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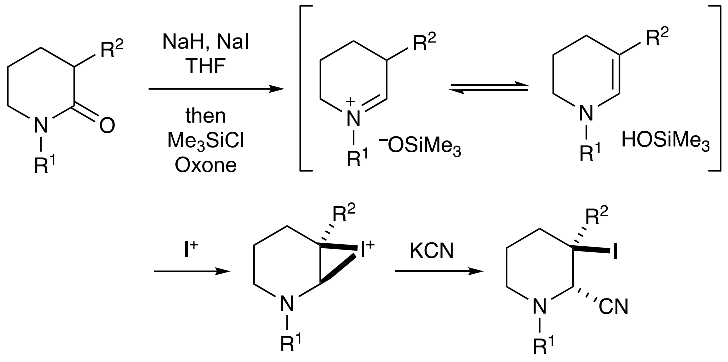

Interception of enamine intermediates in reductive functionalization of lactams by sodium hydride: synthesis of 2-cyano-3-iodo piperidines and pyrrolidines

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ABSTRACT

Facile conversion of 2-piperidones and 2-pyrrolidones into 2-cyano-3-iodo piperidines or pyrrolidines has been accomplished by the sequence of 1) controlled hydride reduction of lactams using sodium hydride (NaH) in the presence of sodium iodide (NaI); 2) silylation of anionic hemiaminal intermediates to facilitate deoxygenation to form an equilibrium mixture of iminium cations and enamines-silanol pair; 3) interception of enamine intermediates by electrophilic iodination to generate iodonium ions; 4) nucleophilic cyanation of the resultant iminium cations. The overall transformation proceeded in highly diastereoselective fashion. The resultant 2-cyano-3-iodo piperidines were converted into 2-cyanotetrahydropyridines, which could be used for [2+2]-annulation or ring-expansion reactions with reactive benzyne or alkyne species, respectively.

1. Introduction

Saturated nitrogen-heterocycles are exceptionally valuable due to their prevalence in a multitude of naturally occurring alkaloids, functional fine chemicals, biologically active pharmaceutical compounds, and agrochemicals.[1] Therefore, synthetic protocols that allow for the facile installation of functionalities onto saturated nitrogen-heterocycles are of use in various applications. In this context, deoxygenative reductive functionalization of readily available and bench-stable lactams has been devised as a straightforward access to C2-functionalized saturated nitrogen-heterocycles[2] through electrophilic activation with trifluoromethanesulfonic anhydride[3] or transition-metal-catalyzed hydrosilation[4] of the aminocarbonyl moiety. On the other hand, our group recently demonstrated the reductive functionalization of carboxamides including lactams for the synthesis of α-branched amines via the controlled hydride reduction by the NaH-NaI composite followed by silylation of the resultant anionic hemiaminal intermediates with trimethylsilyl chloride (Me_3SiCl) and the subsequent α-functionalization with carbon-based nucleophiles such as Grignard reagents and tetrabutylammonium cyanide (Scheme 1A).[5,6] The key to success for the efficient installation of the carbon functionalities at α to the nitrogen is the formation of iminium cation intermediates upon O-silylation. On the other hand, we envisaged that electrophilic iminium intermediates could be present with nucleophilic enamines under equilibrium via deprotonation-protonation sequence. Thus, nucleophilic enamines could be intercepted by concomitant electrophiles to reform iminium cations with an additional β-functionality[7] and further treatment with external carbon-nucleophiles would liberate α,β-difunctionalized amines (Scheme 1B). An elegant example of the intramolecular interception of an enamine intermediate generated by Ir-catalyzed hydrosilylation of a lactam was demonstrated in the key step for the total synthesis of vincadifformine by Dixon (Scheme 1C).[8] Huang utilized enamines pre-prepared by Ir-catalyzed hydrosilylation of tertiary carboxamides for the reactions with nitrilium ions derived from secondary carboxamides, providing substituted ketones upon workup with aqueous acid (Scheme 1D).[9] However, as far as we know, no report has been made on the direct intermolecular trap of the enamine intermediates generated *in situ* from lactams via their reductive deoxygenation. It should be noted that Seidel reported redox-neutral α,β-difunctionalization of cyclic amines via the *in-situ* generation of endocyclic enamines starting from cyclic amines and aryl aldehydes (Scheme 1E).[10] The resultant enamine was intercepted by the hetero-Diels-Alder reaction with concomitantly formed *ortho*-quinone methides to furnish polycyclic *N*,*O*-acetals in a diastereoselective manner.

Herein, we report the facile synthesis of 2-cyano-3-iodo piperidines or pyrrolidines by the following sequential processes comprised of: 1) controlled hydride reduction of lactams using the NaH-NaI composite; 2) formation of an iminium-enamine equilibrium mixture upon O-silylation of anionic hemiaminal intermediates; 3) interception of the enamines with iodine cation (I^+) and subsequent C2-functionalization with KCN (Scheme 1F).

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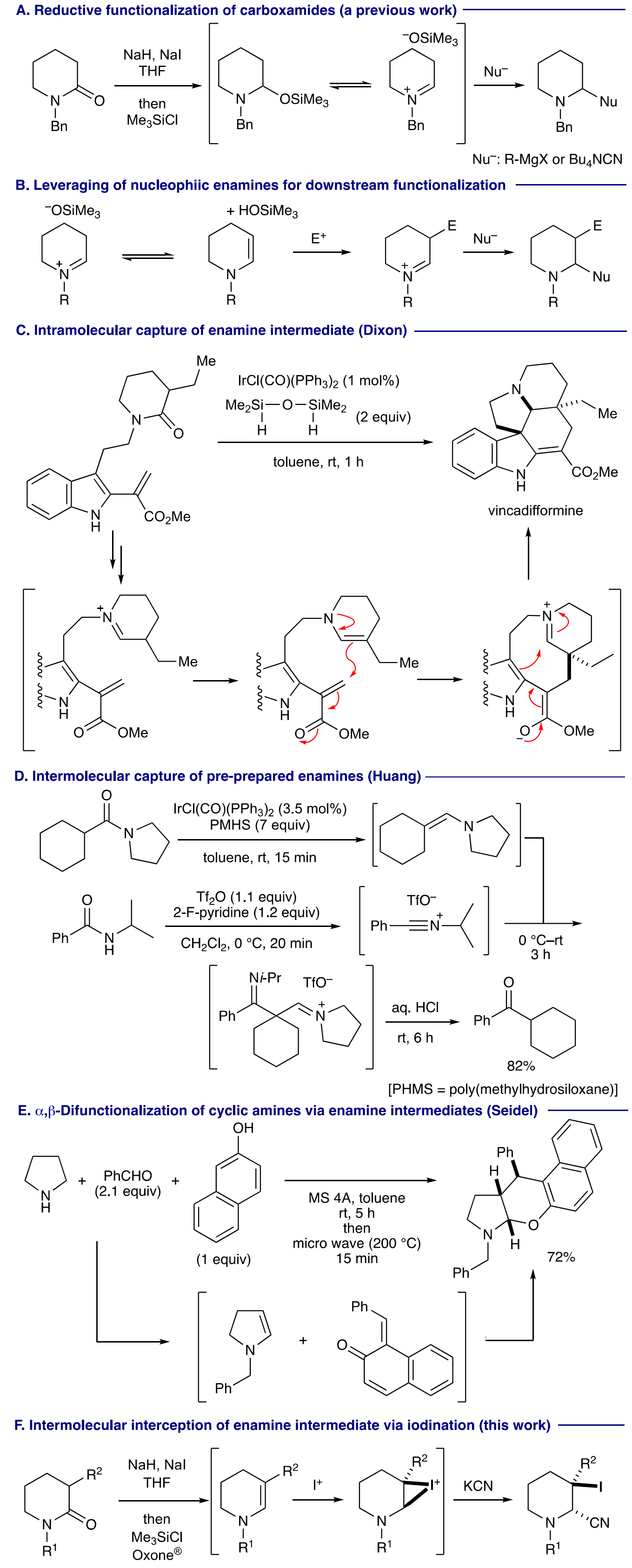
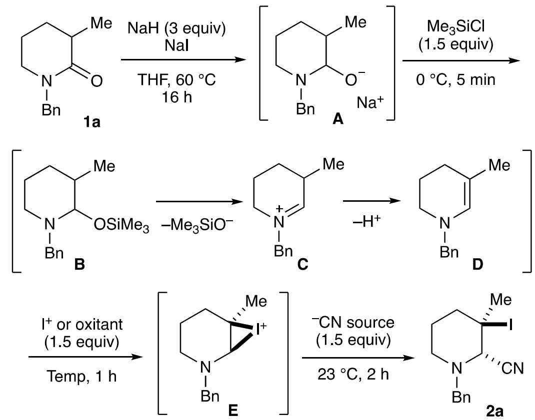


Scheme 1. Synthesis of functionalized saturated nitrogen-heterocycles.

2. Results and Discussion

We commenced our investigations using 2-piperidone **1a** (Table 1). Reduction of **1a** with NaH (3 equiv) and NaI (1 equiv) in THF at 60 °C allowed for a full conversion of **1a** within 16 h. Subsequent treatment of the reaction mixture with chlorotrimethylsilane (Me_3SiCl) (1.5 equiv) at 0 °C formed silyl ether **B**, which underwent elimination of a siloxide ion to form an equilibrium mixture of iminium cation **C** and enamine **D**-silanol couple. It should be noted that aqueous work up of the mixture affords enamine **D** in 58% yield based on the ^1H NMR spectroscopy with an internal standard.[11] We then utilized molecular iodine (I_2) to continuously intercept enamine **D** and attempted to trap the resultant iodonium ion **E** with KCN, affording the desired 2-cyano-3-iodo piperidine **2a** as a single diastereomer in 57% yield (entry 1). The stereoselective feature in the formation of **2a** supported the presence of iodonium ion intermediate **E** that is attacked from the backside by a cyanide ion. The use of *N*-iodosuccinimide (NIS), however, resulted in lower yield of **2a** (entry 2). We next sought for a possibility to use iodide ion derived from NaI, which was used for the activation of NaH in the first controlled hydride reduction step, for the ensuing electrophilic iodination of enamine **D**. For this purpose, we screened oxidants to convert iodide ion (I^-) to iodine cation (I^+).[12] Although the use of iodobenzene diacetate [$PhI(OAc)_2$] resulted in poor yield of **2a** along with the formation of a complex mixture of unidentified compounds (entry 3), employment of Oxone® rendered the process smoothly proceeding to afford **2a** in 77% yield (entry 4). Further optimization of the reaction conditions revealed that increase of the amount of NaI from 1 equiv to 1.2 equiv (entry 5) and raise of the reaction temperature for the iodination step to 60 °C (entry 6) could improve the yield of **2a** to 95% yield (80% isolated yield). Different cyanide sources such as trimethylsilylcyanide (Me_3SiCN) and tetrabutylammonium cyanide (nBu_4NCN) showed similar reactivity as the nucleophile for the formation of **2a** (entries 7 and 8).

Table 1. Reaction optimization[a]



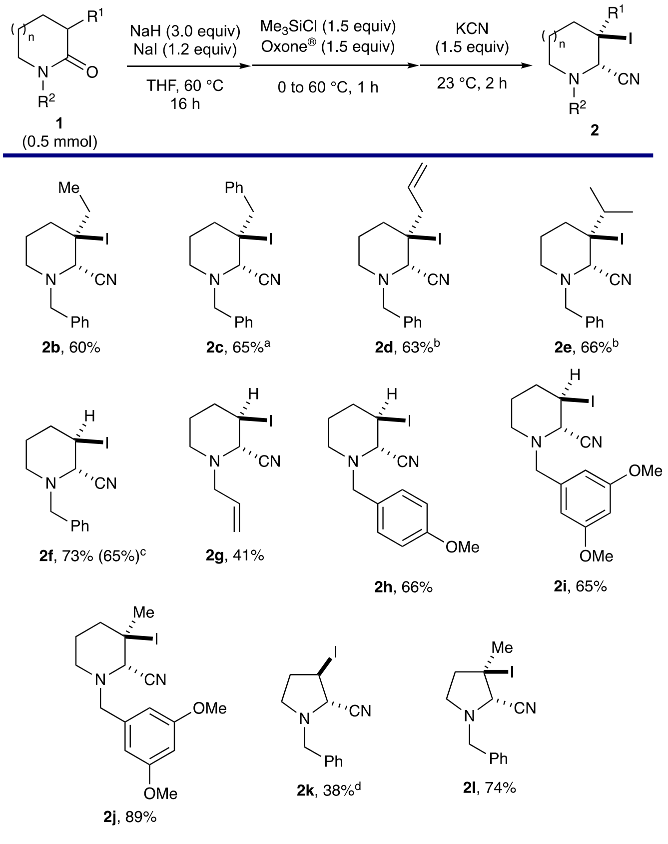
Entry	NaI (equiv)	I^+ or oxidant	Temp (°C)	$^-$CN source	**2a** (%)[b]
1	1	I_2	0 to 23	KCN	57
2	1	NIS	0 to 23	KCN	22
3	1	$PhI(OAc)_2$	0 to 23	KCN	5
4	1	Oxone®	0 to 23	KCN	77
5	1.2	Oxone®	0 to 23	KCN	87
6[c]	1.2	Oxone®	60	KCN	95 (80)[d]
7[c]	1.2	Oxone®	60	Me_3SiCN	94
8[c]	1.2	Oxone®	60	nBu_4NCN	90

[a] The reaction was conducted using 0.5 mmol of **1a**.

[b] ^1H NMR yields based on the internal standard.

[c] The reaction time for the iodination was 1 h.
[d] The isolated yield is in parentheses.
NIS = *N*-iodosuccinimide; Oxone® = 2KHSO$_5$•KHSO$_4$•K$_2$SO$_4$.

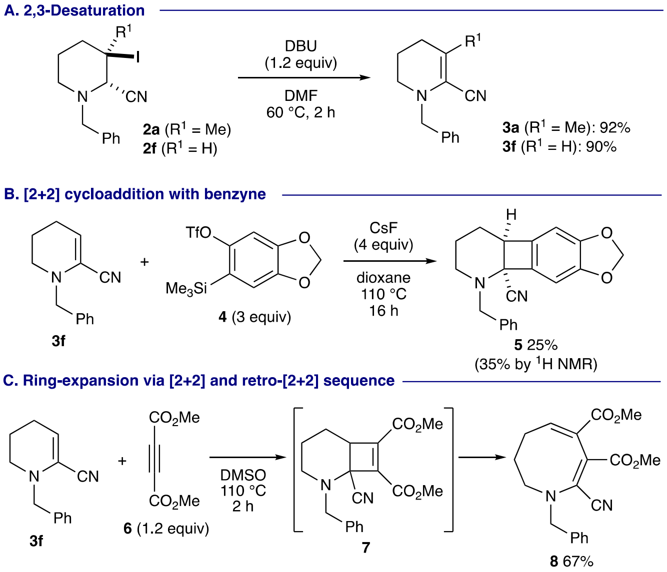
Having optimized the reaction conditions in hands, we next investigated the substrate scope with respect to the lactam substrates **2** (Scheme 2). As for the α-substituent (R^1) of 2-piperidones, installation of ethyl (for **2b**), benzyl (for **2c**), allyl (for **2d**), and sterically demanding isopropyl (for **2e**) groups were found to be compatible. It should be noted that the use of NIS (for **2c**) or I$_2$ (for **2d** and **2e**) instead of Oxone® worked more efficiently for several cases. The reaction of 1-benzyl-2-piperidone (**1f**, R^1 = H) proceeded smoothly to provide **2f** in 73% yield. The synthesis of **2f** in 5 mmol scale could be performed without any detrimental impact to the process efficiency. With respect to the substituent R^2 on the lactam nitrogen, allyl (for **2g**), *para*-methoxybenzyl (for **2h**), and 3,5-dimethoxybenzyl (for **2i** and **2j**) moieties could be installed, providing the corresponding piperidines as a single diastereomer. The structure of **2i** was unambiguously confirmed by the X-ray crystallographic analysis.[13] We also found that this process was amenable to construct pyrrolidines (n = 0) (for **2k** and **2l**), despite diminished yield for **2k** presumably due to its instability.



Scheme 2. Substrate scope.

[a] After addition of Me$_3$SiCl, NIS (1.5 equiv) was added at 23 °C instead of Oxone® and stirred for 2 h before addition of KCN.
[b] After addition of Me$_3$SiCl, I$_2$ (1.5 equiv) was added at 23 °C instead of Oxone® and stirred for 2 h before addition of KCN.
[c] The yield of **2f** from the reaction using 5 mmol of **1f**.
[d] After addition of Oxone®, reaction mixture was stirred at 23 °C for 2 h before addition of KCN.

We explored further molecular transformation of 2-cyano-3-iodo piperidines **2** to showcase their synthetic utility. Desaturation of **2a** and **2f** could proceed efficiently by the treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMF at 60 °C, providing 2-cyanotetrahydropyridines **3a** and **3f** in 92% and 90% yield, respectively.[14] Hsung reported [2+2]-cycloaddition of enamides and benzynes for the construction of benzocyclobutanes.[15] We wondered if the push-pull alkene moiety of **3f** could exhibit similar reactivity with enamides toward benzyne. Thus, we examined the reaction of **3f** and benzyne precursor **4** in the presence of CsF in dioxane at 110 °C (sealed conditions), which afforded benzocyclobutane **5** in moderate yield. By following the protocol developed by Kunesch and Husson,[16] we also performed a sequential [2+2]- and retro-[2+2]-cycloaddition between **3f** and dimethyl acetylenedicarboxylate (**6**), enabling the facile construction of tetrahydroazocine **8** via cyclobutene intermediate **7** in 67% yield.



Scheme 3. Functionalization of 2-cyano-3-iodo piperidines.

3. Conclusions

In summary, we have demonstrated a highly diastereoselective synthesis of 2-cyano-3-iodo piperidines or pyrrolidines from readily available lactams under transition-metal-free conditions. The process leverages controlled hydride reduction of lactams by the NaH-NaI system. Subsequent O-silylation of the resultant anionic hemiaminal intermediates induces generation of an equilibrium mixture of iminium cation and enamine/silanol pair. The interception of the nucleophilic enamine species by iodine cation and ensuing cyanation liberates the products. 2-Cyano-3-iodo piperidines could be converted to 2-cyanotetrahydropyridines, which showed unique reactivity toward [2+2]-cycloadditions with benzyne or dimethyl acetylenedicarboxylate. Further exploration of the synthetic application of this strategy for the synthesis of complex molecules is currently underway in our laboratory.

4. Experimental section

4.1. General experimental methods

^{1}H NMR spectra (400 MHz) were recorded on a Bruker Avance 400 MHz NMR, QNP probe or Bruker Avance III 400 MHz NMR, BBFO probe in CDCl$_3$ [using TMS (for ^{1}H, δ = 0.00) as internal standard]. ^{13}C NMR spectra (100 MHz) were recorded on a Bruker Avance 400 MHz NMR, QNP probe or Bruker Avance III 400 MHz NMR, BBFO probe in CDCl$_3$ [using CDCl$_3$ (for ^{13}C, δ = 77.00) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet. High-resolution mass spectra (ESI) were obtained with a Waters Q-Tof Premier mass spectrometer. Melting points (uncorrected) were recorded on an MPA 100 OptiMelt Automated Melting Point System. IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR spectrometer. The absorption data were recoded only for the key functional groups in the characterization of the respective substrates. X-ray data collection and structural refinement, intensity data for **2i** were collected on a Bruker D8 Quest diffractometer. All anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under an argon atmosphere. All glassware was oven dried for at least 24 h at 140 °C before use. Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl and stored over 4Å molecular sieves. Sodium hydride (NaH, 60 % dispersion in mineral oil, Sigma-Aldrich 452912) and Oxone® (TCI O0310) were purchased and used as received. Sodium iodide (NaI, Sigma-Aldrich 383112) was dried over P_2O_5 under vacuum at 70 °C.[17] Synthetic protocols and characterization of lactam substrates **1** were described in the supplementary material.

4.2. Synthesis of 2-cyano-3-iodo piperidines or pyrrolidines.

General Procedure A: Under an argon atmosphere, in a 25 mL sealed tube containing NaH (1.50 mmol, 3.0 equiv) and NaI (0.600 mmol, 1.2 equiv) was added a solution of **1** (0.500 mmol, 1.0 equiv) in anhydrous THF (2.5 mL) at 23 °C. The reaction mixture was heated at 60 °C (oil bath temperature) for 16 h. The reaction mixture was then cooled to 0 °C (ice-water bath). chlorotrimethylsilane (Me_3SiCl) (0.750 mmol, 1.5 equiv) was added via a micro syringe in one portion, and the mixture was stirred for 5 min at 0 °C. Oxone® (0.750 mmol, 1.5 equiv) was added and the mixture was heated at 60 °C (oil bath) for 1 h. After the reaction mixture was cooled to 23 °C, KCN (0.750 mmol, 1.5 equiv) was added, and the mixture was stirred for another 2 h. The mixture was carefully quenched with pH 10 aqueous NH_4Cl-NH_3 buffer (10 mL) at 0 °C and the organic materials were extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with aqueous sodium thiosulfate solution (1 M), dried over $MgSO_4$, and filtered. The volatile materials were removed, and the resulting residue was purified by flash column chromatography on silica gel to give **2**.

4.2.1. (2S,3R*)-1-Benzyl-3-iodo-3-methylpiperidine-2-carbonitrile (**2a**)*

According to the general procedure A (section 4.2), 1-benzyl-3-methylpiperidin-2-one (**1a**) (102 mg, 0.502 mmol) was converted into **2a** (137 mg, 0.403 mmol) in 80% yield (dr = >99:1 by ^{1}H NMR) as a light yellow oil after purified by flash column chromatography. The NMR yield (95%) was recodrded based on ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane (31.7 mg, 0.189 mmol) as an internal standard. Purification: silica gel, hexane/ethyl acetate = 100:0 to 100:10. R_f = 0.32 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.2 Hz, 2H), 7.35 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 3.81 (d, *J* = 13.4 Hz, 1H), 3.63 (s, 1H), 3.59 (d, *J* = 13.4 Hz, 1H), 2.84 – 2.81 (m, 1H), 2.43 (ddd, *J* = 12.1, 12.1, 3.1 Hz, 1H), 2.19 (s, 3H), 2.08 (dddd, *J* = 12.3, 12.9, 4.4, 4.4 Hz, 1H), 2.01 – 1.97 (m, 1H), 1.70 – 1.67 (m, 1H), 1.18 (ddd, *J* = 15.0, 12.1, 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.2, 129.0, 128.5, 127.7, 111.5, 65.4, 60.1, 48.2, 45.1, 39.4, 34.9, 24.1. IR (KBr, neat, cm^{-1}): 2232 [*v* (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{14}H_{18}IN_2$ $[(M+H)^+]$: 341.0515, found: 341.0515.

4.2.2 (2S,3R*)-1-Benzyl-3-ethyl-3-iodopiperidine-2-carbonitrile (**2b**)*

According to the general procedure A (section 4.2), 1-benzyl-3-ethylpiperidin-2-one (**1b**) (109 mg, 0.502 mmol) was converted into **2b** (106 mg, 0.301 mmol) in 60% yield (dr = >99:1 by ^{1}H NMR) as a light yellow oil after purified by flash column chromatography. Purification: silica gel, hexane/ethyl acetate = 100:0 to 100:15. R_f = 0.18 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 7.2 Hz, 2H), 7.35 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 3.80 (d, *J* = 13.4 Hz, 1H), 3.69 (s, 1H), 3.62 (d, *J* = 13.4 Hz, 1H), 2.85 – 2.81 (m, 1H), 2.44 (ddd, *J* = 12.1, 12.1, 3.0 Hz, 1H), 2.20 – 2.01(m, 3H), 1.89 (dq, *J* = 14.2, 7.2 Hz, 1H), 1.71 – 1.64 (m, 1H), 1.20 (ddd, *J* = 14.9, 12.6, 4.3 Hz, 1H), 1.09 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 129.0, 128.5, 127.7, 111.7, 63.8, 60.2, 56.0, 48.5, 38.2, 37.8, 23.7, 11.2. IR (KBr, neat, cm^{-1}): 2217 [*v* (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{15}H_{20}IN_2$ $[(M+H)^+]$: 355.0671, found: 355.0671.

4.2.3 (2S,3S*)-1,3-Dibenzyl-3-iodopiperidine-2-carbonitrile (**2c**)*

Piperidine **2c** was synthesized according to the general procedure A (section 4.2) with the following modification: After the addition of Me_3SiCl, the mixture was stirred for 5 min at 0 °C. NIS (168 mg, 0.750 mmol, 1.5 equiv) was added and the mixture was stirred at 23 °C for 2 h before the addition of KCN. 1,3-Dibenzylpiperidin-2-one (**1c**) (140 mg, 0.502 mmol) was converted into **2c** (135 mg, 0.324 mmol) in 65% yield (dr = >99:1 by ^{1}H NMR) as a light yellow oil after purified by flash column chromatography. Purification: silica gel, hexane/ethyl acetate = 100:0 to 100:10. R_f = 0.29 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.42 (m, 4H), 7.38 – 7.30 (m, 6H), 3.81 (d, *J* = 13.3 Hz, 1H), 3.70 (s, 1H), 3.67 (d, *J* = 13.3 Hz, 1H), 3.43 (d, *J* = 14.4 Hz, 1H), 3.36 (d, *J* = 14.4 Hz, 1H), 2.88 – 2.84 (m, 1H), 2.50 (ddd, *J* = 12.3, 12.3, 3.1 Hz, 1H), 2.15 (ddddd, *J* = 13.0, 12.3, 12.3, 4.5, 4.5 Hz, 1H), 2.04 – 2.00 (m, 1H), 1.77 – 1.70 (m, 1H), 1.47 (ddd, *J* = 14.9, 12.4, 4.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 135.2, 131.4, 129.0, 128.4, 127.9, 127.7, 127.3, 112.4, 64.4, 60.2, 55.0, 49.9, 47.9, 37.4, 23.7. IR (KBr, neat, cm^{-1}) 2217 [*v* (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{20}H_{22}IN_2$ $[(M+H)^+]$: 417.0828, found: 417.0829.

4.2.4 (2S,3S*)-3-Allyl-1-benzyl-3-iodopiperidine-2-carbonitrile (**2d**)*

Piperidine **2d** was synthesized according to the general procedure A (section 4.2) with the following modification: After the addition of Me_3SiCl, the mixture was stirred for 5 min at 0 °C. Iodine (190 mg, 0.749 mmol, 1.5 equiv) was added and the mixture was stirred at 23 °C for 2 h before the addition of KCN. 3-Allyl-1-benzylpiperidin-2-one (**1d**) (115 mg, 0.502 mmol) was converted into **2d** (121 mg, 0.329 mmol) in 66% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography. Purification: silica gel, hexane/ethyl acetate = 100:0 to 100:10. R_f = 0.32 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.34 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 5.94 (dddd, *J* = 17.0, 10.2, 7.8, 6.1 Hz, 1H), 5.33 (ddd, *J* = 17.0, 2.9, 1.7 Hz, 1H), 5.28 – 5.25 (m, 1H), 3.77 (d, *J* = 13.4 Hz, 1H), 3.62 (d, *J* = 13.4 Hz, 1H), 3.62 (s, 1H), 2.86 (dd, *J* = 15.0, 5.9 Hz, 1H), 2.85 – 2.80 (m, 1H), 2.69 (dd, *J* = 15.0, 7.9 Hz, 1H), 2.43 (ddd, *J* = 12.3, 12.3, 3.0 Hz, 1H), 2.15 (ddddd, *J* = 13.9, 12.3, 12.3, 4.3, 4.3 Hz, 1H), 2.06 – 2.02 (m, 1H), 1.71 – 1.64 (m, 1H), 1.29 (ddd, *J* = 15.1, 12.3, 4.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 133.4, 129.0, 128.5, 127.7, 120.5, 111.9, 63.7, 60.2, 51.9, 48.9, 48.3, 37.8, 23.5. IR

(KBr, neat, cm^{-1}): 2222 [*v* (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{16}H_{20}IN_2$ [(M+H)$^+$]: 369.0828, found: 368.0825.

4.2.5 (2S,3S*)-1-Benzyl-3-iodo-3-isopropylpiperidine-2-carbonitrile (**2e**)*

Piperidine **2e** was synthesized according to the general procedure A (section 4.2) with the following modification: After the addition of Me$_3$SiCl, the mixture was stirred for 5 min at 0 °C. Iodine (190 mg, 0.749 mmol, 1.5 equiv) was added and the mixture was stirred at 23 °C for 2 h before the addition of KCN. 1-Benzyl-3-isopropylpiperidin-2-one (**1e**) (116 mg, 0.502 mmol) was converted into **2e** (122 mg, 0.333 mmol) in 67% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography. Purification: silica gel, hexane/ethyl acetate = 100:0 to 100:10. R$_f$ = 0.36 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.44 (d, *J* = 7.2 Hz, 2H), 7.34 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.28 (t, *J* = 7.2 Hz, 1H), 3.85 (s, 1H), 3.77 (d, *J* = 13.4 Hz, 1H), 3.64 (d, *J* = 13.4 Hz, 1H), 2.82 – 2.79 (m, 1H), 2.41 (ddd, *J* = 12.2, 12.2, 3.0 Hz, 1H), 2.26 – 2.10 (m, 2H), 1.69 – 1.63 (m, 1H), 1.19 (ddd, *J* = 14.8, 12.3, 4.2 Hz, 1H), 1.06 – 1.00 (m, 4H), 0.92 (d, *J* = 5.9 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 136.5, 128.9, 128.4, 127.6, 112.1, 65.7, 63.4, 60.2, 47.9, 38.2, 36.4, 23.5, 20.9, 19.8. IR (KBr, neat, cm^{-1}): 2222 [*v* (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{16}H_{22}IN_2$ [(M+H)$^+$]: 367.0671, found: 367.0674.

4.2.6 (2S,3R*)-1-Benzyl-3-iodopiperidine-2-carbonitrile (**2f**)*

According to the general procedure A (section 4.2), 1-benzylpiperidin-2-one (**1f**) (94.6 mg, 0.500 mmol) was converted into **2f** (119 mg, 0.365 mmol) in 73% yield (dr = >99:1 by ^{1}H NMR) as a light yellow oil after purified by flash column chromatography. The reaction in 5 mmole scale was conducted with 1-benzylpiperidin-2-one (**1f**) (946 mg, 5.01 mmol) to give **2f** (1.06 g, 3.25 mmol) in 65% yield (dr = >99:1 by ^{1}H NMR) as light yellow oil after purified by flash column chromatography. Purification: silica gel, hexane/ethyl acetate = 100:0 to 100:10. R$_f$ = 0.25 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.41 (d, *J* = 6.9 Hz, 2H), 7.34 (dd, *J* = 6.9, 6.9 Hz, 2H), 7.28 (t, *J* = 6.9 Hz, 1H), 4.56 – 4.54 (m, 1H), 3.81 (d, *J* = 13.4 Hz, 1H), 3.71 (d, *J* = 2.3 Hz, 1H), 3.55 (d, *J* = 13.4 Hz, 1H), 2.85 – 2.80 (m, 1H), 2.52 (ddd, *J* = 12.0, 12.0, 2.9 Hz, 1H), 2.09 (ddddd, *J* = 12.7, 12.7, 12.7, 4.2, 4.2 Hz, 1H), 2.01 – 1.95 (m, 1H), 1.86 (dddd, *J* = 15.6, 11.8, 3.7, 3.7 Hz, 1H), 1.63 – 1.58 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 136.1, 128.9, 128.5, 127.8, 113.3, 60.1, 58.3, 49.2, 30.5, 24.6, 21.8. IR (KBr, neat, cm^{-1}): 2222 [*v* (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{13}H_{16}IN_2$ [(M+H)$^+$]: 327.0358, found: 327.0353.

4.2.7 (2S,3R*)-1-Allyl-3-iodopiperidine-2-carbonitrile (**2g**)*

According to the general procedure A (section 4.2), 1-allylpiperidin-2-one (**1g**) (69.6 mg, 0.500 mmol) was converted into **2g** (56.6 mg, 0.205 mmol) in 41% yield (dr = >99:1 by ^{1}H NMR) as a light yellow oil after purified by flash column chromatography. Purification: silica gel, hexane/ethyl acetate = 100:0 to 100:10. R$_f$ = 0.29 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). ^{1}H NMR (400 MHz, CDCl$_3$): δ 5.79 (dddd, *J* = 17.4, 9.9, 7.7, 5.0 Hz, 1H), 5.37 – 5.33 (m, 1H), 5.25 – 5.23 (m, 1H), 4.61 – 4.60 (m, 1H), 3.92 (d, *J* = 1.8 Hz, 1H), 3.29 (dd, *J* = 13.6, 4.9 Hz, 1H), 3.07 (dd, *J* = 13.6, 7.9 Hz, 1H), 2.81 – 2.78 (m, 1H), 2.48 (ddd, *J* = 11.9, 11.9, 2.7 Hz, 1H), 2.12 – 1.96 (m, 2H), 1.87 (dddd, *J* = 15.4, 11.8, 3.7, 3.7 Hz, 1H), 1.63 – 1.59 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 133.2, 119.6, 113.4, 58.8, 58.6, 49.4, 30.7, 24.4, 21.9. IR (KBr, neat, cm^{-1}): 2217 [*v* (C≡N)]. HRMS (ESI): *m/z* calcd for $C_9H_{14}IN_2$ [(M+H)$^+$]: 277.0202, found: 277.0199.

4.2.8 (2S,3R*)-3-Iodo-1-(4-methoxybenzyl)piperidine-2-carbonitrile (**2h**)*

According to the general procedure A (section 4.2), 1-(4-methoxybenzyl)piperidin-2-one (**1h**) (110 mg, 0.502 mmol) was converted into **2h** (118 mg, 0.331 mmol) in 66% yield (dr = >99:1 by ^{1}H NMR) as a light yellow oil after purified by flash column chromatography. Purification: silica gel, hexane/ethyl acetate = 100:0 to 100:10. R$_f$ = 0.21 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.31 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.55 – 4.54 (m, 1H), 3.80 (s, 3H), 3.76 (d, *J* = 13.1 Hz, 1H), 3.69 (d, *J* = 2.3 Hz, 1H), 3.47 (d, *J* = 13.1 Hz, 1H), 2.83 – 2.81 (m, 1H), 2.50 (ddd, *J* = 12.0, 12.0, 2.9 Hz, 1H), 2.08 (ddddd, *J* = 13.0, 12.4, 12.4, 4.1, 4.1 Hz, 1H), 2.00 – 1.95 (m, 1H), 1.85 (dddd, *J* = 15.3, 12.1, 3.6, 3.6 Hz, 1H), 1.62 – 1.58 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 159.2, 130.1, 128.0, 113.8, 113.3, 59.5, 58.1, 55.2, 49.2, 30.6, 24.7, 21.8. IR (KBr, neat, cm^{-1}) 2228 [*v* (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{14}H_{18}IN_2O$ [(M+H)$^+$]: 357.0464, found: 357.0462.

4.2.9 (2S,3R*)-1-(3,5-Dimethoxybenzyl)-3-iodopiperidine-2-carbonitrile (**2i**)*

According to the general procedure A (section 4.2), 1-(3,5-dimethoxybenzyl)piperidin-2-one (**1i**) (125 mg, 0.501 mmol) was converted into **2i** (126 mg, 0.326 mmol) in 65% yield (dr = >99:1by ^{1}H NMR) as a white solid after purified by flash column chromatography. Purification: silica gel, hexane/ethyl acetate = 100:0 to 100:15. R$_f$ = 0.33 (eluent: hexane/ethyl acetate = 10:1, visualized by 254 nm UV or iodine). Recrystallization from hexane:dichloromethane gave a single crystal, the structure of which could be confirmed by X-ray crystallographic analysis (CCDC-2156051). M.p.: 101 – 104 °C (decomposed). ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.60 (d, *J* = 2.2 Hz, 1H), 6.38 (t, *J* = 2.2 Hz, 2H), 4.59 – 4.58 (m, 1H), 3.80 (s, 6H), 3.79 (d, *J* = 13.5 Hz, 1H), 3.48 (d, *J* = 13.5 Hz, 1H), 2.87 – 2.84 (m, 1H), 2.55 (ddd, *J* = 12.1, 12.1, 2.9 Hz, 1H), 2.13 (ddddd, *J* = 12.6, 12.6, 12.6, 4.0, 4.0 Hz, 1H), 2.03 – 1.98 (m, 1H), 1.88 (dddd, *J* = 15.2, 12.1, 3.8, 3.8 Hz, 1H), 1.65 – 1.61 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 160.9, 138.6, 113.2, 106.3, 100.2, 60.2, 58.0, 55.4, 49.4, 30.5, 24.9, 21.8. IR (KBr, neat, cm^{-1}): 2222 [*v* (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{15}H_{20}IN_2O_2$ [(M+H)$^+$]: 387.0569, found: 387.0565.

4.2.10 (2S,3R*)-1-(3,5-Dimethoxybenzyl)-3-iodo-3-methylpiperidine-2-carbonitrile (**2j**)*

According to the general procedure A (section 4.2), 1-(3,5-dimethoxybenzyl)-3-methylpiperidin-2-one (**1j**) (132 mg, 0.501 mmol) was converted into **2j** (177 mg, 0.442 mmol) in 89% yield (dr = >99:1 by ^{1}H NMR) as a light yellow solid after purified by flash column chromatography. Purification: silica gel, hexane/ethyl acetate = 100:0 to 100:15. R$_f$ = 0.18 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). M.p.: 110 – 116 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.64 (d, *J* = 2.0 Hz, 2H), 6.39 (t, *J* = 2.0 Hz, 1H), 3.80 – 3.78 (m, 7H), 3.67 (s, 1H), 3.52 (d, *J* = 13.5 Hz, 1H), 2.87 – 2.84 (m, 1H), 2.46 (ddd, *J* = 12.2, 12.2, 2.9 Hz, 1H), 2.21 (s, 3H), 2.15 – 1.99 (m, 2H), 1.73 – 1.70 (m, 1H), 1.20 (ddd, *J* = 15.1, 12.2, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 160.9, 138.7, 111.4, 106.4, 100.2, 65.1, 60.2, 55.4, 48.4, 45.6, 39.4, 34.9, 24.2. IR (KBr, neat, cm^{-1}): 2222 [*v* (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{16}H_{22}IN_2O_2$ [(M+H)$^+$]: 401.0726, found: 401.0725.

4.2.11 (2S,3R*)-1-Benzyl-3-iodopyrrolidine-2-carbonitrile (**2k**)*

According to the general procedure A (section 4.2), 1-benzylpyrrolidin-2-one (**1k**) (110 mg, 0.500 mmol) was converted into **2k** (59.1 mg, 0.189 mmol) in 38% yield (dr = >99:1 by ^{1}H NMR) as a light yellow oil after purified by flash column chromatography. Purification: silica gel, hexane/ethyl acetate = 100:0 to 100:10. R_f = 0.21 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 4H), 7.29 (t, *J* = 6.9 Hz, 1H), 4.43 (ddd, *J* = 7.8, 3.1, 3.1 Hz, 1H), 4.04 (d, *J* = 13.2 Hz, 1H), 3.84 (d, *J* = 2.7 Hz, 1H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.05 (ddd, *J* = 8.8, 8.8, 5.0 Hz, 1H), 2.74 (ddd, *J* = 8.8, 8.8, 5.5 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.36 (dddd, *J* = 14.1, 8.8, 5.3, 3.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 128.6, 127.7, 115.4, 63.9, 56.1, 50.5, 36.6, 17.5. IR (KBr, neat, cm^{-1}) 2224 [ν (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{12}H_{14}IN_2$ $[(M+H)^+]$: 313.0202, found: 313.0204.

4.2.12 (2S,3R*)-1-Benzyl-3-iodo-3-methylpyrrolidine-2-carbonitrile (**2l**)*

According to the general procedure A (section 4.2), 1-benzyl-3-methylpyrrolidin-2-one (**1l**) (94.6 mg, 0.500 mmol) was converted into **2l** (122 mg, 0.374 mmol) in 74% yield (dr = >99:1 by ^{1}H NMR) as a light yellow oil after purified by flash column chromatography. Purification: silica gel, hexane/ethyl acetate = 100:0 to 100:10. R_f = 0.24 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.35 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 4.05 (d, *J* = 13.3 Hz, 1H), 3.98 (s, 1H), 3.81 (d, *J* = 13.3 Hz, 1H), 3.20 (ddd, *J* = 9.5, 8.5, 6.8 Hz, 1H), 2.81 (ddd, *J* = 9.5, 9.5, 4.0 Hz, 1H), 2.56 (ddd, *J* = 14.8, 8.5, 4.0 Hz, 1H), 2.23 (s, 3H), 2.10 (ddd, *J* = 14.8, 9.7, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 128.6, 113.7, 70.0, 56.3, 50.2, 45.1, 40.3, 33.2. IR (KBr, neat, cm^{-1}): 2216 [ν (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{13}H_{16}IN_2$ $[(M+H)^+]$: 327.0358, found: 327.0359.

4.3. Synthesis of 2-cyanotetrahydropyridines.

General Procedure B: To a 25 mL sealed tube containing diazabicyclo[5.4.0]undec-7-ene (DBU, 0.600 mmol, 1.2 equiv) was added a solution of **2** (0.500 mmol, 1.0 equiv) in anhydrous DMF (2.5 mL) under an argon atmosphere. The reaction mixture was heated at 60 °C (oil bath) for 2 h. The mixture was quenched with water (50 mL) and the organic materials were extracted with diethyl ether (10 mL × 3). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and filtered. The volatile materials were removed, and the resulting residue was purified by flash column chromatography on neutral aluminum oxide to give **3**.

*4.3.1 1-Benzyl-3-methyl-1,4,5,6-tetrahydropyridine-2-carbonitrile (**3a**)*

According to the general procedure B (section 4.3), **2a** (170 mg, 0.500 mmol) was converted into **3a** (97.5 mg, 0.459 mmol) in 92% yield as a light yellow oil after purified by flash column chromatography. Purification: neutral aluminum oxide, hexane/ethyl acetate = 100:0 to 100:5. R_f = 0.32 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.33 (m, 2H), 7.30 – 7.26 (m, 3H), 5.42 (t, *J* = 4.4 Hz, 1H), 4.25 (s, 2H), 2.92 – 2.90 (m, 2H), 2.11 – 2.07 (m, 2H), 1.74 – 1.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 128.5, 128.2, 127.5, 121.9, 116.4, 115.7, 56.7, 46.5, 22.4, 20.5. IR (KBr, neat, cm^{-1}): 2222 [ν (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{18}H_{17}O$ $[(M+H)^+]$: 213.1392, found: 213.1391.

*4.3.2 1-Benzyl-1,4,5,6-tetrahydropyridine-2-carbonitrile (**3f**)*

According to the general procedure B (section 4.3), **2f** (163 mg, 0.500 mmol) was converted into **3f** (88.9 mg, 0.448 mmol) in 90% yield as a light yellow oil after purified by flash column chromatography. Purification: neutral aluminum oxide, hexane/ethyl acetate = 100:0 to 100:5. R_f = 0.30 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV or iodine). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.27 (m, 5H), 4.18 (s, 2H), 2.83 – 2.80 (m, 2H), 2.05 (t, *J* = 6.2 Hz, 2H), 1.96 (s, 3H), 1.66 (tt, *J* = 5.8, 5.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 128.4, 128.3, 127.5, 127.3, 118.0, 115.7, 57.1, 46.2, 28.6, 21.0, 19.7. IR (KBr, neat, cm^{-1}): 2228 [ν (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{18}H_{17}O$ $[(M+H)^+]$: 199.1235, found: 199.1234.

*4.4. Synthesis of 5-benzyl-6,7,8,8a-tetrahydro-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':3,4]cyclobuta[1,2-b]pyridine-4b(5H)-carbonitrile (**5**).*

To a 25 mL sealed tube containing CsF (182.4 mg, 1.20 mmol, 4.0 equiv) was added **4** (309 mg, 0.904 mmol, 3.0 equiv),[18] and a solution of **3f** (59.6 mg, 0.301 mmol) in anhydrous dioxane (3.0 mL) under an argon atmosphere. The reaction mixture was heated at 110 °C (oil bath) for 16 h. The mixture was then filtered through a short plug of silica gel and rinsed with ethyl acetate (10 mL × 3). The volatile materials were removed and the resulting residue was analyzed by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (31.7 mg, 0.189 mmol) as an internal standard, which indicated 35% NMR yield of **5**. Further purification by flash column chromatography on silica gel (hexane/ethyl acetate = 100:0 to 100:20) gave **5** (23.9 mg, 0.0751 mmol) in 25% yield as a pale yellow oil. R_f = 0.23 (eluent: hexane/ethyl acetate = 10:1, visualized by 254 nm UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.27 (m, 5H), 6.58 (s, 1H), 5.82 (s, 1H), 5.81 (d, *J* = 1.2 Hz, 1H), 5.80 (d, *J* = 1.2 Hz, 1H), 4.39 (d, *J* = 16.4 Hz, 1H), 4.37 (d, *J* = 16.4 Hz, 1H), 4.04 – 4.01 (m, 1H), 2.23 – 2.13 (m, 1H), 2.06 – 1.99 (m, 1H), 1.91 – 1.81 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.5, 144.9, 140.6, 137.9, 128.8, 127.4, 126.8, 121.8, 120.8, 105.3, 100.9, 91.7, 73.3, 53.8, 51.0, 38.8, 34.7, 25.4. IR (KBr, neat, cm^{-1}) 2239 [ν (C≡N)]. HRMS (ESI): *m/z* calcd for $C_{20}H_{19}N_2O_2$ $[(M+H)^+]$: 319.1447, found: 319.1451.

*4.5. Synthesis of dimethyl (2E,4E)-1-benzyl-2-cyano-1,6,7,8-tetrahydroazocine-3,4-dicarboxylate (**8**).*

To a 25 mL sealed tube containing 1-benzyl-1,4,5,6-tetrahydropyridine-2-carbonitrile (**3f**) (59.5 mg, 0.301 mmol) was added a solution of dimethyl acetylenedicarboxylate (**6**) (45 μL, 0.366 mmol, 1.2 equiv) (Alfa Aesar 45131) in anhydrous DMSO (1.5 mL) under an argon atmosphere. The reaction mixture was heated at 110 °C (oil bath) for 2 h. The mixture was then filtered through a short plug of silica gel, and rinsed with ethyl acetate (10 mL × 3). The volatile materials were removed, and the resulting residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 100:0 to 100:10) to give **8** (68.5 mg, 0.201 mmol) in 67% yield as a pale yellow oil. R_f = 0.21 (eluent: hexane/ethyl acetate = 20:1, visualized by 254 nm UV). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.32 (m, 5H), 6.64 (t, *J* = 8.7 Hz, 1H), 5.07 (d, *J* = 15.1 Hz, 1H), 4.19 (d, *J* = 15.1 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.68 (brs, 1H), 2.94 – 2.91 (m, 1H), 2.48 (brs, 1H), 2.32 (brs, 1H), 1.69 (brs, 1H), 1.00 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 167.5, 138.4, 135.2, 132.3, 129.5, 128.9, 128.2, 127.7, 114.2, 106.2, 56.8, 52.23, 52.19, 44.5, 24.4, 13.1. IR (KBr, neat, cm^{-1}) 2216 [ν (C≡N)], 1711 [ν (C=O)]. HRMS (ESI): *m/z* calcd for $C_{19}H_{21}N_2O_4$ $[(M+H)^+]$: 341.1501, found: 341.1500.

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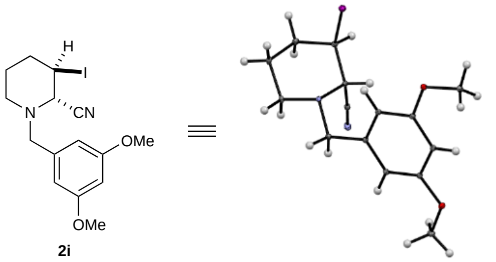

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.