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Intramolecular cyanoamidation of unsaturated cyanoformamides catalyzed by palladium: an efficient synthesis of multi-functionalized lactams

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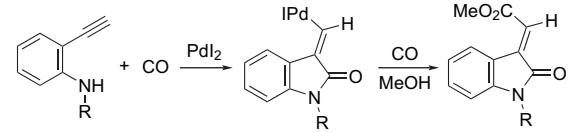
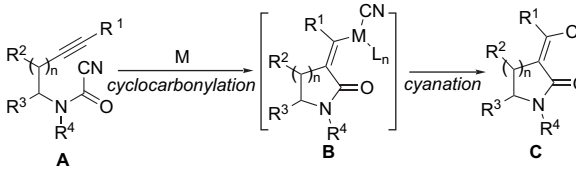
Abstract—The Pd(0)-catalyzed intramolecular cyanoamidation of several unsaturated cyanoformamides with alkenyl, allenyl, and alkynyl groups was investigated. In the cases of alkynyl and 1,1-disubstituted alkenyl cyanoformamides, the Pd(0)-catalyzed C–CN activation and subsequent insertion reaction proceeded smoothly and gave the corresponding lactams bearing a cyano group at the β-position in good yields. The mechanism of the reaction was also discussed.

1. Introduction

Transition-metal-catalyzed carbonylative cyclization of unsaturated amines using carbon monoxide is a powerful tool for the synthesis of lactams and various heterocyclic compounds.[1] Especially, the cyclocarbonylation–esterification represents an efficient and versatile approach to the one-step synthesis of functionalized lactams (Eq. 1).[2] Recently, through the use of well-designed substrates, several efficient methods for the carbonylative cyclization without the use of toxic carbon monoxide have been explored.[3–5] These methods, however, have not been applied to the synthesis of α-alkylidene lactams bearing a cyano group at the β-position. This prompted us to investigate the transition-metal-catalyzed cyclocarbonylation–cyanation of unsaturated cyanoformamides **A** into functionalized lactams **C** (Eq. 2). Such multi-functionalized lactams **C** obtained by this method would be versatile building blocks in organic synthesis and are seen in many natural products.[6] Although direct activation of unstrained C–C single bond by transition metals and subsequent addition of the metal complex to C–C unsaturated bond should be of great synthetic value because such a reaction provides a simultaneous installation of two C–C bonds with perfect atom economy, only a few reports are available.[7–9] We report here the details of the palladium-catalyzed intramolecular cyanoamidation of alkynyl cyanoformamides[10] as well as other several unsaturated cyanoformamides.



(1)



(2)

2. Results and discussion

We first examined the several methods to prepare the requisite unsaturated cyanoformamides (Scheme 1). Although the chemistry of acyl cyanides has been well investigated,[11] there are not so many reports concerning the preparations[12] and the reactions[13] of cyanoformamides. Using carbonyl cyanide generated in situ according to the literature,[12] the primary and secondary unsaturated amines were converted to the corresponding cyanoformamides in moderate to good yield (Method A). This method, however, is not suitable for the large scale preparation of cyanoformamide due to the production of toxic hydrogen cyanide. Then, we

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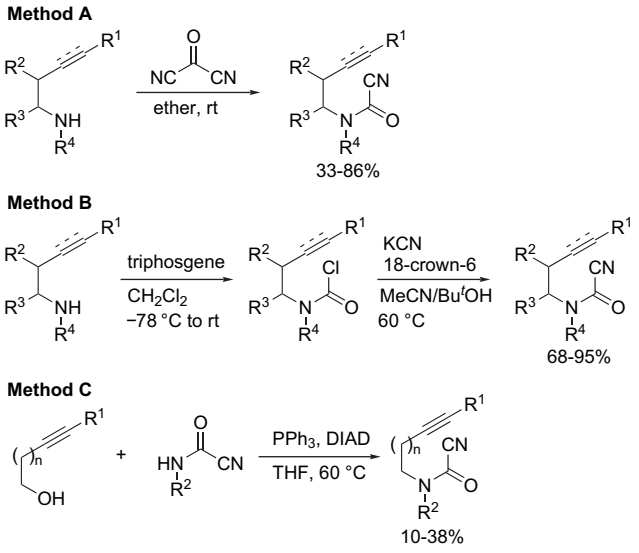
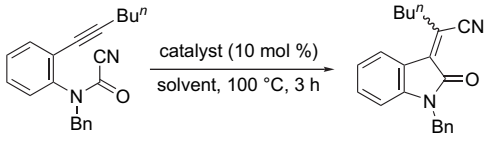
next investigated alternative method (Method B) and found that the reaction of the corresponding chlorocarbamates with KCN in the presence of 18-crown-6 provided the aimed compounds in good yield. Furthermore, it was revealed that the unsaturated cyanoformamides could be prepared from the primary unsaturated alcohol and cyanoformamide under the Mitsunobu conditions albeit in low yield (Method C).



Scheme 1. Preparation of the unsaturated cyanoformamide.

We next investigated the reaction conditions for the intramolecular cyanoamidation of cyanoformanilide **1a** prepared as described above. Representative results are summarized in Table 1. Although we carried out the reaction of **1a** with $Rh_4(CO)_{12}$ at 130 °C according to the previous report,[5] the desired product **2a** could not be obtained. Likewise other metal complexes such as $Ru_3(CO)_{12}$, $Pt(PPh_3)_4$, $Ni(PPh_3)_4$, and $RhCl(PPh_3)_3$ were totally ineffective for the desired reaction. Although the reaction did not proceed at all using $Pd(dba)_2$ or $Pd(acac)_2$ without phosphine ligands (entries 1 and 2), we found that the desired α-alkylidene lactams **2a** could be obtained in moderate yields by using the appropriate combination of Pd(II) and phosphine ligands such as PPh_3 and dppb (entries 3–5). After further experiments on the cyclization, we found that $Pd(PPh_3)_4$ was an effective catalyst for the cyanoamidation, and the oxindole **2a** was obtained in 97% yield as a mixture of (*E*)- and (*Z*)-isomer (entry 6). We next examined the effect of the solvent on the chemical yield. Among the solvents examined, toluene and xylene gave good results in terms of chemical yield and the ratio of *Z*/*E* isomers (entries 6 and 7). When a polar solvent such as DMF was used, both the chemical yield and the *Z*/*E* ratio decreased (entry 8).

Table 1. Survey of the intramolecular cyanoamidation of **1a**[a]

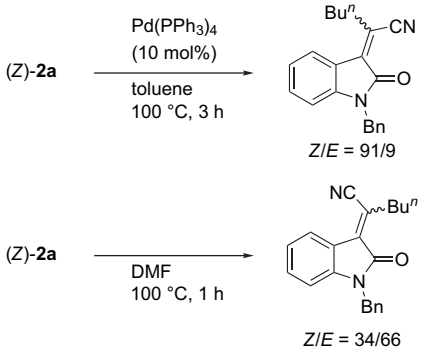


1a **2a**

Entry	Catalyst	Solvent	Yield[b] (%)	*Z*/*E* Ratio
1	$Pd(dba)_2$	Toluene	0	—
2	$Pd(acac)_2$	Toluene	0	—
3	$Pd(acac)_2/4P^nBu_3$	Toluene	0	—
4	$Pd(acac)_2/4PPh_3$	Toluene	39	[c]
5	$Pd(acac)_2$/2dppb[d]	Toluene	45	[c]
6	$Pd(PPh_3)_4$	Toluene	97	73/27
7[e]	$Pd(PPh_3)_4$	Xylene	97	69/31
8	$Pd(PPh_3)_4$	DMF	71	21/79

[a] All reactions were carried out under Ar.
[b] Isolated yield.
[c] A trace amount of (*E*)-isomer was obtained.
[d] 1,4-Bis(diphenylphosphino)butane.
[e] The reaction was carried out at 130 °C.

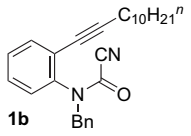
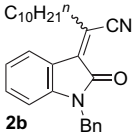
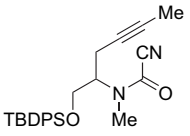
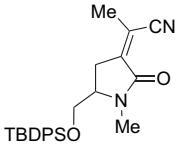
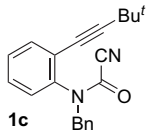
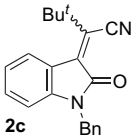
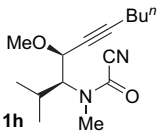
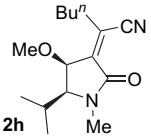
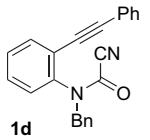
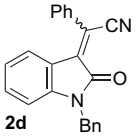
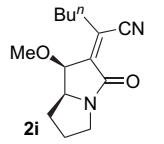
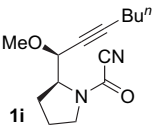
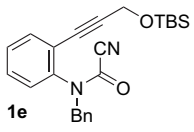
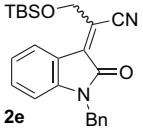
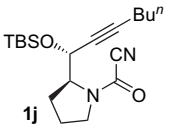
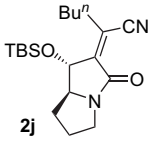
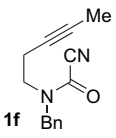
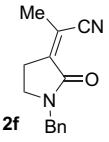
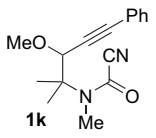
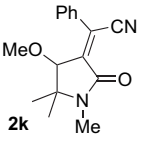
To clarify the mechanism of production of (*E*)-**2a**, we carried out the isomerization experiment (Scheme 2). Although no isomerization occurred only by heating the isolated (*Z*)-isomer in toluene, the slow isomerization from (*Z*)-**2a** to (*E*)-**2a** was observed when (*Z*)-**2a** was subjected to the reaction condition (*Z*/*E*=91/9). In addition, (*Z*)-**2a** easily isomerized to (*E*)-**2a** in DMF (100 °C, 1 h, *Z*/*E*=34/66). These results are consistent with the ratio in Table 1 and suggest that the reaction proceeds stereoselectively to afford (*Z*)-**2a**, which then isomerizes to (*E*)-isomer in the presence of $Pd(PPh_3)_4$ and polar solvent.[14]



Scheme 2. Isomerization experiments of (*Z*)-**2a**.

Having established the optimum reaction conditions, we next investigated the cyanoamidation of several alkynyl cyanoformanilides **1b–e** and alkynyl cyanoformamides **1f–k** (Table 2). The palladium-catalyzed cyclization of formanilides **1b–c**, which have different alkyl substituents such as *n*-$C_{10}H_{21}$ and *t*-Bu, occurred to give the corresponding oxindoles in good yields (entries 1 and 2). The reaction of **1d**,**e** having Ph and CH_2OTBS as an alkynyl side chain proceeded slowly even at 130 °C, and gave the corresponding oxindoles **2d** and **2e** in moderate yields (entries 3 and 4). In contrast to these results, the same reaction of acyclic cyanoformamide **1f** took place smoothly to furnish the desired lactam **2f** in 84% yield as a single isomer (entry 5). The reaction of cyanoformamide **1g**, which was easily prepared from α-amino acid derivative, also occurred cleanly to provide the monosubstituted lactam **2g** in 67% yield. The reaction of L-valine and L-proline derivatives **1h–j** provided the disubstituted lactam **2h** and bicyclic lactams **2i**,**j** in good yields (entries 7–9). Furthermore, the cyclization of α,α-disubstituted amino acid derivative **1k** afforded the desired product **2k** without any troubles (entry 10). In this way, the Pd-catalyzed carbonylative cyclization of non-aromatic substrates **1f–k** proceeds exclusively in a 5-*exo* mode with (*Z*)-selectivity, which

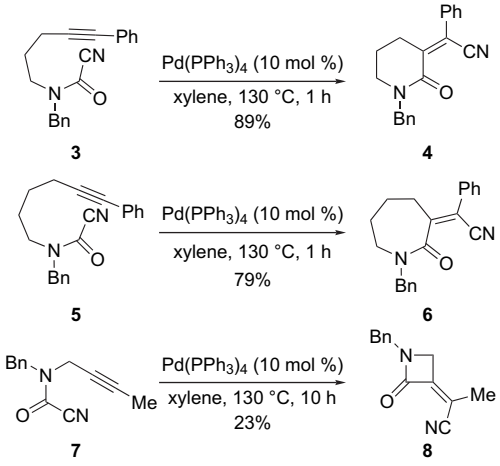
Table 2. Pd-catalyzed cyanoamidation of alkynes **1b–k**[a]

Entry	Substrates	Time (h)	Products	Yield[b] (%)	Entry	Substrates	Time (h)	Products	Yield (%)
1	 **1b**	3	 **2b**	98[c]	6	 **1g**	3	 **2g**	67
2	 **1c**	3	 **2c**	88[d]	7	 **1h**	4	 **2h**	68
3	 **1d**	8	 **2d**	45[e]	8	 **2i**	1	 **1i**	77
4	 **1e**	8	 **2e**	57[e]	9	 **1j**	1	 **2j**	82
5	 **1f**	1	 **2f**	84	10	 **1k**	4	 **2k**	84

[a] All reactions were carried out using 10 mol % of $Pd(PPh_3)_4$ in xylene at 130 °C.
[b] Isolated yield.
[c] *Z*/*E* Ratio was 64/36.
[d] *Z*/*E* Ratio was 86/14.
[e] *Z*/*E* Ratio was >90/10.

means that the substituents have little effect on this cyclization.

We further examined the scope and limitations of the palladium-catalyzed intramolecular cyanoamidation. For this purpose, this protocol was applied to the cyclization of cyanoformamides **3**, **5**, and **7** possessing alkyl chains of different lengths (Scheme 3). As expected, cyanoformamide **3** was successfully cyclized in the presence of 10 mol % of $Pd(PPh_3)_4$. The reaction gave the desired six-membered lactam **4** regio- and stereoselectively in 89% yield. Furthermore, by the same treatment of **5** as **3**, the corresponding seven-membered lactam **6** was obtained in good yield as a single isomer. This method could be also applied to the synthesis of β-lactam, while the chemical yield of **8** was somewhat low due to the poor reactivity of the substrate and the instability of the product. The stereochemistry of all products was determined to be *Z* by NOE experiments.

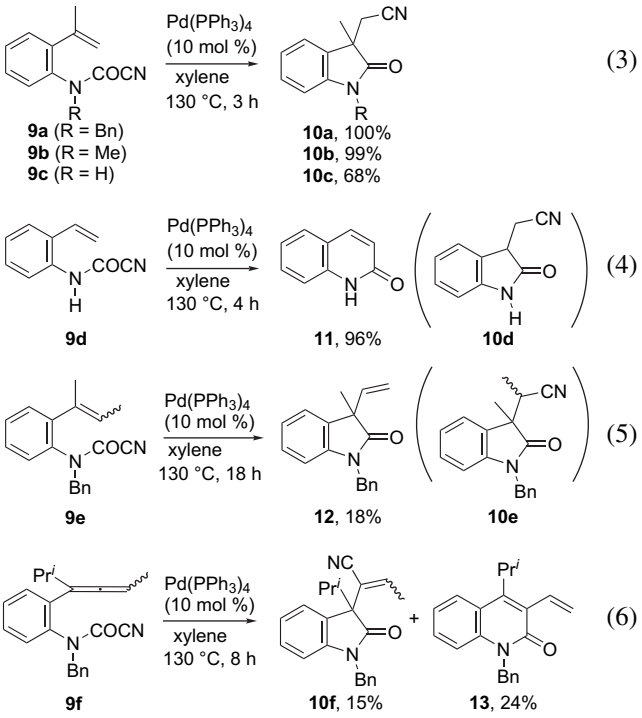


Scheme 3. Application to the synthesis of four-, six-, and seven-membered lactams.

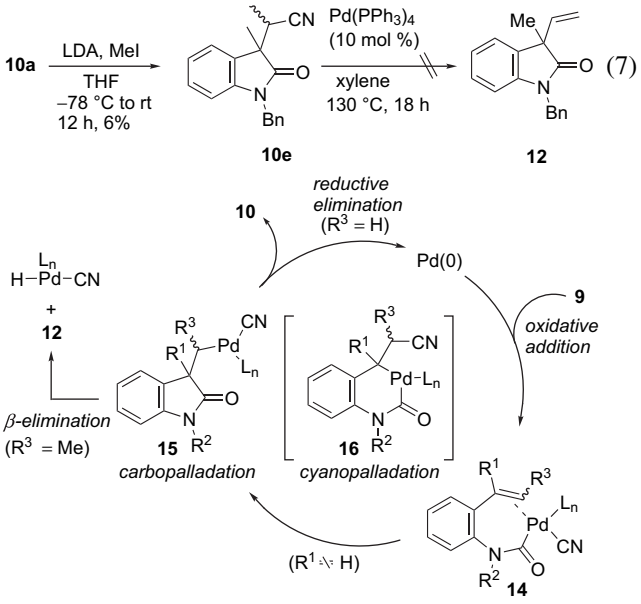
To expand the utility of this reaction, we next investigated the intramolecular cyanoamidation of various unsaturated cyanoformamides (Eqs. 3–6). As reported in our preliminary communication,[10] the reaction of 1,1-disubstituted alkenes **9a**,**b** proceeded cleanly with perfect regioselectivity to afford the cyclized adducts **10a**,**b**, which had a quaternary carbon center, in excellent yield. The presence of a protecting group was not critical, since N–H cyanoformamide **9c** was similarly transformed into its lactam **10c** in 68% yield (Eq. 3). Unexpectedly, the reaction of monosubstituted alkene **9d** did not afford the desired product **10d** and six-membered

lactam **11**, whose structure was identical with the authentic 2-quinolinol, was obtained in high yield as the single product (Eq. 4). On the other hand, in the case of trisubstituted alkene **9e**, the reaction did occur in *exo* mode, giving Heck-type adduct **12** in 18% yield, but not the desired product **10e**, together with 59% yield of the starting material (Eq. 5). Finally, we applied this reaction to the allenyl cyanoformamides **9f** under the same reaction conditions (Eq. 6). In fact, the desired cyanide **10f** was obtained only in 15% yield along with 24% of the six-membered lactam **13**. In all cases except for the 1,1-disubstituted alkenes **9a–c**, the products derived from elimination of HCN were obtained (Eqs. 4–6).

Although it was revealed that this reaction could not be applied to various unsaturated cyanoformamides, we considered these results would be useful for the mechanistic study on the intramolecular cyanoamidation, in short, the elimination of HCN would occur via β-hydride elimination from the reaction intermediate. Alternative possibility of direct elimination from **10** can be ruled out based on the following experiment (Eq. 7). When **10e**, prepared from **10a**, was treated with the same reaction conditions as the Pd(0)-catalyzed cyclization, the production of **12** was not observed at all.[15] Taking into account these results, a plausible mechanism of the intramolecular cyanoamidation is shown in Scheme 4. The reaction would be initiated by the oxidative addition of the C–CN bond of **9** to Pd(0) giving the Pd(II) complex **14**.



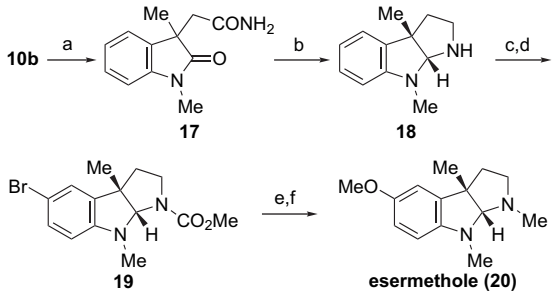
The subsequent insertion of the alkene moiety of **14** into the Pd–CN bond via carbopalladation should afford the intermediate **15**, which would produce cyanoamidation product **10** and Pd(0) catalyst in the case of the substrates without β-proton (R^3=H). In contrast, from the substrates bearing a β-proton (R^3=CH_3), β-hydride elimination proceeds predominantly to provide the alkene **12** and inactive



Scheme 4. A plausible mechanism of the Pd(0)-catalyzed intramolecular cyanoamidation of **9**.

palladium(II) cyano complex,[16] which lead to the low yield of the Heck-type adduct. Alternative possibility of the insertion process via cyanopalladation can be ruled out[17] from the results that cyanoamidation product **10e** was not detected at all in Eq. 5 as well as in the results of Eq. 7. Further detailed mechanistic aspects are under investigations.

Finally, application of this method to the synthesis of esermethole[18] **20** was examined (Scheme 5) by using the cyclized adduct **10b** bearing both a quaternary carbon center and a β-cyano group. Hydrolysis of nitrile **10b** into amide **17** with hydrogen peroxide was followed by the reductive cyclization with $LiAlH_4$ to give the tricyclic product **18**, which possesses a core structure of pyrrolo[2,3-*b*]indole alkaloids. The functionalization of the aromatic ring of **18** was accomplished by the two-step sequence: methoxycarbonylation and bromination with NBS (*N*-bromosuccinimide) to give **19** in good yield. The successive treatment with sodium methoxide in the presence of cuprous iodide[19] and $LiAlH_4$ afforded the desired esermethole **20**. Consequently, it has been shown that the intramolecular cyanoamidation of 1,1-disubstituted alkenyl cyanoformamides would be a novel method for the preparation of related alkaloids.[20,21]



Scheme 5. Application to the synthesis of esermethole (**20**). *Reagents and conditions*: (a) 30% H_2O_2, 1 N NaOH, MeOH, 0 °C, 5 h, 77%; (b) $LiAlH_4$, THF, reflux, 2 h, 57%; (c) $ClCO_2Me$, Et_3N, DMAP, CH_2Cl_2, 0 °C, 2 h, 78%; (d) *N*-bromosuccinimide, DMF, 0 °C, 2 h, 92%; (e) CuI, NaOMe, MeOH/DMF, 120 °C, 2 h, 70%; (f) $LiAlH_4$, THF, reflux, 2 h, 96%.

In summary, we have developed a novel method for the synthesis of four- to seven-membered functionalized lactams by the palladium-catalyzed intramolecular cyanoamidation of alkynyl and alkenyl cyanoformamides. Further detailed investigations of another type of cyclization and further applications of the obtained products are underway in this laboratory.

3. Experimental

3.1. General

Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. ^{1}H and ^{13}C NMR spectra were registered on JEOL JNM-LA500 using TMS as an internal standard (s=singlet, d=doublet, dd=double doublet, ddd=doublet of double doublets, t=triplet, q=quartet, m=multiplet, br=broad). Optical rotations were measured in $CHCl_3$ with a JASCO DIP-360 digital polarimeter unless otherwise noted. For column chromatography, Kanto Silica gel 60 (spherical, 63–210 μm) was employed and preparative thin-layer chromatography (PTLC) was carried out using Silica gel 60 (Merck).

3.2. Materials

Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used without purification. TCNEO (=tetracyanoethyleneoxide) was prepared according to the literature procedure.[12a]

3.3. General procedure for the preparation of unsaturated cyanoformamides (Methods A–C)

Cyanoformamides **1a–e**[10] were prepared according to our preliminary report. Cyanoformamides **1g–k** and **9a–f** were prepared from the corresponding unsaturated amines by using Method A or Method B. Cyanoformamides **1f**, **3**, **5** and **7** were prepared from the corresponding alkynol by using Method C.

3.3.1. General procedure for Method A. Carbonyl cyanide was prepared according to the reported paper.[12a]

To a suspension of TCNEO (5.00 g, 34.7 mmol) in ether (20 mL) was added Me_2S (2.59 mL, 34.0 mmol) at 0 °C. After stirred at 0 °C for 1 h, the mixture was filtered with ether (15 mL) to give the carbonyl cyanide solution (~1.0 M) in ether, which was used for the following reaction without further purification. This material is stable for a few months in a refrigerator.

To a solution of *N*-benzyl-2-isopropenylaniline[3b] (500 mg, 2.24 mmol) in ether (2.5 mL) was added an ether solution of carbonyl cyanide (3.5 mL), as described above, at room temperature and the reaction mixture was stirred at the same temperature for 4 h. The organic solution was washed with saturated aqueous NaOH solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel with hexane/EtOAc (10/1) to give **9a** (502 mg, 81%).

3.3.2. General procedure for Method B. To a solution of *N*-benzyl-2-isopropenylaniline (3.20 g, 14.6 mmol) in CH_2Cl_2 (30 mL) was added pyridine (1.77 mL, 21.9 mmol) followed by triphosgene (1.51 g, 5.10 mmol) at −78 °C. The reaction mixture was warmed up to room temperature, diluted with $CHCl_3$, and washed with 1 N HCl and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude chlorocarbamate. To a solution of the crude chlorocarbamate in a mixture of MeCN (25 mL) and *t*-BuOH (5.0 mL) were added 18-crown-6 (392 mg, 1.46 mmol) and KCN (1.43 g, 21.9 mmol), and the resulting mixture was stirred at 60 °C for 2 h. After removal of the solvents and addition of water, the aqueous solution was extracted with $CHCl_3$ (three times). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel with hexane/EtOAc (95/5) to give **9a** (3.83 g, 95%).

3.3.3. General procedure for Method C. *N*-Benzylcyanoformamide was prepared according to Method A.

To a solution of benzylamine (1.00 g, 9.34 mmol) in ether (10 mL) was added an ether solution of carbonyl cyanide (15 mL), as described above, at room temperature and the reaction mixture was stirred at the same temperature for 2 h. The organic solution was washed with saturated aqueous NaOH and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was purified by recrystallization from hexane/AcOEt to give *N*-benzylcyanoformamide (1.28 g, 86%) as a yellow solid.

3.3.3.1. *N*-Benzylcyanoformamide. Yellow solid; mp 70–72 °C (hexane/EtOAc); ^{1}H NMR ($CDCl_3$, 500 Hz) δ 4.39 (d, 2H, J=6.1 Hz), 7.23 (d, 2H, J=6.7 Hz), 7.33–7.36 (m, 3H), 7.53 (br, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 44.1, 111.3, 127.9, 128.2, 128.9, 135.1, 143.2; IR ($CHCl_3$) 2237, 1709, 1520 cm^{-1}; MS (EI$^+$) 160 (M$^+$, 100). Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.55; H, 5.10; N, 17.63.

To a solution of 3-pentyn-1-ol (500 mg, 5.95 mmol), *N*-benzylcyanoformamide (1.05 g, 6.55 mmol), and triphenylphosphine (1.87 g, 7.14 mmol) in THF (20 mL) was added diisopropyl azodicarboxylate (3.90 mL, 40% solution in toluene) and the reaction mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel with hexane/EtOAc (5/1) to give **1f** (517 mg, 38%).

3.3.3.2. *N*-Benzyl-*N*-[2-(hex-1-ynyl)phenyl]cyanoformamide (1a). Colorless oil; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 0.96 (m, 3H), 1.46 (m, 2H), 1.57 (m, 2H), 2.40 (t, 2H, J=7.2 Hz), 4.49 (d, 1H, J=14.0 Hz), 5.31 (d, 1H, J=14.0 Hz), 6.86 (d, 1H, J=7.9 Hz), 7.16–7.36 (m, 7H), 7.51 (dd, 1H, J=1.4, 7.8 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 13.4, 19.1, 21.9, 30.4, 52.0, 75.7, 97.9, 110.8, 124.4, 128.3, 128.6, 129.4, 129.5, 129.8, 133.5, 134.5, 139.1, 145.3; IR ($CHCl_3$): 2232.2, 1680.7 cm^{-1}; MS (EI$^+$) *m/z*

(relative intensity) 316 (M^+, 25), 184 (100). HRMS (EI^+) $C_{21}H_{20}N_2O$: (M^+) 316.1576. Found: 316.1569.

3.3.3.3. *N*-Benzyl-*N*-[2-(dodec-1-ynyl)phenyl]cyanoformamide (1b). Yellow oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 0.87 (t, 1H, J=7.0 Hz), 1.27–1.31 (m, 12H), 1.42 (m, 2H), 1.59 (m, 2H), 2.39 (t, 1H, J=7.2 Hz), 4.49 (d, 1H, J=14.0 Hz), 5.32 (d, 1H, J=14.3 Hz), 6.86 (d, 1H, J=7.9 Hz), 7.18 (m, 2H), 7.22 (m, 1H), 7.27 (m, 3H), 7.35 (m, 1H), 7.51 (dd, 1H, J=7.8, 1.4 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 14.0, 19.4, 22.6, 28.4, 28.9, 29.0, 29.2, 29.4, 29.5, 31.8, 52.0, 75.7, 98.0, 110.8, 124.4, 128.3, 128.5, 128.6, 129.5, 129.8, 133.5, 134.6, 139.1, 145.3; IR ($CHCl_3$) 2231, 1682 cm^{-1}; MS (CI^+) m/z (relative intensity) 401 (MH^+, 100). HRMS (CI^+) $C_{27}H_{33}N_2O$: (MH^+) 401.2593. Found: 401.2602.

3.3.3.4. *N*-Benzyl-*N*-[2-(3,3-dimethylbut-1-ynyl)phenyl]cyanoformamide (1c). Yellow oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.30 (s, 9H), 4.50 (d, 1H, J=14.3 Hz), 5.28 (d, 1H, J=14.3 Hz), 6.88 (dd, 1H, J=8.1, 1.1 Hz), 7.17 (m, 2H), 7.22 (dd, 1H, J=7.8, 7.8 Hz), 7.27 (m, 1H), 7.33 (dd, 1H, J=7.6, 7.6 Hz), 7.49 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 28.0, 30.5, 52.0, 74.4, 105.8, 110.9, 124.4, 128.3, 128.6, 129.1, 129.4, 129.7, 133.1, 134.4, 139.2, 145.4; IR ($CHCl_3$) 2360, 2235, 1680 cm^{-1}; MS (EI^+) m/z (relative intensity) 316 (M^+, 12). HRMS (EI^+) $C_{21}H_{20}N_2O$: (M^+) 316.1576. Found: 316.1580.

3.3.3.5. *N*-Benzyl-*N*-[2-(2-phenylethynyl)phenyl]cyanoformamide (1d). Red oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 4.63 (d, 1H, J=14.3 Hz), 5.29 (d, 1H, J=14.3 Hz), 6.95 (d, 1H, J=7.9 Hz), 7.21 (m, 6H), 7.35 (m, 4H), 7.48 (m, 2H), 7.59 (dd, 1H, J=1.5, 7.6 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 52.1, 84.1, 95.9, 110.7, 121.8, 123.5, 128.3, 128.4, 128.5, 129.0, 129.3, 129.4, 129.9, 131.6, 133.1, 134.1, 138.9, 145.2; IR ($CHCl_3$) 2220, 1680, 1496, 1394 cm^{-1}; MS (EI^+) m/z (relative intensity) 336 (M^+, 22), 91 (100). HRMS (EI^+) $C_{23}H_{16}N_2O$: (M^+) 336.1263. Found: 336.1257.

3.3.3.6. *N*-Benzyl-*N*-{2-[3-(*tert*-butyldimethylsilyloxy)-prop-1-ynyl]phenyl}cyanoformamide (1e). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 0.01 (s, 6H), 0.78 (s, 9H), 4.30 (d, 1H, J=14.3 Hz), 4.35 (s, 2H), 5.21 (d, 1H, J=14.0 Hz), 6.69 (d, 1H, J=7.9 Hz), 7.00 (m, 2H), 7.11 (m, 4H), 7.22 (t, 1H, J=7.6 Hz), 7.41 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 5.3, 18.2, 25.7, 51.9, 52.0, 79.5, 94.8, 110.6, 123.2, 128.4, 128.7, 129.4, 129.5, 129.9, 130.0, 133.8, 134.5, 139.0, 145.1; IR ($CHCl_3$) 2232, 1680 cm^{-1}; MS (FAB^+) m/z (relative intensity) 405 (M^+, 4), 91 (100). HRMS (FAB^+) $C_{24}H_{28}N_2OSi$: (MH^+) 405.1998. Found: 405.1983.

3.3.3.7. *N*-Benzyl-*N*-(pent-3-ynyl)cyanoformamide (1f). White solid; mp 63–65 °C; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.80 (m, 3H), 2.43 (m, 2H), 3.43 (t, 1H, J=6.9 Hz), 3.62 (t, 1H, J=6.4 Hz), 4.65 (s, 1H), 4.90 (s, 1H), 7.21–7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 Hz, mixture of the rotamers) δ 3.4, 17.0, 18.7, 43.9, 46.8, 47.7, 53.2, 74.0, 75.0, 78.1, 80.5, 110.6, 110.7, 127.7, 128.3, 128.4, 128.7, 128.8, 128.9, 129.0, 129.2, 134.0, 134.4, 144.8, 145.6; IR ($CHCl_3$) 2232, 1684 cm^{-1}; MS (FAB^+) m/z (relative intensity) 227 (M^+, 41), 91 (100). HRMS (FAB^+) $C_{14}H_{14}N_2O$: (MH^+) 227.1184. Found: 227.1190.

3.3.3.8. *N*-(1-*tert*-Butyldiphenylsilyloxyhex-4-yn-2-yl)-*N*-methylcyanoformamide (1g). White solid; mp 82–84 °C; ^1H NMR ($CDCl_3$, 500 Hz, mixture of the rotamers) δ 1.06 (s, 9H), 1.73 (s, 3H), 2.30–2.43 (m, 2H), 2.80 (s, 2H), 3.22 (s, 1H), 3.58–3.78 (m, 2H), 4.41–4.53 (m, 1H), 7.38–7.46 (m, 6H), 7.61–7.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 Hz, mixture of the rotamers) δ 3.3, 14.0, 18.4, 18.9, 19.0, 19.2, 22.6, 26.6, 26.7, 26.8, 31.5, 32.6, 55.6, 60.6, 62.2, 62.7, 72.7, 73.5, 78.6, 79.9, 110.7, 110.8, 127.9, 128.0, 130.06, 130.08, 130.11, 130.15, 132.38, 132.41, 132.6, 132.7, 135.52, 135.56, 135.59, 145.8, 146.2; IR ($CHCl_3$) 2236, 1674 cm^{-1}; MS (EI^+) m/z (relative intensity) 361 ($M-t$-Bu, 100). Anal. Calcd for $C_{25}H_{31}N_2O_2Si$: C, 71.73; H, 7.22; N, 6.69. Found: C, 71.73; H, 7.25; N, 6.68.

3.3.3.9. *N*-((3*S*,4*S*)-4-Methoxy-2-methyl-6-phenylhex-5-yn-3-yl)-*N*-methylcyanoformamide (1h). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 0.82–0.95 (m, 6H), 0.96–1.08 (m, 3H), 1.40 (m, 2H), 1.50 (m, 2H), 2.14–2.37 (m, 3H), 2.97–3.24 (m, 3H), 3.35 (m, 3H), 3.69 (dd, 1H, J=10.4 Hz, 3.7 Hz), 4.17–4.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz, mixture of the rotamers) δ 13.4, 18.2, 19.0, 19.1, 19.6, 19.9, 21.8, 21.9, 25.2, 25.7, 29.9, 30.3, 30.5, 56.8, 57.0, 69.4, 70.9, 71.7, 75.0, 88.8, 90.6, 110.8, 110.9, 146.4, 147.2; IR ($CHCl_3$) 2360, 1670 cm^{-1}; MS (EI^+) m/z (relative intensity) 264 (M^+, 1), 207 (21), 44 (100). HRMS (EI^+) $C_{15}H_{24}N_2O_2$: (M^+) 264.1838. Found: 264.1846.

3.3.3.10. 2-[(*S*)-2-((*S*)-1-Methoxyhept-2-ynyl)pyrrolidin-1-yl]-2-oxoacetonitrile (1i). Colorless oil; $[\alpha]_D^{20}$ −139 (c 1.03, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 Hz, mixture of the rotamers) δ 0.85 (m, 3H), 1.33–1.45 (m, 4H), 1.77–1.86 (m, 1H), 2.02–2.27 (m, 5H), 3.26–3.33 (m, 3H), 3.34–3.78 (m, 2H), 4.09 (m, 1H), 4.23–4.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz, mixture of the rotamers) δ 13.3, 18.08, 18.16, 21.6, 21.7, 22.2, 23.7, 25.8, 26.7, 30.2, 30.4, 46.6, 49.6, 56.6, 56.7, 61.3, 62.6, 69.8, 73.5, 75.0, 75.5, 88.2, 89.8, 111.1, 111.3, 142.7, 142.9; IR ($CHCl_3$) 2935, 2231, 1661, 1413 cm^{-1}; MS (FAB^+) m/z (relative intensity) 249 (MH^+, 100). Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.42; H, 8.02; N, 11.25.

3.3.3.11. 2-[(*S*)-2-((*R*)-1-*tert*-Butyldimethylsilyloxyhept-2-ynyl)pyrrolidin-1-yl]-2-oxoacetonitrile (1j). Colorless oil; $[\alpha]_D^{24}$ −106 (c 0.81, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 Hz) δ −0.07 to 0.15 (m, 6H), 0.74–0.96 (m, 12H), 1.26–1.54 (m, 4H), 1.79 (m, 1H), 1.99–2.19 (m, 4H), 2.31 (m, 1H), 3.23–3.90 (m, 2H), 3.96–4.28 (m, 1H), 4.40–5.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz, mixture of rotamers) δ −5.5, −5.4, −5.1, −5.0, 13.3, 17.7, 17.8, 18.0, 18.1, 21.6, 21.7, 22.4, 23.9, 25.4, 25.5, 26.3, 30.1, 30.3, 46.9, 49.8, 61.2, 62.7, 64.1, 65.4, 77.9, 78.3, 86.6, 88.1, 110.9, 111.3, 142.6; IR ($CHCl_3$) 2360, 2232, 1672 cm^{-1}; MS (EI^+) m/z (relative intensity) 291 ($M-t$-Bu, 57), 225 (48), 73 (100). Anal. Calcd for $C_{19}H_{32}N_2O_2Si$: C, 65.47; H, 9.25; N, 8.04. Found: C, 65.46; H, 9.10; N, 8.00.

3.3.3.12. *N*-(3-Methoxy-2-methyl-5-phenylpent-4-yn-2-yl)-*N*-methylcyanoformamide (1k). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.58 (s, 3H), 1.59 (s, 3H), 3.34 (s, 3H), 3.45 (s, 3H), 5.08 (s, 1H), 7.33 (m, 3H), 7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 22.0, 22.3, 35.6, 57.4, 64.3, 73.9, 84.9, 87.3, 111.4, 122.2, 128.4, 128.7, 131.8,

145.6; IR ($CHCl_3$) 2360, 2229.3, 1672 cm^{-1}; MS (EI^+) *m/z* (relative intensity) 270 (M^+, 1), 186 (42), 145 (100). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.33; H, 6.75; N, 10.23.

3.3.3.13. *N*-Benzyl-*N*-(5-phenylpent-4-ynyl)cyanoformamide (3). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.82 (m, 1H), 1.92 (m, 1H), 2.42 (t, 1H, *J*=6.9 Hz), 2.49 (t, 1H, *J*=6.7 Hz), 3.49 (m, 1H), 3.68 (m, 1H), 4.64 (s, 1H), 4.80 (s, 1H), 7.23–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 126 Hz, mixture of the rotamers) δ 16.6, 16.8, 25.4, 27.1, 44.0, 47.0, 48.0, 52.8, 81.9, 82.3, 87.2, 88.0, 110.6, 110.8, 123.2, 123.3, 127.8, 127.9, 128.0, 128.3, 128.4, 128.5, 128.8, 129.0, 129.2, 131.5, 131.6, 134.0, 134.6, 144.9, 145.4; IR ($CHCl_3$) 2231, 1677, 1429 cm^{-1}; MS (EI^+) *m/z* (relative intensity) 302 (M^+, 8), 211 (47), 91 (100). HRMS (EI^+) $C_{20}H_{18}N_2O$: (M^+) 302.1419. Found: 302.1416.

3.3.3.14. *N*-Benzyl-*N*-(6-phenylhex-5-ynyl)cyanoformamide (5). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.51 (m, 1H), 1.58 (m, 1H), 1.66 (m, 1H), 1.77 (m, 1H), 2.37 (t, 1H, *J*=6.9 Hz), 2.41 (t, 1H, *J*=6.9 Hz), 3.33 (m, 1H), 3.50 (m, 1H), 4.58 (s, 1H), 4.71 (s, 1H), 7.20–7.39 (m, 10H); ^{13}C NMR ($CDCl_3$, 126 Hz, mixture of the rotamers) δ 18.6, 25.1, 25.4, 27.1, 44.1, 47.6, 47.7, 52.2, 81.2, 81.4, 88.6, 88.9, 110.6, 110.8, 123.5, 123.6, 127.4, 127.6, 128.0, 128.1, 128.2, 128.6, 128.8, 129.0, 131.4, 134.5, 144.7, 145.1; IR ($CHCl_3$) 2232, 1675 cm^{-1}; MS (EI^+) *m/z* (relative intensity) 316 (M^+, 9), 225 (20), 91 (100). HRMS (EI^+) $C_{21}H_{20}N_2O$: (M^+) 316.1576. Found: 316.1567.

3.3.3.15. *N*-Benzyl-*N*-(but-2-ynyl)cyanoformamide (7). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.84 (s, 3H), 4.06 (s, 1H), 4.18 (s, 1H), 4.71 (s, 1H), 4.88 (s, 1H), 7.27–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 Hz, mixture of the rotamers) δ 3.4, 33.5, 38.0, 47.3, 51.3, 70.9, 71.0, 82.0, 83.0, 110.2, 110.5, 128.0, 128.5, 128.7, 128.8, 129.0, 129.2, 133.6, 134.1, 144.3, 144.6; IR ($CHCl_3$) 2360, 2236, 1678 cm^{-1}; MS (EI^+) *m/z* (relative intensity) 212 (M^+, 13), 91 (100). HRMS (EI^+) $C_{13}H_{12}N_2O$: (M^+) 212.0950. Found: 212.0956.

3.3.3.16. *N*-Benzyl-*N*-[2-(prop-1-en-2-yl)phenyl]cyanoformamide (9a). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 2.11 (s, 3H), 4.09 (d, 1H, *J*=14.3 Hz), 5.08 (s, 1H), 5.34 (s, 1H), 5.50 (d, 1H, *J*=14.0 Hz), 6.75 (d, 1H, *J*=7.9 Hz), 7.15 (m, 1H), 7.18 (m, 1H), 7.28 (m, 3H), 7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 23.5, 52.2, 110.8, 118.2, 128.3, 128.4, 128.7, 129.3, 130.2, 130.3, 130.5, 134.5, 134.8, 141.9, 142.2, 145.4; IR ($CHCl_3$) 2231, 1677 cm^{-1}; MS (EI^+) *m/z* (relative intensity) 276 (M^+, 1), 184 (64), 130 (100). HRMS (EI^+) $C_{18}H_{16}N_2O$: (M^+) 276.1263. Found: 276.1267.

3.3.3.17. *N*-Methyl-*N*-[2-(prop-1-en-2-yl)phenyl]cyanoformamide (9b). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 2.08 (s, 3H), 3.27 (s, 3H), 5.03 (s, 1H), 5.32 (s, 1H), 7.25 (m, 1H), 7.39 (m, 2H), 7.46 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 23.4, 36.6, 110.8, 118.0, 128.6, 128.9, 130.2, 130.3, 136.8, 141.6, 142.3, 145.2; IR ($CHCl_3$) 2232, 1690 cm^{-1}; MS (EI^+) *m/z* (relative intensity) 200 (M^+, 0.2). HRMS (EI^+) $C_{12}H_{12}N_2O$: (M^+) 200.0950. Found 200.0959.

3.3.3.18. *N*-[2-(Prop-1-en-2-yl)phenyl]cyanoformamide (9c). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 2.11 (s, 3H), 5.07 (m, 1H), 5.49 (m, 1H), 7.24 (m, 2H), 7.31 (m, 1H), 8.10 (d, 1H, *J*=8.2 Hz), 8.31 (br, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 24.3, 111.6, 118.1, 121.7, 121.8, 126.3, 128.1, 131.4, 134.5, 140.4, 141.6; IR ($CHCl_3$) 3361, 1708, 1522 cm^{-1}; MS (EI^+) *m/z* (relative intensity) 186 (M^+, 13), 117 (100). HRMS (EI^+) $C_{11}H_{10}N_2O$: (M^+) 186.0793. Found: 186.0796.

3.3.3.19. *N*-Benzyl-*N*-[2-(but-2-en-2-yl)phenyl]cyanoformamide (9e). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.55–2.03 (m, 6H), 3.99–4.11 (m, 1H), 5.42–5.56 (m, 1H), 5.58–5.77 (m, 1H), 6.76 (m, 1H), 7.10–7.30 (m, 7H), 7.37–7.44 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz, major peaks of the rotamers) δ 14.1, 17.1, 51.9, 111.0, 127.6, 128.1, 128.3, 128.7, 129.3, 130.2, 130.6, 131.6, 133.2, 134.7, 135.0, 144.2, 145.5; IR ($CHCl_3$): 2360, 1678 cm^{-1}; MS (FAB^+) *m/z* (relative intensity) 291 (M^+, 100). HRMS (FAB^+) $C_{19}H_{19}N_2O$: (MH^+) 291.1497. Found: 291.1505.

3.3.3.20. *N*-Benzyl-*N*-[2-(2-methylhexa-3,4-dien-3-yl)-phenyl]cyanoformamide (9f). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.08 (d, 1H, *J*=6.7 Hz), 1.12 (d, 2H, *J*=7.0 Hz), 1.18 (d, 3H, *J*=6.6 Hz), 1.74 (d, 1H, *J*=7.3 Hz), 1.80 (d, 2H, *J*=7.0 Hz), 2.80 (m, 1H), 3.97 (m, 1H), 5.43–5.61 (m, 2H), 6.61–6.68 (m, 1H), 7.09–7.14 (m, 3H), 7.24–7.31 (m, 3H), 7.40–7.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 Hz, mixture of the rotamers) δ 14.3, 21.7, 21.9, 22.4, 22.8, 30.1, 30.2, 51.5, 51.6, 89.5, 89.7, 107.1, 107.4, 110.8, 111.0, 127.5, 128.3, 128.4, 128.7, 128.9, 129.1, 129.4, 129.5, 130.3, 130.4, 131.5, 131.6, 134.8, 134.9, 135.6, 135.8, 136.4, 136.5, 146.0, 146.1, 203.8, 203.9; IR ($CHCl_3$) 2222, 1680 cm^{-1}; MS (FAB^+) *m/z* (relative intensity) 331 (MH^+, 14), 91 (100). HRMS $C_{22}H_{23}N_2O$: (MH^+) 331.1810. Found: 331.1812.

3.4. General procedure for the palladium-catalyzed intramolecular cyanoamidation

Under an argon atmosphere, a solution of **1a** (50.0 mg, 0.158 mmol) and $Pd(PPh_3)_4$ (18.2 mg, 10 mol %) in toluene (1.6 mL) was stirred at 100 °C for 2 h. Purification by column chromatograph on silica gel (AcOEt/hexane=1/10 to 1/3 as eluant) gave the products (*Z*)-**2a** (35.3 mg, 71%) and (*E*)-**2a** (12.9 mg, 26%) as yellow solids.

3.4.1. 2-(1-Benzyl-2-oxoindolin-3-ylidene)hexanenitrile (2a). Compound (*Z*)-**2a**: yellow solid; mp 123–124 °C; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.00 (m, 3H), 1.53 (m, 2H), 1.81 (m, 2H), 2.83 (t, 2H, *J*=7.2 Hz), 4.95 (s, 2H), 6.77 (d, 1H, *J*=7.9 Hz), 7.04 (dd, 1H, *J*=7.6, 7.6 Hz), 7.26–7.34 (m, 6H), 7.52 (d, 1H, *J*=7.6 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 13.7, 22.4, 29.3, 32.5, 43.8, 109.8, 117.4, 119.8, 120.6, 122.7, 125.4, 127.6, 127.9, 128.9, 132.1, 135.4, 136.7, 143.8, 164.6; IR ($CHCl_3$) 2210, 1713, 1606, 1467, 1379, 1354 cm^{-1}; MS (EI^+) *m/z* (relative intensity) 316 (M^+, 12), 91 (100). Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.94; H, 6.33; N, 8.86.

Compound (*E*)-**2a**: yellow solid; mp 102–103 °C; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.03 (m, 3H), 1.51 (m, 2H), 1.68 (m, 2H), 3.23 (m, 2H), 4.92 (s, 2H), 6.72 (d, 1H, *J*=7.9 Hz), 7.07 (dd,

1H, J=7.8, 7.8 Hz), 7.26–7.34 (m, 6H), 8.23 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 13.7, 22.3, 29.3, 30.4, 43.5, 109.2, 118.1, 120.2, 121.4, 122.9, 123.8, 127.3, 127.8, 128.9, 131.9, 135.3, 135.4, 142.9, 166.0. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 9.72; H, 6.37; N, 8.85. Found: C, 79.42; H, 6.26; N, 8.83.

3.4.2. 2-(1-Benzyl-2-oxoindolin-3-ylidene)dodecanenitrile (2b). Compound (*Z*)-**2b**: yellow solid; mp 92–94 °C; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 0.88 (t, 3H, J=6.6 Hz), 1.26–1.32 (m, 10H), 1.37 (m, 2H), 1.49 (m, 2H), 1.82 (m, 2H), 2.82 (m, 2H), 4.94 (s, 2H), 6.76 (d, 1H, J=7.9 Hz), 7.04 (dd, 1H, J=7.6 Hz), 7.25–7.33 (m, 6H), 7.52 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 14.1, 22.6, 27.3, 29.2, 29.3, 29.4, 29.5, 31.8, 32.7, 43.8, 109.7, 117.4, 119.9, 120.6, 122.7, 125.4, 127.6, 127.9, 128.9, 132.1, 135.4, 136.7, 143.8, 164.5; IR ($CHCl_3$) 1714 cm^{-1}; MS (EI$^+$) m/z (relative intensity) 400 (M$^+$, 17), 91 (100). Anal. Calcd for $C_{27}H_{32}N_2O$: C, 80.96; H, 8.05; N, 6.99. Found: C, 81.10; H, 8.02; N, 7.11.

Compound (*E*)-**2b**: yellow oil; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 0.88 (t, 3H, J=6.6 Hz), 1.27–1.32 (m, 10H), 1.36 (m, 2H), 1.44 (m, 2H), 1.74 (m, 2H), 3.21 (m, 2H), 4.92 (s, 2H), 6.72 (d, 1H, J=7.6 Hz), 7.07 (dd, 1H, J=7.6 Hz), 7.25–7.33 (m, 6H), 8.22 (d, 1H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 14.0, 22.6, 28.4, 29.1, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 43.5, 109.2, 118.1, 120.2, 121.5, 122.9, 123.8, 127.3, 127.8, 128.9, 131.9, 135.3, 135.4, 143.0, 166.0; IR ($CHCl_3$) 1702 cm^{-1}; MS (EI$^+$) m/z (relative intensity) 400 (M$^+$, 17), 91 (100). Anal. Calcd for $C_{27}H_{32}N_2O$: C, 80.96; H, 8.05; N, 6.99. Found: C, 81.03; H, 8.05; N, 6.70.

3.4.3. 2-(1-Benzyl-2-oxoindolin-3-ylidene)-3,3-dimethylbutanenitrile (2c). Compound (*Z*)-**2c**: orange solid; mp 210–212 °C; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 1.57 (s, 9H), 4.97 (s, 2H), 6.78 (d, 1H, J=7.9 Hz), 7.05 (dd, 1H, J=7.8, 7.8 Hz), 7.26–7.35 (m, 6H), 7.78 (d, 1H, J=7.9 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 28.8, 34.9, 43.9, 109.7, 116.6, 119.1, 122.0, 127.6, 127.8, 128.8, 129.4, 130.7, 132.1, 135.4, 137.4, 144.1, 165.4; IR ($CHCl_3$) 2360, 1714 cm^{-1}; MS (EI$^+$) m/z (relative intensity) 316 (M$^+$, 23). Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.47; H, 6.43; N, 8.73.

Compound (*E*)-**2c**: orange oil; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 1.59 (s, 9H), 4.93 (s, 2H), 6.71 (d, 1H, J=7.6 Hz), 7.06 (dd, 1H, J=7.8, 7.8 Hz), 7.27–7.34 (m, 6H), 8.45 (d, 1H, J=7.9 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 29.1, 36.1, 43.7, 109.0, 118.0, 121.1, 122.8, 124.8, 127.3, 127.8, 128.9, 131.3, 131.8, 135.5, 143.3, 144.1, 164.5; IR ($CHCl_3$) 1707 cm^{-1}; MS (EI$^+$) m/z (relative intensity) 316 (M$^+$, 25). HRMS (EI$^+$) $C_{21}H_{20}N_2O$: (M$^+$) 316.1576. Found: 316.1569.

3.4.4. 2-(1-Benzyl-2-oxoindolin-3-ylidene)-2-phenylacetonitrile (2d). Compound (*Z*)-**2d**: red solid; mp 170–172 °C; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 4.99 (s, 2H), 6.72 (t, 2H, J=7.3 Hz), 6.86 (m, 1H), 7.21 (m, 1H), 7.30 (m, 1H), 7.32–7.40 (m, 4H), 7.51–7.58 (m, 3H), 7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 43.9, 109.7, 117.0, 117.1, 120.0, 122.3, 124.8, 127.6, 127.9, 128.8, 129.5, 130.8, 132.9, 135.3, 137.3, 144.1, 164.9; IR ($CHCl_3$) 2212, 1713, 1603, 1469, 1353 cm^{-1}; MS (EI$^+$) m/z (relative intensity) 336 (M$^+$, 28), 91 (100). HRMS (EI$^+$) $C_{23}H_{16}N_2O$: (M$^+$) 336.1263. Found: 336.1266.

3.4.5. 2-(1-Benzyl-2-oxoindolin-3-ylidene)-3-*tert*-butyldimethylsilyloxypropanenitrile (2e). Compound (*Z*)-**2e**: colorless oil; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 0.20 (s, 6H), 0.95 (s, 9H), 4.77 (s, 2H), 4.95 (s, 2H), 6.76 (d, 1H, J=7.9 Hz), 7.05 (t, 1H, J=7.3 Hz), 7.30 (m, 6H), 7.46 (d, 1H, J=7.6 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ −5.3, 18.2, 25.7, 43.8, 61.3, 109.7, 115.8, 118.6, 120.1, 122.8, 126.8, 127.5, 127.9, 128.9, 132.8, 135.3, 137.5, 143.9, 164.3; IR ($CHCl_3$) 2232, 1680 cm^{-1}; MS (FAB$^+$) m/z (relative intensity) 405 (M$^+$, 14), 91 (100). HRMS (FAB$^+$) $C_{24}H_{28}N_2OSi$: (MH$^+$) 405.1998. Found: 405.2002.

3.4.6. 2-(1-Benzyl-2-oxopyrrolidin-3-ylidene)propanenitrile (2f). Colorless oil; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 2.04 (s, 3H), 2.78 (t, 2H, J=4.7 Hz), 3.35 (t, 2H, J=6.1 Hz), 4.57 (s, 2H), 7.22–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 18.8, 23.8, 42.8, 47.2, 108.9, 117.2, 127.9, 128.4, 128.7, 135.6, 146.3, 163.9; IR ($CHCl_3$) 2218, 1692 cm^{-1}; MS (EI$^+$) m/z (relative intensity) 226 (M$^+$, 72), 91 (100). Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.04; H, 6.24; N, 12.12.

3.4.7. 2-[5-(*tert*-Butyldiphenylsilyloxymethyl)-1-methyl-2-oxopyrrolidin-3-ylidene]propanenitrile (2g). Yellow solid; mp 157–162 °C; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 1.00 (s, 9H), 1.97 (s, 3H), 2.61 (m, 1H), 2.77 (m, 1H), 2.81 (s, 3H), 3.61 (d, 1H, J=8.9 Hz), 3.73 (m, 1H), 7.35–7.43 (m, 6H), 7.55–7.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 18.7, 19.0, 26.5, 28.0, 28.4, 57.7, 63.0, 107.5, 117.2, 127.9, 130.0, 130.1, 132.4, 132.7, 135.4, 135.5, 146.3, 164.5; MS (EI$^+$) m/z (relative intensity) 361 (M−*t*-Bu, 100). Anal. Calcd for $C_{25}H_{30}N_2O_2Si$: C, 71.73; H, 7.22; N, 6.69. Found: C, 71.46; H, 7.15; N, 6.65.

3.4.8. 2-[(4*S*,5*S*)-5-Isopropyl-4-methoxy-1-methyl-2-oxopyrrolidin-3-ylidene]-2-phenylacetonitrile (2h). Colorless oil; $[\alpha]_D^{20}$ −0.24 (*c* 0.81, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 Hz) δ 0.85 (d, 3H, J=7.0 Hz), 0.94 (t, 3H, J=7.3 Hz), 1.09 (d, 3H, J=7.3 Hz), 1.38 (m, 2H), 1.63 (m, 2H), 2.12 (m, 1H), 2.49 (m, 2H), 3.02 (s, 3H), 3.46 (s, 2H), 3.65 (dd, 1H, J=7.0, 2.1 Hz), 4.58 (d, 1H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 13.7, 16.7, 20.6, 22.2, 28.7, 29.8, 30.6, 31.2, 58.7, 65.3, 78.8, 116.7, 117.4, 144.0, 163.9; IR ($CHCl_3$) 2360, 1692 cm^{-1}; MS (EI$^+$) m/z (relative intensity) 264 (M$^+$, 7), 98 (100). HRMS (EI$^+$) $C_{15}H_{24}N_2O_2$: (M$^+$) 264.1838. Found: 264.1840.

3.4.9. 2-((1*S*,7a*S*)-Tetrahydro-1-methoxy-3-oxo-1*H*-pyrrolizin-2(5*H*)-ylidene)hexanenitrile (2i). Colorless oil; $[\alpha]_D^{20}$ +37.7 (*c* 1.12, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 Hz) δ 0.94 (m, 3H), 1.37 (m, 3H), 1.65 (m, 2H), 2.13 (m, 3H), 2.45 (m, 2H), 3.24 (m, 1H), 3.41 (m, 3H), 3.71 (m, 2H), 4.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 13.6, 22.1, 25.5, 29.4, 30.4, 31.4, 41.9, 56.3, 64.6, 79.5, 116.0, 120.8, 146.8, 164.0; IR ($CHCl_3$) 1693 cm^{-1}; MS (EI$^+$) m/z (relative intensity) 248 (M$^+$, 12), 109 (100). HRMS (EI$^+$) $C_{14}H_{20}N_2O_2$: (M$^+$) 248.1525. Found: 248.1530.

3.4.10. 2-((1*R*,7a*S*)-Tetrahydro-1-*tert*-butyldimethylsilyloxy-3-oxo-1*H*-pyrrolizin-2(5*H*)-ylidene)hexanenitrile

(2j). White solid; $[\alpha]_D^{20}$ +46.1 (*c* 0.70, $CHCl_3$); mp 113–115 °C; ^1H NMR ($CDCl_3$, 500 Hz) δ −0.01 (s, 3H), 0.00 (s, 3H), 0.75 (s, 9H), 1.12 (m, 1H), 1.21 (m, 2H), 1.46 (m, 2H), 1.86 (m, 1H), 1.93 (m, 1H), 2.03 (m, 1H), 2.28 (t, 2H, *J*=7.8 Hz), 3.06 (m, 1H), 3.41 (m, 1H), 3.56 (m, 1H), 4.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ −5.0, −4.0, 13.7, 17.7, 22.3, 25.2, 25.5, 29.5, 29.8, 31.2, 42.0, 68.0, 72.3, 116.2, 120.0, 149.2, 164.1; IR ($CHCl_3$) 1693 cm^{-1}; MS (EI^+) *m*/*z* (relative intensity) 348 (M^+, 1), 291 (55), 69 (100). Anal. Calcd for $C_{19}H_{32}N_2O_2Si$: C, 65.47; H, 9.25; N, 8.04. Found: C, 65.37; H, 9.35; N, 7.91.

3.4.11. 2-(4-Methoxy-1,5,5-trimethyl-2-oxopyrrolidin-3-ylidene)-2-phenylacetonitrile (2k). Pale yellow solid; mp 172–178 °C; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.24 (s, 3H), 1.30 (s, 3H), 2.92 (s, 3H), 3.12 (s, 3H), 4.21 (s, 1H), 7.47 (m, 3H), 7.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 19.9, 24.6, 25.5, 58.0, 62.1, 82.0, 116.2, 118.9, 128.8, 128.9, 130.1, 133.3, 145.2, 163.0; IR ($CHCl_3$) 1690 cm^{-1}; MS (EI^+) *m*/*z* (relative intensity) 270 (M^+, 100), 199 (55), 143 (54). Anal Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 69.78; H, 6.65; N, 10.02.

3.4.12. (*Z*)-2-(1-Benzyl-2-oxopiperidin-3-ylidene)-2-phenylacetonitrile (4). Yellow oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.79 (dd, 2H, *J*=12.1, 5.7 Hz), 2.63 (m, 2H), 3.33 (m, 2H), 4.74 (s, 2H), 7.26–7.44 (m, 10H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 22.3, 28.2, 46.8, 51.0, 118.5, 118.8, 127.7, 128.5, 128.7, 128.8, 129.0, 129.4, 134.4, 136.5, 144.7, 161.6; IR ($CHCl_3$) 3013, 1645, 1599, 1490, 1450 cm^{-1}; MS (EI^+) *m*/*z* (relative intensity) 302 (M^+, 29), 91 (100). HRMS (EI^+) $C_{20}H_{18}N_2O$: (M^+) 302.1419. Found: 302.1424.

3.4.13. (*Z*)-2-(1-Benzyl-2-oxoazepan-3-ylidene)-2-phenylacetonitrile (6). Colorless crystal; mp 142–143 °C; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.55 (m, 2H), 1.71 (m, 2H), 2.49 (m, 2H), 3.32 (m, 2H), 4.72 (s, 2H), 7.30–7.44 (m, 10H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 26.1, 27.1, 28.5, 47.3, 50.0, 113.8, 117.4, 127.8, 128.4, 128.6, 128.8, 129.0, 129.3, 132.2, 136.7, 156.3, 169.6; IR ($CHCl_3$) 1641 cm^{-1}; MS (EI^+) *m*/*z* (relative intensity) 316 (M^+, 18), 91 (100). HRMS (EI^+) $C_{21}H_{20}N_2O$: (M^+) 316.1576. Found: 316.1582.

3.4.14. (*Z*)-2-(1-Benzyl-2-oxoazetidin-3-ylidene)propanenitrile (8). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.93 (s, 3H), 3.72 (s, 3H), 4.54 (s, 3H), 7.25 (m, 1H), 7.34–7.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 17.1, 46.4, 47.0, 104.0, 115.4, 128.2, 128.4, 129.1, 134.5, 151.8, 159.2; MS (EI^+) *m*/*z* (relative intensity) 212 (M^+, 12), 91 (100). HRMS (M^+) $C_{13}H_{12}N_2O$: (M^+) 212.0950. Found: 212.0946.

3.4.15. 2-(1-Benzyl-3-methyl-2-oxoindolin-3-yl)acetonitrile (10a). Yellow oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.57 (s, 3H), 2.64 (d, 1H, *J*=16.5 Hz), 2.90 (d, 1H, *J*=16.5 Hz), 4.93 (s, 2H), 6.78 (d, 1H, *J*=7.6 Hz), 7.09 (t, 1H, *J*=7.6 Hz), 7.27 (m, 6H), 7.47 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 22.4, 26.2, 43.8, 44.8, 109.7, 116.6, 123.1, 123.2, 127.1, 127.8, 128.9, 129.2, 130.9, 135.3, 141.8, 177.7; IR ($CHCl_3$) 1714 cm^{-1}; MS (EI^+) *m*/*z* (relative intensity) 276 (M^+, 19), 236 (23), 91 (100). HRMS (EI^+) $C_{18}H_{16}N_2O$: (M^+) 276.1263. Found: 276.1261.

3.4.16. 2-(1,3-Dimethyl-2-oxoindolin-3-yl)acetonitrile (10b). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.49 (s, 3H), 2.59 (d, 1H, *J*=16.8 Hz), 2.83 (d, 1H, *J*=16.8 Hz), 3.22 (s, 3H), 6.92 (d, 1H, *J*=7.6 Hz), 7.12 (dd, 1H, *J*=7.6, 7.6 Hz), 7.33 (dd, 1H, *J*=7.6, 7.6 Hz), 7.45 (d, 1H, *J*=7.3 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 21.7, 25.6, 26.0, 44.4, 108.3, 116.3, 122.6, 122.7, 128.8, 130.6, 142.4, 177.1; IR ($CHCl_3$) 1716 cm^{-1}; MS (EI^+) *m*/*z* (relative intensity) 200 (M^+, 44), 160 (100). HRMS (EI^+) $C_{12}H_{12}N_2O$: (M^+) 200.0950. Found: 200.0952.

3.4.17. 2-(3-Methyl-2-oxoindolin-3-yl)acetonitrile (10c). Yellow oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.56 (s, 3H), 2.64 (d, 1H, *J*=16.8 Hz), 2.85 (d, 1H, *J*=16.5 Hz), 7.00 (d, 1H, *J*=7.6 Hz), 7.12 (t, 1H, *J*=7.6 Hz), 7.30 (t, 1H, *J*=7.8 Hz), 7.45 (d, 1H, *J*=7.3 Hz), 9.15 (br, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 22.1, 26.1, 45.3, 110.6, 116.5, 123.2, 123.4, 129.2, 131.4, 139.9, 180.2; IR ($CHCl_3$) 3208, 1719 cm^{-1}; MS (EI^+) *m*/*z* (relative intensity) 186 (M^+, 62), 145 (100), 128 (95). HRMS (EI^+) $C_{11}H_{10}N_2O$: (M^+) 186.0793. Found: 186.0790.

3.4.18. 2-Quinolinol (11). ^1H NMR ($CDCl_3$, 500 Hz) δ 6.73 (d, 1H, *J*=9.5 Hz), 7.22 (dd, 1H, *J*=7.5, 7.5 Hz), 7.50–7.52 (m, 2H), 7.56 (m, 1H), 7.83 (d, 1H, *J*=9.5 Hz), 12.7 (br, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 116.3, 119.9, 121.3, 122.7, 127.7, 130.6, 138.6, 141.1, 164.8.

3.4.19. 1-Benzyl-3-methyl-3-vinylindolin-2-one (12). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.56 (s, 3H), 4.87 (d, 1H, *J*=15.6 Hz), 4.95 (d, 1H, *J*=15.6 Hz), 5.18 (m, 2H), 6.02 (dd, 1H, *J*=17.4, 10.4 Hz), 6.73 (d, 1H, *J*=7.6 Hz), 7.04 (dd, 1H, *J*=7.6, 7.6 Hz), 7.15 (d, 1H, *J*=7.9 Hz), 7.19 (dd, 1H, *J*=6.5, 6.5 Hz), 7.25 (m, 3H), 7.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 22.6, 43.6, 51.2, 109.3, 115.4, 122.6, 123.9, 127.1, 127.6, 128.0, 132.8, 136.0, 138.2, 142.1, 178.9; IR ($CHCl_3$) 1712, 1610, 1489, 1351, 1180 cm^{-1}; MS (EI^+) *m*/*z* (relative intensity) 263 (M^+, 71), 91 (100). HRMS (EI^+) $C_{18}H_{17}NO$: (M^+) 263.1310. Found: 263.1303.

3.4.20. 2-(1-Benzyl-3-isopropyl-2-oxoindolin-3-yl)but-2-enenitrile (10f). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 0.94 (d, 3H, *J*=6.9 Hz), 0.96 (d, 1H, *J*=6.9 Hz), 1.29 (d, 3H, *J*=7.6 Hz), 2.83 (m, 1H), 4.85 (d, 1H, *J*=15.3 Hz), 4.96 (d, 1H, *J*=15.3 Hz), 6.59 (q, 1H, *J*=7.3 Hz), 6.84 (d, 1H, *J*=7.6 Hz), 7.06 (dd, 1H, *J*=7.6, 7.6 Hz), 7.23–7.27 (m, 4H), 7.32 (dd, 1H, *J*=7.5, 7.5 Hz), 7.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 15.4, 16.7, 17.4, 35.9, 44.2, 56.1, 109.2, 116.8, 119.5, 122.9, 124.3, 127.9, 128.7, 128.8, 129.6, 135.6, 142.9, 148.1, 175.8; MS (EI^+) *m*/*z* (relative intensity) 330 (M^+, 9), 91 (100). HRMS (EI^+) $C_{22}H_{22}N_2O$: (M^+) 330.1732. Found: 330.1734.

3.4.21. 1-Benzyl-4-isopropyl-3-vinylquinolin-2(1*H*)-one (13). Colorless oil; ^1H NMR ($CDCl_3$, 500 Hz) δ 1.54 (d, 6H, *J*=7.3 Hz), 3.94 (m, 1H), 5.56 (m, 2H), 5.64 (m, 2H), 6.85 (m, 1H), 7.17 (dd, 1H, *J*=7.8, 7.8 Hz), 7.22–7.30 (m, 5H), 7.36 (dd, 1H, *J*=7.6, 7.6 Hz), 8.07 (d, 1H, *J*=7.9 Hz); MS (EI^+) *m*/*z* (relative intensity) 303 (M^+, 49), 212 (100). HRMS (EI^+) $C_{21}H_{21}NO$: (M^+) 303.1626. Found: 303.1623.

3.5. Mechanistic study

To a solution of diisopropylamine (234 mg, 2.31 mmol) in THF (5.0 mL), *n*-BuLi (1.6 M in hexane, 1.44 mL) was

added at −78 °C. The reaction mixture was allowed to warm up to 0 °C, stirred for additional 15 min, and cooled again to −78 °C. A solution of **10a** (580 mg, 2.10 mmol) in THF (5.0 mL) was added slowly to the mixture. After being stirred for 30 min, the mixture was quenched with MeI (0.39 mL, 6.30 mmol) and warmed up to room temperature (approx. 12 h). After successive addition of Et_2O and a saturated NH_4Cl solution, the organic layer was separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remaining product was purified by chromatography with hexane/EtOAc (3/1) to give **10e** (35.6 mg, 6%) as colorless oil.

3.5.1. 2-(1-Benzyl-3-methyl-2-oxoindolin-3-yl)propanenitrile (10e). Colorless oil; ^{1}H NMR ($CDCl_3$, 500 Hz) δ 0.93 (d, 3H, J=7.0 Hz), 1.63 (m, 3H), 3.24 (q, 1H, J=7.0 Hz), 4.91 (m, 2H), 6.81 (d, 1H, J=7.6 Hz), 7.11 (dd, 1H, J=7.6, 7.3 Hz), 7.23–7.35 (m, 6H), 7.60 (d, 1H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 13.6, 23.1, 33.0, 44.0, 49.0, 109.5, 120.7, 123.4, 123.7, 127.3, 127.9, 128.8, 128.9, 129.0, 129.3, 135.5, 142.5, 177.5; IR ($CHCl_3$) 2244, 1712 cm^{-1}; MS (EI$^+$) m/z (relative intensity) 290 (M$^+$, 25), 236 (53), 91 (100). HRMS (EI$^+$) $C_{19}H_{18}N_2O$: (EI$^+$) 290.1419. Found: 290.1418.

3.6. Synthesis of esermethole (20)

To a solution of nitrile **10b** (100 mg, 0.499 mmol) in MeOH (5.0 mL), a solution of aqueous 30% hydrogen peroxide (2.0 mL) and 1 M NaOH (2.5 mL) was added at 0 °C. The mixture was stirred at room temperature for 5 h. After adding saturated aqueous Na_2SO_3, the mixture was evaporated under reduced pressure. The residue was purified by recrystallization from AcOEt to give amide **17** (84.0 mg, 77%) as white solid.

3.6.1. 2-(1,3-Dimethyl-2-oxoindolin-3-yl)acetamide (17). ^{1}H NMR ($CDCl_3$, 500 Hz) δ 1.46 (s, 3H), 2.69 (d, 1H, J=15.0 Hz), 2.81 (d, 1H, J=15.0 Hz), 3.25 (s, 3H), 5.22 (br, 1H), 6.42 (br, 1H), 6.87 (d, 1H, J=7.6 Hz), 7.09 (dd, 1H, J=7.5, 7.5 Hz), 7.27 (m, 1H), 7.29 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 23.4, 26.4, 43.4, 45.9, 108.4, 122.7, 123.0, 128.3, 133.3, 142.8, 171.3, 180.7; IR ($CHCl_3$) 1693, 1612 cm^{-1}; MS (EI$^+$) m/z (relative intensity) 218 (M$^+$, 54), 160 (100). HRMS (M$^+$) $C_{12}H_{14}N_2O_2$: (M$^+$) 218.1055. Found: 218.1052.

To a solution of amide **17** (80.0 mg, 0.367 mmol) in THF (3.0 mL) was added $LiAlH_4$ (189 mg, 4.99 mmol) at room temperature and the reaction mixture was heated under reflux for 2 h. After cooling to 0 °C, the reaction mixture was treated with a mixture of THF and H_2O (10/1) and diluted with AcOEt. The mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue, which was diluted with AcOEt. The organic solution was washed with saturated aqueous Na_2CO_3 and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel with $CHCl_3$/MeOH (9/1) to give pyrrolo[2,3-*b*]indole **18** (39.3 mg, 57%).

3.6.2. 1,2,3,3a,8,8a-Hexahydro-3a,8-dimethylpyrrolo[2,3-*b*]indole (18). ^{1}H NMR ($CDCl_3$, 500 Hz) δ 1.43 (s, 3H), 1.79 (m, 1H), 2.02 (m, 1H), 2.15 (br, 1H), 2.75 (m, 1H), 2.83 (s, 3H), 3.05 (m, 1H), 4.49 (s, 1H), 6.32 (d, 1H, J=7.6 Hz), 6.63 (dd, 1H, J=7.3, 7.3 Hz), 7.01 (d, 1H, J=7.3 Hz), 7.06 (dd, 1H, J=7.6, 7.6 Hz); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 26.2, 31.7, 42.7, 46.1, 52.1, 92.3, 105.0, 116.8, 122.5, 127.8, 135.7, 151.0; MS (EI$^+$) 188 m/z (relative intensity) (M$^+$, 100). HRMS (EI$^+$) $C_{12}H_{16}N_2$: (M$^+$) 188.1313. Found: 188.1309.

To a solution of **18** (38.0 mg, 0.202 mmol), Et_3N (40.8 mg, 0.404 mmol), and DMAP (1 mol %) in CH_2Cl_2 (2.0 mL) was added $ClCO_2Me$ (23 μL, 0.303 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel with hexane/EtOAc (10/1) to give carbamate[18i] (39.1 mg, 78%).

N-Bromosuccinimide (14.3 mg, 0.080 mmol) was added to a solution of carbamate (18.0 mg, 0.073 mmol) in DMF (0.7 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C. After addition of water, the aqueous solution was extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated. Purification by silica gel column chromatography with hexane/AcOEt (8/1) provided **19** (21.8 mg, 92%) as a colorless oil.

3.6.3. Methyl 5-bromo-3,3a,8,8a-tetrahydro-3a,8-dimethylpyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate (19). ^{1}H NMR ($CDCl_3$, 500 Hz) δ 1.40 (s, 3H), 1.92 (m, 1H), 2.07 (m, 1H), 2.85–2.95 (m, 3H), 3.11 (m, 1H), 3.72–3.86 (m, 4H), 5.09–5.21 (m, 1H), 6.24 (d, 1H, J=8.2 Hz), 7.07 (s, 1H), 7.18 (d, 1H, J=10.0 Hz); MS (EI$^+$) m/z (relative intensity) 326 (83), 324 (84), 222 (100). HRMS (EI$^+$) $C_{14}H_{17}BrN_2O_2$: (M$^+$) 324.0473. Found: 324.0469.

To a suspension of **19** (20.0 mg, 0.062 mmol) and CuI (11.6 mg, 0.062 mmol) in DMF (0.3 mL) was added a sodium methoxide solution (0.3 mL, 0.61 mmol) prepared from a lump of sodium (141 mg, 6.13 mmol) and absolute MeOH (3.0 mL). After the resulting mixture was stirred at 120 °C for 2 h, the reaction mixture was cooled and the insoluble materials were filtered off. The filtrate was concentrated in vacuo and H_2O was added to the residue. The aqueous layer was extracted with ether and the extract was washed with brine and dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel with hexane/AcOEt (5/1) to give methyl 3,3a,8,8a-tetrahydro-5-methoxy-3a,8-dimethylpyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate[18i] (11.9 mg, 70%).

To a solution of methyl 3,3a,8,8a-tetrahydro-5-methoxy-3a,8-dimethylpyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate (11.0 mg, 0.039 mmol) in THF (1.0 mL) was added $LiAlH_4$ (15.0 mg, 0.39 mmol) at room temperature and the reaction mixture was heated under reflux for 2 h. After cooling to 0 °C, the reaction mixture was treated with a mixture of THF and H_2O (10/1) and diluted with AcOEt. The mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to give a residue, which was diluted

with AcOEt. The organic solution was washed with saturated aqueous Na_2CO_3 and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel with $CHCl_3$/MeOH (10/1) to give esermethole (**20**) (8.9 mg, 96%).

3.6.4. Esermethole (20). ^{1}H NMR ($CDCl_3$, 500 Hz) δ 1.43 (s, 3H), 1.95 (dd, 1H, J=7.5, 5.3 Hz), 2.53 (s, 3H), 2.64 (m, 1H), 2.72 (m, 1H), 2.89 (s, 3H), 3.75 (s, 3H), 4.06 (s, 1H), 6.36 (d, 1H, J=8.2 Hz), 6.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 Hz) δ 27.4, 37.9, 38.1, 40.8, 52.8, 53.2, 56.0, 98.3, 107.5, 109.9, 112.3, 138.3, 146.6, 153.1; MS (EI$^+$) m/z (relative intensity) 232 (M^+, 100). HRMS (EI$^+$) $C_{14}H_{20}N_2O$: (M^+) 232.1576. Found: 232.1579.

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