1-aminocyclopropanecarboxylate (**5i**)*[8]

Yield 23.7 mg (96%) of **5i** as a TFA salt from 78 mg of **4i**; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.39–1.44 (2H, m), 1.90–1.95 (2H, m), 3.82 (3H, s); MS (ESI) m/z=116 $[M+H]^+$.

4.4. General procedure of N-alkylation of resin-bound carbamates for the synthesis of secondary aryl amines (10–13)

A mixture of **1** (1.0 g, 1.2 mmol; loading 1.2 mmol/g), carboxylic acid **2a** or **6** (3.6 mmol), diphenylphosphoryl azide (1.3 ml, 6 mmol), and triethylamine (1.67 ml, 12 mmol) in toluene (10 ml) was heated at 100 °C for 16 h. The resin was washed successively with DMF (4×15 ml), DMF/H_2O (1:1) (4×15 ml), MeOH (4×15 ml), and CH_2Cl_2 (4×15 ml). The resin was dried under high vacuum for 10 h. The resin (30 mg, 0.036 mmol) and NaH (60% in oil, 7.2 mg, 0.18 mmol) were shaken in DMF (0.5 ml) for 1.5 h. Then, alkylating agent (0.36 mmol) was added and heated at 80 °C for 16 h. The resin was washed successively with DMF (3×3 ml), MeOH (3×3 ml), and CH_2Cl_2 (3×3 ml). The product resin was shaken with 50% TFA/CH_2Cl_2 for 5 min, filtered, washed, and evaporated to dryness to leave desired secondary aryl amines **10–13**.

*4.4.1. 3-(4-Methylphenylamino)-1-propene (**10**)*

Yield 8.0 mg (85%) of **10** as a TFA salt from 489 mg of **2a** and 44 mg of allyl bromide; ^{1}H NMR (300 MHz, CD_3OD) δ 2.39 (3H, s), 3.98 (2H, d, J=7.4 Hz), 5.43–5.52 (2H, m), 5.88–6.02 (1H, m), 7.30 (2H, d, J=8.5 Hz), 7.37 (2H, d, J=8.5 Hz); EI-HRMS calcd for $C_9H_{13}N$ ($M^{+\bullet}$): 147.1048, found 147.1055.

*4.4.2. 2-(4-Methylphenylamino)ethane (**11**)*

Yield 8.3 mg (92%) of **11** as a TFA salt from 56 mg of iodoethane; ^{1}H NMR (300 MHz, CD_3OD) δ 1.28 (3H, t, J=7.8 Hz), 2.36 (3H, s), 3.31 (2H, q, J=7.8 Hz), 7.18 (2H, d, J=8.6 Hz), 7.29 (2H, d, J=8.6 Hz); EI-HRMS calcd for $C_{10}H_{13}N$ ($M^{+\bullet}$): 135.1048, found 135.1039.

*4.4.3. 3-(6-Methyl-2-pyridylamino)-1-propene (**12**)*

Yield 13.3 mg (98%) of **12** as two TFA salts from 493 mg of **6** and 44 mg of allyl bromide; ^{1}H NMR (300 MHz, CD_3OD) δ 2.52 (3H, s), 4.03–4.08 (2H, m), 5.25–5.36 (2H, m), 5.87–6.01 (1H, m), 6.72 (1H, d, J=8.1 Hz), 6.88 (1H, d, J=9.4 Hz), 7.82 (1H, d, J=9.4 Hz), 7.84 (1H, d, J=8.1 Hz); EI-HRMS calcd for $C_9H_{12}N_2$ ($M^{+\bullet}$): 148.1000, found 148.0994.

*4.4.4. 2-(6-Methyl-2-pyridylamino)ethane (**13**)*

Yield 12.7 mg (97%) of **13** as two TFA salts from 56 mg of iodoethane; ^{1}H NMR (300 MHz, CD_3OD) δ 1.32 (3H, t, J=7.5 Hz), 2.50 (3H, s), 3.43 (2H, q, J=7.5 Hz), 6.67 (1H, d, J=6.9 Hz), 6.84 (1H, d, J=9.6 Hz), 7.76 (1H, d, J=6.9 Hz), 7.78 (1H, d, J=9.6 Hz); EI-HRMS calcd for $C_8H_{12}N_2$ ($M^{+\bullet}$): 136.1000, found 136.1003.

4.5. General procedure of N-alkylation of resin-bound carbamates for the synthesis of secondary alkyl amines (14, 15)

A mixture of **1** (1.0 g, 0.82 mmol; loading 0.82 mmol/g), 1-phenylcyclopropanecarboxylic acid **4b** (4.1 mmol), diphenylphosphoryl azide (0.88 ml, 4.1 mmol), and triethylamine (1.14 ml, 8.2 mmol) in toluene (10 ml) was heated at 120 °C for 16 h. The resin was washed successively with DMF (4×15 ml), DMF/H_2O (1:1) (4×15 ml), MeOH (4×15 ml), and CH_2Cl_2 (4×15 ml). The resin was dried under high vacuum for 10 h. The resin (100 mg, 0.082 mmol) and LiHMDS (1 M solution in THF: 0.82 ml, 0.82 mmol) were shaken in DMF (1.0 ml) for 1.0 h. Then, alkylating agent (0.82 mmol) was added and heated at 120 °C for 16 h. The resin was washed successively with DMF (3×3 ml), MeOH (3×3 ml), and CH_2Cl_2 (3×3 ml). The product resin was shaken with 50% TFA/CH_2Cl_2 for 5 min, filtered, washed, and evaporated to dryness to leave desired secondary alkyl amines (**14**, **15**).

*4.5.1. N-Ethyl-1-phenylcyclopropanamine (**14**)*

Yield 15.2 mg (67%) of **14** as a TFA salt from 128 mg of iodoethane; ^{1}H NMR (400 MHz, CD_3OD) δ 1.18 (3H, t, J=7.4 Hz), 1.22–1.26 (2H, m), 1.37–1.41 (2H, m), 2.94 (2H, q, J=7.4 Hz), 7.42–7.55 (5H, m); ESI-HRMS calcd for $C_{11}H_{15}N$ $[M+H]^+$: 162.1283, found 162.1283.

*4.5.2. N-Benzyl-1-phenylcyclopropanamine (**15**)*

Yield 20.7 mg (75%) of **15** as a TFA salt from 140 mg of benzyl bromide; ^{1}H NMR (400 MHz, CD_3OD) δ 1.25–1.45 (4H, m), 4.85 (2H, s), 7.28–7.63 (10H, m); ESI-HRMS calcd for $C_{16}H_{17}N$ $[M+H]^+$: 224.1439, found 224.1444.

4.6. Synthesis of biaryl amines

*4.6.1. Biphenyl-2-amine (**19**)*[8]

The resin-bound carbamate of 2-iodoaniline **16** (100 mg, 0.12 mmol), **17** (72.6 mg, 0.6 mmol), $Pd(PPh_3)_4$ (7 mg, 5 mol %), and 2 M Na_2CO_3 (0.2 ml, 0.4 mmol) were shaken in DME (2 ml) at 100 °C for 16 h. The resin was washed successively with DMF/H_2O (1:1, 3×3 ml), MeOH (3×3 ml), and CH_2Cl_2 (3×3 ml). The product resin was shaken with 50% TFA/CH_2Cl_2 for 30 min, filtered, washed, and evaporated to dryness to give TFA salt of **19** as a colorless oil (28.9 mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12–7.64 (9H, m); MS (ESI) m/z=170 $[M+H]^+$.

*4.6.2. 2′,6′-Dimethylbiphenyl-2-amine (**24**)*

A mixture of **1** (100 mg, 0.12 mmol; loading 1.2 mmol/g), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid **20** (89 mg, 0.36 mmol), diphenylphosphoryl azide (0.13 ml, 0.66 mmol), and triethylamine (0.17 ml, 1.2 mmol) in toluene (5 ml) was heated at 100 °C for 16 h. The resin was washed successively with DMF (4×15 ml), DMF/H_2O (1:1) (4×15 ml), MeOH (4×15 ml), and CH_2Cl_2 (4×15 ml). The resin, **22** (139.2 mg, 0.6 mmol), $Pd(PPh_3)_4$ (7 mg, 5 mol %) and 2 M Na_2CO_3 (0.2 ml, 0.4 mmol) were shaken in DME (2 ml) at 100 °C for 16 h. The resin was washed successively with DMF/H_2O (1:1, 3×3 ml), MeOH (3×3 ml), and CH_2Cl_2 (3×3 ml). The product resin was shaken with 50% TFA/CH_2Cl_2 for 30 min, filtered, washed, and evaporated to dryness to give TFA salt of **24** as a colorless oil (36.6 mg, 98%); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94 (6H, s), 7.02 (1H, t, J=1.5 Hz), 7.07–7.19 (4H, m), 7.24–7.30 (1H, m), 7.52 (1H, t, J=7.8 Hz); ESI-HRMS calcd for $C_{14}H_{16}N$ $(M+H)^+$: 198.1283, found 198.1286.

Acknowledgements

The authors thank Mr. H. Ohsawa for HRMS measurements.

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