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A base-modulated chemoselective synthesis of 3-cyanoindoles or 4-cyanoquinolines using a palladium-catalyzed N-heterocyclization

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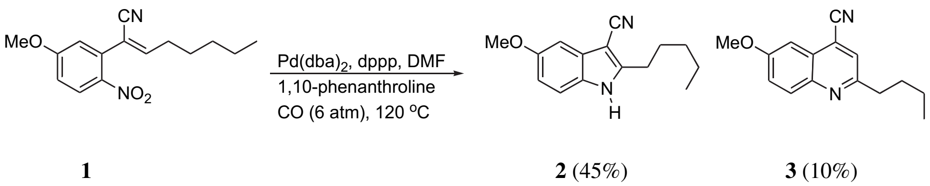
ABSTRACT

A selective methodology for the synthesis of either 3-cyanoindoles or 4-cyanoquinolines via a base-modulated palladium-catalyzed reductive N-heterocyclization from a common 1-cyano-1-(2-nitrophenyl)-1-alkene precursor is described. The required starting materials were prepared either by a Kosugi–Migita–Stille coupling of 2-halo-1-nitrobenzenes with a tributyl(1-alkenyl)stannane or by a vicarious nucleophilic substitution (VNS) of nitrobenzenes followed by a Knoevenagel condensation with an aldehyde.

1. Introduction

A variety of functionalized indoles can be synthesized via palladium-catalyzed reductive N-heterocyclization of 1-alkenyl-2-nitrobenzenes, using carbon monoxide as the ultimate reducing agent.[1–3] 3-Aryl indoles are formed in a related reaction starting from 2,2-diaryl-1-nitroethenes.[4] The reductive heterocyclization to form indoles and other nitrogen heterocycles is related to the Cadogan–Sundberg type cyclization using, for example, triethylphosphite as the reducing agent.[5]

In a palladium-catalyzed synthesis of 3-cyano-substituted indoles, compound **1** was reacted with carbon monoxide and the expected indole **2** was isolated in moderate yield (Scheme 1). The yield of indole was lower compared to related examples and, surprisingly, a small amount of quinoline **3** was also obtained.[6] Considering the presence of a base (1,10-phenanthroline) in the above reaction, we postulated that the presence or absence of a base may modulate the selectivity of the cyclization reaction. Herein is reported a selective route to either 3-cyanoindoles or 4-cyanoquinolines from a common precursor, 1-cyano-1-(2-nitrophenyl)-1-alkenes. In addition, reactions of the corresponding alkyl 2-(2-nitrophenyl)-2-alkenoates affording only or predominantly indoles will be discussed.



Scheme 1.

2. Results and discussions

The question whether an indole or a quinoline could be obtained selectively from a common precursor was first examined. Compound **4** was selected as the substrate for the initial study since gram amounts of this compound were already available from a previous project. Results of this small study are summarized in Scheme 2. Reaction of **4** using bis(dibenzylideneacetone)palladium-1,3-bis(diphenylphosphino)propane (Pd(dba)$_2$-dppp) in the absence of 1,10-phenanthroline gave indole **5**, quinoline **6**, and quinoline-*N*-oxide **7**,[7] all in low isolated yields (entry 1). Addition of triethylamine to the reaction mixture eliminated the *N*-oxide **7** but the reaction was still nonselective and low yielding (entry 2). Next, 1.05 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added

Based on this result, we decided to investigate the feasibility of preparing either an indole or a quinoline from a common precursor simply by varying additives in the reaction.

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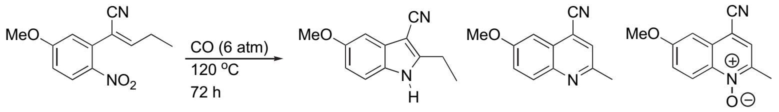


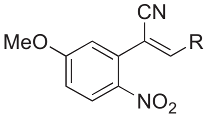
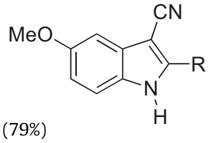
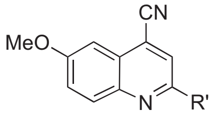
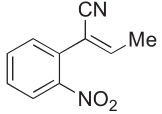
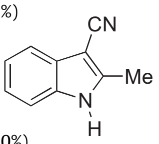
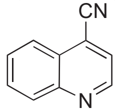
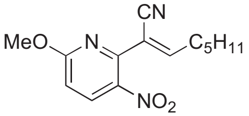
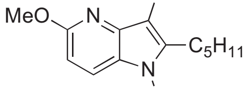
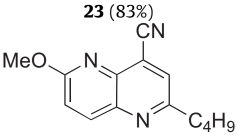
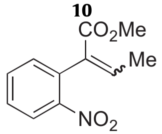
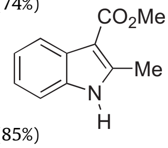
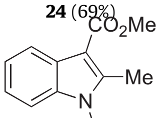
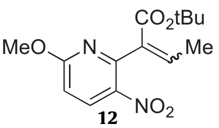
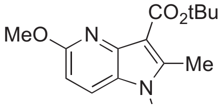
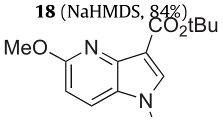
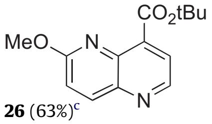
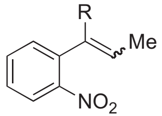
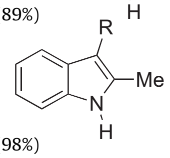
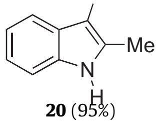
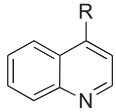
	4	5	6	7
1	$Pd(dba)_2$ – dppp	6%	8%	7%
2	$Pd(dba)_2$ – dppp – NEt_3	3%	5%	---
3	$Pd(dba)_2$ – dppp – phen – DBU	---	11%	---
4	**$Pd(OAc)_2$ – PPh_3**	**79%**	---	---
5	**$Pd(OAc)_2$ – PPh_3 – DBU**	---	**88%**	---

phen = 1,10-phenanthroline, dppp = 1,3-bis(diphenylphosphino)propane, DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene.

Scheme 2.

to the original catalyst mixture. Gratifyingly, the reaction was now selective for the formation of quinoline **6**, however the yield was still very low (entry 3). Palladium diacetate ($Pd(OAc)_2$) and triphenylphosphine (PPh_3) in DMF has been used as the catalyst system in related cyclization reactions to afford indoles.[8] Employing these conditions, indole **5** was isolated as the *sole product* in 79% yield (entry 4). The yield and selectivity was very encouraging for the synthesis of 3-cyanoindoles. With the intention of diverting the reaction to the formation of quinoline **6**, DBU was added to the reaction mixture. In the event, treatment of **4** with

Table 1
Cyclizations to afford 3-cyanoindoles or 4-cyanoquinolines

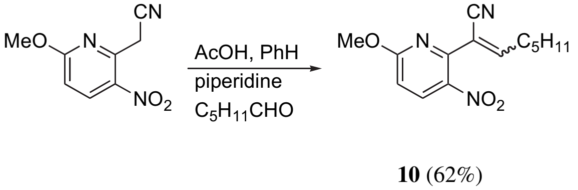
Entry	Nitroalkene	Conditions A[a]	Conditions B[b]	
				
1	**4** (R=Et)	**5** (79%)	**6** (R′=Me, 88%)	
2	**8** (R=Me)	**15** (82%)	**22** (R′=H, 88%)	
3	**1** (R=Pent)	**2** (91%)	**3** (R′=Bu, 79%)	
				
4	**9**	**16** (80%)	**23** (83%)	
				
5	**10**	**17** (74%)	**24** (69%)	
				
6	**11**	**18** (85%)	**18** (DBU, 87%)	
7			**18** (NEt_3, 78%)	
8			**18** (*t*-BuOK, 35%)	
9			**18** (NaHMDS, 84%)	
				
10	**12**	**19** (89%)	**25** (24%)[c]	**26** (63%)[c]
				
11	**13** (R=Ph)	**20** (98%)	**20** (95%)	—
12			—	**27** (79%)[c]
13	**14** (R=H)	**21** (96%)[d]	**21** (89%)[c]	—

[a] Conditions A: $Pd(OAc)_2$, PPh_3, DMF, CO (6 atm), 120 °C, 72 h.

[b] Conditions B: $Pd(OAc)_2$, PPh_3, DBU, DMF, CO (6 atm), 120 °C, 72 h.

[c] *t*-BuOK in place of DBU.

[d] $Pd(OAc)_2$, PPh_3, MeCN, CO (4 atm), 70 °C, 15 h. See Ref. 4.



Scheme 3.

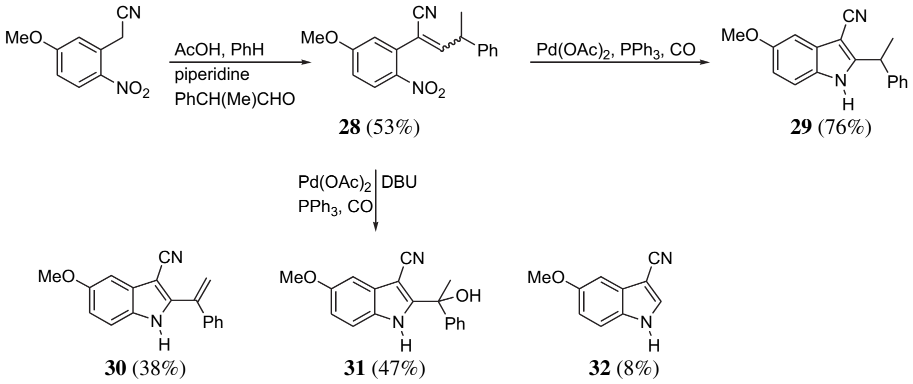
a catalytic amount of $Pd(OAc)_2$–PPh_3 in the presence of a slight excess of DBU gave *exclusively* quinoline **6** in 88% yield (entry 5). Thus, the goal of preparing either an indole or a quinoline ring system from a common precursor was realized, at least for this substrate.

Having developed conditions for selective synthesis of either indole **5** or quinoline **6** from compound **4**, a number of additional substrates were prepared and subjected to the two slightly different reaction conditions (Table 1). Four unsaturated nitriles (**1**, **8**–**10**) were prepared using a Knoevenagel condensation[9] of the corresponding 2-arylacetonitrile with ethanal or hexanal. For example, reaction of 6-methoxy-3-nitro-2-pyridineacetonitrile[10] with hexanal gave **10** (Scheme 3). In addition to the nitriles, two ester-functionalized starting materials (**11** and **12**) were prepared by the same methodology. It should be noted that the condensation reactions using ethanal are very sensitive to the purity of the reagents used. Several of the attempts did not furnish the desired product. The yields reported for the new compounds in the experimental section represent the maximum single reaction yield from, in some cases, over 20 reactions. The last two substrates (**13** and **14**) in Table 1 were prepared via a Kosugi–Migita–Stille cross-coupling between 2-iodo-1-nitrobenzene and 1-propene-1-yltributyltin and 1-phenyl-1-propen-1-yltributyltin, respectively.

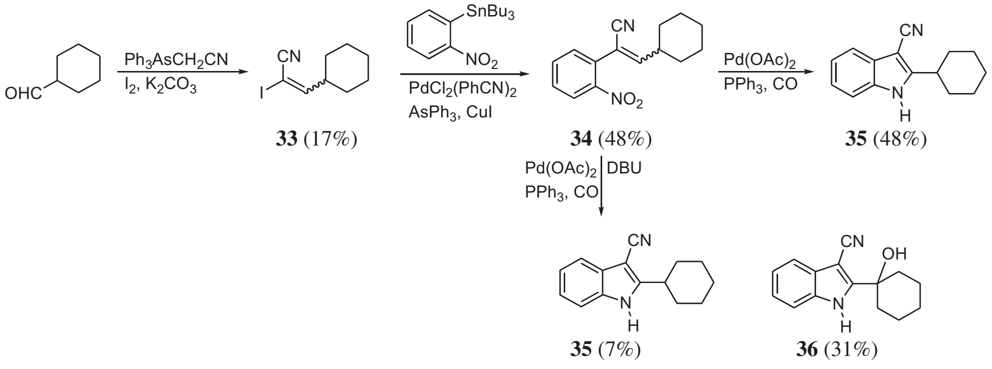
Cyclization of **1**, **4**, and **8**–**14** using $Pd(OAc)_2$–PPh_3 as the catalyst system (conditions A) gave in all cases studied exclusively indoles (**2**, **5**, and **15**–**21**) in good isolated yields (Table 1, entries 1–6 and 10, 11, 13). The corresponding quinolines were not observed in the crude spectra from these reactions. Reaction of the same substrates but using the $Pd(OAc)_2$–PPh_3–DBU system (conditions B) gave different results depending on the substituent on the alkene. The nitrile-functionalized substrates furnished the corresponding quinolines **3**, **6**, **22**–**24** (entries 1–5). Disappointingly, the ester **11** did not undergo cyclization to afford a quinoline under the basic conditions B. Three additional bases were examined for **11** however, indole **18** was formed in all cases (entries 6–9). It appears that the quinoline forming reaction is limited to the nitriles. In contrast, the azaquinoline **26** was formed upon reaction of the pyridine derivative **12** (entry 10). In addition to **26**, one additional product was isolated and identified as the azaindole **25**. Note that **25** has lost a methyl group compared to azaindole **19** formed under conditions A. DBU was apparently sufficiently basic to deprotonate all nitriles and esters examined (compounds **1**, **4**, and **8**–**12**). This was evidenced by the immediate change in color of the reaction mixtures upon addition of the base.

In contrast, no color change was observed for the significantly less acidic substrates **13** and **14**. Reaction of **13** using DBU as the base furnished only indole **20** in 95% yield (entry 11). However, reaction of **13** with $Pd(OAc)_2$–PPh_3–KO*t*-Bu did produce an initial deep blue color and smoothly furnished quinoline **27** (entry 12). In the last example in Table 1, the less acidic substrate **14** was reacted with carbon monoxide in the presence of $Pd(OAc)_2$–PPh_3. Only indole **21** was obtained independent of what base was used.

Two substrates **28** and **34**, which cannot form fully aromatic quinolines without migration or loss of a carbon chain were also examined. Compound **28** was prepared by condensation of 2-nitro-5-methoxy-1-cyanomethylbenzene with 2-phenylpropanal. This compound was subjected to reaction conditions A and B. Not



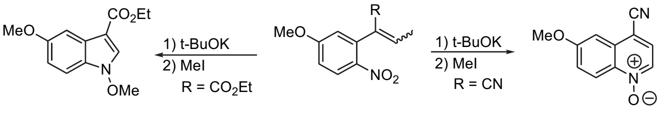
Scheme 4.



Scheme 5.

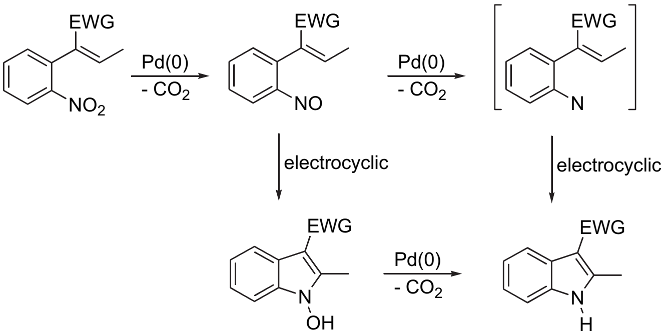
surprising, under neutral conditions (A) the expected indole **29** was isolated in good yield (Scheme 4). In contrast, three different indoles, **30** and an inseparable mixture of **31** and **32**, were obtained under the basic conditions B. The structures of **31** and **32** were elucidated using 2D NMR techniques including COSY, HMQC, HMBC, and NOESY. Indole **32** is interesting in that a significant part of the starting material has been lost.

Compound **34** was prepared cyclohexane carbaldehyde via a Wittig reaction forming **33** followed by a Kosugi–Migita–Stille reaction (Scheme 5). Again, the expected indole **35** was formed albeit in relatively low isolated yield under conditions A. Under the basic conditions B, a low yield of indole **35** in addition to indole **36** having an oxidized cyclohexyl group was isolated. This outcome was interpreted as the result of a competing cyclization of **34** to **35** and cyclization of the anion formed from **34** to give **36**.



38 (83%) **8** (R=CN) **37** (R=CO$_2$Et) **39** (53%)

Scheme 6.



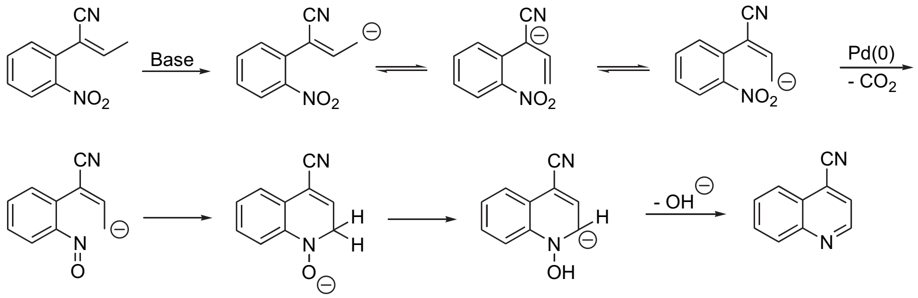
Scheme 7.

The difference in chemoselectivity between the nitriles and the esters is puzzling. It is unclear why either indoles or quinolines can be obtained from the nitrile-substituted substrates while the esters afford exclusively indoles under either of the conditions. Although not known for the compounds examined in this study, the pK_a for the substrates having a CN versus COOR group must be of very similar in magnitude. For example, the pK_a values for CH_3CN and CH_3CO_2Et have been reported as 24.5 and 25.0, respectively.[11]

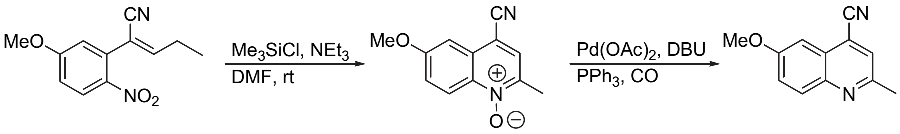
Two closely related substrates **8** and **37** differing only in the electron-withdrawing group, CN versus CO_2Et, were prepared. The substrates were deprotonated with *t*-BuOK in *t*-BuOH and methyl iodide was added to the mixture with the intent to trap the intermediate and perhaps give insight into the electronic distribution of the formed anion (Scheme 6). In the event, two different products were obtained. After workup and purification, ester **37** gave exclusively *N*-methoxyindole **38** while on the other hand nitrile **8** furnished the quinoline-*N*-oxide **39**. As was noticed for two previous products, **25** and **32**, part of the alkene-chain was lost during the reaction forming **38**. It is again evident from these two experiments that under identical reaction conditions, the esters and the nitriles have different chemoselectivity. The reason for this is presently unknown.

The mechanisms for the reactions leading to either indole or quinoline products and indoles wherein a carbon–carbon bond has been broken and/or a side-chain oxidized are not clear at this moment. In the absence of a base, the reaction probably proceeds via a deoxygenation producing a nitroso compound followed by either (a) a second deoxygenation to give a nitrenenoid intermediate and ultimately an indole or (b) an electrocyclic ring closure to afford an *N*-hydroxy indole followed by a palladium-catalyzed deoxygenation (Scheme 7).[12] This mechanism rationale accounts for the formation of indoles without carbon–carbon bond cleavage or side-chain oxidation.

The mechanistic picture is a little more complex in the presence of a base. Addition of a sufficiently strong base results in the formation of the conjugate base as is evident by the immediate formation of a deep blue solution (Scheme 8). The nitro group is probably deoxygenated by the catalyst system to form a nitrosarene. Nucleophilic addition of the carbanion to the nitroso group followed by protonation–deprotonation and elimination of hydroxide would furnish a quinoline.

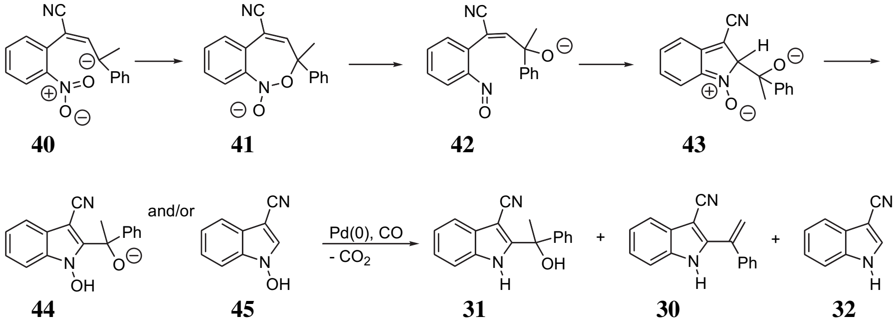


Scheme 8.



4 **7** (90%) **6** (24%)

Scheme 9.



Scheme 10.

Makosza and Wrobel have reported the formation of quinoline-*N*-oxides (such as **7**, Scheme 2) by treatment of compound **4**, and related substrates, with triethylamine–trimethylsilyl chloride (Scheme 9).[7] This result raises the question whether the base-modulated cyclization forming quinolines (conditions B) is just a simple palladium-catalyzed reduction of the formed quinoline-*N*-oxide. Submitting **7** to conditions B did furnish quinoline **6**. However, the yield of **6** was only 24% after the same length of time required to produce quinoline **6** directly from **4** using our methodology. This result is not conclusive but indicates that the major reaction path is probably not substrate (**4**)→quinoline-*N*-oxide (**7**)→quinoline (**6**) for the palladium-catalyzed reaction. Perhaps the formation of the nitroso-intermediate is faster compared to nucleophilic addition to the nitro-group in cases wherein a quinoline is formed. Nucleophilic addition to the nitro-group may also be a reversible reaction under basic conditions while the reduction to a nitrosarene is not.

The final mechanistic question is the formation of indoles with concurrent carbon–carbon bond fission (**25**, **32**), oxidation (**31**, **36**), or alkene formation (**30**). This transformation may occur via addition of the allylic carbanion **40** to the nitro-group affording the seven-membered intermediate **41** (Scheme 10). Ring-opening of **41** would give nitrosarene **42** followed by electrocyclic ring-closure to produce **43**. Rearomatization can now occur either by loss of acetophenone-protonation to give **44** or loss of a proton to give **45**. Palladium-catalyzed deoxygenation of **44** would after subsequent protonation afford **31** or protonation–elimination produce **30**. Deoxygenation of **45** would result in the formation of **32**.

The mechanism seen in Scheme 10 is supported by related observations reported in the literature.[13,14] In addition, the addition of carbanions to aromatic nitro-groups has been proposed as one of the steps in the Bartoli indole synthesis using nitroarenes and an excess alkenyl Grignard reagents.[15]

3. Conclusion

We have successfully developed a synthetic methodology for the formation of various 4-cyanoquinolines and 3-cyanoindoles from a common 1-cyano-1-(2-nitrophenyl)alkene precursor. Quinolines are formed in the presence of a base and indoles in the absence. Mechanistic rationales for the formation of both products and side product have been presented.

4. Experimental section

4.1. General procedures

NMR spectra were determined in $CDCl_3$ at 600 MHz (^{1}H NMR) and 150 MHz (^{13}C NMR). The chemical shifts are expressed in δ values relative to $SiMe_4$ (0.0 ppm, ^{1}H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) internal standards.

Anhydrous benzene, *N*-methylpyrrolidone, and *N*,*N*-dimethylformamide were used as received. Hexanes and ethyl acetate were distilled over calcium hydride. Chemicals prepared according to literature procedures have been footnoted the first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in oven-dried glassware. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure unless otherwise stated. Melting points (uncorrected) were recorded directly from products obtained by chromatography.

*4.1.1. 1-Cyano-1-(2-nitrophenyl)propene (**9**).* To a solution of 2-nitrophenylacetonitrile (508 mg, 3.13 mmol) in benzene (10 mL) was added acetic acid (60 μL), piperidine (50 μL), and freshly distilled ethanal (900 μL, 15.6 mmol). The flask was fitted with a Dean–Stark trap and the mixture was heated at reflux (20 h). The solvents were removed under reduced pressure and the resulting crude product was purified by chromatography (hexanes/EtOAc, 8:2) to give **9** (118 mg, 0.67 mmol, 21%) as a pale yellow oil. ^{1}H NMR δ 8.06 (dd, J=8.4, 1.2 Hz, 1H), 7.66 (dt, J=8.4, 1.2 Hz, 1H), 7.57 (dt, J=8.4, 1.2 Hz, 1H), 7.41 (dt, J=8.4, 1.2 Hz, 1H), 6.56 (q, J=7.2 Hz, 1H), 2.23 (d, J=7.2 Hz, 3H); ^{13}C NMR δ 146.8, 133.6, 131.7, 130.1, 129.7, 129.6, 125.1, 114.9, 114.0, 17.8; IR (ATR) 2935, 1604, 1509, 1309 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_9N_2O_2$ (M+H^{+}) 189.0640; found, 189.0658.

*4.1.2. 2-(6-Methoxy-3-nitro-2-pyridyl)-2-heptenenitrile (**10**).* To a solution of 2-cyanomethyl-6-methoxy-3-nitropyridineacetonitrile (456 mg, 2.34 mmol) in benzene (10 mL) was added acetic acid (60 μL), piperidine (50 μL), and freshly distilled hexanal (400 μL, 3.45 mmol). The flask was fitted with a Dean–Stark trap and the mixture was heated at reflux (20 h). The solvents were removed under reduced pressure and the crude product was purified by chromatography (hexanes/EtOAc, 8:2) affording **10** (397 mg, 1.44 mmol, 62%) as a pale yellow oil. A 1.6:1 isomer ratio was obtained. Spectral data for the major isomer: ^{1}H NMR δ 8.23 (d, J=9.0 Hz, 1H), 7.05 (t, J=7.8 Hz, 1H), 6.83 (d, J=9.0 Hz, 1H), 4.05 (s, 3H), 2.64 (q, J=7.8 Hz, 2H), 1.41 (m, 4H), 1.24 (m, 2H), 0.93 (t, J=7.2 Hz, 3H). Spectral data for the minor isomer: ^{1}H NMR δ 8.37 (d, J=9.0 Hz, 1H), 6.90 (d, J=9.6 Hz, 1H), 6.80 (t, J=7.8 Hz, 1H), 4.04 (s, 3H), 2.10 (q, J=7.8 Hz, 2H), 1.61 (p, J=7.8 Hz, 2H), 1.4 (m, 4H), 0.85 (t, J=7.2 Hz, 3H); both isomers: ^{13}C NMR δ 165.4, 164.8, 156.0, 152.9, 145.8, 145.2, 139.5, 138.0, 136.1, 136.0, 116.9, 114.3, 113.6, 112.7, 112.3, 111.7, 55.0, 54.8, 32.0, 31.2, 31.2 29.9, 27.8, 27.7 22.3, 22.2, 13.9, 13.8; IR (ATR) 2931, 2222, 1579, 1320, 1277 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{17}N_3NaO_3$ (M+Na^{+}) 298.1168; found, 298.1162.

*4.1.3. 1,1-Dimethylethyl 2-(6-methoxy-3-nitro-2-pyridyl)-2-butenoate (**12**).* To a −78 °C cold solution of 1,1-dimethylethyl (6-methoxy-3-nitrophenyl)ethanoate[6] (577 mg, 2.14 mmol) and 18-crown-6 (176 mg, 0.67 mmol) in dry THF (15 mL) under a nitrogen atmosphere was added a solution of potassium *tert*-butoxide (624 mg, 5.56 mmol) in THF (3 mL). The solution turned deep blue immediately upon addition of the base: freshly distilled ethanal (1.25 mL, 21.4 mmol) was added dropwise to the solution and the mixture was allowed to stir at −78 °C (2 h). A saturated solution of NH_4Cl (aqueous, 2 mL) was added to the resulting brown solution. The solution was extracted with CH_2Cl_2 (20 mL) and the organic phase was washed with saturated NaCl (aqueous, 2×20 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvents were evaporated under reduced pressure. The resulting dark crude oil was purified by a chromatography (hexanes/EtOAc, 9:1) to give **12** (*E*/*Z*, 4.6:1, 468 mg, 1.57 mmol, 73%) as a pale yellow oil. Analytical data for the major isomer: ^{1}H NMR δ 8.30 (d, *J*=8.4 Hz, 1H), 7.15 (q, *J*=7.2 Hz, 1H), 6.75 (d, *J*=9.0 Hz, 1H), 3.97 (s, 3H), 1.77 (d, *J*=7.2 Hz, 3H), 1.36 (s, 9H); ^{13}C NMR δ 164.9, 163.6, 149.9, 144.5, 140.6, 135.4, 134.0, 110.2, 81.3, 54.5, 27.7, 15.1. Partial data for the minor isomer from the mixture: ^{1}H NMR (600 MHz) δ 8.20 (d, *J*=8.4 Hz, 1H), 6.79 (q, *J*=7.2 Hz, 1H), 6.70 (d, *J*=9.0 Hz, 1H), 3.99 (s, 3H), 2.27 (d, *J*=7.2 Hz, 3H), 1.37 (s, 9H); ^{13}C NMR δ 164.8, 163.4, 151.6, 140.3, 136.0, 133.8, 109.8, 81.6, 54.8, 27.8, 15.9; both isomers: IR (ATR) 1710, 1680, 1540, 1338, 1289 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}N_2O_5$ (M+H$^+$) 295.1294; found, 295.1289.

*4.1.4. 1-Phenyl-1-(2-nitrophenyl)-1-propene (**13**).* A solution of 2-iodo-1-nitrobenzene (257 mg, 1.03 mmol), 1-(tributylstannyl)-1-phenyl-1-propene[16] (478 mg, 1.17 mmol), $PdCl_2(PhCN)_2$ (21 mg, 0.06 mmol), $AsPh_3$ (31 mg, 0.10 mmol), and CuI (32 mg, 0.16 mmol) in NMP (2 mL) was heated at 80 °C for 72 h. The solvent was removed under reduced pressure, and the dark crude oil was purified by chromatography (hexanes/EtOAc, 95:5) to give **13** (209 mg, 0.86 mmol, 84%) as a pale yellow oil. A 9:1 ratio of isomers was obtained. Analytical data for the major isomer: ^{1}H NMR δ 7.73 (d, *J*=7.8 Hz, 1H) 7.50 (td, *J*=7.8, 1.2 Hz, 1H), 7.37 (d, *J*=7.8 Hz, 2H), 7.35 (d, *J*=7.8 Hz, 2H), 7.30 (t, *J*=7.8 Hz, 1H), 7.23 (t, *J*=7.8 Hz, 1H), 7.19 (dd, *J*=7.8, 1.2 Hz, 1H), 5.89 (q, *J*=7.2 Hz, 1H), 1.87 (d, *J*=7.2 Hz, 3H); ^{13}C NMR δ 149.3, 138.7, 138.5, 137.8, 133.7, 132.2, 132.0, 129.7, 127.7, 127.4, 127.2, 123.9, 15.5; IR (ATR) 2942, 2232, 1526, 1353 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}NNaO_2$ (M+Na$^+$) 262.0844; found, 262.0839.

4.2. Method A

*4.2.1. 3-Cyano-2-ethyl-5-methoxyindole (**5**).* To an oven-dried ACE glass pressure tube was added **4**[7] (155 mg, 0.67 mmol), $Pd(OAc)_2$ (15.0 mg, 0.07 mmol), PPh_3 (61 mg, 0.23 mmol), and DMF (5 mL). The tube was fitted with a pressure head and the solution was then saturated with CO (three cycles to 6 atm of CO). The reaction mixture was heated at 120 °C under CO (6 atm, 72 h). The solvents were removed under reduced pressure and the crude product was purified by chromatography (hexanes/EtOAc, 8:2) affording **5** (107 mg, 0.53 mmol, 79%) as a pale yellow solid. Mp 145–150 °C; ^{1}H NMR δ 8.27 (s, 1H), 7.24 (d, *J*=9.0 Hz, 1H), 7.10 (d, *J*=2.4 Hz, 1H), 6.88 (dd, *J*=9.0, 2.4 Hz, 1H), 3.86 (s, 3H), 2.97 (q, *J*=7.2 Hz, 2H), 1.41 (t, *J*=7.2 Hz, 3H); ^{13}C NMR δ 156.0, 150.5, 129.4, 128.8, 116.7, 113.8, 112.4, 100.8, 84.3, 56.0, 21.2, 13.4; IR (ATR) 3243, 2973, 2212, 1477, 1218 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{13}N_2O$ (M+H$^+$) 201.1028; found, 201.1023.

*4.2.2. 3-Cyano-5-methoxy-2-methylindole (**15**)*[17]. Reaction of **8**[7] (130 mg, 0.56 mmol), $Pd(OAc)_2$ (13.0 mg, 0.05 mmol), PPh_3 (61 mg, 0.23 mmol), and CO (6 atm) in DMF (5 mL), as described for **5**, gave after chromatography (hexanes/EtOAc, 7:3) **15** (87 mg, 0.47 mmol, 82%) as a pale yellow solid. Mp 180–182 °C; ^{1}H NMR δ 8.34 (s, 1H), 7.22 (d, *J*=9.0 Hz, 1H), 7.09 (d, *J*=2.4 Hz, 1H), 6.87 (dd, *J*=9.0, 2.4 Hz, 1H), 3.86 (s, 3H), 2.60 (s, 3H); ^{13}C NMR δ 156.1, 144.7, 129.5, 128.7, 116.5, 113.9, 112.2, 100.9, 85.9, 56.0, 13.3; IR (ATR) 3255, 2211 cm^{-1}.

*4.2.3. 3-Cyano-2-pentyl-5-methoxyindole (**2**).* Reaction of **1**[6] (112 mg, 0.43 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), PPh_3 (55 mg, 0.20 mmol), and CO (6 atm) in DMF (5 mL), as described for **5**, gave after chromatography (hexanes/EtOAc, 8:2) **17** (90 mg, 0.39 mmol, 91%) as a pale yellow solid. Mp 98 °C (lit.[6] 98–99 °C).

*4.2.4. 3-Cyano-2-methyl indole (**16**).* Reaction of **9** (88 mg, 0.50 mmol), in presence of $Pd(OAc)_2$ (12 mg, 0.05 mmol), PPh_3 (55 mg, 0.28 mmol), and CO (6 atm) in DMF (5 mL), and described for **5**, gave after solvents removal and purification by chromatography (hexanes/EtOAc, 95:5) **16** (58 mg, 0.40 mmol, 80%) as a pale yellow solid. Mp 203 °C (lit.[18] 204–206 °C).

*4.2.5. 4-Aza-3-cyano-5-methoxy-2-pentylindole (**17**).* Reaction of **10** (100 mg, 0.36 mmol), $Pd(OAc)_2$ (10 mg, 0.05 mmol), PPh_3 (45 mg, 0.24 mmol), and CO (6 atm) in DMF (5 mL) as described for **5** gave after chromatography (hexanes/EtOAc, 9:1) **17** (66 mg, 0.27 mmol, 74%) as a pale yellow solid. Mp 129 °C; ^{1}H NMR δ 9.53 (s, 1H), 7.69 (d, *J*=9.0 Hz, 1H), 6.88 (d, *J*=9.0 Hz, 1H), 4.07 (s, 3H), 3.23 (t, *J*=7.2 Hz, 2H), 1.81 (p, *J*=7.2 Hz, 2H), 1.49 (sextet, *J*=7.2 Hz, 2H), 1.26 (m, 2H), 0.99 (t, *J*=7.2 Hz, 3H); ^{13}C NMR δ 162.4, 142.6, 137.7, 124.6, 123.6, 114.2, 113.2, 90.2, 54.0, 39.8, 29.7, 26.3, 22.3, 13.9; IR (ATR) 3246, 2219, 1477, 1218 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}N_3O$ (M+H$^+$) 244.1450; found, 244.1444.

*4.2.6. Methyl 2-methyl-indole-3-carboxylate (**18**).* Reaction of methyl 2-(2-nitrophenyl)-2-butenoate (**11**)[19] (88 mg, 0.40 mmol), $Pd(OAc)_2$ (14 mg, 0.05 mmol), PPh_3 (54 mg, 0.20 mmol), and CO (6 atm) in DMF (5 mL) as described for **5** gave after chromatography (hexanes/EtOAc, 9:1) **18** (64 mg, 0.34 mmol, 85%) as a pale yellow solid. Mp 161 °C (lit.[20] 162–163 °C).

*4.2.7. 1,1-Dimethylethyl 4-aza-5-methoxy-2-methylindole-3-carboxylate (**19**).* Reaction of **12** (234 mg, 0.79 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol), PPh_3 (55 mg, 0.28 mmol), and CO (6 atm) in DMF (5 mL) as described for **5** gave after chromatography (hexanes/EtOAc, 9:1) **19** (185 mg, 0.70 mmol, 89%) as a white solid. Mp 222–224 °C; ^{1}H NMR δ 8.50 (br s, 1H), 7.45 (d, *J*=9.0 Hz, 1H), 6.56 (d, *J*=9.0 Hz, 1H), 4.01 (s, 3H), 2.71 (s, 3H), 1.66 (s, 9H); ^{13}C NMR δ 164.6, 160.9, 144.5, 141.8, 123.1, 121.1, 106.3, 105.3, 79.8, 53.2, 30.9, 28.7; IR (ATR) 3321, 1700, 1669, 1525, 1284, 1144 cm^{-1}; HRMS calcd for $C_{14}H_{19}N_2O_3$ (M+H$^+$) 263.1396; found, 263.1389.

*4.2.8. 2-Methyl-3-phenylindole (**21**).* Reaction of **14** (103 mg, 0.43 mmol), $Pd(OAc)_2$ (10.5 mg, 0.048 mmol), PPh_3 (51 mg, 19 mmol), and CO (6 atm) in DMF (5 mL), as described for **5**, gave after chromatography (hexanes/EtOAc, 9:1) **21** (89 mg, 0.42 mmol, 98%) as a pale yellow solid. Mp 58 °C (lit.[21] 58–60 °C).

*4.2.9. 2-(5-Methoxy-2-nitrophenyl)-3-phenyl-2-pentenenitrile (**28**).* Reaction of 5-methoxy-2-nitrophenylacetonitrile[22] (213 mg, 1.11 mmol), AcOH (60 μL), piperidine (50 μL), and 2-phenylpropanal (150 μL, 1.11 mmol) in benzene (10 mL) as described for **10** (80 °C for 16 h) gave after chromatography (hexanes/EtOAc, 9:1) **28** (177 mg, 0.58 mmol, 53%) as a pale yellow oil. A 34:1 ratio of alkene isomers was observed. ^{1}H NMR δ 8.15 (d, *J*=9.0 Hz, 1H), 7.35 (m, 4H), 7.27 (m, 1H), 6.97 (dd, *J*=9.0, 3.0 Hz, 1H), 6.76 (d, *J*=3.0 Hz, 1H), 6.46 (d, *J*=10.2 Hz, 1H), 4.25 (dq, *J*=10.2, 7.2 Hz, 1H), 3.89 (s, 3H), 1.57 (d, *J*=7.2 Hz, 3H); ^{13}C NMR δ 163.5, 154.1, 142.0, 140.4, 132.2, 128.9, 127.9, 127.2, 126.9, 117.6, 115.1, 114.2, 111.9, 56.2, 41.9, 20.0; IR (ATR) 2933, 1603, 1586, 1504, 1328, 1243 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{16}N_2NaO_3$ (M+Na$^+$) 331.1059; found, 331.1052.

*4.2.10. 3-Cyano-2-(1-phenylethyl)-5-methoxyindole (**29**).* Reaction of **28** (88 mg, 0.29 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), PPh_3 (49 mg, 0.191 mmol), and CO (6 atm) in DMF (4 mL) as described for **5** gave after chromatography (hexanes/EtOAc, 9:1) **29** (60 mg, 0.22 mmol, 76%) as a pale yellow solid. Mp 167–168 °C; ^{1}H NMR δ 8.00 (s, 1H), 7.38 (t, *J*=7.8 Hz, 2H), 7.33 (d, *J*=7.2 Hz, 2H), 7.31 (t, *J*=7.2 Hz, 1H), 7.15 (d, *J*=9.0 Hz, 1H), 7.11 (d, *J*=2.4 Hz, 1H), 6.86 (dd, *J*=9.0, 2.4 Hz, 1H), 4.59 (q, *J*=7.2 Hz, 1H), 3.85 (s, 3H), 1.84 (d, *J*=7.2 Hz, 3H); ^{13}C NMR δ 155.9, 151.5, 141.3, 129.2, 128.9, 128.7, 127.6, 127.4, 116.3, 114.1, 112.3, 100.7, 55.8, 38.4, 20.0;[23] IR (ATR) 3243, 2212 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}N_2O$ (M+H$^+$) 277.1341; found, 277.1335.

4.3. Method B

*4.3.1. 4-Cyano-2-methyl-6-methoxyquinoline (**6**).* Reaction of **4** (101 mg, 0.43 mmol), Pd(OAc)$_2$ (15 mg, 0.05 mmol), PPh$_3$ (63 mg, 0.23 mmol), DBU (72 μL, 0.48 mmol), and CO (6 atm) in DMF (5 mL), as described for **5** gave after chromatography (hexanes/EtOAc, 8:2) **6** (76 mg, 0.38 mmol, 88%) as a pale yellow solid. Mp 156 °C; ^{1}H NMR δ 7.98 (d, *J*=9.6 Hz, 1H), 7.57 (s, 1H), 7.44 (dd, *J*=9.6, 3.0 Hz, 1H), 7.33 (d, *J*=2.4 Hz, 1H), 3.99 (s, 3H), 2.75 (s, 3H); ^{13}C NMR δ 159.4, 155.6, 144.3, 131.2, 125.9, 125.7, 124.3, 117.4, 116.2, 102.3, 56.0, 24.9; IR (ATR) 3009, 2230, 1475 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{11}N_2O$ (M+H$^+$) 199.0871; found, 199.0866.

*4.3.2. 4-Cyano-6-methoxyquinoline (**22**).* Reaction of **8** (87 mg, 0.40 mmol), Pd(OAc)$_2$ (14 mg, 0.05 mmol), PPh$_3$ (60 mg, 0.23 mmol), DBU (65 μL, 0.43 mmol), and CO (6 atm) in DMF (5 mL), as described for **6**, gave after chromatography (hexanes/EtOAc, 8:2) **22** (65 mg, 0.35 mmol, 88%) to afford a pale yellow solid. Mp 145 °C (lit.[24] 157 °C).

4.3.3. 2-Butyl-4-cyano-6-methoxyquinoline (3)[2]. Reaction of **1** (105 mg, 0.38 mmol), Pd(OAc)$_2$ (11 mg, 0.04 mmol), PPh$_3$ (45 mg, 0.16 mmol), DBU (60 μL, 0.41 mmol), and CO (6 atm) in DMF (5 mL) as described for **6** gave after chromatography (hexanes/EtOAc, 8:2) **3** (72 mg, 0.30 mmol, 79%) as a pale yellow solid.

*4.3.4. 4-Cyanoquinoline (**23**).* Reaction of **9** (156 mg, 0.83 mmol), Pd (OAc)$_2$ (16 mg, 0.07 mmol), PPh$_3$ (55 mg, 0.21 mmol), DBU (170 μL, 1.14 mmol), and CO (6 atm) in DMF (5 mL) as described for **6** gave after chromatography (hexanes/EtOAc, 9:1) **23** (106 mg, 0.69 mmol, 83%) as a pale yellow solid. Mp 106–107 °C (lit.[25] 103–104 °C).

*4.3.5. 5-Aza-2-butyl-4-cyano-6-methoxyquinoline (**24**).* Reaction of **10** (159 mg, 0.58 mmol), Pd(OAc)$_2$ (12.1 mg, 0.06 mmol), PPh$_3$ (61 mg, 23 mmol), DBU (90 μL, 0.61 mmol), and CO (6 atm) in DMF (5 mL) as described for **6** gave after chromatography (hexanes/EtOAc, 98:2) **24** (99 mg, 0.40 mmol, 69%) as a pale yellow solid. Mp 68 °C; ^{1}H NMR δ 8.18 (d, *J*=9.0 Hz, 1H), 7.70 (s, 1H), 7.20 (d, *J*=9.6 Hz, 1H), 4.16 (s, 3H), 2.98 (t, *J*=7.8 Hz, 2H), 1.80 (p, *J*=7.8 Hz, 2H), 1.43 (sextet, *J*=7.8 Hz, 2H), 0.97 (t, *J*=7.8 Hz, 3H); ^{13}C NMR δ 163.3, 160.2, 141.9, 139.7, 139.0, 127.4, 118.6, 118.2, 115.4, 54.4, 38.1, 31.9, 22.4, 13.9; IR (ATR) 2233 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}N_3O$ (M+H$^+$) 242.1293; found, 242.1288.

4.3.6. 1,1-Dimethylethyl 4-aza-5-methoxyindole-3-carboxylate (25)[6] *and 1,1-dimethylethyl 5-aza-6-methoxyquinoline-4-carboxylate (**26**).* Reaction of **12** (234 mg, 0.79 mmol), Pd(OAc)$_2$ (16 mg, 0.06 mmol), PPh$_3$ (56 mg, 0.30 mmol), *t*-BuOK (92 mg, 0.82 mmol), and CO (6 atm) in DMF (5 mL), as described for **6**, gave after chromatography (hexanes/EtOAc, 9:1) in order of elution **26** (130 mg, 0.50 mmol, 63%) and **25** (48 mg, 0.19 mmol, 24%) both as pale yellow solids. Analytical data for **26**: mp 126–127 °C; ^{1}H NMR δ 8.80 (d, *J*=4.8 Hz, 1H), 8.20 (d, *J*=9.0 Hz, 1H), 7.60 (d, *J*=4.2 Hz, 1H), 7.15 (d, *J*=9.0 Hz, 1H), 4.08 (s, 3H), 1.68 (s, 9H); ^{13}C NMR δ 166.3, 162.4, 147.4, 142.6, 139.9, 139.2, 138.3, 121.8, 117.2, 82.8, 54.0, 28.3; IR (ATR) 1694, 1592, 1508, 1346, 1204 cm^{-1}; HRMS calcd for $C_{14}H_{16}N_2O_3$ (M+H$^+$) 261.1239; found, 261.1233.

*4.3.7. 4-Phenylquinoline (**27**).* Reaction of **13** (167 mg, 0.70 mmol), Pd(OAc)$_2$ (16 mg, 0.07 mmol), PPh$_3$ (60 mg, 0.23 mmol), *t*-BuOK (88 mg, 0.78 mmol), and CO (6 atm) in DMF (5 mL), as described for **6**, gave after chromatography (hexanes/EtOAc, 9:1) **27** (112 mg, 0.55 mmol, 79%) as a pale yellow solid. Mp 61 °C (lit.[26] 61–62 °C).

*4.3.8. 2-Methylindole (**21**).* Reaction of **14** (158 mg, 0.97 mmol), Pd (OAc)$_2$ (16 mg, 0.06 mmol), PPh$_3$ (61 mg, 0.23 mmol), *t*-BuOK (86 mg, 0.77 mmol), and CO (6 atm) in DMF (5 mL), as described for **6**, gave after chromatography (hexanes/EtOAc, 9:1) **21** (113 mg, 0.86 mmol, 89%) as a pale yellow solid.

*4.3.9. 3-Cyano-2-(1-phenyl-1-ethenyl)-5-methoxyindole (**30**), 3-cyano-2-(1-methyl-1-hydroxybenzyl)-6-methoxyindole (**31**), and 3-cyano-6-methoxyindole (**32**)*[27]. Reaction of **28** (86 mg, 0.28 mmol), Pd(OAc)$_2$ (10 mg, 0.04 mmol), PPh$_3$ (44 mg, 0.17 mmol), DBU (50 μL, 0.33 mmol), and CO (6 atm) in DMF (4 mL), as described for **6**, gave after chromatography (hexanes/EtOAc, 95:5) in order of elution **30** (29 mg, 0.08 mmol, 38%) and a 7:1 mixture of **31** and **32** (44 mg, 47% and 8%) as pale yellow solids. Spectral data for **30**: mp 160 °C; ^{1}H NMR δ 8.16 (s, 1H), 7.44 (m, 3H), 7.39 (m, 2H), 7.27 (d, *J*=9.0 Hz, 1H), 7.17 (d, *J*=3.0 Hz, 1H), 6.93 (dd, *J*=9.0, 3.0 Hz, 1H), 6.19 (s, 1H), 5.78 (s, 1H), 3.89 (s, 3H); ^{13}C NMR δ 156.7, 144.3, 138.7, 138.2, 129.4, 129.2, 129.1, 129.0, 128.2, 120.0, 116.4, 115.5, 112.6, 100.5, 85.5, 55.8; IR (ATR) 3287, 2217 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}N_2O$ (M+H$^+$) 275.1184; found, 275.1179. Spectral data for **31** from the mixture: ^{1}H NMR δ 9.03 (s, 1H), 7.52 (dt, *J*=7.2, 1.2 Hz, 2H), 7.36 (t, *J*=7.2 Hz, 2H), 7.31 (t, *J*=7.2 Hz, 1H), 7.26 (t, *J*=9.0 Hz, 1H), 7.08 (d, *J*=2.4 Hz, 1H), 6.90 (dd, *J*=9.0, 2.4 Hz, 1H), 3.87 (s, 3H), 2.75 (br s, 1H), 2.22 (s, 3H); ^{13}C NMR δ 155.9, 152.0, 144.1, 129.6, 128.8, 128.4, 127.9, 125.3, 116.2, 114.6, 112.7, 100.5, 82.35, 73.81, 55.8, 29.1. HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2$ (M+H$^+$) 293.1291; found, 293.1285. Spectral data for **32** from the mixture: ^{1}H NMR δ 8.74 (s, 1H), 7.65 (d, *J*=9.0 Hz, 1H), 7.33 (d, *J*=9.0 Hz, 1H), 7.17 (d, *J*=2.4 Hz, 1H), 6.96 (dd, *J*=9.0, 2.4 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR δ 156.1, 131.8, 129.7, 128.9, 116.0, 115.2, 112.9, 100.6, 87.2, 55.8. HRMS (ESI) calcd for $C_{10}H_9N_2O$ (M+H$^+$) 173.0715; found, 173.0710.

*4.3.10. 3-Cyclohexyl-2-iodo-2-propenenitrile (**33**).* To a solution of cyanomethyltriphenylarsonium bromide[28] (1.66 g, 3.90 mmol) in MeCN (15 mL) at 10 °C was added potassium carbonate (536 mg, 3.88 mmol) and iodine (997 mg, 3.93 mmol). The solution was stirred under a nitrogen atmosphere (ambient temperature, 30 h) where after potassium carbonate (564 mg, 4.08 mmol), cyclohexylcarboxaldehyde (556 mg, 5.00 mmol) and H$_2$O (0.5 mL) were added.

After additional 48 h, the solvents were removed under reduced pressure and the resulting crude product was purified by chromatography (hexanes/EtOAc, 95:5) to give **33** (171 mg, 0.65 mmol, 17%)[29] as a brown oil. ^{1}H NMR δ 6.89 (d, *J*=10.2 Hz, 1H), 2.54 (qt, *J*=10.8, 3.6 Hz, 1H), 1.77–1.73 (m, 6H), 1.25–1.14 (m, 4H); ^{13}C NMR δ 167.3, 116.1, 49.7, 45.7, 45.0, 31.4, 25.3, 25.0; IR (ATR) 2935, 2851, 2211, 1447, 1148 cm^{-1}; HRMS (ESI) calcd for $C_9H_{12}NaNI$ (M+Na$^+$) 283.9912; found, 283.9906.

*4.3.11. 3-Cyclohexyl-2-(2-nitrophenyl)-2-propenenitrile (**34**).* Reaction of tributyl(2-nitrophenyl) stannane[30] (273 mg, 0.66 mmol), **33** (171 mg, 0.65 mmol), PdCl$_2$(PhCN)$_2$ (16 mg, 0.04 mmol), AsPh$_3$ (22 mg, 0.07 mmol), and CuI (22 mg, 0.12 mmol) in NMP (3 mL), as described for **13** (80 °C, 76 h), gave after chromatography (hexanes/EtOAc, 9:1) **34** (82 mg, 0.32 mmol, 48%, as a 14:1 mixture of isomers) as a pale brown oil.[31] ^{1}H NMR δ 8.03 (d, *J*=9.6 Hz, 1H), 7.65 (t, *J*=7.2 Hz, 1H), 7.55 (t, *J*=7.2 Hz, 1H), 7.41 (d, *J*=7.8 Hz, 1H), 6.31 (d, *J*=10.2 Hz, 1H), 2.78 (tq, *J*=4.2, 0.8 Hz, 1H), 1.87 (d, *J*=2.6 Hz, 2H), 1.79 (dt, *J*=13.8 Hz, 3.0 Hz, 2H), 1.72 (dt, *J*=13.2, 3.6 Hz, 1H), 1.40 (tq, *J*=12.6, 3.6 Hz, 2H), 1.23 (m, 3H); ^{13}C NMR δ 156.7, 147.8, 133.5, 131.7, 129.9, 129.7, 124.9, 115.2, 110.6, 41.2, 31.6, 25.5, 25.1; IR (ATR) 2928, 2853, 2221, 1526, 1345, 854, 731 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}NaN_2O_2$ (M+Na$^+$) 279.1110; found 279.1104.

*4.3.12. 3-Cyano-2-cyclohexylindole (**35**).* Reaction of **34** (73 mg, 0.31 mmol), PPh_3 (26.2 mg, 0.10 mmol), Pd(OAc) (7.6 mg, 0.03 mmol), and CO (6 atm) in DMF (5 mL), as described in for **5**, gave after chromatography (hexanes/EtOAc, 7:3) **35** (34 mg, 0.15 mmol, 48%) as a pale yellow solid. Mp 171–173 °C; ^{1}H NMR δ 8.54 (br s, 1H), 7.67 (d, J=4.8 Hz, 1H), 7.38 (d, J=7.2 Hz, 1H), 7.26–7.23 (m, 2H), 3.05 (tt, J=8.4, 3.6 Hz, 1H), 2.08 (d, J=12.0 Hz, 2H), 1.90 (dt, J=13.8, 3.0 Hz, 2H), 1.80 (d, J=12.6 Hz, 1H), 1.61 (dq, J=12.6, 3.6 Hz, 2H), 1.46 (tq, J=13.2, 3.6 Hz, 2H), 1.31 (tq, J=12.6, 3.6 Hz, 1H); ^{13}C NMR δ 153.4, 134.1, 127.8, 123.3, 122.0, 119.0, 116.4, 111.3, 83.4, 37.6, 32.4, 26.1, 25.7; IR (ATR) 3227, 2919, 2849, 2215, 1439, 737 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}NaN_2$ (M+Na$^+$) 247.1211; found, 247.1199.

*4.3.13. 3-Cyano-2-cyclohexylindole (**35**) and 3-cyano-2-(1-hydroxycyclohexyl)indole (**36**).* Reaction of **34** (82 mg, 0.32 mmol), PPh_3 (42 mg, 0.16 mmol), DBU (53 mg, 0.36 mmol), and $Pd(OAc)_2$ (10 mg, 0.05 mmol) in DMF (5 mL) as described for **6** gave after chromatography (hexanes/EtOAc, 8:2) **35** (5 mg, 0.02 mmol, 7%) and **36** (24 mg, 0.10 mmol, 31%) as a pale yellow oil. ^{1}H NMR δ 9.25 (br s, 1H), 7.68 (d, J=6.6 Hz, 1H), 7.40 (d, J=6.6 Hz, 1H), 7.25 (m, 2H), 2.47 (br s, 1H), 2.25 (dt, J=13.8, 4.8, 2H), 1.89 (d, J=13.8 Hz, 2H), 1.82–1.64 (m, J=16.2 Hz, 5H), 1.43 (m, 1H); ^{13}C NMR δ 154.6, 133.1, 129.2, 123.7, 122.3, 119.4, 116.8, 112.0, 80.7, 72.3, 37.4, 24.9, 21.6; IR (ATR) 3330, 2938, 2214, 1737, 1241, 1044 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}NaN_2O$ (M+Na$^+$) 263.1160; found, 263.1155.

*4.3.14. Ethyl 2-(5-methoxy-2-nitrophenyl)-2-butenoate (**37**).* To a solution of ethyl 2-(5-methoxy-2-nitrophenyl)ethanoate[32] (260 mg, 1.18 mmol) and 18-crown-6 (125 mg, 0.473 mmol) in dry THF (8 mL) was a solution of *t*-BuOK (400 mg, 3.56 mmol) in THF (2 mL) at −78 °C: freshly distilled ethanal (1 mL, 17.8 mmol) was added to the resulting deep blue solution. The reaction mixture was stirred at −78 °C (1 h) and then at ambient temperature (30 min). The reaction was quenched with NH_4Cl (aqueous-saturated, 1 mL) and $MgSO_4$ was added. The mixture was filtered, the solvents were removed under reduced pressure, and the crude product was purified by chromatography (hexanes/EtOAc, 8:2) affording **37** (138 mg, 0.53 mmol, 47%) as a faint yellow oil. ^{1}H NMR δ 8.22 (d, J=9.0 Hz, 1H), 7.17 (q, J=7.8 Hz, 1H), 6.95 (dd, J=9.0, 2.4 Hz, 1H), 6.70 (d, J=2.4 Hz, 1H), 4.15 (very broad apparent doublet, 2H), 3.90 (s, 3H), 1.73 (d, J=7.2 Hz, 3H), 1.20 (t, J=7.2 Hz, 3H); ^{13}C NMR δ 165.3, 163.1, 141.6, 138.5, 133.7, 133.1, 127.4, 117.6, 113.2, 60.9, 55.9, 15.3, 14.0; IR (ATR) 1710, 1576, 1510, 1336, 1233, 1043, 1028 cm^{-1}; HRMS calcd for $C_{13}H_{15}NNaO_5$ (M+Na$^+$) 288.0848; found, 288.0842.

*4.3.15. Ethyl 5-methoxy-N-methoxyindole-3-carboxylate (**38**).* To a solution of **37** (107 mg, 0.46 mmol) in *t*-BuOH (2 mL) was added a solution of *t*-BuOK (0.65 g, 5.30 mmol) in *t*-BuOH (3 mL) under nitrogen. The deep blue reaction mixture was cooled in an ice bath for 10 min. Methyl iodide (110 μL, 0.69 mmol) was added dropwise over a period of 2 min. The solution was allowed to warm up to room temperature, and stirred for 3 h. The reaction was quenched with a solution of saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (30 mL). The organic phase was then washed with water (3×30 mL) and dried over magnesium sulfate ($MgSO_4$). After solvent evaporation, the crude was purified by chromatography (hexanes/EtOAc, 8:2), **38** (53 mg, 0.38 mmol, 83%) as a pale yellow oil. ^{1}H NMR δ 7.83 (s, 1H), 7.60 (d, J=2.4 Hz, 1H), 7.27 (d, J=8.9 Hz, 1H), 6.89 (dd, J=8.9, 2.4 Hz, 1H), 4.30 (q, J=6.9 Hz, 2H), 4.05 (s, 3H), 3.82 (s, 3H), 1.34 (t, J=6.9 Hz, 3H); ^{13}C NMR δ 164.7, 156.2, 128.1, 126.9, 123.7, 114.1, 109.5, 102.9, 66.9, 59.8, 55.7, 14.6;[23] IR (ATR) 3128, 2942, 1696, 1534, 1206, 1023, 772 cm^{-1}; HRMS calcd for $C_{13}H_{16}NO_4$ (M+H$^+$) 250.1079; found, 250.1071.

*4.3.16. 4-Cyano-6-methoxyquinoline-N-oxide (**39**).* A solution of **8** (150 mg, 0.73 mmol) and *t*-BuOH (3 mL) was added slowly to a preformed solution of *t*-BuOK (1.00 g, 8.16 mmol) in *t*-BuOH (3 mL) under nitrogen. The reaction was cooled in an ice bath for 10 min. Methyl iodide (170 μL, 1.10 mmol) was added dropwise over a period of 2 min. The solution was allowed to warm up to ambient temperature, and stirred for 3 h. The reaction was quenched with a solution of saturated NH_4Cl (10 mL) and extracted with dichloromethane (30 mL). The organic phase was washed with water (3×30 mL) and dried over magnesium sulfate ($MgSO_4$). The solvents were removed under reduced pressure and the resulting residue was purified by chromatography (hexanes/EtOAc, 9:1) to afford **39** (78.1 mg, 0.39 mmol, 53%) as a pale yellow solid.[7]

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