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Chlorosilane-Promoted Addition Reaction of Isocyanides to 3,4-Dihydroisoquinoline *N*-Oxides

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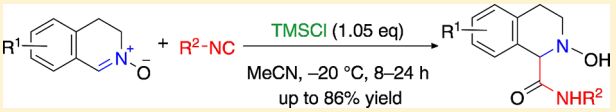
Supporting Information

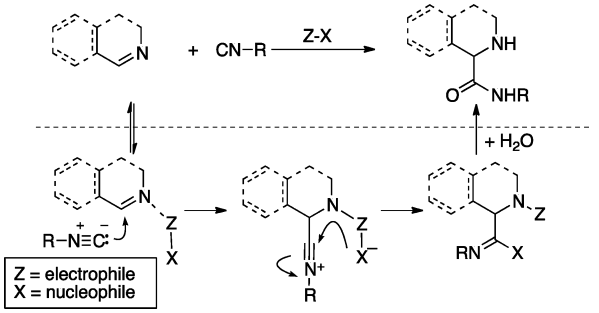
ABSTRACT: The addition reaction of isocyanides to 3,4-dihydroisoquinoline *N*-oxides in the presence of TMSCl has been demonstrated, with the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylamides being obtained in moderate to high yields. A wide range of 3,4-dihydroisoquinoline *N*-oxides and isocyanides were applicable to this reaction.



Isoquinoline alkaloids, especially 1,2,3,4-tetrahydroisoquinolines (THIQs), have long attracted significant attention due to their biological activity and also because they are important building blocks in natural product synthesis and drug discovery.[1] The majority of these compounds have a substituent at the C1 position of the isoquinoline moiety, and therefore the development of practical methods for the synthesis of THIQs bearing substituents at this position is important. Various reliable methods involving asymmetric synthesis have been reported to date.[2] The compound 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid and its derivatives are of particular interest as potential building blocks of modified peptides or other pharmacologically active compounds.[3] Such derivatives have been produced via Ugi-type reactions, which have also been applied to the synthesis of medicinally relevant heterocycles,[4] although the practical applications of this approach remain limited.[5] Herein, we report the addition of isocyanides to 3,4-dihydroisoquinoline *N*-oxides via an innovation of the Ugi reaction utilizing a chlorosilane without a carboxylic acid, to give the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylamide derivatives in good to high yields.

In general, Ugi reactions require a carboxylic acid that activates an imine and traps a nitrilium ion to form an acyloxylated intermediate. Subsequent acyl transfer leads to the corresponding α-amino amide. A carboxylic acid is therefore typically a necessary component of the sequence within the Ugi synthesis involving a reaction of an isocyanide with an imine. This requirement for a carboxylic acid, however, limits the applications of the reaction and prevents the synthesis of a broad range of molecules. To overcome this limitation, we have reasoned that a compound (which we write in the generic format as Z–X) composed of an electrophile (Z) and a nucleophilic group (X), could essentially perform the same function as the carboxylic acid in an Ugi-type reaction (Scheme 1). On the basis of this hypothesis, we have previously developed an *O*-silylative Passerini reaction and the borinic acid-catalyzed α-addition of isocyanide.[6]

Scheme 1. Hypothetical Modified Ugi-Type Reaction Mechanism



We initially investigated the feasibility of using metal halides as the Z–X species to induce the addition reaction of an isocyanide to a nitrone.[7] Among the imine analogues, nitrones appear to be a promising candidate[8] since they possess an electronegative oxygen that can activate the C=N bond and strongly coordinate to metals.

Our initial attempts involved using 3,4-dihydroisoquinoline *N*-oxide (**1a**) and *tert*-butyl isocyanide (**2a**) in the presence of $MgCl_2$, $ZnCl_2$, and other metal halides in dichloromethane. However, none of these reactions were successful; the reactions either did not proceed and only starting materials were recovered, or the reactions gave a very complex mixture of products. In contrast, when this reaction was carried out in the presence of chlorotrimethylsilane (TMSCl) in dichloromethane at −20 °C, the reaction resulted in the 1,2,3,4-tetrahydroisoquinoline-1-carboxylamide **3aa** in 53% yield, as well as the dehydrated compound **4aa** in 23% yield (Table 1, entry 1).[9] With the use of toluene and THF as solvents, mixtures of **3aa** and **4aa** were again obtained, but in lower yields. Reactions carried out in DMF and acetonitrile (MeCN), however, gave **3aa** as the sole product in 78% and 82% yields, respectively

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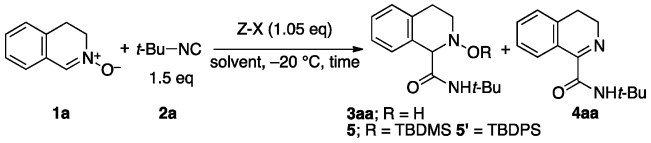
Table 1. Reaction Conditions and Results for Ugi-Type Reactions



1a 2a 3aa; R = H 5; R = TBDMS 5′ = TBDPS 4aa

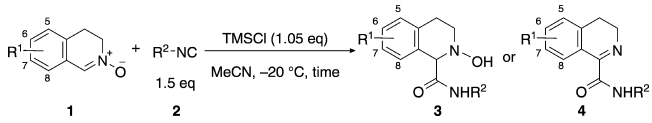
entry	ZX	solvent	time (h)	yield of 3aa (%)	yield of 4aa (%)	yield of 5 or 5′ (%)
1	TMSCl	CH_2Cl_2	8	53	23	
2	TMSCl	toluene	12	7	12	
3	TMSCl	THF	12	23	9	
4	TMSCl	DMF	12	78		
5	TMSCl	MeCN	12	82		
6	TESCl	MeCN	12	59	29	
7	TIPSCl	MeCN	12	47		
8	TBDMSCl	MeCN	24	11		51
9	TBDPSCl	MeCN	24			76

(entries 2–5). The structure of product **3aa** was obtained by X-ray crystallography.

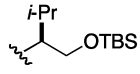
Having established an efficient method for the addition of an isocyanide to a nitrone, we set out to evaluate the use of chlorosilane derivatives bearing other substituents (entries 6–9). Using chlorotriethylsilane (TESCl), a mixture of **3aa** and **4aa** was obtained with yields of 59% and 29%, respectively (entry 6), whereas chlorotriisopropylsilane (TIPSCl) exhibited decreased reactivity and gave solely **3aa** in 47% yield (entry 7). When employing the more sterically hindered silyl compounds *tert*-butylchlorodimethylsilane (TBDMSCl) and *tert*-butylchlorodiphenylsilane (TBDPSCl), the *O*-silylated products **5** and **5′** were obtained with yields of 51% and 76%, respectively (entries 8 and 9). These results indicate that minimal steric hindrance at the Si atom is crucial for the reaction to proceed efficiently.

We subsequently attempted to expand the scope of isocyanides and nitrones to which this Ugi-type reaction utilizing TMSCl might be applied, as detailed in Table 2. In these reactions, optimal molar quantities of nitrones **1a–h** (1.0 equiv) and isocyanides **2a–h** (1.5 equiv) were used in the presence of 1.05 equiv of TMSCl. From this work we determined that these reaction conditions were applicable to a wide variety of nitrones and isocyanides and that most reactions were complete within 24 h at either −20 or 0 °C. The reaction of the aliphatic isocyanides **2a** and **2b** (R^2 = *t*-Bu, *c*-Hex) with **1a** in the presence of TMSCl resulted in the product in good to high yields (entries 1 and 2). In the case of the primary alkyl isocyanide **2c**, however, lower reactivity was observed with the corresponding product **3ac** produced in 73% yield (entry 3). The chiral isocyanide **2d**, which was prepared from the corresponding amino acid,[10] gave the product **3ad** in good yield; however, no chiral induction was observed (entry 4). Aromatic isocyanides were also investigated, although low reactivities resulted from their use (entries 5–8). When phenylisocyanide (**2e**) was used, only the corresponding dehydrated compound **4ae** was obtained in 32% yield (entry 5). Aromatic isocyanides bearing an electron-donating group at the *para* position also exhibited low reactivities with the corresponding products produced in 42% and 53% yields, respectively (entries 6 and 7). In the case of an aromatic isocyanide bearing an electron-withdrawing group at the *para* position, the reaction did not proceed at all (entry 8). The reactivity of various nitrones in conjuction with *tert*-

Table 2. Summary of Isocyanides and Nitrones Investigated



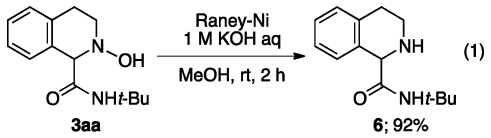
1 2 3 4

entry	R^1	R^2	time / h	yield / %
1	H (**1a**)	*t*-Bu (**2a**)	12	82 (**3aa**)
2	H (**1a**)	*c*-Hex (**2b**)	8	86 (**3ab**)
3	H (**1a**)	Bn (**2c**)	24	73 (**3ac**)
4	H (**1a**)	 (**2d**)	12	70 (**3ad**)
5	H (**1a**)	Ph (**2e**)	24	32 (**4ae**)
6	H (**1a**)	4-$MeOC_6H_4$ (**2f**)	24	42 (**3af**)
7	H (**1a**)	4-$Me_2NC_6H_4$ (**2g**)	24	53 (**3ag**)
8	H (**1a**)	4-BrC_6H_4 (**2h**)	24	nr
9	5-Me (**1b**)	*t*-Bu (**2a**)	8	78 (**3ba**)
10	6-Me (**1c**)	*t*-Bu (**2a**)	24	26 (**3ca**)
11	7-Me (**1d**)	*t*-Bu (**2a**)	8	82 (**3da**)
12	8-Me (**1e**)	*t*-Bu (**2a**)	24	64 (**3ea**)
13[a]	5,6-MeO (**1f**)	*t*-Bu (**2a**)	24	75 (**3fa**)
14[a]	6,7-MeO (**1g**)	*t*-Bu (**2a**)	24	78 (**3ga**)
15	7-Cl (**1h**)	*t*-Bu (**2a**)	15	77 (**3ha**)

[a]Reaction was carried out at 0 °C.

butylisocyanide (**2a**) was next examined, via the reaction of 1.0 equiv of nitrones **1a–h** with 1.5 equiv of **2a** in the presence of 1.05 equiv of TMSCl. With regard to the substituents of the nitrones, those nitrones having 5-, 7-, and 8-methyl substituents were all reactive, furnishing the corresponding heterocycles (entries 9, 11, and 12). The only exception was the incorporation of the 6-methyl substituent, which resulted in a very sluggish reaction to give the product **3ca** in 26% yield (entry 10). The nitrones **1f** and **1g** with dimethoxy groups showed low reactivity with **2a** and TMSCl at −20 °C, but at 0 °C both compounds reacted to give the corresponding products **3fa** and **3ga** in 75% and 78% yields, respectively (entries 13 and 14). In addition, the nitrone **1g** with an electron-withdrawing group on the aromatic ring reacted to afford the product **3ha** in 77% yield (entry 15).

The hydroxyl group of **3aa** was easily removed by the reaction with Raney nickel to give the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylamide **6** in 92% yield (eq 1).



3aa 6; 92% (1)

To elucidate the reaction mechanism, we performed ^1H and ^{13}C NMR analyses in MeCN-d_3. Treatment of nitrone **1a** with 1.0 equiv of TMSCl induced a downfield shift of the iminium hydrogen atom from 7.65 to 8.10 ppm. The same behavior was observed with ^{13}C NMR, where the carbon of the imino group (at 133.6 ppm) moved downfield (to 148.1 ppm). In contrast, treatment of **2a** with 1.0 equiv of TMSCl did not result in the shift of any hydrogen or carbon atoms. On the basis of these results and the data presented in Table 1 (entries 8 and 9), we propose a mechanism for this Ugi-type reaction as shown in

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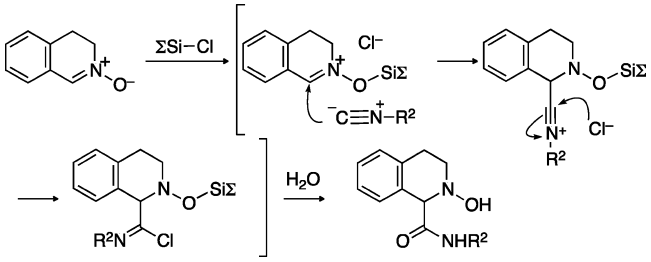
Scheme 2. We propose that this reaction likely proceeds by initial activation of the nitrone via coordination of its oxygen

Scheme 2. Plausible Reaction Mechanism



with TMSCl. This is followed by stabilization of the nitrilium intermediate by the addition of the chloride anion to form the imidoyl chloride,[11] which is then hydrolyzed by water to give the final product. In the case of phenyl isocyanide (R^2 = Ph; **2e**), conjugation between C═N bond and aromatic ring on the nitrogen atom of imidoyl chloride might make C1 proton of the tetrahydroisoquinoline ring more acidic. Therefore, deprotonation at the C1 position readily occurred followed by elimination of the silyloxy anion to give **4ae**. On the other hand, introduction of an electron-donating group on the aromatic ring such as **2f** and **2g** made the C1 proton of the corresponding imidoyl chloride less acidic to prevent the deprotonation.

In conclusion, we have designed and demonstrated the addition reaction of isocyanides to nitrones in the presence of TMSCl to afford the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylamides in moderate to high yields. A wide range of 3,4-dihydroisoquinoline *N*-oxides and isocyanides were applicable to this reaction.

EXPERIMENTAL SECTION

General Method. ^{1}H NMR was 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 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.

3,4-Dihydroisoquinoline 2-oxides were prepared according to the reported procedure.[12]

General Procedure. To a solution of 2-(2-bromoethyl)-benzaldehyde derivative (2.0 mmol) in MeOH (2.0 mL) was added hydroxylamine hydrogenchloride (4.0 mmol) at room temperature, and the whole was refluxed for 1 h. The 1 N NaOH aq (5 mL) was added at room temperature. After removal of the MeOH under reduced pressure, the aqueous solution was extracted with $CHCl_3$ (3 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4, followed by evaporation.

5-Methyl-3,4-dihydroisoquinoline 2-Oxide (1b). Silica gel column chromatography (ethyl acetate/MeOH = 10/1) gave **1b** (595 mg, 74%, 5.0 mmol scale) as a white solid of mp = 84.5−85.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.28 (s, 3H), 3.10 (t, J = 7.8 Hz, 2H), 4.09 (t, J = 7.8 Hz, 2H), 6.96 (d, J = 7.1 Hz, 1H), 7.15 (t, J = 7.1 Hz, 2H), 7.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 18.9, 24.7, 57.4, 123.6, 127.3, 128.2, 128.4, 131.5, 134.4, 135.2. IR (KBr): 3370, 2910, 1610, 1580, 1450, 1250, 1170 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{10}H_{12}NO$ [M^+ + H] 162.0919; found 162.0923.

6-Methyl-3,4-dihydroisoquinoline 2-Oxide (1c). Silica gel column chromatography (ethyl acetate/MeOH = 10/1) gave **1c** (507 mg, 63%, 5.0 mmol scale) as a white solid of mp = 109−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.32 (s, 3H), 3.12 (t, J = 7.7 Hz, 2H), 4.06 (t, J = 7.7 Hz, 2H), 7.02 (d, J = 7.7 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 7.15 (t, J = 7.7 Hz, 1H), 7.97 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 18.4, 28.1, 57.6, 124.9, 126.7, 129.1, 129.4, 130.5, 132.2, 133.7. IR (KBr): 3380, 2970, 1600, 1560, 1470, 1260, 1190 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{10}H_{12}NO$ [M^+ + H] 162.0919; found 162.0918.

7-Methyl-3,4-dihydroisoquinoline 2-Oxide (1d). Silica gel column chromatography (ethyl acetate/MeOH = 10/1) gave **1d** (515 mg, 64%, 5.0 mmol scale) as a white solid of mp = 90.5−91.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.27 (s, 3H), 3.07 (t, J = 7.8 Hz, 2H), 4.02 (t, J = 7.8 Hz, 2H), 6.84 (s, 1H), 7.03 (s, 2H), 7.64 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 20.9, 27.3, 58.1, 126.0, 127.1, 128.2, 130.1, 134.2, 137.3. IR (KBr): 3430, 2960, 1590, 1570, 1500, 1280, 1200 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{10}H_{12}NO$ [M^+ + H] 162.0919; found 169.0922.

8-Methyl-3,4-dihydroisoquinoline 2-Oxide (1e). Silica gel column chromatography (ethyl acetate/MeOH = 10/1) gave **1e** (572 mg, 71%, 5.0 mmol scale) as a white solid of mp = 75−76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.33 (s, 3H), 3.12 (t, J = 7.7 Hz, 2H), 4.06 (t, J = 7.7 Hz, 2H), 6.97−7.01 (m, 2H), 7.05 (d, J = 7.8 Hz, 1H), 7.71 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.4, 27.7, 57.8, 125.4, 125.7, 128.1, 128.2, 130.0, 134.2, 139.9. IR (KBr): 3360, 2980, 1600, 1560, 1440, 1270, 1170 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{10}H_{12}NO$ [M^+ + H] 162.0919; found 162.0920.

5,6-Dimethoxy-3,4-dihydroisoquinoline 2-Oxide (1f). Silica gel column chromatography (ethyl acetate/MeOH = 10/1) gave **1f** (672 mg, 65%, 5.0 mmol scale) as a white solid of mp = 124.5−125 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.14 (t, J = 7.7 Hz, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 3.98 (t, J = 7.7 Hz, 2H), 6.74 (d, J = 8.3 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 7.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.9, 55.8, 57.0, 60.6, 110.9, 121.7, 121.9, 123.9, 133.8, 145.8, 154.0. IR (KBr): 3430, 2940, 1590, 1490, 1310, 1270, 1090 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{11}H_{14}NO_3$ [M^+ + H] 208.0974; found 208.0979.

7-Chloro-3,4-dihydroisoquinoline 2-Oxide (1h). Silica gel column chromatography (ethyl acetate/MeOH = 10/1) gave **1h** (288 mg, 78%, 2.0 mmol scale) as a white solid of mp = 109−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.09 (t, J = 7.8 Hz, 2H), 4.04 (t, J = 7.8 Hz, 2H), 7.04−7.09 (m, 2H), 7.15−7.19 (m, 1H), 7.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 27.3, 58.2, 124.9, 128.2, 128.5, 129.0, 130.0, 132.8, 133.5. IR (KBr): 3360, 3030, 2830, 1590, 1490, 1410, 1270, 1190 cm^{-1}. HRMS−FAB (m/z): calcd for C_9H_9ClNO [M^+ + H] 182.0373; found 182.0369.

General Procedure for the Addition of Isocyanide to Nitrones in the Presence of TMSCl. To a solution of nitrone (0.5 mmol) in MeCN (1.0 mL) was added TMSCl (0.525 mmol) in MeCN (0.5 mL) at −20 °C. After 10 min, isocyanide (1.0 mmol) in MeCN (0.5 mL) was added dropwise at −20 °C and stirred at that temperature. After reaction completion (monitored by TLC), water (3 mL) was added at −20 °C and warmed to room temperature, and then ethyl acetate was added. Aqueous layer was separated and extracted with ethyl acetate (5 mL × 3). Combined organic layers were washed with brine and dried over Na_2SO_4. The residue was purified by silica gel column chromatography to give the corresponding products.

***N*-(*tert*-Butyl)-2-hydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3aa).** Silica gel column chromatography (hexane/ethyl acetate = 3/1−1/1) gave **3aa** (151 mg, 82%) as a white solid of mp = 156−157 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.31 (s, 9H), 2.76−2.80 (m, 1H), 2.94−3.01 (m, 1H), 3.06−3.14 (m, 1H), 3.39−3.43 (m, 1H), 4.21 (s, 1H), 5.70 (br, 1H), 6.42 (brs, 1H), 7.02 (d, J = 6.9 Hz, 1H), 7.09−7.12 (m, 2H), 7.41 (d, J = 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.6, 29.1, 50.8, 54.2, 74.0, 126.2, 126.4, 127.2, 128.2, 132.0, 132.3, 170.5. IR (KBr): 3370, 2970, 2830, 1650, 1530, 1450,

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1360, 1230 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{14}H_{21}N_2O_2$ [M$^+$ + H] 249.1603; found 249.1609.

***N*-Cyclohexyl-2-hydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3ab).** Silica gel column chromatography (hexane/ethyl acetate = 3/1−1/1) gave **3ab** (118 mg, 86%) as a white solid of mp = 178−179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 0.73−1.90 (m, 10 H), 2.78−2.82 (m, 1H), 2.96−3.02 (m, 1H), 3.08−3.17 (m, 1H), 3.41−3.45 (m, 1H), 3.68−3.77 (m, 1H), 4.31 (s, 1H), 5.36 (brs, 1H), 6.41 (d, J = 6.3 Hz, 1H), 7.03 (d, J = 6.9 Hz, 1H), 7.07−7.14 (m, 2H), 7.41 (d, J = 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 24.7, 24.9, 25.5, 29.1, 32.7, 32.9, 48.0, 54.3, 73.3, 126.2, 126.4, 127.2, 128.2, 131.9, 132.4, 170.6. IR (KBr): 3230, 2970, 2920, 1640, 1560, 1450, 1370, 1250 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{16}H_{23}N_2O_2$ [M$^+$ + H] 275.1770; found 275.1760.

***N*-Benzyl-2-hydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3ac).** Silica gel column chromatography (hexane/ethyl acetate = 3/1−1/1) gave **3ac** (103 mg, 73%) as a white solid of mp = 176−177 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.75−2.79 (m, 1H), 2.95−3.00 (m, 1H), 3.04−3.13 (m, 1H), 3.38−3.41 (m, 1H), 4.26 (dd, J = 15.5, 5.5 Hz, 1H), 4.42 (s, 1H), 4.50−4.56 (m, 1H), 5.54 (brs, 1H), 6.97 (brs, 1H), 7.02−7.04 (m, 1H), 7.12−7.22 (m, 7H), 7.48 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 29.2, 43.0, 54.3, 73.1, 126.4, 126.5, 127.4, 127.4, 127.5, 128.2, 128.6, 138.3, 171.4. IR (KBr): 3290, 2930, 2840, 1660, 1530, 1490, 1360, 1250 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{17}H_{19}N_2O_2$ [M$^+$ + H] 283.1447; found 283.1446.

***N*-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-methylbutan-2-yl)-2-hydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3ad).** Silica gel column chromatography (hexane/ethyl acetate = 5/1−1/1) gave **3ad** (138 mg, 70%). Diastereomeric ratio was determined to be 1:1 by ^{1}H NMR.

Diastereomer (R_f = 0.4, hexane/ethyl acetate = 7/1 × 2). ^{1}H NMR (400 MHz, $CDCl_3$): −0.28 (s, 3H), −0.14 (s, 3H), 0.74 (s, 9H), 0.96 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 1.93 (sep, J = 6.6 Hz, 1H), 2.83−2.88 (m, 1H), 3.03−3.19 (m, 2H), 3.35 (dd, J = 10.5, 3.2 Hz, 1H), 3.48−3.52 (m, 1H), 3.64−3.70 (m, 2H), 4.43 (s, 1H), 5.34 (brs, 1H), 6.86 (d, J = 9.2 Hz, 1H), 7.06−7.08 (m, 1H), 7.12−7.18 (m, 2H), 7.48−7.51 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): −6.1, −5.8, 18.0, 19.5, 19.7, 25.7, 28.8, 29.2, 54.2, 55,4, 62.6, 73.3, 126.3, 126.5, 127.3, 128.2, 131.8, 132.3, 170.8. IR (KBr): 3360, 2930, 2820, 1640, 1530, 1260, 1100 cm^{-1} HRMS−FAB (m/z): calcd for $C_{21}H_{37}N_2O_3Si$ [M$^+$ + H] 393.2573; found 393.2566.

Diastereomer (R_f = 0.55, hexane/ethyl acetate = 7/1 × 2). ^{1}H NMR (400 MHz, $CDCl_3$): 0.09 (s, 3H), 0.10 (s, 3H), 0.75 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.91 (s, 9H), 2.6−2.90 (m, 1H), 3.03−3.09 (m, 1H), 3.18−3.26 (m, 1H), 3.47−3.50 (m, 1H), 3.63−3.66 (m, 1H), 3.74−3.81 (m, 2H), 4.40 (s, 1H), 6.07 (s, 1H), 6.86 (d, J = 9.2 Hz, 1H), 7.11 (d, J = 7.3 Hz, 1H), 7.13−7.20 (m, 3H), 7.49 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): −5.5, −5.4, 18.3, 19.0, 19.5, 25.8, 29.3, 29.3, 53.3, 55.6, 63.4, 73.9, 126.1, 126.4, 127.3. 128.2, 131.8, 132.2, 171.3. IR (KBr): 3360, 2930, 2820, 1640, 1530, 1260, 1100 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{21}H_{37}N_2O_3Si$ [M$^+$ + H] 393.2573; found 393.2562

2-Hydroxy-*N*-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3af). Silica gel column chromatography (hexane/ethyl acetate = 3/1−1/1) gave **3af** (63 mg, 42%) as a white solid of mp = 158−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.81−2.86 (m, 1H), 3.02−3.08 (m, 1H), 3.15−3.23 (m, 1H), 3.47−3.52 (m, 1H), 3.70 (s, 3H), 4.45 (s, 1H), 5.58 (brs, 1H), 6.76 (d, J = 8.9 Hz, 2H), 7.05−7.16 (m, 3H), 7.39 (d, J = 8.9 Hz, 2H), 7.51 (d, J = 6.9 Hz, 1H), 8.37 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 29.2, 54.2, 55.4, 73.5, 114.0, 121.5, 126.3, 126.6, 127.5, 128.3, 130.8, 131.3, 132.5, 156.2, 169.4. IR (KBr): 3330, 2960, 2840, 1650, 1510, 1460, 1250 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{17}H_{19}N_2O_3$ [M$^+$ + H] 299.1396; found 299.1397.

***N*-(4-(Dimethylamino)phenyl)-2-hydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3ag).** Silica gel column chromatography (hexane/ethyl acetate = 8/1−5/1−1/1) gave **3ag** (82 mg, 53%) as a white solid of mp = 173−175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.83 (s, 6H), 2.85−2.88 (m, 1H), 3.03−3.08 (m, 1H), 3.15−3.23 (m, 1H), 3.47−3.51 (m, 1H), 4.44 (s, 1H), 5.48 (brs, 1H), 6.61 (d, J = 8.7 Hz, 2H), 7.06 (d. J = 7.3 Hz, 1H), 7.09−7.13 (m, 2H), 7.34 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 7.3 Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 29.2, 41.0, 54.2, 73.6, 113.1, 121.4, 126.4, 126.5, 127.4, 127.7, 128.2, 131.5, 132.5, 147.8, 169.1. IR (KBr): 3340, 2950, 2840, 1640, 1540, 1360, 1230 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{18}H_{22}N_3O_2$ [M$^+$ + H] 312.1712; found 312.1716.

***N*-(*tert*-Butyl)-2-hydroxy-5-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3ba).** Silica gel column chromatography (hexane/ethyl acetate = 4/1−2/1−1/1) gave **3ba** (102 mg, 78%) as a white solid of mp = 173−174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.26 (s, 9H), 2.16 (s, 3H), 2.72−2.76 (m, 1H), 2.82−2.90 (m, 1H), 2.94−3.00 (m, 1H), 3.44−3.49 (m, 1H), 4.20 (s, 1H), 5.31 (brs, 1H), 6.29 (brs, 1H), 6.98−7.04 (m, 2H), 7.25 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 19.4, 26.9, 28.6, 50.8, 54.1, 74.4, 123.8, 126.3, 128.6, 131.0, 131.9, 135.8, 170.7. IR (KBr): 3360, 2970, 2830, 1650, 1530, 1360, 1230 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{15}H_{23}N_2O_2$ [M$^+$ + H] 263.1760; found 263.1755.

***N*-(*tert*-Butyl)-2-hydroxy-6-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3ca).** Silica gel column chromatography (hexane/ethyl acetate = 4/1−2/1−1/1) gave **3ca** (102 mg, 26%) as a white solid of mp = 160−170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.26 (s, 9H), 2.22 (s, 3H), 2.72−2.76 (m, 1H), 2.95−2.98 (m, 1H), 3.01−3.03 (m, 1H), 3.38−3.43 (m, 1H), 4.16 (s, 1H), 5.48 (brs, 1H), 6.37 (brs, 1H), 6.84 (brs, 1H), 6.91 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 20.9, 28.6, 29.1, 50.7, 54.3, 73.9, 126.1, 127.3, 128.7, 129.0, 132.1, 136.9, 170.1 IR (KBr): 3370, 2970, 2840, 1650, 1540, 1360, 1230 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{15}H_{23}N_2O_2$ [M$^+$ + H] 263.1760; found 263.1765.

***N*-(*tert*-Butyl)-2-hydroxy-7-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3da).** Silica gel column chromatography (hexane/ethyl acetate = 4/1−2/1−1/1) gave **3da** (108 mg, 82%) as a white solid of mp = 114−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.27 (s, 9H), 2.21 (s, 3H), 2.72−2.77 (m, 1H), 2.91−2.98 (m, 1H), 3.01−3.09 (m, 1H), 3.38−3.42 (m, 1H), 4.16 (s, 1H), 5.50 (brs, 1H), 6.38 (brs, 1H), 6.90−6.92 (m, 2H), 7.21 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.1, 28.6, 28.7, 50.8, 54.4, 74.0, 126.5, 128.0, 128.1, 129.5, 131.2, 136.0, 170.7. IR (KBr): 3330, 2970, 2830, 1660, 1530, 1360, 1230 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{15}H_{23}N_2O_2$ [M$^+$ + H] 263.1760; found 263.1764.

***N*-(*tert*-Butyl)-2-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3ea).** Silica gel column chromatography (hexane/ethyl acetate = 4/1−2/1−1/1) gave **3ea** (84 mg, 64%) as a white solid of mp = 162−164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.26 (s, 9H), 2.23 (s, 3H), 2.72−2.76 (m, 1H), 2.92−2.98 (m, 1H), 3.02−3.11 (m, 1H), 3.38−3.42 (m, 1H), 4.16 (s, 1H), 5.49 (brs, 1H), 6.37 (brs, 1H), 6.84 (brs, 1H), 6.91 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 20.9, 28.6, 29.0, 50.7, 54.3, 73.9, 126.1, 127.3, 128.7, 129.1, 132.1, 136.9, 170.7. IR (KBr): 3300, 2970, 2840, 1650, 1530, 1530, 1230. cm^{-1}. HRMS−FAB (m/z): calcd for $C_{15}H_{23}N_2O_2$ [M$^+$ + H] 263.1760; found 263.1759.

***N*-(*tert*-Butyl)-2-hydroxy-5,6-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3fa).** Silica gel column chromatography (hexane/ethyl acetate = 5/1−2/1−1/1) gave **3fa** (115 mg, 75%) as a white solid of mp = 158−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.27 (s, 9H), 2.81−2.98 (m, 3H), 3.40−3.43 (m, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 4.11 (s, 1H), 5.31 (brs, 1H), 6.34 (brs, 1H), 6.70 (d, J = 8.7 Hz, 1H), 7.10 (d, J = 8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 23.8, 28.6, 50.8, 53.9, 55.7, 60.0, 73.5, 110.9, 121.7, 125.1, 126.9, 145.7, 151.3, 170.5. IR (KBr): 3380, 2970, 2840, 1650, 1540, 1280, 1230 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{16}H_{25}N_2O_4$ [M$^+$ + H] 309.1814; found 309.1818.

***N*-(*tert*-Butyl)-2-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3ga).** Silica gel column chromatography (hexane/ethyl acetate = 5/1−2/1−1/1) gave **3ga** (120 mg, 78%) as a white solid of mp = 194−195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.27 (s, 9H), 2.68−2.72 (m, 1H), 2.92−2.98 (m, 1H), 3.01−3.09 (m, 1H), 3.37−3.42 (m, 1H), 3.75 (s, 3H), 3.78 (s, 3H), 4.12 (s, 1H), 5.21 (brs, 1H), 6.37 (brs, 1H), 6.49 (s, 1H), 6.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.6, 28.8, 50.7, 54.4, 55.8, 55.9, 73.8, 108.6, 110.4, 123.8, 124.3, 147.6, 148.2, 170.6. IR (KBr): 3360, 2970,

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2840, 1650, 1520, 1300, 1220 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{16}H_{25}N_2O_4$ [M^+ + H] 309.1814; found 309.1823.

***N*-(*tert*-Butyl)-7-chloro-2-hydroxy-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (3ha).** Silica gel column chromatography (hexane/ethyl acetate = 5/1−2/1−1/1) gave **3ha** (108 mg, 77%) as a white solid of mp = 137−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.27 (s, 9H), 2.72−2.77 (m, 1H), 2.92−3.06 (m, 2H), 3.37−3.40 (m, 1H), 4.17 (s, 1H), 6.17 (brs, 1H), 6.52 (brs, 1H), 6.95 (d, J = 8.1 Hz, 1H), 7.09 (d, J = 8.1 Hz, 1H), 7.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.3, 28.6, 51.0, 53.9, 73.2, 126.2, 127.5, 129.5, 131.0, 132.2, 133.8, 170.0. IR (neat): 3360, 2970, 2830, 1650, 1530, 1290, 1230 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{14}H_{20}ClN_2O_2$ [M^+ + H] 283.1213; found 283.1220.

***N*-(*tert*-Butyl)-3,4-dihydroisoquinoline-1-carboxamide (4aa).** Silica gel column chromatography (hexane/ethyl acetate = 10/1−5/1) gave **4aa** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 1.45 (s, 9H), 2.70 (t, J = 7.3 Hz, 2H), 3.73 (t, J = 7.3, 2H), 7.17 (d, J = 7.3 Hz, 1H), 7.28−7.38 (m, 3H), 8.17 (d, J = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 25.6, 28.5, 46.9, 50.8, 126.1, 126.6, 126.9, 128.4, 130.9, 137.9, 160.3, 163.6. IR (neat): 3360, 2970, 1680, 1610, 1510, 1360. 1250, 1130 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{14}H_{19}N_2O$ [M^+ + H] 231.1497; found 231.1499.

***N*-(Phenyl)-3,4-dihydroisoquinoline-1-carboxamide (4ae).** Silica gel column chromatography (hexane/ethyl acetate = 10/1−5/1) gave **4ae** (40 mg, 32%) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): 2.70 (t, J = 7.3 Hz, 2H), 3.79 (t, J = 7.3 Hz, 2H), 7.07 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 7.26−7.36 (m, 4H), 7.63 (d, J = 8.2 Hz, 2H), 8.26 (d, J = 7.8 Hz, 1H). 9.43 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 25.9, 47.2, 119.6, 124.2, 126.0, 127.0, 127.2, 128.7, 129.0, 131.4, 137.7, 138.1, 159.3, 161.6. IR (neat): 3320, 2920, 1690, 1600, 1520, 1440, 1290 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{16}H_{15}N_2O$ [M^+ + H] 251.1184; found 251.1180.

***N*-(*tert*-Butyl)-2-((*tert*-butyldimethylsilyl)oxy)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (5).** Silica gel column chromatography (hexane/ethyl acetate = 10/1−5/1) gave **5** (55 mg, 51%, 0.3 mmol scale) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 0.08 (s, 3H), 0.10 (s, 3H), 0.81 (s, 9H), 1.29 (s, 9H), 2.43−2.46 (m, 1H), 3.02−3.12 (m, 3H), 4.36 (s, 1H), 6.68 (brs, 1H), 6.96−6.99 (m, 1H), 7.07 (m, 2H), 7.29 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): −4.8, −3.6, 17.8, 25.6, 26.0, 28.7, 50.8, 51.5, 71.4, 125.6, 126.8, 128.0, 129.3, 130.4, 133.2, 169.0. IR (KBr): 3290, 2930, 1660, 1550, 1450, 1360, 1250 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{20}H_{35}N_2O_2Si$ [M^+ + H] 363.2468; found 363.2471.

***N*-(*tert*-Butyl)-2-((*tert*-butyldiphenylsilyl)oxy)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (5′).** Silica gel column chromatography (hexane/ethyl acetate = 10/1−5/1) gave **5′** (110 mg, 76%, 0.3 mmol scale) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 0.98 (s, 9H), 1.01 (s, 9H), 2.43−2.47 (m, 1H), 3.02−3.12 (m, 3H), 4.36 (s, 1H), 6.15 (brs 1H), 6.98−7.00 (m, 1H), 7.07−7.10 (m, 2H), 7.26−7.41 (m, 6H), 7.60−7.66 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 0.98, 19.1, 27.2, 28.3, 50.5, 50.7, 70.8, 125.5, 126.8, 127.6, 127.6, 127.9, 129.5, 129.7, 129.9, 129.9, 133.2, 133.3, 133.6, 134.8, 136.0, 168.3. IR (neat): 3390, 2930, 2820, 1690, 1510, 1430, 1220, 1110 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{30}H_{39}N_2O_2Si$ [M^+ + H] 487.2781; found 487.2777.

***N*-(*tert*-Butyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (6).** To a solution of **3aa** (59.5 mg, 0.24 mmol) in MeOH (1.1 mL) were subsequently added potassium hydroxide (26.9 mg, 0.48 mmol) in H_2O and nickel/aluminum alloy (421 mg) at room temperature.[13] The whole was stirred at room temperature for 2 h and filtrated through Celite. The filtrate was concentrated to afford the crude prodtct. Silica gel column chromatography (ethyl acetate/MeOH = 10/1) gave **6** (51 mg, 92%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): 1.25 (s, 9H), 2.03 (brs, 1H), 2.63−2.70 (m, 1H), 2.74−2.81 (m, 1H), 2.98 (t, J = 5.9 Hz, 2H), 4.34 (s, 1H), 6.97 (brs, 1H), 7.00−7.02 (m, 1H), 7.09−7.11 (m, 2H), 7.40−7.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 28.6, 29.2, 41.1, 50.6, 60.6, 125.8, 126.8, 127.9, 129.0, 132.9, 134.4, 171.7. IR (neat): 3310, 2970, 1660, 1510, 1390, 1230 cm^{-1}. HRMS−FAB (m/z): calcd for $C_{14}H_{21}N_2O$ [M^+ + H] 233.1654; found 233.1658.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra of products and X-ray crystallographic data of **3aa** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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