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Palladium-Catalyzed Enantioselective Domino Heck–Cyanation Sequence: Development and Application to the Total Synthesis of Esermethole and Physostigmine

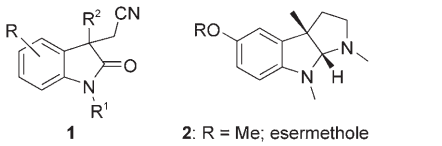
Artur Pinto, Yanxing Jia, Luc Neuville, and Jieping Zhu*[a]

Abstract: An efficient synthesis of functionalized 3-alkyl-3-cyanomethyl-2-oxindole **1** by a palladium-catalyzed domino Heck–cyanation reaction has been developed. Reaction of *ortho*-iodoanilide **5** with potassium ferro(II)cyanide, $K_4[Fe(CN)_6]$, dissolved in DMF in the presence of palladium acetate and sodium carbonate afforded oxindole **1** in good to excellent yields. An enantioselective domino Heck–cyanation process has been developed for the first time using (*S*)-DIFLUORPHOS as a chiral supporting ligand, and an enantioselectivity of up to 79% *ee* in the enantiomerically enriched oxindole was obtained under optimized conditions. A concise total synthesis of esermethole and physostigmine, powerful inhibitors of acetyl- and butyryl-cholinesterase, is documented.

Keywords: alkaloids · asymmetric synthesis · cyanation · domino reactions · oxindoles

Introduction

The development of catalytic processes allowing the formation of multiple chemical bonds in a single synthetic operation represents an attractive and very active research field of synthetic organic chemistry.[1] The high bond-forming efficiency of such domino processes is ideally suited for generating molecular complexity and for reducing waste production.[2] The importance and reliability of transition-metal-catalyzed transformations has made them ideal starting points for the elaboration of such domino processes, and indeed, significant progress has been achieved in this regard.[3] Among them, palladium-catalyzed carbopalladation, especially the Heck reaction,[4] has played a prominent role in developing some of the most powerful domino processes. In particular, the oligocyclization of a halogenated polyene[5] and sequences of intramolecular Heck reaction–anion capture[6] have met with great success in the synthesis of structurally diverse heterocycles and spirocycles. A variety of nucleophiles including organoboronic acids, organotin derivatives, enolates, and π nucleophiles have been utilized to trap the stable σ-alkylpalladium complex; while alkynes, allenes, and carbon monoxide have served as relays to propagate the reaction sequence before the terminating step.[7] On the other hand, cyanide has rarely been used as a terminating agent, aside from two examples reported independently by the groups of Torii and Grigg.[8] We report herein, the development of an efficient synthesis of 3,3-disubstituted 2-oxindole **1** by a domino intramolecular Heck–cyanation sequence using potassium ferro(II)cyanide (**4**)[9] as a cyanide donor. An enantioselective version of this process is also documented for the first time, and its utility is illustrated by the development of an efficient synthesis of esermethole (**2**) and physostigmine (**3**), which is a powerful inhibitor of acetyl- and butyrylcholinesterase, isolated from the seeds of *physostigma venenosum*.[10]



1

2: R = Me; esermethole
3: R = CONHMe; physostigmine

Results and Discussion

Heck–cyanation process: Metal-catalyzed cyanation of aryl halides, including the classic Rosenmund–von Braun reac-

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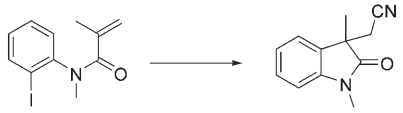
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. It contains copies of ^1H and ^{13}C NMR spectra of compounds **1a**–**1k**, esermethole (**2**) and physostigmine (**3**), and chiral HPLC diagrams of racemic and enantiomerically enriched oxindole **1k**.

tion and its palladium-catalyzed version, is a common and useful transformation as a result of the versatility of the cyano group in synthesis and its prevalence in pharmaceutical agents.[11] It has long been known that the palladium-catalyzed cyanation reaction is very sensitive to the reaction conditions, and in particular, the cyanide source. Indeed, it has been proposed that the presence of two or more equivalents of cyanide relative to palladium, in solution, can interrupt the catalytic cycle by forming a stable palladium cyanate complex.[12] To prevent catalyst deactivation, a variety of cyanide sources, such as alkali cyanide, zinc cyanide, acetone cyanohydrine, and trimethylsilyl cyanide, in combination with different solvents, have been proposed to fine-tune the cyanide concentration.[13] Recently Beller et al.,[14] and subsequently Weissman et al.[15] have demonstrated that potassium ferro(II)cyanide (**4**) is an excellent cyanide source for the palladium-catalyzed cyanation of aryl halides. Following these observations, an intramolecular Heck–cyanation sequence involving a palladium catalyst was investigated by using *o*-iodoanilide **5a** as the test substrate with **4** as the terminating agent. The results are summarized in Table 1.

Table 1. Palladium-catalyzed domino Heck–cyanation sequence: a survey of reaction conditions.[a]

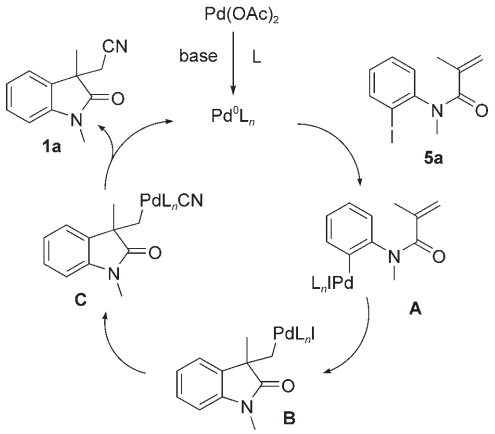


Entry	Catalyst	Solvent	Base	Time [h]	Conv. [%]	Yield [%]
1	$Pd(OAc)_2$	DMF	Na_2CO_3	3	>99	83
2	$Pd(OAc)_2$	DMA	Na_2CO_3	24	59	55
3	$Pd(OAc)_2$	NMP	Na_2CO_3	24	>99	82
4	$[Pd(dba)_2]$	DMF	Na_2CO_3	27	78	68
5	$Pd(OAc)_2$	DMF	K_2CO_3	20	>99	47
6	$Pd(OAc)_2$	DMF	$CaCO_3$	20	34	65
7	$Pd(OAc)_2$	DMF	Ag_3PO_4	–	0	0

[a] All reactions were carried out under an argon atmosphere using 1.0 equiv of **5a**, 0.015 equiv of Pd catalyst, 0.22 equiv of **4**, 1.0 equiv of base, and solvent (0.2 M) at 120 °C.

Under the ligandless conditions employed by Weissman et al., the reaction outcome was both solvent and base dependent. Sodium carbonate (entry 1) was a superior base to potassium carbonate (entry 5), calcium carbonate (entry 6), and silver phosphate (entry 7) when palladium acetate was used as a palladium source. Results also indicate that DMF or *N*-methylpyrrolidinone (NMP) (entries 1 and 3) were better reaction media than *N*,*N*-dimethylacetamide (DMA) (entry 2). Bis(dibenzylideneacetone)palladium, $[Pd(dba)_2]$, can also catalyze the domino sequence, albeit less efficiently (entry 4). Under optimized conditions ($Pd(OAc)_2$ (1.5 mol%), $K_4[Fe(CN)_6]$ (0.22 equiv), Na_2CO_3, (1.0 equiv), DMF, 0.2 M, 120 °C), cyclic cyanation of **5a** afforded the desired 3-methyl-3-cyanomethyl-2-oxindole (**1a**) in an isolated yield of 83%. As in the case of cyanation of aryl halides, all six cyanide anions bound to iron are transferable.

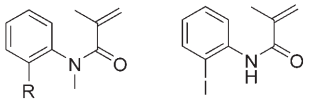
The possible reaction path is depicted in Scheme 1. Oxidative addition of an aryl iodide to a Pd^0 species generated in situ gives intermediate **A**, which undergoes 5-*exo*-trig cyclization to afford the σ-alkylpalladium complex **B**. Displacement of the iodide by cyanide would afford palladium complex **C**, which upon reductive elimination, would produce desired oxindole **1** with the concurrent regeneration of the Pd^0 species.



Scheme 1. Domino Heck–cyanation sequence, a plausible reaction path.

To probe the scope and limitation of this new protocol, cyclic cyanation of a range of substituted *o*-iodoanilides[16] were examined and the results are shown in Table 2. The outcome of this domino process is not sensitive to the electronic properties of the aryl halide, and a variety of oxindoles substituted at C-4, C-5, C-6, and C-7 by an electron-donating or an electron-withdrawing group can be prepared in good to excellent yields. Even the electron-rich and sterically encumbered 2,6-disubstituted aryl iodide **5b** participated in the reaction to provide the desired oxindole **1b** in 78% yield (entry 1). A chlorine atom was also tolerated (entry 4), which provides the potential for further functionalization. *N*-Benzyl anilide **5i** underwent cyclic cyanation, albeit with a slightly decreased yield (entry 8). As an *N*-benzyl group is readily removed, it constituted a route to N-unsubstituted oxindole. Lastly, *tert*-butyldimethylsilyl (TBDMS)-functionalized 3-hydroxymethyl-3-cyanomethyl oxindole **1j** was synthesized from **5j** without any problems. Partial cleavage of the TBDMS ether under the basic reaction conditions may account for the reduced yield of **1j** (entry 9).

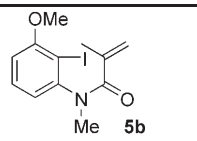
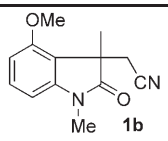
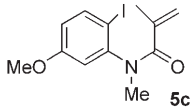
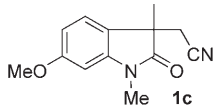
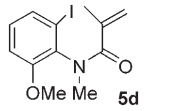
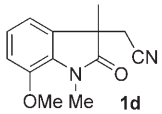
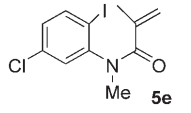
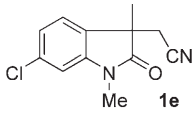
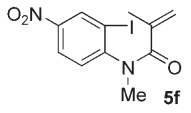
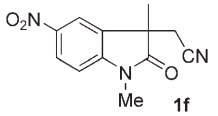
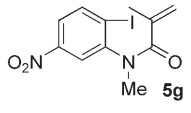
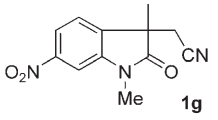
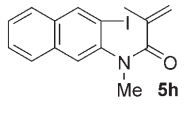
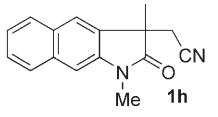
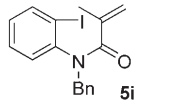
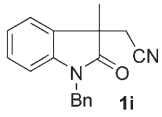
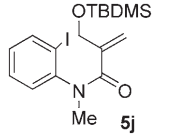
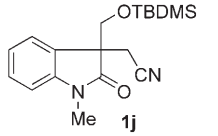
o-Bromoanilide **5l** participated in the domino process leading to the formation of **1a** in 63% yield at a higher cata-



5l: R = Br
5m: R = OTf

5n

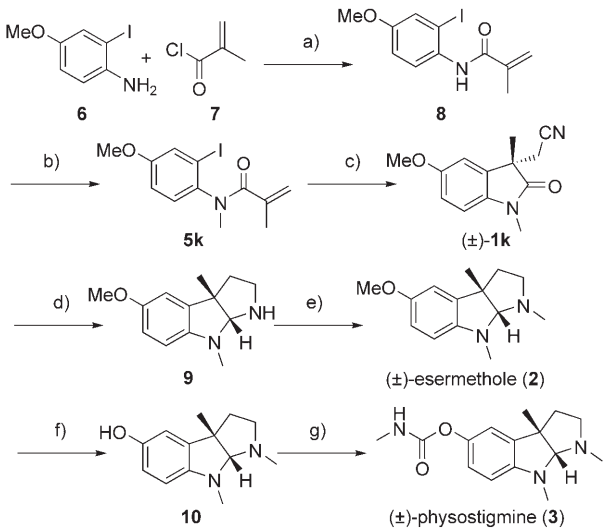
Table 2. Scope of the palladium-catalyzed Heck–cyanation reaction of *o*-iodoanilides **5b–5j**.[a]

Entry	Substrate	Product	Yield [%][b]
1	 **5b**	 **1b**	78
2	 **5c**	 **1c**	78
3	 **5d**	 **1d**	70
4	 **5e**	 **1e**	72
5	 **5f**	 **1f**	90
6	 **5g**	 **1g**	71
7	 **5h**	 **1h**	80
8	 **5i**	 **1i**	61
9	 **5j**	 **1j**	51

[a] All reactions were carried out under an argon atmosphere using 0.015 equiv of Pd catalyst, 0.22 equiv of **4**, 1.0 equiv of Na_2CO_3 dissolved in DMF (0.2 M) at 120 °C. [b] Isolated yield after flash column chromatography.

lyst loading ($Pd(OAc)_2$ 0.1 equiv). Cyclic cyanation of *o*-trifluorosulfonyl anilide **5m** under standard conditions afforded **1a** in a low yield (22%) owing to competitive hydrolysis of the triflate (OTf) function. On the other hand, the secondary amide **5n** failed to produce the desired compound probably as a result of an unfavorable conformational preference.

Total synthesis of physostigmine: The utility of this domino process is illustrated by the total synthesis of physostigmine (**3**) (Scheme 2).[17] Acylation of 2-iodo-4-methoxyaniline (**6**) with methacryloyl chloride (**7**) afforded anilide **8**, which was *N*-methylated to give **5k** in 93% yield. Treatment of **5k** under established palladium-catalysis conditions provided



Scheme 2. Total synthesis of physostigmine. Reagents and conditions: a) Et_3N, CH_2Cl_2, 76%; b) NaH, MeI, THF, 93%; c) $Pd(OAc)_2$ (1.5 mol%), $K_4[Fe(CN)_6]$ (0.22 eqiv), Na_2CO_3 (1.0 eqiv), DMF, 80%; d) LAH, THF, 85%; e) HCHO, $NaBH_4$, Et_3N, MeOH, 70%; f) HBr (48% aqueous solution), reflux; g) NaH, THF, **11**, 44% for two steps.

oxindole **1k** in 80% yield. Reductive cyclization of oxindole **1k** using conditions optimized by Brossi and Yu provided hexahydropyrroloindole **9** in 85% yield.[18] N-Methylation under reductive amination conditions afforded esermethole **2** in 70% yield. Cleavage of the methyl ether group under acidic conditions (aqueous HBr) afforded the corresponding phenol **10**. Previously, methyl isocyanate has been used to provide the urea functionality. However, we found that reaction of sodium phenoxide with *N*-succinimidyl-*N*-methylcarbamate (**11**) provided the desired (±)-physostigmine in comparable yield (44% yield over two steps compared with 31% reported by Overman et al.[17a]). Potentially, this modification could be useful for large-scale synthesis because **11** is much cheaper and easier to handle than methyl isocyanate.[19]

Enantioselective Heck–cyanation process: A number of palladium-catalyzed enantioselective Heck cyclizations and oligocyclizations have been developed since the seminal contributions of the groups of Shibasaki[20] and Overman, respectively.[21] Whereas examples of enantioselective Heck cyclization–anion capture of resulting π-allyl–Pd^{II} complexes are known,[22] to the best of our knowledge, the corresponding enantioselective Heck cyclization–anion capture of the resulting σ-alkyl–Pd^{II} complex is unknown. Initial investigations into reaction conditions using (*R*)-BINAP (see Figure 1, below), a highly efficient ligand in oxindole synthesis,[23] are summarized in Table 3. The domino sequence of **5k** proceeded efficiently in the presence of (*R*)-BINAP to provide **1k** in 90% yield although the enantioselectivities achieved remained low (entry 1). Addition of silver phosphate (Ag_3PO_4) (entry 2) did not disrupt the reaction (cf. Table 1, entry 7); however, no enantioselectivity was ob-

Table 3. Palladium-catalyzed enantioselective Heck–cyanation reaction of **5k** using (*R*)-BINAP as ligand.[a]

Entry	Catalyst	Additive	Solvent	Time [h]	Yield [%]	*ee* [%][b]
1	$Pd(OAc)_2$	–	DMF	3	90	7
2	$Pd(OAc)_2$	Ag_3PO_4	DMF	3	65	0
3	$[Pd(dba)_2]$	Ag_3PO_4	DMF	5	89	13
4	$[Pd(dba)_2]$	Ag_3PO_4	DMA	5	76	24
5	$[Pd(dba)_2]$	Ag_3PO_4	NMP	3	56	22
6	$[Pd(dba)_2]$	PMP[c]	DMA	3	54	0

[a] Pd catalyst (5 mol%) was treated with (*R*)-BINAP (12 mol%) and Ag_3PO_4 (2.0 equiv) at RT for 40 min before the addition of Na_2CO_3 (1.0 equiv), **4** (0.22 equiv), and **7c**. The reaction was then maintained at 120°C. [b] Determined by chiral HPLC. [c] PMP = 1,2,2,6,6-pentamethylpiperidine (5 equiv).

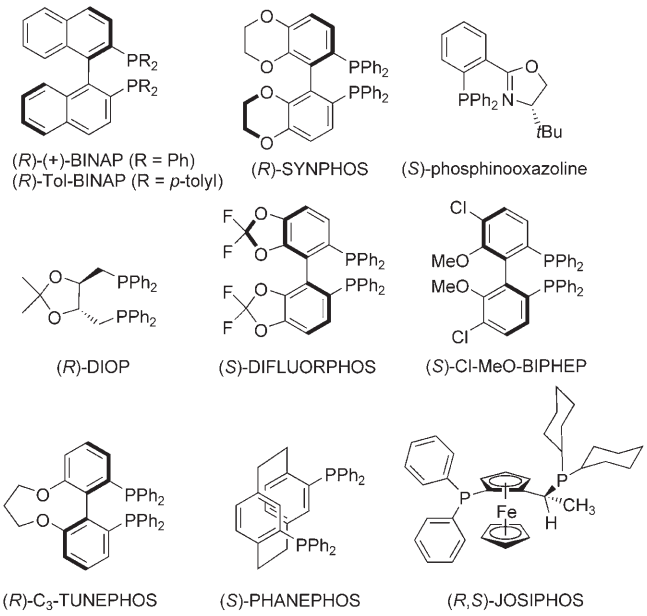
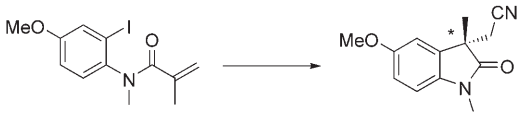


Figure 1. Structure of chiral bidentate ligands screened for the enantioselective palladium-catalyzed Heck–cyanation sequence.

served under these conditions. The palladium source can also influence the reaction outcome, and in general, better enantioselectivities were obtained when using $[Pd(dba)_2]$ relative to $Pd(OAc)_2$ (entry 2 vs. entries 3–5). Using 1,2,2,6,6-pentamethylpiperidine (PMP) as an additive led to a racemic compound (entry 6), which indicates that the cation mechanism might be essential for enantioselectivity.

The low enantioselectivity observed (24%, entry 4) is in sharp contrast to the high *ee* value obtained by Overman in his synthesis of oxindole by means of an intramolecular Heck reaction.[24] It is reasonable to assume that the presence of cyanide may modify the coordination sphere of palladium prior to the key C–C bond-forming step. To raise the *ee* to a synthetically useful level, a screening of bidentate ligands (Figure 1) was performed and the results are summarized in Table 4. The enantioselectivity of the present domino process is very sensitive to the ligand structure. Thus, a simple switch from BINAP to Tol-BINAP (entry 1) decreased the enantioselectivity and the yield of **1k** significantly. Similarly, (*S*)-phosphinooxazoline (entry 3), (*R*)-DIOP (entry 4), (*S*)-PHANEPHOS (entry 12), and (*R*,*S*)-JOSIPHOS (entry 13) were found to be less efficient as ligands than BINAP for this transformation. Alternatively, chiral biaryl-based ligands such as (*R*)-SYNPHOS, (*S*)-Cl-MeO-BIPHEP, (*R*)-TUNEPHOS, and (*S*)-DIFLUORPHOS gave superior results to BINAP in terms of enantioselectivity. Among them, (*S*)-DIFLUORPHOS[25] proved to be the most effective ligand. Under optimized conditions, cyclic cyanation of **5k** in the presence of (*S*)-DIFLUORPHOS afforded (*S*)-**1k** in 78% yield and with 72% *ee* (entry 10).

Table 4. Enantioselective Heck–cyanation reaction of **5k**: effect of ligand structure.[a]



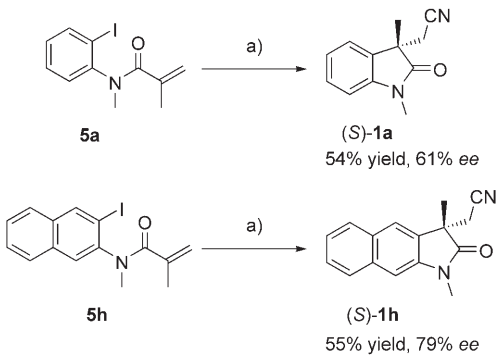
5k **1k**

Entry	Ligand	Base	Time [h]	Yield [%]	Config.[b]	*ee* [%]
1	(*R*)-Tol-BINAP	Na_2CO_3	3	20	*R*	6
2	(*R*)-SYNPHOS	Na_2CO_3	3	84	*R*	33
3	(*S*)-phosphino oxazoline	Na_2CO_3	24	12[c]	*R*	26
4	(*R*)-DIOP	Na_2CO_3	24	20	–	*rac*
5	(*R*)-SYNPHOS	K_2CO_3	3	69	*R*	46
6	(*S*)-DIFLUORPHOS	K_2CO_3	3	57	*S*	66
7	(*S*)-Cl-MeO-BIPHEP	K_2CO_3	3	46	*S*	52
8	(*R*)-C_{13}-TUNEPHOS	K_2CO_3	6	63	*R*	48
9	(*S*)-DIFLUORPHOS[d]	K_2CO_3	24	25[c]	*S*	53
10	(*S*)-DIFLUORPHOS[e]	K_2CO_3	3	35	*S*	37
10	(*S*)-DIFLUORPHOS[f]	K_2CO_3	3	78	*S*	72
11	(*S*)-DIFLUORPHOS[g]	K_2CO_3	3	44	*S*	72
12	(*S*)-PHANEPHOS[f]	K_2CO_3	6	41	*R*	16
13	(*R*)-(*S*)-JOSIPHOS[f]	K_2CO_3	22	28	*R*	3

[a] $[Pd(dba)_2]$ (5 mol%) was treated with a ligand (12 mol%) and Ag_3PO_4 (2.0 equiv) at RT for 40 min before the addition of a base (1 equiv), **4** (0.22 equiv), and **5k**. The reaction was then maintained at 120°C. [b] Absolute configuration. [c] Anilide **5k** was not fully consumed. [d] The reaction was maintained at 90°C. [e] Same as conditions [a] with 5 mol% $Pd_2(dba)_3$. [f] Same as conditions [a] with no pre-treatment. [g] Same as conditions [a] with 10 mol% of $[Pd(dba)_2]$.

Applying these enantioselective domino Heck–cyanation conditions to anilides **5a** and **5h** led to the formation of the corresponding oxindoles **1a** and **1h** with 61 and 79% *ee*, respectively (Scheme 3).

The absolute configuration of **1k** was determined by comparison of the optical rotation value with that reported in the literature.[26] As a result of converting (*S*)-**1k** into



Scheme 3. Palladium-catalyzed enantioselective Heck–cyanation reaction. Reagents and conditions: a) $[Pd(dba)_2]$ (5 mol%), (*S*)-DIFLUORPHOS (12 mol%), Ag_3PO_4 (2 equiv), K_2CO_3 (1 equiv), $K_4[Fe(CN)_6]$ (0.22 equiv), 120°C.

(−)-physostigmine, the present work represents a formal synthesis of this natural product.

Conclusion

We have developed an efficient synthesis of 3-substituted-3-cyanomethyl-2-oxindoles by using a palladium-catalyzed domino intramolecular Heck–cyanation sequence employing potassium ferro(II)cyanide, $K_4[Fe(CN)_6]$, as a trapping agent for the σ-alkylpalladium intermediate.[27] The reaction is applicable to a wide range of substrates with different electronic properties. In addition, a concise synthesis of physostigmine utilizing this key domino process for the construction of the core framework has been accomplished. An enantioselective version of this domino process has also been developed by using (*S*)-DIFLUORPHOS as a chiral ligand and represents, to the best of our knowledge, the first such example of this type of domino process.

Experimental Section

Typical procedure for palladium-catalyzed domino Heck–cyanation sequence: Potassium ferrocyanide (0.22 equiv), Na_2CO_3 (1.0 equiv), and $Pd(OAc)_2$ (1.5 mol%) were added to a degassed 0.2 M solution of iodoanilide **5** dissolved in DMF. After being stirred at 120°C under an argon atmosphere for 3 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by using flash chromatography to give the corresponding oxindole **1**.

(1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (1a): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.53$ (dd, $J=7.5$, 1.5 Hz, 1H), 7.42 (dt , $J=7.5$, 1.5 Hz, 1H), 7.19 (dt, $J=7.5$, 1.1 Hz, 1H), 6.93 (dd, $J=7.5$, 1.1 Hz, 1H), 3.25 (s, 3H), 2.98 (AB, $J=16.6$ Hz, $\Delta\nu_{AB}=87.3$ Hz, 2H), 1.55 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=177.5$, 142.7, 131.0, 129.2, 123.3, 123.1, 116.6, 108.7, 44.8, 26.5, 26.3, 22.2 ppm; IR ($CHCl_3$): $\tilde{\nu}=2255$, 1715 cm^{-1}.

(4-Methoxy-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (1b): Colorless oil; yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.30$ (dd, $J=8.4$, 7.9 Hz, 1H), 6.65 (dd, $J=8.4$, 0.4 Hz, 1H), 6.56 (dd, $J=7.9$, 0.4 Hz, 1H), 3.90 (s, 3H), 3.20 (s, 3H), 2.98 (AB, $J=16.3$ Hz, $\Delta\nu_{AB}=53.2$ Hz, 2H), 1.50 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=177.8$, 156.1, 144.3, 130.4, 116.2, 106.1, 102.0, 55.4, 46.0, 26.7, 24.0, 21.0 ppm; IR ($CHCl_3$): $\tilde{\nu}=1708$, 1606, 1474, 1260, 1067 cm^{-1}; HRMS: *m/z* calcd for $C_{13}H_{14}N_2NaO_2$ [M^++Na]: 253.0953; found: 253.0944.

(6-Methoxy-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (1c): Colorless oil; yield 78%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.36$ (d, $J=8.2$ Hz, 1H), 6.62 (dd, $J=8.2$, 2.3 Hz, 1H), 6.47 (d, $J=2.3$ Hz, 1H), 3.84 (s, 3H), 3.21 (s, 3H), 2.65 (AB, $J=16.6$ Hz, $\Delta\nu_{AB}=86.3$ Hz, 2H), 1.50 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=178.1$, 161.0, 155.6, 144.0, 123.8, 122.9, 116.7, 106.8, 96.8, 55.6, 44.5, 26.6, 26.5, 22.4 ppm; IR ($CHCl_3$): $\tilde{\nu}=1713$, 1625, 1380, 1096, 729, 702 cm^{-1}; HRMS: *m/z* calcd for $C_{13}H_{14}N_2NaO_2$ [M^++Na]: 253.0953; found: 253.0962.

(7-Methoxy-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (1d): Colorless oil; yield 70%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.05$ (m, 2H), 6.90 (dd, $J=8.1$, 2.2 Hz, 1H), 3.87 (s, 3H), 3.21 (s, 3H), 2.70 (AB, $J=16.4$ Hz, $\Delta\nu_{AB}=78.2$ Hz, 2H), 1.42 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=177.7$, 153.2, 145.7, 132.6, 123.9, 116.6, 115.6, 112.9, 56.0, 44.9, 29.8, 26.5, 22.4 ppm; IR ($CHCl_3$): $\tilde{\nu}=2251$, 1702, 1252, 734 cm^{-1}; HRMS: *m/z* calcd for $C_{13}H_{14}N_2NaO_2$ [M^++Na]: 253.0953; found: 253.0928.

(6-Chloro-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (1e): Colorless oil; yield 72%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.33$ (d, $J=8.0$ Hz, 1H), 7.04 (dd, $J=8.0$, 1.8 Hz, 1H), 6.84 (d, $J=1.8$ Hz, 1H), 3.16 (s, 3H), 2.64 (AB, $J=16.6$ Hz, $\Delta\nu_{AB}=85.0$ Hz, 2H), 1.45 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=177.4$, 143.9, 135.2, 129.2, 124.1, 123.1, 116.4, 109.5, 44.6, 26.6, 26.2, 22.1 ppm; IR ($CHCl_3$): $\tilde{\nu}=1718$, 1610, 1495, 1370 cm^{-1}; HRMS: *m/z* calcd for $C_{12}H_{11}ClN_2NaO$ [M^++Na]: 257.0458; found: 257.0453.

(1,3-Dimethyl-5-nitro-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (1f): Yellow solid; yield 90%; m.p. 94–96°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.28$ (dd, $J=8.6$, 2.2 Hz, 1H), 8.24 (d, $J=2.2$ Hz, 1H), 6.94 (d, $J=8.6$ Hz, 1H), 3.26 (s, 3H), 2.76 (AB, $J=16.7$ Hz, $\Delta\nu_{AB}=46.2$ Hz), 1.51 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=177.5$, 148.5, 143.9, 131.6, 126.5, 119.1, 115.6, 108.5, 45.2, 27.0, 26.1, 22.3 ppm; IR ($CHCl_3$): $\tilde{\nu}=1656$, 1521, 1343 cm^{-1}; HRMS: *m/z* calcd for $C_{12}H_{11}N_3NaO_3$ [M^++Na]: 268.0698; found: 268.0673.

(1,3-Dimethyl-6-nitro-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (1g): Yellow oil; yield 71%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.06$ (dd, $J=8.2$, 2.1 Hz, 1H), 7.74 (d, $J=2.1$ Hz, 1H), 7.64 (d, $J=8.2$ Hz, 1H), 3.33 (s, 3H), 2.79 (AB, $J=16.7$ Hz, $\Delta\nu_{AB}=84.1$ Hz, 2H), 1.57 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=176.8$, 149.1, 144.1, 137.6, 123.7, 118.8, 115.9, 103.8, 45.1, 26.9, 25.9, 22.0 ppm; IR ($CHCl_3$): $\tilde{\nu}=1722$, 1528, 1348 cm^{-1}; HRMS: *m/z* calcd for $C_{12}H_{11}N_3NaO_3$ [M^++Na]: 268.0698; found: 268.0689.

(1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-benzo[*f*]indol-3-yl)acetonitrile (1h): Colorless oil; yield 80%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.92$ (s, 1H), 7.85 (d, $J=8.1$ Hz, 1H), 7.80 (d, $J=8.1$ Hz, 1H), 7.51 (ddd, $J=8.2$, 6.9, 1.4 Hz, 1H), 7.42 (ddd, $J=8.2$, 7.0, 1.4 Hz, 1H), 7.18 (s, 1H), 3.35 (s, 3H), 2.80 (AB, $J=16.6$ Hz, $\Delta\nu_{AB}=89.2$ Hz, 2H), 1.62 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=177.0$, 140.7, 134.0, 131.6, 130.4, 128.4, 127.14, 127.12, 124.8, 122.9, 116.6, 104.5, 44.4, 26.8, 26.7, 22.7 ppm; IR ($CHCl_3$): $\tilde{\nu}=1715$, 1645, 1470, 1381, 1050, 750 cm^{-1}; HRMS: *m/z* calcd for $C_{16}H_{14}N_2NaO$ [M^++Na]: 273.1004; found: 273.0985.

(1-Benzyl-3-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (1i): Colorless oil; yield 61%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.41$ (d, $J=7.4$ Hz, 1H), 7.25–7.13 (m, 6H), 7.02 (dt, $J=7.6$, 0.8 Hz, 1H), 6.71 (d, $J=7.8$ Hz, 1H), 4.86 (s, 2H), 2.72 (AB, $J=16.6$ Hz, $\Delta\nu_{AB}=80.5$ Hz, 2H), 1.51 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=177.7$, 141.8, 135.3, 131.0, 129.1, 128.9, 127.8, 127.2, 123.3, 123.2, 109.8, 44.9, 44.0, 26.4, 22.5 ppm; IR ($CHCl_3$): $\tilde{\nu}=2248$, 1712, 1612, 1488, 1380, 1362, 1178, 753 cm^{-1}; HRMS: *m/z* calcd for $C_{18}H_{16}N_2NaO$ [M^++Na]: 299.1160; found: 299.1125.

{3-[(*tert*-Butyldimethylsilyloxy)methyl]-1-methyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl}acetonitrile (1j): Colorless oil; yield 51%; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.52$ (dd, $J=7.4$, 0.7 Hz, 1H), 7.41 (dt, $J=7.8$, 1.2 Hz, 1H), 7.17 (dt, $J=7.6$, 0.9 Hz, 1H), 6.94 (d, $J=7.8$ Hz, 1H), 3.91 (AB, $J=9.5$ Hz, $\Delta\nu_{AB}=54.1$ Hz, 2H), 3.29 (s, 3H), 2.93 (AB, $J=16.7$ Hz, $\Delta\nu_{AB}=77.3$ Hz, 2H), 0.79 (s, 9H), −0.02 (s, 3H), −0.06 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=175.3$, 143.7, 129.3, 128.5, 124.1, 122.9, 116.4, 108.4,

66.5, 51.0, 29.7, 26.4, 25.6, 21.5, 18.0, −5.7, −5.8 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1718, 1614, 1471, 1121, 839 cm^{-1}; HRMS: *m/z* calcd for $C_{18}H_{26}N_2NaO_2Si$ [M^++Na]: 353.1661; found: 353.1635.

***N*-(2-Iodo-4-methoxyphenyl)-2-methylacrylamide (8)**: Triethylamine (3.16 mL, 22.3 mmol) was added to a stirred solution of 2-iodo-4-methoxyaniline (**6**) (4.28 g, 17.2 mmol) dissolved in CH_2Cl_2 (15 mL) at RT, and 2-methylacryloyl chloride (**7**) (2.16 mL, 22.3 mmol) was added dropwise at 0 °C. The resulting solution was stirred at RT for 2 h. After addition of water, the mixture was extracted with CH_2Cl_2. The organic layers were then combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by using flash column chromatography (heptanes/EtOAc 9:1) to give **8** as a colorless solid (4.12 g, 76%). M.p. 74–75 °C ; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, J = 9.0 Hz, 1H), 7.66 (br s, 1H), 7.26 (d, J = 2.8 Hz, 1H), 6.85 (dd, J = 9.0, 2.8 Hz), 5.87 (s, 1H), 5.43 (s, 1H), 3.71 (s, 3H), 2.04 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 156.7, 140.3, 131.7, 123.8, 122.8, 120.7, 114.7, 90.9, 55.7, 18.7 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 3279, 2922, 2851, 1655, 1620, 1531 cm^{-1}; HRMS: *m/z* calcd for $C_{11}H_{12}INNaO_2$ [M^++Na]: 339.9811; found: 339.9796.

***N*-(2-Iodo-4-methoxyphenyl)-*N*,2-dimethylacrylamide (5k)**: A solution of **8** (4.09 g, 12.9 mmol) in THF (20 mL) was added dropwise at 0 °C to a stirring suspension of NaH (60%, 774 mg, 19.3 mmol) and THF (14 mL). The resulting mixture was stirred at 0 °C for 40 min, and then MeI (2 mL, 32.25 mmol) was added. The resulting mixture was maintained at RT for 3 h, quenched with water, and extracted with EtOAc. The organic layers were then combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by using flash column chromatography (heptanes/EtOAc 4:1) to give **5k** as a colorless solid (3.97 g, 93%). M.p. 82–84 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (d, J = 2.8 Hz, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.88 (dd, J = 8.7, 2.7 Hz, 1H), 5.08 (s, 1H), 5.00 (s, 1H), 3.81 (s, 3H), 3.22 (s, 3H), 1.83 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 158.9, 140.4, 139.8, 129.4, 124.7, 115.1, 99.4, 55.7, 37.0, 20.6 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1652, 1625, 1491, 1285, 1224, 1030 cm^{-1}; HRMS: *m/z* calcd for $C_{12}H_{14}INNaO_2$ [M^++Na]: 353.9967; found: 330.9941.

(5-Methoxy-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (1k): By following the general procedure, **5k** was converted to **1k** in 80% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 8.6, 2.0 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 3.82 (s, 3H), 3.22 (s, 3H), 2.84 (AB, J = 16.5 Hz, $\Delta\nu_{AB}$ = 85.6 Hz, 2H), 2.55 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.2, 157.6, 136.9, 133.0, 116.1, 113.9, 111.0, 109.4, 57.6, 45.2, 26.9, 26.4, 22.5 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1710, 1655, 1504, 1363, 1292, 668 cm^{-1}; HRMS: *m/z* for $C_{13}H_{14}N_2NaO_2$ [M^++Na]: calcd 253.0953; found: 253.0937.

5-Methoxy-8-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (9): Oxindole **1k** (187 mg, 0.81 mmol) was dissolved in THF (16 mL), and $LiAlH_4$ (142 mg, 3.74 mmol) was added. The reaction mixture was stirred under an Ar atmosphere for 1 h and then heated to reflux. After heating at reflux for 10 min, the mixture was quenched at 0 °C with water and extracted with EtOAc. The organic layers were then combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by using flash column chromatography (CH_2Cl_2/MeOH 9:1) to give **9** as a yellow oil (150 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.67 (d, J = 2.5 Hz, 1H), 6.35 (dd, J = 8.3, 2.5 Hz, 1H), 6.27 (d, J = 8.3 Hz, 1H), 5.0 (br s, 1H), 4.44 (s, 1H), 3.75 (s, 3H), 3.06 (ddd, J = 10.4, 7.2, 3.0 Hz, 1H), 2.84–2.78 (m, 4H), 2.01 (ddd, J = 9.3, 6.3, 3.0 Hz, 1H), 1.79 (ddd, J = 12.2, 9.7, 7.1 Hz, 1H), 1.42 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.5, 145.5, 137.3, 111.9, 110.4, 105.6, 93.2, 56.0, 52.2, 46.1, 42.2, 33.1, 26.1 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1496, 1278, 1219 cm^{-1}.

(±)-Esermethole (2): Hexahydropyrroloindole (**9**) was dissolved in MeOH (2 mL), and Et_3N (0.14 mL, 0.95 mmol) and an aqueous solution of CH_2O (37%, 0.37 mL, 13.3 mmol) were added. The reaction mixture was stirred for 1 h at RT, then cooled to 0 °C before $NaBH_4$ (56 mg, 1.48 mmol) was added slowly, and the mixture stirred for 3 h at RT. The mixture was quenched at 0 °C with water and extracted with EtOAc. The organic layers were then combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by using flash column chromatography (CH_2Cl_2:MeOH 9:1) to give **2** as a yellow oil (60 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.58 (m, 2H), 6.31 (d, J = 8.2 Hz, 1H), 4.08 (s, 1H), 3.68 (s, 3H), 2.84 (s, 3H), 2.74 (ddd, J = 9.8, 6.1, 4.4 Hz, 1H), 2.55 (m, 1H), 2.48 (s, 3H), 1.92 (m, 2H), 1.38 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.2, 146.3, 138.0, 112.4, 109.8, 107.7, 98.0, 56.0, 53.1, 52.9, 40.5, 38.1, 37.6, 27.3 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1496, 1279, 1220, 1032 cm^{-1}.

Physostigmine (3): Esermethole (**2**) (92 mg, 0.40 mmol) was dissolved in an aqueous solution of HBr (48%, 1 mL) and stirred at reflux for 19 h. The mixture was then cooled and poured into cold water. The acidic solution was basified by using a solution of NaOH (10%), then extracted with EtOAc, dried (Na_2SO_4), and evaporated to dryness. The crude product was used directly in the next step of the reaction without purification. A mixture of the resulting phenol **10** (53.0 mg, 0.24 mmol), NaH (60%, 22 mg, 0.54 mmol), and THF (2 mL) was stirred at 0 °C for 5 min before *N*-succinimidyl-*N*-methylcarbamate (**11**) was added at this temperature. The resulting mixture was stirred at RT for 1 h, quenched with water, and extracted with EtOAc. The organic layers were then combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by using flash column chromatography (heptanes/EtOAc 9:1) to give **3** as a colorless oil (48 mg, 44%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.86 (dd, J = 8.5, 2.3 Hz, 1H), 6.79 (d, J = 2.3 Hz, 1H), 6.40 (d, J = 8.5 Hz, 1H), 4.92 (br s, 1H), 4.37 (s, 1H), 2.98 (s, 3H), 2.89 (d, J = 4.8 Hz, 3H), 2.65 (m, 2H), 2.60 (s, 3H), 2.07 (m, 2H), 1.47 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 149.5, 143.2, 137.4, 120.5, 116.2, 106.6, 97.9, 53.1, 52.6, 40.7, 38.2, 37.1, 27.7, 27.2 ppm; IR ($CHCl_3$): $\tilde{\nu}$ = 1730, 1496, 1256, 1202 cm^{-1}.

Typical procedure for enantioselective palladium-catalyzed domino Heck–cyanation sequence—Synthesis of (5-methoxy-1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetonitrile (1k): Potassium ferrocyanide (14 mg, 0.03 mmol), K_2CO_3 (16 mg, 0.15 mmol), silver phosphate (126 mg, 0.3 mmol), [Pd(dba)$_2$] (4.34 mg, 0.008 mmol), and (*S*)-DIFLUORPHOS (12.3 mg, 0.033 mmol) were added to a degassed solution of **5k** (50 mg, 0.15 mmol) in DMA (1 mL). After being stirred at 120 °C under an argon atmosphere for 3 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by using flash chromatography (silica gel, heptanes/EtOAc 3:1) to give **1k** as a colorless oil (26.8 mg, 78%). The *ee* of **1k** was determined to be 72% by chiral column HPLC analysis (AD column; flow rate: 1 mL min^{-1}; eluent: hexane/EtOH 4:1; $t_{R(minor)}$ = 8.21 min, $t_{R(major)}$ = 18.82 min; cf. the Supporting Information).

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