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A three-component reaction of *C*,*N*-cyclic *N*′-acyl azomethine imines, isocyanides, and azide compounds: effective synthesis of 1,5-disubstituted tetrazoles with tetrahydroisoquinoline skeletons†

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A multicomponent reaction of isocyanides and *C*,*N*-cyclic *N*′-acyl azomethine imines in the presence of TMSCl and NaN_3 leads to tetrazole derivatives. These reactions proceeded cleanly to afford the corresponding 1,5-disubstituted tetrazoles containing a tetrahydroisoquinoline skeleton in high to excellent yields.

Introduction

The multi-component reactions of isocyanides are powerful synthetic tools for preparation of diverse complex molecules in practical, time-saving one-pot operations through combinatorial strategies or parallel syntheses. Classically, the reaction of an isocyanide with an imine and a carboxylic acid—the Ugi reaction—is one of the most important multi-component reactions to synthesize α-amino amides.[1] After discovery around 1960, various modifications have been developed;[2] however, the use of components other than carboxylic acids has been limited. One of the reasons why carboxylic acid is crucial in this reaction depends on the reaction mechanism. The mechanism of the Ugi reaction has been studied thoroughly and involves activation of the imine by a carboxylic acid followed by addition of an isocyanide and trapping of the resulting nitrilium intermediate by the carboxylate to afford the final product by migration of the acyl group onto the nitrogen atom originating from the imine. Therefore, a carboxylic acid is necessary for the reaction of an isocyanide with an imine in the Ugi reaction, *i.e.*, the use of a carboxylic acid limits application of this reaction to the construction of a broad range of molecules. However, after considering these issues, an azide compound was chosen for the isocyanide-based multicomponent reaction. Ugi first reported that the reaction of an aldehyde with an isocyanide in the presence of hydrazoic acid instead of a carboxylic acid afforded 1*H*-tetrazoles *via* 1,3-dipolar cycloaddition between a nitrilium intermediate and hydrazoic acid.[3,4] Tetrazoles have long been recognized as carboxylic acid isosters[5] and are important heterocycles in medicinal chemistry because of greater stability toward the metabolic degradation pathway.[6] The 1,5-disubstituted tetrazole is an analog for the *cis*-amide bond, making it a valuable tool in the design of conformationally constrained peptidemimetics.[7] Several methods have been developed for the synthesis of 1,5-disubstituted tetrazoles.[8] This is the first example of the synthesis of novel 1,5-disubstituted tetrazoles containing tetrahydroisoquinoline skeletons based on the isocyanide-based multicomponent reaction.[9,10]

Among the imine analogs, *C*,*N*-cyclic *N*′-acyl azomethine imines are promising candidates[11] because they possess an acyl group, which can activate the C═N bond and strongly coordinate to metals. A previous study already reported that [5 + 1] cycloaddition of isocyanides and *C*,*N*-cyclic *N*′-acyl azomethine imines as an "isocyanophile" gave imin-1,3,4-oxadiazin-6-one derivatives in high yields.[12,13] This cyclization reaction was expanded to a three-component reaction. Therefore, a molecule (Z–X) consisting of an electrophilic (Z) and a nucleophilic group (X) could suppress the intramolecular trapping of the nitrilium intermediate through an *N*′-acyl group (**A**) and undergo nucleophilic trapping by X (**B**) to achieve a multicomponent reaction (Scheme 1).

Results and discussion

Initial studies began using the *C*,*N*-cyclic *N*′-acyl azomethine imine **1a**[14] and *tert*-butyl isocyanide (**2a**) in the presence of $MgCl_2$ or $ZnCl_2$ in acetonitrile (MeCN); however, only the cyclization product imin-1,3,4-oxadiazin-6-one derivative **3aa** was obtained in 70% yield (eqn (1)).[12] In contrast, when the

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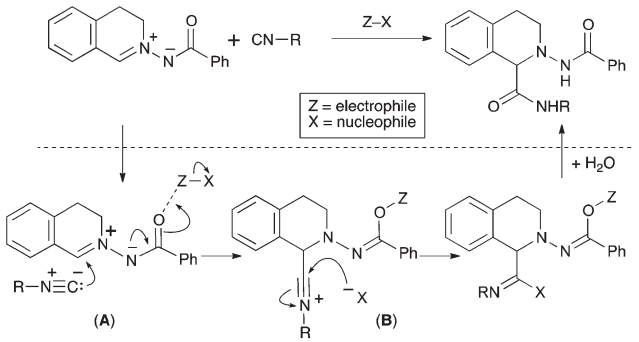
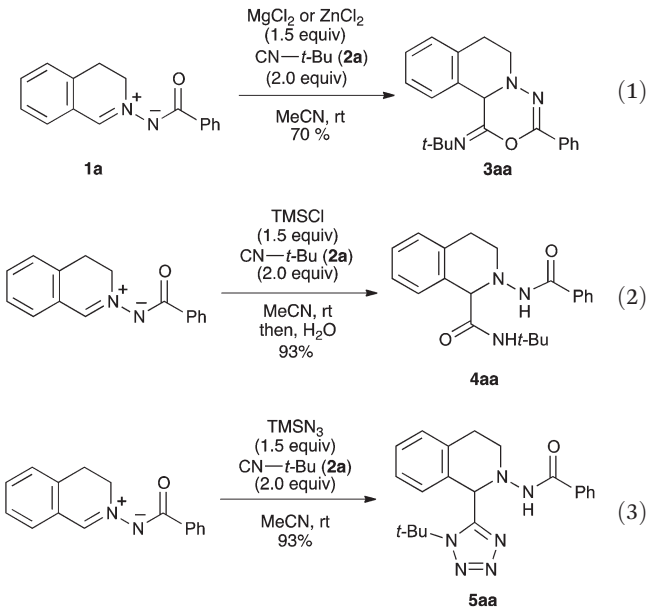


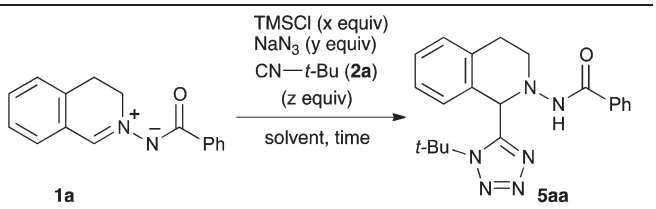
Scheme 1 Working hypothesis.

reaction was conducted in the presence of chlorotrimethylsilane (TMSCl) in MeCN at room temperature, the reaction gave the 1,2,3,4-tetrahydroisoquinoline-1-carboxylamide **4aa** in 93% yield (eqn (2)). As expected, TMSCl suppressed the cyclization pathway and the nitrilium intermediate was trapped by a chloride anion, followed by hydrolysis to afford **4aa**.[15] Based on this result, the reaction of **1a** and **2a** in the presence of trimethylsilyl azide ($TMSN_3$) in MeCN was examined. The reaction was complete within 10 min to afford the 1,5-disubstituted tetrazole **5aa** in 93% yield (eqn (3)). In addition, the X-ray structure of the product **5aa** was obtained,



Furthermore, the combination of TMSCl and sodium azide, which are less expensive than $TMSN_3$, was also effective in this reaction to afford the tetrazole **5aa** in 94% yield after 10 min (Table 1, entry 1). This reaction proceeded smoothly in toluene, ethyl acetate, dichloromethane, and ether to afford **5aa** in good to high yields (entries 2–5). In THF, the reaction was sluggish to afford **5aa** in a lower yield (entry 6). The solvent MeOH was very effective in this reaction, affording the product in 99% yield, probably due to the solubility of the substrate **1a** (entry 7). By decreasing the amount of TMSCl, NaN_3, and/or the isocyanide to 1.0 equiv., **5aa** was still obtained in 90% yield (entries 8–10). The cyclized compound **4aa** was obtained in 45% yield when 0.5 equiv. of TMSCl was used (entry 11).

Table 1 Reaction conditions for a three-component reaction

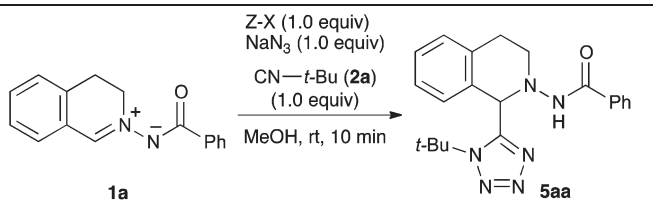


Entry	Solvent	*x* Equiv.	*y* Equiv.	*z* Equiv.	Yield/%
1	MeCN	1.5	2.0	2.0	94
2	Toluene	1.5	2.0	2.0	82
3	CH_2Cl_2	1.5	2.0	2.0	84
4	AcOEt	1.5	2.0	2.0	93
5	Et_2O	1.5	2.0	2.0	96
6	THF	1.5	2.0	2.0	66
7	MeOH	1.5	2.0	2.0	99
8	MeOH	1.5	1.0	2.0	89
9	MeOH	1.5	1.0	1.0	93
10	MeOH	1.0	1.0	1.0	90
11	MeOH	0.5	1.0	1.0	45[a]

[a] **3aa** was also obtained in 45% yield.

After an efficient method for addition of the isocyanide to the *C*,*N*-cyclic *N*′-acyl azomethine imine was established, silyl halides containing other substituents were evaluated (Table 2). The use of bromotrimethylsilane (TMSBr) or iodotrimethylsilane (TMSI) resulted in lower reactivity to afford **5aa** in 86% or 85% yield, respectively (entries 2 and 3). For chlorotriethylsilane (TESCl), chlorotriisopropylsilane (TIPSCl), or *tert*-butylchlorodimethylsilane (TBDMSCl), reactivity similar to TMSCl was observed (entries 4–6). Using a more hindered silyl compound such as *tert*-butylchlorodiphenylsilane (TBDPSCl), **3aa** was formed in 26% yield and **5aa** was produced in 65% yield (entry 7). These results indicate that the less sterically

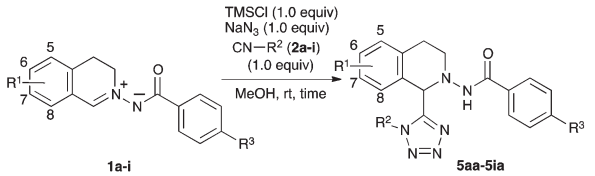
Table 2 Effect of silyl halides for a three-component reaction

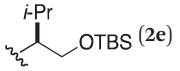


Entry	Z–X	Yield/%
1	TMSCl	90
2	TMSBr	86
3	TMSI	85
4	TESCl	92
5	TIPSCl	88
6	TBDMSCl	90
7[a]	TBDPSCl	65

[a] **3aa** was also obtained in 26% yield.

Table 3 Scope of isocyanides and azomethine imines



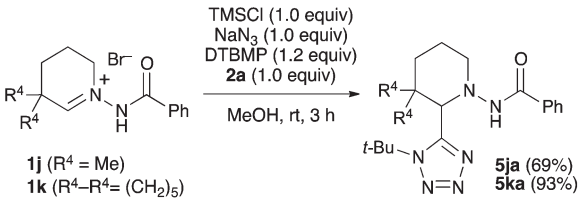
Entry[a]	R^1	R^2	Time	Yield/%
1	H (**1a**)	*t*-Bu (**2a**)	10 min	90 (**5aa**)
2	H (**1a**)	*t*-Oct (**2b**)	20 min	90 (**5ab**)
3[b]	H (**1a**)	*c*-Hex (**2c**)	20 min	89 (**5ac**)
4[b]	H (**1a**)	Bn (**2d**)	3 h	99 (**5ad**)
5[b]	H (**1a**)	 (**2e**)	30 min	91 (**5ae**)
6[b]	H (**1a**)	Ph (**2f**)	3 h	82 (**5af**)
7[b]	H (**1a**)	4-$MeOC_6H_4$ (**2g**)	3 h	95 (**5ag**)
8[b]	H (**1a**)	4-BrC_6H_4 (**2h**)	4 min	84 (**5ah**)
9[b]	H (**1a**)	4-$O_2NC_6H_4$ (**2i**)	27 h	91 (**5ai**)
10	5-Me (**1b**)	*t*-Bu (**2a**)	10 min	95 (**5ba**)
11	6-Me (**1c**)	*t*-Bu (**2a**)	10 min	97 (**5ca**)
12	7-Me (**1d**)	*t*-Bu (**2a**)	10 min	92 (**5da**)
13	8-Me (**1e**)	*t*-Bu (**2a**)	24 h	— (**5ea**)
14	6-MeO (**1f**)	*t*-Bu (**2a**)	10 min	89 (**5fa**)
15	7-Cl (**1g**)	*t*-Bu (**2a**)	1 h	64 (**5ga**)
16[c]	H (**1h**)	*t*-Bu (**2a**)	10 min	90 (**5ha**)
17[d]	H (**1i**)	*t*-Bu (**2a**)	16 h	77 (**5ia**)

[a] R^3 = H otherwise mentioned. [b] Reaction was conducted at 50 °C. [c] R^3 = Me. [d] R^3 = Cl.

hindered Si atom and Cl anion were crucial for efficient completion of the reaction.

The scope of isocyanides and *C*,*N*-cyclic *N*′-acyl azomethine imines applicable to the multicomponent reaction was investigated as shown in Table 3. For isocyanides, optimal amounts of the azomethine imine **1a** (1.0 equiv.) and isocyanides **2a–i** (1.0 equiv.) in the presence of TMSCl (1.0 equiv.) and NaN_3 (1.0 equiv.) were used in MeOH (entries 1–9).

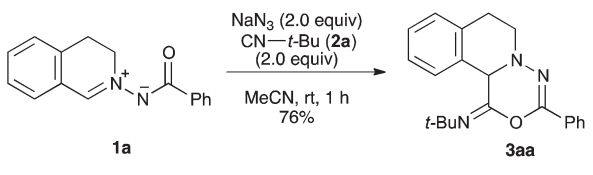
The results showed that the conditions were applicable to a wide variety of isocyanides. Most of the reactions were complete within 24 h. The reaction of aliphatic isocyanides (R^3 = *t*-Bu, *t*-Oct, *c*-Hex, and Bn) with **1a** gave the 1,5-disubstituted tetrazole derivatives in high yields (entries 1–4). The azomethine imine **1a** was consumed within 20 min when *tert*-octylisocyanide (**2b**) was used, giving **5ab** in 90% yield (entry 2). For cyclohexylisocyanide (**2c**) and benzylisocyanide (**2d**), reactivity was lower at room temperature; however, the desired tetrazoles were obtained in 89% and 99% yields, respectively, when the reactions were conducted at 50 °C (entries 3 and 4). The chiral isocyanide **2e**, prepared from the corresponding amino acid, gave the desired product in 91% yield; however, no chiral induction was observed (entry 5). Phenylisocyanide (**2f**) and aromatic isocyanides with electron-withdrawing or -donating groups at the *para* position also afforded the corresponding tetrazoles in high yields, although the reactions were performed at 50 °C (entries 6–9). Reactivity toward various *C*,*N*-cyclic *N*′-acyl azomethine imines using *tert*-butylisocyanide (**2a**) was examined using 1.0 equiv. of azomethine imines **1a–i** and 1.0 equiv. of **2a**. The 5-, 6-, and 7-methyl substituents were all tolerated, furnishing the corresponding tetrazoles (entries 10–12). The only exception was incorporation of the 8-methyl substituent, which did not result in the desired product **5ea** due to a complicated reaction (entry 13). The *C*,*N*-cyclic azomethine imine **1f** with an electron-donating group was utilized as well (entry 14). In addition, the *C*,*N*-cyclic azomethine imine **1g** with an electron-withdrawing group on the aromatic ring reacted slowly to afford the product **5ga** in 64% yield (entry 15). The influence of the substituent of the benzoyl group on the nitrogen was also examined. The results showed that a methyl group on the aromatic moiety was more effective than a chloride group to afford the products in 90% and 77% yields, respectively (entries 16 and 17).



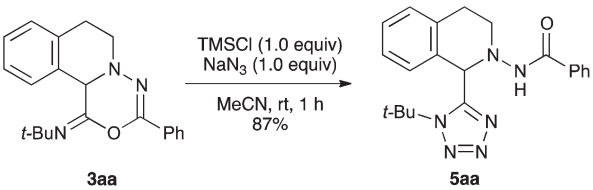
(4)

In addition, structurally distinct azomethine imine was examined. The reaction of *C*,*N*-cyclic azomethine imines not fused to the aromatic ring, which were generated *in situ* from **1j** and **1k** in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a base, was conducted with *tert*-butylisocyanide (**2a**) in the presence of TMSCl and NaN_3 to afford the products **5ja** and **5ka** in 69% and 93% yields, respectively (eqn (4)).

To determine the reaction mechanism, control experiments were conducted. The reaction of the isocyanide **2a** to the *C*,*N*-cyclic azomethine imine **1a** in the presence of NaN_3 without TMSCl afforded the cyclized compound **3aa** (eqn (5)). In addition, when the reaction of the cyclized compound **3aa** with TMSCl and NaN_3 was conducted, the desired tetrazole **5aa** was obtained (eqn (6)).

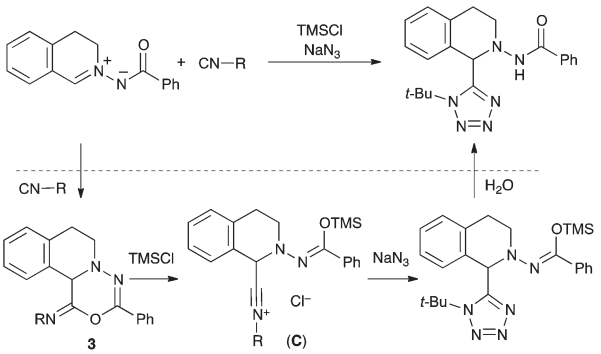


(5)



(6)

These results indicate that the [5 + 1] cycloaddition of isocyanides and *C*,*N*-cyclic *N*′-acyl azomethine imines proceeded very quickly to afford **3**, whose imin-1,3,4-oxadiazin-6-one ring was cleaved by TMSCl to generate the corresponding nitrilium intermediate (**C**) *in situ*. Subsequent 1,3-dipolar cycloaddition between the nitrilium intermediate (**C**) and an azide ion proceeded to afford the corresponding tetrazole (Scheme 2).



Scheme 2 Proposed reaction mechanism.

Conclusions

In conclusion, a multicomponent reaction of isocyanides, *C*,*N*-cyclic *N*′-acyl azomethine imines, and azide compounds was developed. The reaction proceeded cleanly to afford 1,5-disubstituted tetrazole derivatives containing a tetrahydroisoquinoline skeleton in high yields. A wide range of *C*,*N*-cyclic *N*′-acyl azomethine imines and isocyanides were suitable for this reaction.

Experimental section

General method

^{1}H NMR spectra were recorded on a 400 MHz NMR spectrometer. Chemical shifts δ are reported in ppm using TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (*J*) and integration. ^{13}C NMR spectra were recorded on a 100 MHz NMR spectrometer. The chemical shifts were determined in the δ-scale relative to $CDCl_3$ (δ = 77.0 ppm). The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. HRMS (FAB, positive) was measured with a quadrupole mass spectrometer. All of the melting points were measured with a micro melting point apparatus. Toluene was dried and distilled over sodium. THF was freshly distilled from sodium diphenylketyl. All other solvents were distilled and stored over drying agents.

General procedure for the multicomponent reaction of azomethine imines, isocyanides, and azide ion

To a suspension of **1** (0.2 mmol, 1.0 equiv.) and NaN_3 (0.2 mmol, 1.0 equiv.) in MeOH (1.1 mL), TMSCl (0.2 mmol, 1.0 equiv.) in MeOH (0.2 mL) was added at room temperature. After stirring for 10 min, **2** (0.2 mmol, 1.0 equiv.) in MeOH (0.2 mL) was added dropwise and stirred at room temperature. After the completion of reaction (monitored by TLC), water (1.5 mL) was added and extracted with ethyl acetate (2 mL × 3). Combined organic layers were washed with sat. $NaHCO_3$ aq (3 mL) and brine (3 mL) and dried over Na_2SO_4, then concentrated. The residue was purified by silicagel column chromatography to give the corresponding product.

N-(1-(1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5aa)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5aa** (68 mg, 90%) as a white solid of mp = 193–194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.67 (s, 9H), 3.01 (m, 1H), 3.38 (m, 2H), 3.67 (m, 1H), 6.15 (s, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.22–7.26 (m, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.35 (s, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 27.8, 30.1, 52.0, 61.4, 63.8, 126.6, 127.1, 128.3, 128.6, 129.1, 131.8, 132.9, 133.1, 133.4, 154.0, 166.2. IR (KBr): 3240, 2940, 1670, 1580, 1530, 1450, 1280 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{21}H_{25}N_6O$ [M^+ + H]: 377.2090. Found: 377.2092.

N-(1-(1-(2,4,4-Trimethylpentan-2-yl)-1*H*-tetrazol-5-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5ab)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5ab** (78 mg, 90%) as a yellow amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$): 0.78 (s, 9H), 1.77 (s, 3H), 1.80 (s, 3H), 2.07 (s, 2H), 2.99 (m, 1H), 3.31 (m, 2H), 3.69 (m, 1H), 6.08 (s, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.23–7.28 (m, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.37 (s, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 27.1, 28.7, 30.4, 30.9, 31.4, 51.3, 54.4, 61.3, 67.8, 126.5, 126.9, 127.1, 127.9, 128.5, 129.2, 131.6, 132.5, 133.1, 133.5, 153.9, 165.9. IR (KBr): 3260, 2960, 1680, 1520, 1490, 1400, 1280 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{25}H_{33}N_6O$ [M^+ + H]: 433.2716. Found: 433.2720.

N-(1-(1-Cyclohexyl-1*H*-tetrazol-5-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5ac)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5ac** (72 mg, 89%) as a white solid of mp = 232–234 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 0.80–2.23 (m, 10H), 3.00 (m, 1H), 3.34 (m, 1H), 3.50 (m, 1H), 3.61 (m, 1H), 4.54 (m, 1H), 5.92 (s, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 7.09 (m, 1H), 7.25 (m, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.45 (m, 2H), 7.56 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.9, 25.4, 25.5, 29.5, 32.0, 32.2, 53.0, 58.7, 60.3, 126.7, 126.9, 127.2, 128.0, 128.5, 128.9, 131.6, 131.7, 133.2, 133.4, 153.6, 166.2. IR (KBr): 3250, 2940, 1670, 1520, 1450, 1310 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{23}H_{27}N_6O$ [M^+ + H]: 403.2246. Found: 403.2254.

N-(1-(1-Benzyl-1*H*-tetrazol-5-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5ad)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5ad** (83 mg, 99%) as a white solid of mp = 188–189 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.94 (m, 1H), 3.45 (m, 2H), 3.58 (m, 1H), 5.59 (d, *J* = 15.1 Hz, 1H), 5.89 (d, *J* = 15.1 Hz, 1H), 5.95 (s, 1H), 6.30 (d, *J* = 7.8 Hz, 1H), 6.83 (m, 3H), 7.08 (t, *J* = 7.3 Hz, 2H), 7.13 (m, 3H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 2H), 7.72 (brs, 1H). ^{13}C NMR

(100 MHz, $CDCl_3$): 29.3, 51.9, 53.0, 60.7, 126.6, 127.0, 127.1, 127.9, 127.9, 128.0, 128.3, 128.5, 128.9, 130.8, 131.7, 132.9, 133.4, 154.1, 166.5. IR (KBr): 3270, 3020, 1650, 1520, 1290 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{24}H_{23}N_6O$ [M^+ + H]: 411.1933. Found: 411.1940.

(2*S*)-*N*-(1-(1-(1-((*tert*-Butyldimethylsilyl)oxy)-3-methylbutan-2-yl)-1*H*-tetrazol-5-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl) benzamide (5ae)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5ae** (95 mg, 91%) as a yellow amorphous solid. Diastereomeric ratio was determined to be *ca.* 1 : 1 by ^1H NMR.

Diastereomer (R_f = 0.3, hexane/ethyl acetate = 2/1 × 2). ^1H NMR (400 MHz, $CDCl_3$): −0.01 (s, 3H), 0.00 (s, 3H), 0.48 (d, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.97 (d, *J* = 6.9 Hz, 3H), 2.07 (m, 1H), 3.08 (m, 1H), 3.23 (m, 1H), 3.48 (m, 1H), 3.84 (m, 1H), 4.16 (m, 1H), 4.24 (t, *J* = 8.7 Hz, 1H), 5.05 (m, 1H), 6.29 (s, 1H), 6.96 (d, *J* = 7.7 Hz, 1H), 7.19 (m, 2H), 7.30 (m, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.51 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): −5.8, −5.7, 18.0, 18.5, 19.4, 25.6, 28.7, 29.1, 51.2, 59.4, 61.3, 65.9, 126.8, 127.0, 128.1, 128.3, 128.6, 129.1, 131.3, 131.9, 133.0, 133.5, 154.7, 166.3. IR (KBr): 3250, 2970, 1690, 1540, 1470, 1290, 1120 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{28}H_{41}N_6O_2Si$ [M^+ + H]: 521.3060. Found: 521.3070.

Diastereomer (R_f = 0.25, hexane/ethyl acetate = 2/1 × 2). ^1H NMR (400 MHz, $CDCl_3$): −0.15 (s, 3H), −0.21 (s, 3H), 0.82 (s, 9H), 0.90 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 2.10 (m, 1H), 2.70 (m, 1H), 3.03 (m, 1H), 3.30 (m, 1H), 3.37 (m, 1H), 3.63 (m, 2H), 4.62 (m, 1H), 6.20 (s, 1H), 6.82 (d, *J* = 7.9 Hz, 1H), 7.19 (t, *J* = 7.3 Hz, 1H), 7.30 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.64 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): −5.8, −5.7, 18.0, 18.5, 19.4, 25.6, 28.7, 29.1, 51.2, 59.4, 61.3, 65.9, 126.8, 127.0, 127.5, 128.1, 128.6, 129.1, 131.3, 131.9, 133.0, 133.5, 154.7, 166.3. IR (KBr): 3250, 2970, 1690, 1540, 1470, 1290, 1120 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{28}H_{41}N_6O_2Si$ [M^+ + H]: 521.3060. Found: 521.3054.

N-(1-(1-Phenyl-1*H*-tetrazol-5-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5af)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5af** (65 mg, 82%) as a yellow solid of mp = 177–178 °C. ^1H NMR (400 MHz, $CDCl_3$): 2.73 (m, 1H), 2.91 (m, 1H), 3.29 (m, 1H), 3.57 (m, 1H), 5.90 (s, 1H), 6.61 (d, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 7.02 (t, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.3 Hz, 1H), 7.26–7.36 (m, 5H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 3H), 7.64 (d, *J* = 7.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.9, 52.3, 60.3, 126.4, 126.5, 126.5, 127.1, 127.7, 128.3, 128.5, 128.6, 130.0, 131.0, 131.9, 133.0, 133.8, 134.0, 155.0, 166.4. IR (KBr): 3240, 3060, 1650, 1500, 1460, 1280 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{23}H_{21}N_6O$ [M^+ + H]: 397.1777. Found: 397.1774.

N-(1-(1-(4-Methoxyphenyl)-1*H*-tetrazol-5-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5ag)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5ag** (81 mg, 95%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): 2.73 (m, 1H), 2.92 (m, 1H), 3.28 (m, 1H), 3.53 (m, 1H), 3.79 (s, 3H), 5.89 (s, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.97 (d, *J* = 7.8 Hz, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.34–7.41 (m, 5H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.9, 52.2, 55.5, 60.2, 113.6, 126.3, 126.4, 126.5, 126.7, 127.1, 127.7, 127.9, 128.6, 131.1, 131.9, 133.0, 133.8, 155.1, 160.5, 166.4. IR (KBr): 3240, 2940, 1650, 1520, 1460, 1250 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{24}H_{22}N_6O_2$ [M^+ + H]: 427.1882. Found: 427.1878.

N-(1-(1-(4-Bromophenyl)-1*H*-tetrazol-5-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5ah)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5ah** (40 mg, 84%, 0.1 mmol scale) as a white solid of mp = 196–198 °C. ^1H NMR (400 MHz, $CDCl_3$): 2.73 (m, 1H), 2.92 (m, 1H), 3.28 (m, 1H), 3.53 (m, 1H), 5.84 (s, 1H), 6.56 (d, *J* = 7.7 Hz, 1H), 6.99 (m, 2H), 7.11 (t, *J* = 7.3 Hz, 1H), 7.36 (brs, 1H), 7.38–7.51 (m, 7H), 7.63 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 29.0, 52.6, 60.7, 124.2, 126.3, 126.5, 127.1, 127.9, 128.2, 128.6, 128.7, 130.7, 131.6, 131.9, 132.9, 133.0, 133.7, 155.0, 166.4. IR (KBr): 3220, 3060, 1650, 1540, 1490, 1300 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{23}H_{20}BrN_6O$ [M^+ + H]: 475.0882. Found: 475.0883.

N-(1-(1-(4-Nitrophenyl)-1*H*-tetrazol-5-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5ai)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5ai** (40 mg, 91%, 0.1 mmol scale) as a white solid of mp = 223–224 °C. ^1H NMR (400 MHz, $CDCl_3$): 2.78 (m, 1H), 3.00 (m, 1H), 3.21 (m, 1H), 3.66 (m, 1H), 5.83 (s, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.3 Hz, 1H), 7.01 (t, *J* = 7.3 Hz, 1H), 7.09 (t, *J* = 7.3 Hz, 1H), 7.32 (brs, 1H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.94 (m, 2H), 8.12 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 29.1, 52.1, 61.4, 123.6, 126.2, 126.8, 127.1, 127.7, 128.3, 128.7, 128.8, 130.4, 132.1, 132.7, 133.6, 138.9, 148.1, 155.1, 166.6. IR (KBr): 3240, 3070, 2930, 1680, 1600, 1530, 1340, 1110 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{23}H_{20}N_7O_3$ [M^+ + H]: 442.1628. Found: 442.1629.

N-(1-(1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)-5-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5ba)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5ba** (71 mg, 95%) as a white solid of mp = 225–227 °C. ^1H NMR (400 MHz, $CDCl_3$): 1.64 (s, 9H), 2.30 (s, 3H), 2.91 (m, 1H), 3.09 (m, 1H), 3.37 (m, 1H), 3.68 (m, 1H), 6.08 (s, 1H), 6.44 (d, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.34–7.37 (m, 3H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.56 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 19.3, 25.1, 30.1, 51.3, 61.7, 63.7, 124.5, 126.4, 127.0, 128.6, 129.3, 131.8, 131.9, 132.6, 133.0, 136.9, 154.1, 166.1. IR (KBr): 3210, 2940, 1670, 1540, 1460, 1290 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{22}H_{27}N_6O$ [M^+ + H]: 391.2246. Found: 391.2244.

N-(1-(1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)-6-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5ca)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5ca** (36 mg, 97%, 0.1 mmol scale) as a white solid of mp = 166–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.67 (s, 9H), 2.32 (s, 3H), 2.94 (m, 1H), 3.35 (m, 2H), 3.64 (m, 1H), 6.09 (s, 1H), 6.42 (d, J = 7.8 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 7.03 (s, 1H), 7.33 (m, 2H), 7.45 (m, 1H), 7.53 (d, J = 7.3 Hz, 2H), 7.62 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.0, 27.6, 30.1, 52.0, 61.3, 63.7, 126.4, 127.0, 127.4, 128.5, 129.6, 129.9, 131.7, 133.1, 137.6, 154.1, 166.2. IR (KBr): 3260, 2970, 1670, 1530, 1490, 1270 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{22}H_{27}N_6O$ [M^+ + H]: 391.2246. Found: 391.2245.

N-(1-(1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)-7-methyl-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5da)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5da** (76 mg, 92%) as a white solid of mp = 197–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.68 (s, 9H), 2.21 (s, 3H), 2.95 (m, 1H), 3.29 (m, 2H), 3.64 (m, 1H), 6.01 (s, 1H), 6.41 (s, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.21 (brs, 1H), 7.37 (t, J = 7.8 Hz, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.53 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.0, 26.9, 30.1, 51.8, 61.8, 63.7, 127.0, 127.2, 128.7, 129.0, 129.1, 130.1, 131.9, 132.4, 133.1, 136.5, 153.9, 165.9. IR (KBr): 3250, 2920, 1680, 1530, 1490, 1280 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{22}H_{27}N_6O$ [M^+ + H]: 391.2246. Found: 391.2236.

N-(1-(1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)-6-methoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5fa)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5fa** (73 mg, 89%) as a yellow solid of mp = 206–208 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.69 (s, 9H), 2.98 (m, 1H), 3.33 (m, 2H), 3.36 (m, 1H), 3.80 (s, 3H), 6.01 (s, 1H), 6.53 (d, J = 8.2 Hz, 1H), 6.68 (dd, J = 8.2, 2.7 Hz, 1H), 6.74 (d, J = 2.7 Hz, 1H), 7.24 (m, 1H), 7.36 (t, J = 7.3 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.53 (d, J = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 27.9, 30.1, 51.7, 55.2, 61.4, 63.7, 113.0, 113.6, 124.9, 127.0, 127.8, 128.6, 131.8, 133.1, 134.8, 154.2, 159.0, 166.1. IR (KBr): 3240, 2940, 1670, 1610, 1510, 1280 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{22}H_{27}N_6O_2$ [M^+ + H]: 407.2195. Found: 407.2189.

N-(1-(1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)-7-chloro-3,4-dihydroisoquinolin-2(1*H*)-yl)benzamide (5ga)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5ga** (53 mg, 64%) as a white solid of mp = 197–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.71 (s, 9H), 2.99 (m, 1H), 3.26 (m, 1H), 3.46 (m, 1H), 3.65 (m, 1H), 6.13 (s, 1H), 6.55 (s, 1H), 7.17 (d, J = 8.1 Hz, 1H), 7.24 (m, 1H), 7.32 (t, J = 8.1 Hz, 2H), 7.45 (t, J = 7.3 Hz, 1H), 7.53 (d, J = 7.3 Hz, 2H), 7.70 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 26.9, 30.2, 51.1, 60.7, 63.9, 126.7, 127.0, 128.3, 128.7, 130.7, 131.9, 132.0, 132.4, 132.9, 134.5, 153.5, 166.3. IR (KBr): 3210, 2920, 1680, 1490, 1280 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{21}H_{24}ClN_6O$ [M^+ + H]: 411.1700. Found: 411.1692.

N-(1-(1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-methylbenzamide (5ha)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5ha** (35 mg, 90%, 0.1 mmol scale) as a white solid of mp = 221–224 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.65 (s, 9H), 2.32 (s, 3H), 2.97 (m, 1H), 3.35 (m, 2H), 3.67 (m, 1H), 6.18 (s, 1H), 6.51 (d, J = 7.3 Hz, 1H), 7.09 (m, 3H), 7.24 (m, 2H), 7.44 (d, J = 8.3 Hz, 2H), 7.72 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.4, 27.8, 30.1, 52.0, 61.5, 63.8, 126.5, 126.6, 127.0, 127.9, 129.1, 129.2, 130.2, 133.0, 133.4, 142.3, 154.1, 166.2. IR (neat): 3200, 2980, 1670, 1530, 1500, 1290 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{22}H_{27}N_6O$ [M^+ + H]: 391.2246. Found: 391.2254.

N-(1-(1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-chlorobenzamide (5ia)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **5ia** (63 mg, 77%, 0.1 mmol scale) as a white solid of mp = 231–232 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.67 (s, 9H), 2.99 (m, 1H), 3.37 (m, 2H), 3.69 (m, 1H), 6.17 (s, 1H), 6.49 (d, J = 7.3 Hz, 1H), 7.12 (t, J = 7.3 Hz, 1H), 7.22–7.28 (m, 4H), 7.48 (d, J = 8.7 Hz, 2H), 7.82 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 27.7, 30.1, 52.1, 61.6, 63.8, 126.7, 126.8, 128.1, 128.5, 129.0, 129.2, 131.4, 132.7, 133.3, 138.2, 153.9, 165.1. IR (KBr): 3220, 3000, 1670, 1600, 1530, 1480, 1280 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{21}H_{24}ClN_6O$ [M^+ + H]: 411.1700. Found: 411.1709.

N-(2-(1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)-3,3-dimethylpiperidin-1-yl)-benzamide (5ja)

To a suspension of **1j** (0.3 mmol) in MeOH (0.6 mL), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (0.36 mmol, 1.2 equiv.) was added at room temperature. After 30 min, a solution of TMSCl (0.3 mmol) and NaN_3 (0.3 mmol) in MeOH (1.2 mL), which was prepared in another flask, was transferred *via* a cannula at room temperature and the whole mixture was stirred for 30 min. **2** (0.2 mmol, 1.0 equiv.) in MeOH (0.2 mL) was added dropwise and stirred at room temperature. After the completion of reaction (monitored by TLC), water (1.5 mL) was added and extracted with ethyl acetate (2 mL × 3). Combined organic layers were washed with sat. $NaHCO_3$ aq (3 mL) and brine (3 mL) and dried over Na_2SO_4, and then concentrated. Silicagel column chromatography (hexane/diethyl ether = 5/1) gave **5ja** (74 mg, 69%, 0.3 mmol scale) as a white solid of mp = 183–185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 0.87 (s, 3H), 1.25 (s, 3H), 1.72 (s, 9H), 1.82–2.05 (m, 4H), 3.35 (m, 1H), 3.57 (m, 1H), 5.06 (s, 1H), 6.95 (brs, 1H), 7.31–7.46 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.6, 26.0, 28.0, 31.0, 33.9, 36.0, 51.0, 63.2, 64.0, 126.7, 128.6, 131.8, 132.9, 152.6, 166.0. IR (neat): 3210, 3060, 2950, 1650, 1550, 1450, 1300, 1230 cm^{-1}. HRMS–FAB (*m*/*z*): Calcd for $C_{19}H_{29}N_6O$ [M^+ + H]: 357.2403. Found: 357.2404.

N-(1-(1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)-2-azaspiro[5.5]undecan-2-yl)benzamide (5ka)

Silicagel column chromatography (hexane/diethyl ether = 5/1) gave **5ka** (111 mg, 93%, 0.3 mmol scale) as a white solid of

mp = 219–220 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.01 (m, 1H), 1.18 (m, 2H), 1.42 (m, 3H), 1.68 (s, 9H), 1.80–1.83 (m, 3H), 1.99 (m, 1H), 2.13 (m, 1H), 2.30 (brs, 2H), 2.57 (m, 1H), 3.21 (m, 1H), 3.62 (m, 1H), 4.97 (s, 1H), 6.91 (brs, 1H), 7.34 (t, J = 6.9 Hz, 2H), 7.44 (d, J = 6.9 Hz, 1H), 7.49 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 20.6, 21.0, 21.2, 23.9, 26.2, 31.2, 34.5, 34.7, 38.8, 50.2, 63.2, 65.0, 126.9, 128.4, 131.6, 132.9, 151.2, 165.6. IR (KBr): 3240, 2930, 1650, 1540, 1460, 1290 cm^{-1}. HRMS–FAB (m/z): Calcd for $C_{22}H_{33}N_6O$ [M^+ + H]: 397.2716. Found: 397.2723.

2-Benzamido-*N*-(*tert*-butyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (4aa)

Silicagel column chromatography (hexane/ethyl acetate = 1/1) gave **4aa** (68 mg, 93%) as a white solid of mp = 168–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.18 (s, 9H), 2.77 (m, 1H), 2.96 (m, 1H), 3.34 (m, 2H), 4.28 (s, 1H), 7.05–7.17 (m, 3H), 7.31 (brs, 1H), 7.36 (m, 3H), 7.45 (m, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.2, 29.4, 50.8, 52.6, 71.2, 126.2, 126.4, 127.2, 127.2, 128.4, 128.7, 131.8, 131.9, 132.4, 133.3, 166.1, 170.2. IR (KBr): 3310, 2960, 1650, 1540, 1290, 1230 cm^{-1}. HRMS–FAB (m/z): Calcd for $C_{21}H_{26}N_3O_2$ [M^+ + H]: 352.2025. Found: 352.2027.

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Notes and references

1 (*a*) I. Ugi and C. Steinbrückner, *Angew. Chem.*, 1960, **72**, 267–268; (*b*) I. Ugi, R. Meyr, U. Fetzer and C. Steinbrückner, *Angew. Chem.*, 1959, **71**, 386.

2 Recent reviews: (*a*) L. Banfi, R. Riva and A. Basso, *Synlett*, 2010, 23–41; (*b*) L. El Kaim and L. Grimaud, *Tetrahedron*, 2009, **65**, 2153–2171; (*c*) A. Dömling, *Curr. Opin. Chem. Biol.*, 2002, **6**, 306–313; (*d*) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3169–3210; (*e*) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Res.*, 1996, **29**, 123–131.

3 I. Ugi and R. Meyr, *Chem. Ber.*, 1961, **94**, 2229–2233.

4 Recent examples, see: (*a*) T. Yue, M.-X. Wang, D.-X. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2008, **47**, 9454–9457; (*b*) J. Mayer, M. Umkehrer, C. Kalinski, G. Ross, J. Kolb, C. Burdack and W. Hiller, *Tetrahedron Lett.*, 2005, **46**, 7393–7396; (*c*) T. Nixey and C. Hulme, *Tetrahedron Lett.*, 2002, **43**, 6833–6835. Cu-catalyzed [3 + 2] cycloaddition of nitriles and trimethylsilyl azide has been reported. See: (*d*) T. Jin, F. Kitahara, S. Kamijo and Y. Yamamoto, *Chem.–Asian J.*, 2008, **3**, 1575–1580.

5 G. A. Patani and E. J. LaVoie, *Chem. Rev.*, 1996, **96**, 3147–3176.

6 H. Singh, A. S. Chawla, V. K. Kapoor, D. Paul and P. K. Malhotra, *Prog. Med. Chem.*, 1980, **17**, 151–183.

7 J. Zabrocki, G. D. Smith, J. B. Dunbar Jr., H. Iijima and G. R. Marshall, *J. Am. Chem. Soc.*, 1988, **110**, 5875–5880.

8 (*a*) S. J. Gunn, A. Baker, R. D. Bertram and S. L. Warriner, *Synlett*, 2007, 2643–2646; (*b*) V. V. Sureshbabu, R. Venkataramanarao, S. A. Naik and G. Chennakrishnareddy, *Tetrahedron Lett.*, 2007, **48**, 7038–7041; (*c*) B. C. H. May and A. D. Abell, *Tetrahedron Lett.*, 2001, **42**, 5641–5644; (*d*) Y. Satoh and J. Moliterni, *Synlett*, 1998, 528–530; (*e*) S.-E. Yoo and Y.-D. Gong, *Heterocycles*, 1997, **45**, 1251–1255; (*f*) J. V. Duncia, M. E. Pierce and J. B. Santella III, *J. Org. Chem.*, 1991, **56**, 2395–2400.

9 (*a*) N. Isambert and R. Lavilla, *Chem.–Eur. J.*, 2008, **14**, 8444–8454; (*b*) C. Masdeu, E. Gómez, N. A. O. Williams and R. Lavilla, *Angew. Chem., Int. Ed.*, 2007, **46**, 3043–3046; (*c*) N. A. O. Williams, C. Masdeu, J. L. Díaz and R. Lavilla, *Org. Lett.*, 2006, **8**, 5789–5792; (*d*) J. L. Díaz, M. Miguel and R. Lavilla, *J. Org. Chem.*, 2004, **69**, 3550–3553.

10 Tetrahydroisoquinoline-1-carboxyamide derivatives represent a fundamental structural motif found in many biologically active compounds as well as natural products. For example, they were shown to be potent growth hormone secretagogues. (*a*) J. J. Li, H. Wang, F. Qu, C. Musial, J. A. Tino, J. A. Robl, A. Slusarchyk, R. Golla, R. Seethala, K. Dickinson, L. Giupponi, G. Grover, P. Sleph, N. Flynn, B. J. Murphy, D. Gordon, M. Kung and R. Stoffel, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1799–1802. Recently, jasisoquinolines A and B were isolated from marine sponge *Jaspis* sp: (*b*) Y. Imae, K. Takada, S. Murayama, S. Okada, Y. Ise and S. Matsunaga, *Org. Lett.*, 2011, **13**, 4798–4801. Therefore, it is important for organic chemistry and/or medicinal chemistry to construct these structures efficiently.

11 (*a*) T. Sakai, T. Soeta, K. Inomata and Y. Ukaji, *Bull. Chem. Soc. Jpn.*, 2012, **85**, 231–235; (*b*) H. Kawai, Z. Yuan, E. Tokunaga and N. Shibata, *Org. Lett.*, 2012, **14**, 5330–5333; (*c*) T. Hashimoto, M. Omote and K. Maruoka, *Angew. Chem., Int. Ed.*, 2011, **50**, 8952–8955; (*d*) T. Hashimoto, M. Omote and K. Maruoka, *Angew. Chem., Int. Ed.*, 2011, **50**, 3489–3492; (*e*) T. Hashimoto, Y. Maeda, M. Omote, H. Nakatsu and K. Maruoka, *J. Am. Chem. Soc.*, 2010, **132**, 4076–4077.

12 T. Soeta, K. Tamura and Y. Ukaji, *Org. Lett.*, 2012, **14**, 1226–1229.

13 Very recently, an asymmetric version was also reported. See: T. Hashimoto, H. Kimura, Y. Kawamata and K. Maruoka, *Angew. Chem., Int. Ed.*, 2012, **51**, 7279–7281.

14 We chose the *C*,*N*-cyclic *N*′-acyl azomethine imines which are fused to an aromatic ring since the starting substrates are only stable when the aromatic ring is incorporated.

15 We already found that TMSCl was a good promoter for the nucleophilic addition of isocyanides to 3,4-dihydroisoquinoline *N*-oxides to give the corresponding amides. T. Soeta, S. Fujinami and Y. Ukaji, *J. Org. Chem.*, 2012, **77**, 9878–9883.