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A highly active catalyst for the reductive cyclization of *ortho*-nitrostyrenes under mild conditions

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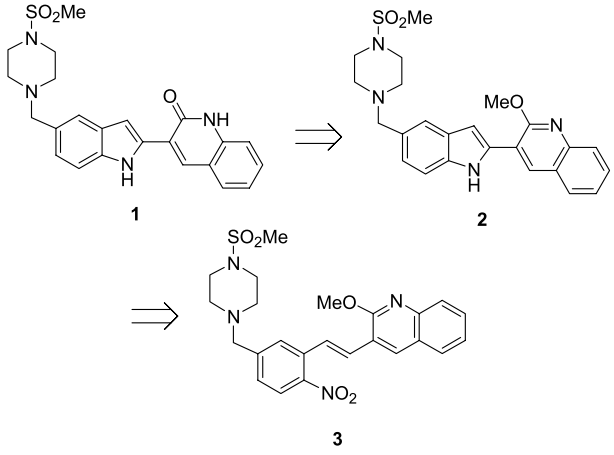
Dedicated to the memory of Jackie Smitrovich – a dear friend and a talented colleague

Abstract—A mild and efficient method for the palladium-catalyzed reductive cyclization of *ortho*-nitrostyrenes to afford indoles is reported. Treatment of *ortho*-nitrostyrenes with 0.1 mol% palladium (II) trifluoroacetate [$Pd(TFA)_2$] and 0.7 mol% 3,4,7,8-tetramethyl-1,10-phenanthroline (tm-phen) in DMF at 15 psig CO and 80 °C afforded indoles in good to excellent yields. When the reaction was conducted in toluene, the corresponding *N*-hydroxyindole was isolated. A mechanism that accounts for the formation of *N*-hydroxyindole is proposed.

1. Introduction

Substituted indoles are privileged structures[1] that are present in a wide range of pharmacophores.[2] As such, the synthesis of indoles represents a long and rich area of synthetic organic chemistry.[3] KDR kinase inhibitor **1** was identified as part of Merck's efforts[4] for blocking tumor-induced angiogenesis.[5] Due to the low solubility of **1** imparted by the quinilone ring, we proposed unmasking the quinolone in the final step, making methoxy-protected **2** our synthetic target (Scheme 1). Of the synthetic approaches investigated,[6] construction of the indol-2-yl methoxy-quinoline core of **2** by reductive cyclization of *ortho*-nitrostyrene **3** was appealing in that this substrate could be convergently assembled in a short number of steps.[7] This strategy would require a mild method for the reductive cyclization.



Scheme 1.

The Cadogan deoxygenation of nitroaromatics using boiling triethyl phosphite is now a classic synthetic method for the construction of a wide range of nitrogen-containing aromatic heterocycles and remains the most common method to affect deoxygenative cyclization.[8,9] While broad in scope, the generation of a large amount of phosphorous waste detracts from this approach. Transition metal promoted deoxygenation of nitroaromatics to give heterocycles was first realized by Waterman and Vivian in 1940 using stoichiometric iron oxalate at 200 °C.[10] In recent years, transition metal catalyzed variants of this reaction using CO as the stoichiometric reductant have been developed,[11] however, the moderate yields and extreme conditions (1175 psi CO and 220 °C) significantly limit the synthetic utility of this system. Palladium-based systems have subsequently been identified as more efficient catalysts for this transformation. The palladium-catalyzed reductive cyclization of *ortho*-nitrostyrenes in the presence of stoichiometric $SnCl_2$ at 100 °C and 275 psi CO was developed by Watanabe.[12] Söderberg reported a Pd/triphenylphoshphine system effective at

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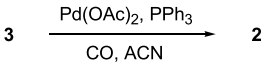
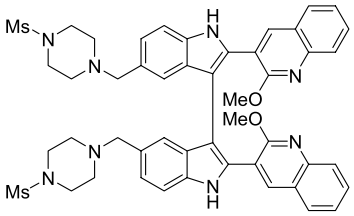
Table 1. Reductive cyclization of **3** using $Pd(OAc)_2$/triphenylphosphine



Entry	$Pd(OAc)_2$ (mol%)	PPh_3 (mol%)	CO (psig)	Temp (°C)	2 (% yield)[a]
1	6	24	60	70	95 (45)[b]
2	6	24	60	40	32
3	6	24	30	70	90
4	6	24	15	70	50
5	2	4	60	70	71
6	1	2	60	70	63

[a] HPLC assay yield.
[b] Yield reported for material isolated by crystallization.



4

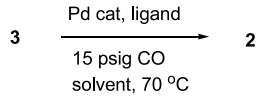
Figure 1.

lower temperatures and pressures (70 °C and 60 psi) at 6 mol% palladium loading.[13] Catalysts derived from palladium(II) salts and bidentate nitrogen ligands effect cyclization of *ortho*-nitrostyrenes at low catalyst loading, however, these reactions require harsh conditions (300 psi CO and 120 °C).[14] Catalytic alternatives effective at mild temperatures and pressures would enhance widespread uptake of this technology. Our approach to developing a highly efficient catalytic system relied upon systematic screening using a 6×8 parallel Parallel Pressure Reactor (PPR®). Results of these studies and investigations into the reaction mechanism are presented herein.

2. Results and discussion

The relatively mild pressure and temperature required for Pd/phosphine catalytic systems motivated us to apply this system towards the reductive cyclization of **3**. Using the conditions reported by Söderberg [6 mol% $Pd(OAc)_2$, 24 mol% PPh_3, CO (60 psig), 70 °C in ACN],[13] indole **2** was produced in high assay yield (95%, Table 1, entry 1). The only by-product was dimer **4** (3%, Fig. 1). Crystallization from the reaction stream resulted in a disappointing isolated yield (45%) due to the presence of triphenylphosphine and triphenylphosphine oxide. Reducing the ligand and catalyst loading resulted in decreased yields due

Table 2. Reductive cyclization using palladium/phenanthroline catalysts[a]



Entry	Catalyst (mol%)	Ligand (mol%)	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$ (1.0)	phen (2.0)	ACN	56
2	$Pd(OAc)_2$ (1.0)	phen (2.0)	THF	37
3	$Pd(OAc)_2$ (1.0)	phen (2.0)	Toluene	40
4	$Pd(OAc)_2$ (1.0)	phen (2.0)	ODCB[c]	58
5	$Pd(OAc)_2$ (1.0)	phen (2.0)	DMF	98 (94)[d]
6	$Pd(OAc)_2$ (0.5)	phen (1.0)	DMF	93
7	$Pd(OAc)_2$ (0.25)	phen (0.5)	DMF	24
8	$Pd(OAc)_2$ (0.10)	phen (0.2)	DMF	0
9	$Pd(OAc)_2$ (0.10)	phen (0.5)	DMF	6
10	$Pd(OAc)_2$ (0.10)	phen (1.0)	DMF	25
11	$Pd(OAc)_2$ (0.10)	tm-phen (0.2)	DMF	25
12	$Pd(OAc)_2$ (0.10)	tm-phen (0.5)	DMF	79
13	$Pd(OAc)_2$ (0.10)	tm-phen (1.0)	DMF	92
14	$phen_2Pd(BF_4)_2$[e] (1.0)	—	DMF	99
15	$phen_2Pd(BF_4)_2$ (0.5)	—	DMF	89
16	$phen_2Pd(BF_4)_2$ (0.25)	—	DMF	74
17	$Pd(TFA)_2$ (0.1)	phen (0.5)	DMF	32
18	$Pd(TFA)_2$ (0.1)	phen (1.0)	DMF	33
19	$Pd(TFA)_2$ (0.1)	tm-phen (0.2)	DMF	68
20	$Pd(TFA)_2$ (0.1)	tm-phen (0.5)	DMF	78
21	$Pd(TFA)_2$ (0.1)	tm-phen (1.0)	DMF	100

[a] Reactions performed at 70 °C and 15 psig CO.
[b] HPLC assay yield.
[c] *ortho*-Dichlorobenzene.
[d] Number in parentheses is yield reported for material isolated by crystallization.
[e] Pre-formed catalyst.

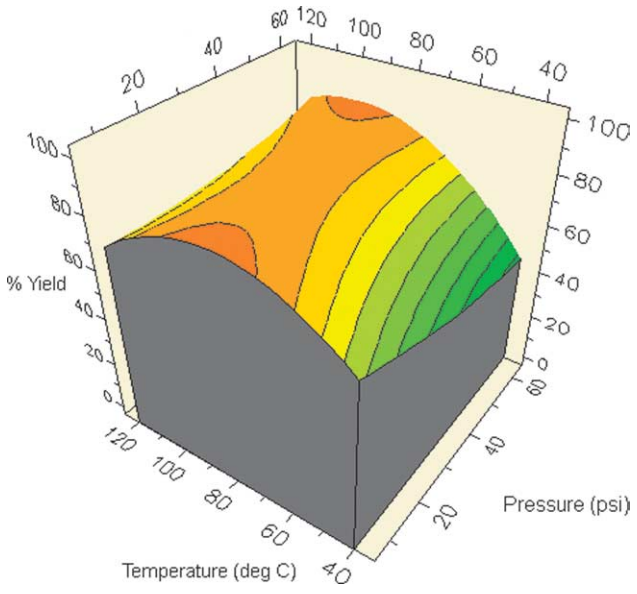
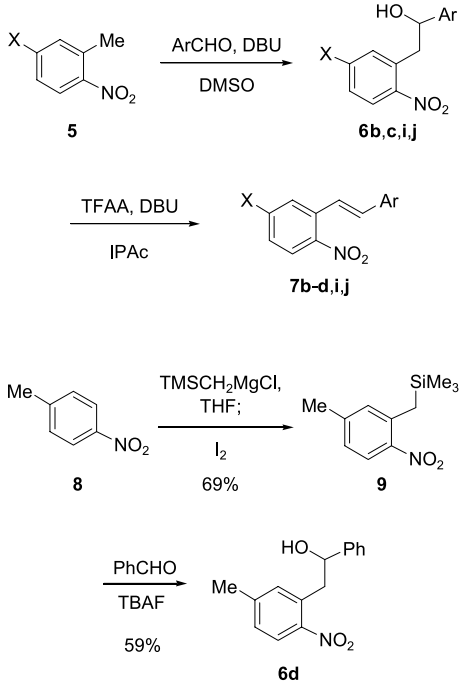


Figure 2. Temperature and pressure response surface for the cyclization of **3**.



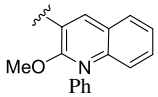
Scheme 2.

to lower conversion (entries 5 and 6). The CO pressure could be reduced to 30 psig without adversely affecting yield, but at 15 psig yield decreased due to lower conversion (entries 3 and 4). Due to the necessity for high catalyst and ligand loading, a more efficient catalytic system was sought.

Catalysts derived from palladium(II) salts and bidentate nitrogen ligands are highly reactive systems for the reduction of nitroarenes to isocyanates and carbamates[15] and have been applied to the reductive cyclization of *ortho*-nitrostyrenes at high temperatures and pressures.[13a,14] The efficiency of these systems, we proposed, may allow the reductive cyclization of **3** to occur at low catalyst and ligand loading and hence simplify isolation of indole **2**. Initial results were encouraging, with the reaction occurring at mild temperature and pressure: treatment of **3** with 1 mol% $Pd(OAc)_2$ and 2 mol% 1,10-phenanthroline (phen) in ACN at 15 psig CO and 70 °C afforded **2** in 56% yield (Table 2, entry 1). A screen of solvents identified DMF as optimal, and under identical conditions **2** was produced in 98% assay yield and 94% isolated yield (entry 5).[16] Other solvents resulted in lower conversion.

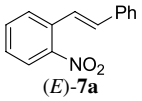
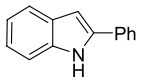
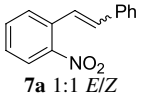
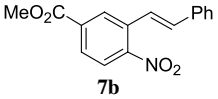
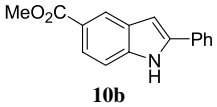
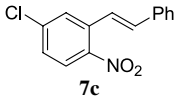
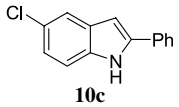
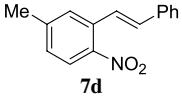
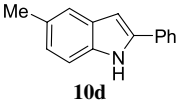
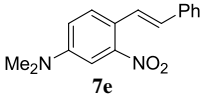
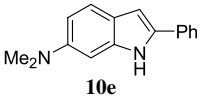
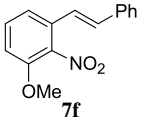
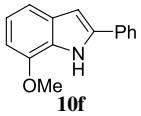
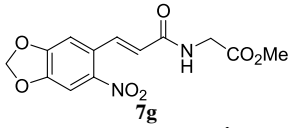
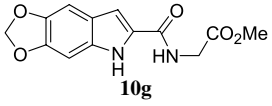
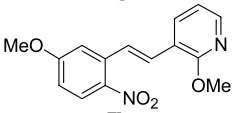
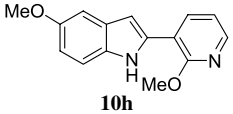
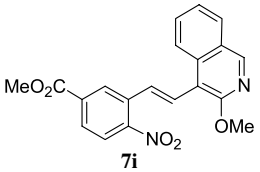
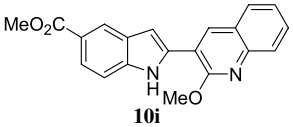
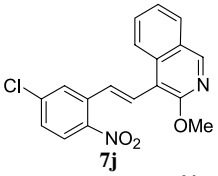
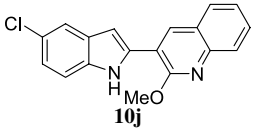
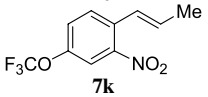
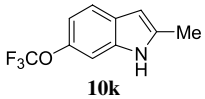
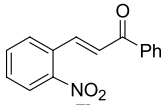
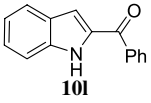
Optimization of reaction parameters was accomplished using a 6×8 module Parallel Pressure Reactor (PPR®) from Symyx Technologies, Inc. With a 1:2 $Pd(OAc)_2$/phen ratio, high yield is maintained at 0.5 mol% palladium (93%, Table 2, entry 6), but at lower palladium loading the yield dropped drastically due to decreased conversion (entry 7) and no reaction occurred at 0.1 mol% catalyst loading (entry 8). The catalyst loading could be reduced to 0.1 mol% by increasing the ligand/palladium ratio,[17] but conversion was low (entries 9 and 10). For the reductive carbonylation of nitro-arenes to afford isocyanates, increased catalytic activity is obtained with palladium (II) salts with non-coordinating counter ions and electron rich phenanthrolines.[15d,e,18] The pre-formed catalyst $phen_2Pd(BF_4)_2$[19] performed similarly to the catalyst generated in situ from 0.5 mol% $Pd(OAc)_2$ and 0.5 mol% phen (compare entries 5 and 14) and conversion dropped with decreased catalyst loading (entries 15 and 16). Due to ease of operation, the in situ catalyst system was chosen for further optimization. Palladium trifluoroacetate [$Pd(TFA)_2$] gave similar results at 0.1 mol% loading with excess phen (entries 17 and 18). Use of the more electron donating ligand and 3,4,7,8-tetramethyl-1,10-phenanthroline (tm-phen) gave higher conversion at a 10:1 ratio with $Pd(OAc)_2$ (92% assay yield, entry 13). Best results were obtained with 0.1 mol% $Pd(TFA)_2$ and 1 mol% tm-phen, affording indole **2** in 100% assay yield (entry 21).

Table 3. Preparation of substituted *ortho*-nitrostyrenes **7b–d,i,j**

Entry	X	Ar	Alcohol	Yield (%)[a]	Styrene	Yield (%)[a]
1	CO_2Me	Ph	**6b**	—	**7b**	75
2	Cl	Ph	**6c**	61	**7c**	64
3	Me	Ph	**6d**	59	**7d**	70
4	CO_2Me		**6i**	80	**7i**	87
5	Cl	Ph	**6j**	84	**7j**	93

[a] Isolated yield.

Table 4. Reductive cyclization of substituted *ortho*-nitrostyrenes[a]

Entry	Substrate	Product	Yield (%)[b]
1[c]	 (*E*)-**7a**	 **10a**	87
2[c]	 **7a** 1:1 *E*/*Z*	**10a**	86
3[d]	 **7b**	 **10b**	98
4	 **7c**	 **10c**	96
5	 **7d**	 **10d**	89
6[e]	 **7e**	 **10e**	61
7[e]	 **7f**	 **10f**	18
8[e]	 **7g**	 **10g**	72
9[f]	 **7h**	 **10h**	72
10[d]	 **7i**	 **10i**	78
11	 **7j**	 **10j**	91
12	 **7k**	 **10k**	84[g]
13	 **7l**	 **10l**	84

[a] Reaction conditions: 1 mol% $Pd(OAc)_2$, 2 mol% phen, 15 psig CO, 80 °C for 16 h in DMF, unless otherwise noted.
[b] Isolated yield.
[c] 1.5 mol% $Pd(OAc)_2$, 3 mol% phen employed.
[d] 0.1 mol% $Pd(TFA)_2$, 0.7 mol% tm-phen employed.
[e] 1.0 mol% $Pd(TFA)_2$, 2.0 mol% tm-phen employed.
[f] 1.5 mol% $Pd(OAc)_2$, 3 mol% phen, 30 psig CO. 70 °C for 16 h in DMF.
[g] HPLC assay yield.

With this catalyst system, the optimal temperature and pressure were identified by DOE (design of experiments, Fig. 2). The ranges investigated spanned 40–120 °C and 5–65 psig CO. Temperature had the greater effect of the two variables. The effect of pressure was minimal, with high yields occurring at both low and high pressure at the optimal temperatures. At 5–15 psig CO, the optimal temperature was 80 °C, with decreased conversion at temperatures <80 °C. At 65 psig, highest yields were obtained at 100 °C. Due to ease of operation, the milder reaction conditions were selected for further optimization.

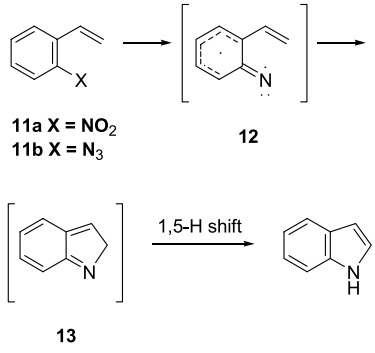
At 15 psig CO and 80 °C the ligand/palladium can be reduced to 7:1 without adversely effecting conversion. At low catalyst loadings, (0.1 mol%) rigorous air free conditions are necessary for reproducibility. Optimized conditions (0.1 mol% $Pd(TFA)_2$, 0.7 mol% tm-phen, 15 psig CO, 80 °C in DMF) afforded **2** in 94% isolated yield.

The scope was investigated using a panel of substituted *ortho*-nitrostyrenes. Substrates were commercially available, previously reported, or readily available in a few steps from commercially available starting materials. Substituted styrenes **7b–d,i,j** were prepared from the corresponding alcohols in a one pot acylation/elimination sequence with TFAA and DBU (Scheme 2, Table 3). Alcohol **6b** was prepared following the literature procedure.[20] Alcohols **6c,d,i,j** were prepared by DBU-mediated addition of the requisite *ortho*-nitrotoluene to either benzaldehyde or 2-methoxyquinoline-3-carboxaldehyde. Alcohol **6d** was prepared using the sequence optimized for **2** (Scheme 2).[6b] Addition of trimethylsilylmethylmagnesium bromide to 4-nitrotoluene followed by oxidation of the resulting nitronate intermediate with iodine afforded **9**. Treatment of **9** with catalytic tetrabutylammonium fluoride (TBAF, 0.20 mol%) in the presence of benzaldehyde afforded **6d** in 59% isolated yield. Styrenes **7e** and **7l** were prepared from the commercially available nitrobenzaldehydes by reaction with diethyl benzylphosphonate.

ortho-Nitrostyrenes **7b–l** were submitted to the reductive cyclization (Table 4). With 1 mol % $Pd(OAc)_2$ and 2 mol% phen, the catalyst and ligand can be weighed in air and added to the reaction as solids. For small scale reactions, solutions of $Pd(OAc)_2$ and phen in DMF were added to a solution of the substrate on the bench top. At 0.1 mol% catalyst loading, solutions of $Pd(TFA)_2$ and tm-phen were prepared on the bench top and then added to a solution of substrate in a nitrogen atmosphere glove box. The reductive conditions tolerate a wide range of functional groups, for example esters, aromatic chlorides, anilines and amides (entries 3, 4, 6 and 8). α,β-Unsaturated amides and ketones undergo the reaction (entries 8 and 13). Methoxy-substituted quinolines and pyridines are compatible with the conditions (entries 9–11). The olefin geometry does not effect the reaction, as demonstrated by reaction of a 1:1 mixture of (*E*)/(*Z*) isomers of **7a**,[21] which gave a comparable yield to reaction of isomerically pure (*E*)-**7a** (compare entries 1 and 2). The alkene is not required to be cross-conjugated as exemplified by entry 12, where the alkene has a methyl substituent. Electron rich substrates gave low yields under standard conditions due to poor conversion. High conversion of **7h** was obtained using 1.5 mol% $Pd(OAc)_2$ and 3 mol% phen at 30 psig CO pressure and 70 °C. Use of 1 mol% of the more reactive catalyst $Pd(TFA)_2$ with 2 mol% tm-phen was required to obtain good conversion with **7e** and **7g** and afforded indoles **10e** and **10g** in 61 and 72% isolated yields, respectively. Even under these conditions, **7f** afforded only an 18% yield due to poor conversion (entry 7).

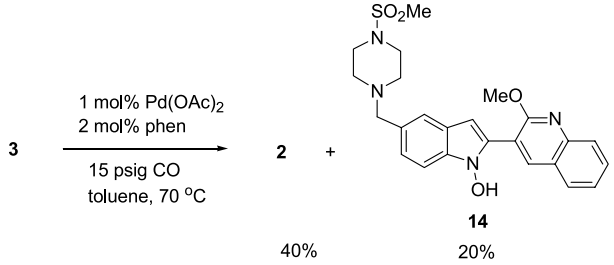
The widely accepted mechanism for the formation of heterocyclic products from nitro aromatics involves exhaustive deoxygenation to a singlet nitrene **12** which undergoes a downstream insertion into the adjacent π-bond to form **13** followed by a hydrogen migration to afford the indole (Scheme 3). This rationalization is primarily supported by the product distribution from reactions of aromatic nitro compounds and their analogous azides.[22] A significant study of the chemistry of biphenylnitrenes by laser flash photolysis and time-resolved IR experiments and by theoretical calculations has recently been published.[23] These data indicate that cyclization proceeds via a singlet nitrene with an open-shell electronic structure to form isocarbazole and a 1,5-hydrogen shift to form carbazole.

N-Hydroxy- and *N*-ethoxyindoles have been observed by Sundberg in the reduction of **11a** with triethylphosphite,

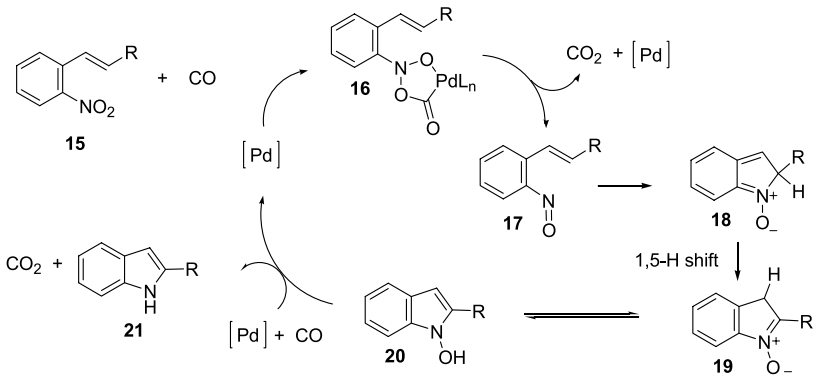


Scheme 3.

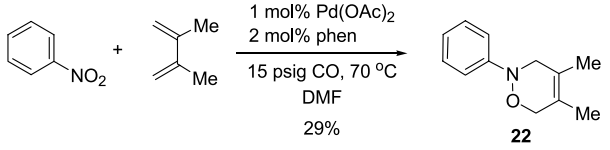
which suggests a competitive pathway might be available involving partially deoxygenated intermediates.[8c] *N*-Hydroxyindoles have been identified in the palladium-catalyzed reductive cyclization of *ortho*-nitrostyrenes in THF at 170 °C and 440 psi CO.[14a] We have observed analogous products under our milder reductive cyclization conditions. When the cyclization of styrene **3** was performed in toluene, two products were formed (Scheme 4). Expected indole **2** was isolated in 40% yield and *N*-hydroxyindole **14** was isolated in 20% yield. When **14**



Scheme 4.



Scheme 5.



Scheme 6.

was resubjected to the standard reductive cylization conditions in DMF, indole **2** was formed quantitatively.

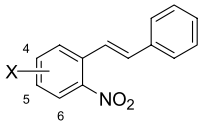
The formation of hydroxyindole **14** and its conversion to indole **2** gives some insight into the reaction mechanism. Reduction of the nitro to the nitrene does not account for the formation of **14**. We propose the following mechanism (Scheme 5). Reaction of the nitrostyrene with the catalyst and carbon monoxide gives palladacycle **16**,[24] which undergoes extrusion of CO_2 to give nitrosostyrene **17**. For the reduction of nitroaromatics to isocyanates, the nitroso species undergoes further reduction and incorporation of CO.[25] We propose that in the presence of the pendant olefin, intramolecular 6π-electron 5-atom electrocyclic reaction occurs faster than reduction, giving nitronate **18**.[26] Subsequent 1,5-hydrogen shift and isomerization affords *N*-hydroxyindole **20**, which is subsequently reduced by a second equivalent of CO to give indole **21**. The viability of the 1,5-electrocylization pathway under experimental reaction conditions has been demonstrated computationally.[27,28]

Attempts to trap nitrosostyrene **17** by conducting the cyclization reaction of *ortho*-nitrostyrene **7a** in the presence of 2,3-dimethylbutadiene were unsuccessful. Oxazine **22**[17] was produced in 29% yield from the reaction of *ortho*-nitrobenzene and 2,3-dimethylbutadiene with 1 mol% $Pd(OAc)_2$ and 2 mol% phen at 15 psig CO and 70 °C (Scheme 6). The remainder of the reaction mixture was starting material. This result indicates that aromatic nitro groups are reduced to the nitroso species under the reaction conditions. For the reaction of **7a**, intramolecular cyclization onto the pendant alkene may be faster than intermolecular cycloaddition with the diene.

In order to explore the electronic effect on the rate of reaction, competition experiments of substituted *ortho*-nitrostyrenes **7b–f** with unsubstituted **7a** (X=H) were conducted (Table 5). A 1:1 molar ratio of the substituted styrene and **7a** was submitted to the following cyclization conditions: 0.1 mol% $Pd(TFA)_2$, 0.7 mol% tm-phen, 15 psi CO, 80 °C, DMF. Relative rates were determined by HPLC assay yield of the amount of starting material remaining in the reaction mixture and are reported as an average of three experiments.

A ρ value of +1.77 was obtained by plotting log k_{rel} versus σ parameter[29] (Fig. 3), indicative of a build-up of negative charge on the nitroarene in the rate determining step of the reaction. This finding is also supported by an increase in reaction rate with the reduction potential of the nitrostyrene[30] (Fig. 4). The rate of reaction **7f**, bearing a methoxy substituent ortho to the nitro group, correlated well with the

Table 5. Substituent effects on the reductive cyclization of substituted *ortho*-nitrostyrenes



Entry	X	Substrate	E^{oa}	k_{rel}	σ_p [b]
1	4-CO_2Me	**7b**	−0.95	6.8	0.50
2	4-Cl	**7c**	−1.09	3.5	0.23
3	H	**7a**	−1.13	—	0
4	4-Me	**7d**	−1.20	0.57	−0.17
5	5-NMe_2	**7e**	−1.23	0.51	−0.15[c]
6	6-OMe	**7f**	−1.40	0.15	—

[a] $E^{o}=(E_{pc}+E_{pa})/2$.
[b] Values from Ref 30.
[c] Value reported is σ_m.

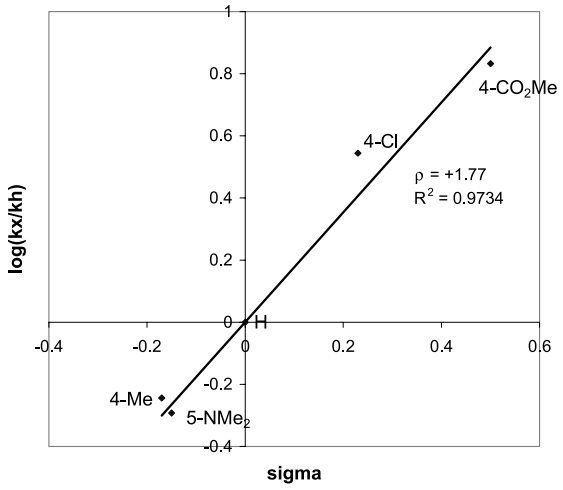


Figure 3. Hammett plot for the reaction of substituted *ortho*-nitrostyrenes **7a–e**.

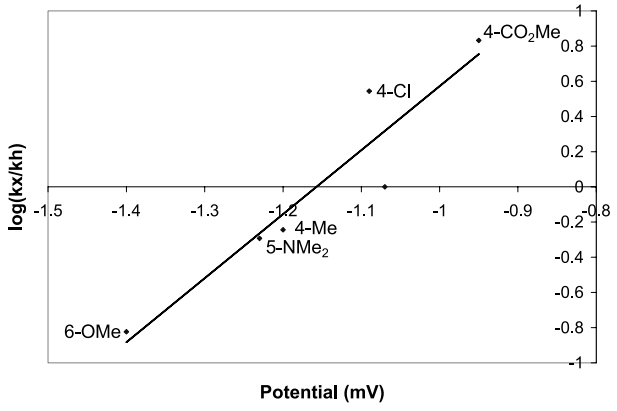


Figure 4. Plot of log k_{rel} versus reduction potential for the reductive cyclization of *ortho*-nitrostyrenes **7a–f**.

reduction potential. Severe drops in the rate of reduction of *ortho*-substituted nitroarenes by Ru(dppe)$(CO)_3$ complexes were found in arenes bearing three or more substituents.[25] Presumably, in these sterically encumbered systems, the nitro group rotates out of plane with the aromatic ring.

The electrocyclization of **17** to give **18** (Scheme 5) would not be expected to be accelerated by electron withdrawing groups.[31] A competition experiment between nitrostyrene **7b** and *N*-hydroxyindole **20a** (Scheme 5, R=Ph) indicated that the reduction of **20a** is faster than the reduction of **7b**. We propose that rate determining reduction of nitroarene **15** to nitroso intermediate **17** is followed by a faster cyclization to *N*-hydroxyindole **20**, which is then reduced to indole **21**.

3. Conclusion

We have developed a palladium-catalyzed reduction of *ortho*-nitrostyrenes to afford indoles in good to excellent yields. A range of functionality is tolerated. The cyclization occurs under much milder conditions and at lower catalyst loadings than previously reported, giving excellent yields at just 15 psig CO. Using CO as the stoichiometric reductant and 0.1 mol% palladium trifluoroacetate, CO_2 is the only stoichiometric by-product, which offers significant economic and environmental advantages over the standard triethylphosphite deoxygenation procedure.

4. Experimental

4.1. General methods

^{1}H NMR and ^{13}C NMR were recorded at ambient temperature at a frequency of 400.13 and 100.61 MHz, respectively. The chemical shifts are reported in ppm relative to residual $CHCl_3$ for proton (δ=7.27) and $CDCl_3$ for carbon (δ=77.0). The data are reported as follows: proton multiplicities (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br=broad), coupling constants, and integration. Microanalyses were performed by Quantitative Technologies, Inc. Melting points are reported uncorrected. Flash chromatography was performed using the indicated solvent system on EM Reagents silica gel (SiO_2) 60 (230–400 mesh). All reactions were carried out under an atmosphere of nitrogen, except where indicated. All reagents used were commercially available from Aldrich Chemical Co., except the following: 2-methoxyquinoline-3-carboxaldehyde[6b] was purchased from Daito Chemix Corporation, **7g** was purchased from Menai Organics, Ltd and **7l** was purchased from Acros. DMF, DMSO, toluene and DBU were dried over 4 Å molecular sieves. Solutions of $Pd(OAc)_2$, $Pd(TFA)_2$, 1,10-phenanthroline (phen) and 3,4,7,8-tetramethyl-1,10-phenanthroline (tm-phen) in DMF were prepared in air.

4.1.1. Reductive cyclization of 3 with $Pd(OAc)_2$ and PPh_3: 2-methoxy-3-(5-{[4-(methylsulfonyl)-1-piperazinyl]-methyl}-1*H*-indol-2-yl)-quinoline (2). An autoclave was charged with **3**[6b] (4.0 g, 8.3 mmol), $Pd(OAc)_2$ (0.112 g, 0.50 mmol), PPh_3 (0.520 g, 2.00 mmol) and acetonitrile (40 mL). The vessel was purged three times successively with N_2 and CO. The reactor was pressurized to 30 psig with CO heated to 70 °C. After 15 h, the reaction mixture was filtered washing with hot acetonitrile, affording dimer **4** as a pale green solid (0.224 g, 0.25 mmol, 3%) in >95% purity as determined by ^{1}H NMR spectroscopic analysis. HPLC analysis of the filtrate indicated a 95% assay yield of **2**. The filtrate was concentrated in vacuo. Crystallization from 2:1 EtOAc/hexanes provided **2** as a pale yellow solid (1.79 g, 45%): mp 197–198 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.68 (br s, 1H), 8.48 (s, 1H), 7.88 (d, J=8.4 Hz, 1H), 7.81 (d, J=8.1 Hz, 1H), 7.64 (t, J=8.4 Hz, 1H), 7.57 (s, 1H), 7.44 (m, 2H), 7.18 (dd, J=8.3, 1.4 Hz, 1H), 7.07 (s, 1H), 4.31 (s, 3H), 3.66 (s, 2H), 3.27 (m, 4H), 2.78 (s, 3H), 2.61 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.3, 145.3, 136.0, 135.2, 134.0, 129.6, 129.0, 128.3, 127.6, 127.0, 125.5, 124.8, 124.2, 121.1, 116.8, 111.3, 101.5, 63.3, 54.1, 52.3, 46.0, 34.0; Anal. Calcd for $C_{24}H_{26}N_4O_3S$: C, 63.98; H, 5.82; N, 12.44. Found: C, 64.28; H, 5.68; N, 12.05.

4.1.2. 2,2′-Bis(2-methoxyquinolin-3-yl)-5,5′-bis{[4-(methylsulfonyl)piperazin-1-yl]methyl}-1*H*,1′*H*-3-3′-biindole (4). Mp 324–326 °C (dec); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.3 (br s, 2H), 7.96 (s, 2H), 7.67 (d, J=8.3 Hz,

2H), 7.57 (dt, $J=7.0$, 1.2 Hz, 2H), 7.50 (d, $J=7.9$ Hz, 2H), 7.37 (d, $J=8.3$ Hz, 2H), 7.29 (dt, $J=7.9$, 0.8 Hz, 2H), 7.01 (m, 4H), 3.67 (s, 6H), 3.44 (d, $J=12.4$ Hz, 2H), 3.22 (d, $J=12.4$ Hz, 2H), 2.92 (m, 8H), 2.82 (s, 6H), 2.22 (m, 4H), 2.15 (m, 4H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 159.0, 144.8, 138.4, 135.6, 130.2, 129.3, 127.3, 126.9, 126.1, 124.3, 123.9, 123.1, 120.2, 118.2, 110.9, 108.2, 62.4, 52.8, 51.3, 45.1, 35.6, 33.8; HRMS calcd for $C_{48}H_{51}N_8O_6S_2$: 899.3373 (M+H). Found: 899.3372 (M+H).

4.1.3. Reductive cyclization of 3 with $Pd(OAc)_2$ and phen: (2). An autoclave was charged with was charged with **3** (45.02 g, 93.3 mmol), $Pd(OAc)_2$ (0.210 g, 0.935 mmol), 1,10-phenathroline (0.336 g, 1.87 mmol) and DMF (1.3 L). The vessel was purged three times successively with N_2 and CO. The reactor was pressurized to 15 psig with CO and the mixture heated to 70 °C. After 14 h, the vessel was allowed to cool to rt. The reaction mixture was filtered through solka flok. The filtrate was concentrated to 150 mL and heated to 50 °C. MeOH (50 mL) was added and the mixture was allowed to cool to rt. Filtration afforded **2** as a pale yellow solid (39.39 g, 94%). Spectral data was identical to that prepared by Method A.

4.1.4. Reductive cyclization of 3 with $Pd(TFA)_2$ and tmphen: (2). An Endeavor™ glass liner was charged with **3** (100 mg, 0.207 mmol) and the liner was inserted into an Endeavor™ pressure reactor. To the liner was charged $Pd(TFA)_2$ (6.02×10^{-3} M solution in DMF, 34 μL, 2.05×10^{-4} mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (1.20×10^{-2} M solution in DMF, 121 μL, 1.45×10^{-3} mmol) and DMF (2.85 mL). The reactor system was sealed and purged three times with N_2 followed by CO. The system was pressurized with CO (15 psig) and heated at 80 °C for 16 h. The mixture was cooled to rt and concentrated in vacuo. Purification by flash chromatography (2:1 EtOAc/hexanes to 4:1 EtOAc/hexanes) afforded **2** as a pale yellow solid (87 mg, 94%). Spectral data was identical to that prepared by Method A.

4.1.5. Methyl 4-nitro-3-[(*E*)-2-phenylvinyl]benzoate (7b). To a solution of **6b**[20] (1.50 g, 4.98 mmol) in isopropyl acetate (IPAc, 20 mL) was added trifluoroacetic anhydride (2.07 mL, 14.9 mmol). After 1 h, DBU (3.72 mL, 24.9 mmol) was added. After 1 h, the reaction was diluted with IPAc (20 mL) and washed with 2 N HCl (10 mL), water (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to a yellow solid. Crystallization from 1:5 EtOAc/hexanes afforded **7b** as yellow needles (1.06 g, 75%): mp 122–123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (d, $J=1.6$ Hz, 1H), 8.03 (dd, $J=8.5$, 1.7 Hz, 1H), 7.96 (d, $J=8.5$ Hz, 1H), 7.58–7.55 (m, 2H), 7.51 (s, 1H), 7.43–7.34 (m, 3H), 7.22 (d, $J=16.1$ Hz, 1H), 4.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 150.3, 136.1, 135.1, 133.9, 132.9, 129.4, 128.9, 128.8, 128.6, 127.2, 124.8, 122.0, 52.8; Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.62; H, 4.53; N, 4.94.

4.1.6. 2-(5-Chloro-2-nitrophenyl)-1-phenylethanol (6c).[20] To a solution of 5-chloro-2-nitrotoluene (9.68 g, 56.0 mmol) and benzaldehyde (4.80 mL, 47.0 mmol) in DMSO (60 mL) was added DBU (8.40 mL, 56.0 mmol). After a 36 h age, the reaction mixture was diluted with IPAc (60 mL) and washed with brine (60 mL). The layers were separated. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash chromatography (1:15 to 1:8 EtOAc/hexanes) afforded **6c** as a green tacky oil (7.03 g, 61%) in >95% purity as determined by ^{1}H NMR spectroscopic analysis: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94–7.91 (m, 1H), 7.44–7.32 (m, 7H), 5.04–5.02 (m, 1H), 3.37 (dd, $J=13.6$, 3.7 Hz, 1H), 3.21 (dd, $J=13.6$, 9.0 Hz, 1H), 2.09 (d, $J=3.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.8, 143.6, 138.7, 135.7, 133.4, 128.5, 127.7, 127.5, 126.1, 125.6, 73.6, 42.4.

4.1.7. 4-Chloro-1-nitro-2[(*E*)-2-phenylvinyl]benzene (7c).[32] To a solution of **6c** (2.01 g, 7.24 mmol) in toluene (25 mL) was added PTSA (0.275 g, 1.45 mmol). The reaction vessel was equipped with a Dean Stark apparatus and heated at 110 °C for 1 h. The mixture was cooled to rt and washed with $NaHCO_3$ (saturated aq, 2×10 mL) and water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to a yellow solid. Crystallization from 1:2 toluene/hexanes afforded **7c** as a yellow solid (0.950 g, 51%). A second crop was obtained by crystallization from 1:5 EtOAc/hexanes (0.247 g, 13%): mp 94.2–95.3 °C (lit.[30] mp 91–93 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, $J=8.8$ Hz, 1H), 7.75 (d, $J=2.2$ Hz, 1H), 7.62–7.55 (m, 3H), 7.43–7.35 (m, 4H); 7.10 (d, $J=16.1$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.0, 139.4, 136.0, 135.0, 134.9, 128.9, 128.8, 127.9, 127.8, 127.2, 126.3, 122.4.

4.1.8. Trimethyl(5-methyl-2-nitrobenzyl)silane (9). To a cooled (−40 °C) solution of 4-nitrotoluene (13.7 g, 99.9 mmol) in THF (200 mL) was added $TMSCH_2MgCl$ (1.0 M in THF, 130 mL, 130 mmol) at such a rate to maintain the reaction temperature < −30 °C. After 1 h, the reaction was warmed to −10 °C. Iodine (1 M aq, 130 mL, 130 mmol) was added and the mixture was allowed to warm to rt. After 15 min, Na_2SO_3 (saturated aq, 75 mL) was charged. The mixture was extracted with MTBE (100 mL). The layers were separated and the organic layer was washed with Na_2SO_3 (saturated aq, 50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to an orange liquid. Purification by flash chromatography (1:20 EtOAc/hexanes) afforded **9** as a pale yellow liquid (15.44 g, 69%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, $J=8.4$ Hz, 1H), 7.00 (dd, $J=8.4$, 1.0 Hz, 1H), 6.94 (s, 1H), 2.58 (s, 2H), 2.37 (s, 3H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.6, 143.7, 137.7, 131.9, 125.7, 125.4, 24.9, 21.3, −1.5; Anal. Calcd for $C_{11}H_{17}NO_2Si$: C, 59.15; H, 7.67; N, 6.27. Found: C, 59.21; H, 7.74; N, 6.16.

4.1.9. 2-(5-Methyl-2-nitrophenyl)-1-phenylethanol (6d). To a solution of **9** (14.21 g, 63.6 mmol) in IPAc (250 mL) was added benzaldehyde (6.75 mL, 66.8 mmol) followed by TBAF (1 M solution in THF, 12.7 mL, 12.7 mmol). After 2 h, NH_4Cl (saturated aq, 100 mL) was added to the reaction mixture. The layers were separated. The organic layer was washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to an orange oil. Purification by flash chromatography (1:7 to 1:3 EtOAc/hexanes) afforded **6d** as an off-white solid (9.59 g, 59%): mp 77.8–78.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, $J=8.3$ Hz, 1H), 7.44–7.36 (m,

4H), 7.32–7.31 (m, 1H), 7.20–7.18 (m, 1H), 7.14 (br s, 1H), 5.07–5.03 (m, 1H), 3.40 (dd, $J=13.5$, 3.7 Hz, 1H), 3.19 (dd, $J=13.5$, 9.1 Hz, 1H), 2.40 (s, 3H), 2.15 (d, $J=3.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.5, 144.0, 143.9, 134.1, 133.6, 128.5, 128.3, 127.8, 125.6, 125.1, 74.3, 43.1, 21.3; Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.95; H, 5.84; N, 5.43.

4.1.10. 4-Methyl-1-nitro-2-[(*E*)-2-phenylvinyl]benzene (7d). To a solution of **6d** (8.56 g, 33.3 mmol) in IPAc (150 mL) was added trifluoroacetic anhydride (14.1 mL, 99.9 mmol). After 1 h, DBU (24.9 mL, 167 mmol) was added. The mixture was heated at reflux for 14 h. Upon cooling to rt, a white solid precipitated. The mixture was filtered, washing with EtOAc. The filtrate was washed with 2 N HCl (75 mL), water (75 mL), brine (75 mL) and concentrated in vacuo to a brown oil. Purification by flash chromatography (1:10 to 1:5 toluene/hexanes) afforded **7d** as a yellow oil (5.6 g, 70%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, $J=8.4$ Hz, 1H), 7.65 (d, $J=16.1$ Hz, 1H), 7.57–7.55 (m, 3H), 7.42–7.38 (m, 2H), 7.35–7.33 (m, 1H), 7.20 (d, $J=8.3$ Hz, 1H), 7.07 (d, $J=16.1$ Hz, 1H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.7, 144.2, 136.6, 133.4, 133.2, 128.7, 128.6, 128.4, 127.0, 125.0, 124.0, 21.5; ^{13}C NMR (CD_3CN, 100 MHz) δ 147.0, 145.8, 137.9, 134.1, 133.7, 130.0, 129.9, 129.7, 129.5, 128.0, 125.9, 124.9, 21.6; Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.59; H, 5.28; N, 5.78.

4.1.11. *N*,*N*-Dimethylamino-3-nitro-4-[(*E*)-2-phenylvinyl]-aniline (7e). To a solution of diethyl benzylphosphonate (0.800 mL, 3.84 mmol) and 4-dimethylamino-2-nitrobenzaldehyde (500 mg, 2.57 mmol) in DMF (20 mL) was added KO*t*-Bu (288 mg, 2.57 mmol). After 14 h, the mixture was diluted with MTBE (20 mL) and washed with water (2×5 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to a red oil. Purification by flash chromatography (1:4 EtOAc/hexanes) afforded **7e** as a red solid (363 mg, 53%): mp 105.8–106.4 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, $J=8.8$ Hz, 1H), 7.52–7.48 (m, 3H), 7.38–7.36 (m, 2H), 7.28–7.25 (m, 1H), 7.17 (d, $J=2.8$ Hz, 1H), 6.95 (d, $J=16.2$ Hz, 1H), 6.93–6.90 (m, 1H), 3.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.6, 149.0, 137.2, 129.6, 128.6, 128.4, 127.6, 126.5, 123.4, 119.7, 116.4, 106.6, 40.1; Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.52; H, 5.96; N, 10.25.

4.1.12. 4-Methoxy-2-nitro-1-[(*E*)-2-phenylvinyl]benzene (7f). To a solution of diethyl benzylphosphonate (0.860 mL, 4.14 mmol) and 3-methoxy-2-nitrobenzaldehyde (500 mg, 2.76 mmol) in DMF (10 mL) was added NaOMe (194 mg, 3.6 mmol). After 14 h, the mixture was partitioned between water (5 mL) and MTBE (10 mL). The layers were separated. The organic layer was washed with water (2× 5 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to an oil that solidified upon standing. Crystallization from 1:9 EtOAc/hexanes afforded **7f** as a pale orange solid (435 mg, 62%): mp 112.0–113.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50–7.48 (m, 2H), 7.43–7.31 (m, 5H), 7.17 (d, $J=16.1$ Hz, 1H); 6.96–6.92 (m, 2H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.8, 140.5, 136.0, 134.1, 130.7, 130.6, 128.74, 128.71, 127.0, 120.1, 117.6, 111.0, 56.3; Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.40; H, 4.92; N, 5.36.

4.1.13. Methyl 3-[2-hydroxy-2-(2-methoxyquinolin-3-yl)ethyl]-4-nitrobenzoate (6i). To a solution of methyl 3-methyl-4-nitrobenzoate (1.19 g, 6.41 mmol) and 2-methoxyquinoline-3-carboxaldehyde (1.00 g, 5.34 mmol) in DMSO (20 mL) was added DBU (0.96 mL, 6.4 mmol). After 3 h the mixture was diluted with IPAc (100 mL) and washed with brine (100 mL). The organic layer was concentrated and purified by chromatography (4:1 EtOAc/hexanes) to afford **6i** as a pale yellow solid (1.60 g, 80%): mp 130.0–131.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (s, 1H), 8.05–8.03 (m, 2H), 7.92–7.86 (m, 2H), 7.73 (d, $J=8.8$ Hz, 1H), 7.65–7.61 (m, 1H), 7.42–7.38 (m, 1H), 5.19 (br s, 1H), 4.17 (s, 3H), 3.94 (s, 3H), 3.55–3.45 (m, 2H), 2.90–2.80 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 159.1, 152.7, 145.6, 135.4, 134.7, 134.3, 133.2, 133.1, 129.3, 128.5, 127.4, 127.1, 126.7, 125.0, 124.2, 70.0, 53.4, 52.6, 39.4; Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.82; H, 4.62; N, 7.30.

4.1.14. Methyl 3-[(*E*)-2-(2-methoxyquinolin-3-yl)vinyl]-4-nitrobenzoate (7i). To a solution of **6i** (1.60 g, 4.18 mmol) in IPAc (60 mL) was added trifluoroacetic anhydride (1.75 mL, 12.6 mmol). After the reaction was aged for 1 h, DBU (1.88 mL, 12.6 mmol) was added. After 14 h, the reaction mixture was washed with brine (20 mL) and concentrated in vacuo. Purification by flash chromatography (1:4 EtOAc/hexanes) afforded **7i** as a white solid (1.32 g, 87%): mp 186–187 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.53 (s, 1H), 8.23 (s, 1H), 8.01 (d, $J=8.4$ Hz, 1H), 8.00 (d, $J=8.4$ Hz, 1H), 7.85 (d, $J=8.1$ Hz, 1H), 7.77 (m, 2H), 7.64 (t, $J=7.6$ Hz, 1H), 7.52 (d, $J=16.8$ Hz, 1H), 7.41 (t, $J=8.4$ Hz, 1H), 4.18 (s, 3H), 4.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 159.7, 150.3, 146.2, 135.4, 133.9, 132.9, 129.9, 129.5, 129.1, 128.8, 127.7, 126.9, 125.1, 124.8, 124.7, 124.4, 121.3, 53.7, 52.8; Anal. Calcd for $C_{19}H_{16}N_2O_4$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.73; H, 4.35; N, 7.63.

4.1.15. 2-(5-Chloro-2-nitrophenyl)-1-(2-methoxyquinolin-3-yl)ethanol (6j). To a solution of 5-chloro-2-nitrotoluene (1.65 g, 9.62 mmol), 2-methoxy-3-quinoline carboxaldehyde (1.64 g, 8.74 mmol) in DMSO (40 mL) was added DBU (1.57 mL, 10.5 mmol). After 3 h, the mixture was diluted with IPAc (100 mL), washed with brine (100 mL) and concentrated in vacuo. Purification by flash chromatography (4:1 EtOAc/hexanes) afforded **6j** as a white solid (2.65 g, 84%): mp 127.1–128.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (s, 1H), 7.98–7.84 (m, 2H), 7.72 (d, $J=$ 7.6 Hz, 1H), 7.64–7.61 (m, 1H), 7.44–7.34 (m, 3H), 5.18 (br s, 1H), 4.15 (s, 3H), 3.47–3.35 (m, 2H), 3.01–2.97 (m, 1H); ^{13}C NMR (CD_3CN, 100 MHz) δ 159.1, 148.3, 145.6, 138.6, 135.4, 134.8, 132.9, 129.3, 127.5, 127.4, 127.1, 126.7, 125.9, 125.0, 124.2, 69.9, 53.4, 39.6. Anal. Calcd for $C_{18}H_{15}ClN_2O_4$: C, 60.26; H, 4.41; N, 7.81. Found: C, 60.13; H, 4.13; N, 7.73.

4.1.16. 3-[(*E*)-2-(5-Chloro-2-nitropheyl)vinyl]-2-methoxyquinoline (7j). To a solution of **6j** (1.00 g, 2.79 mmol) in IPAc (20 mL) was added trifluoroacetic anhydride (1.24 mL, 14.0 mmol). After 1 h, DBU (3.34 mL,

22.3 mmol) was added. After 14 h, the reaction mixture was washed with brine (20 mL) and concentrated in vacuo. Purification by flash chromatography (1:5 EtOAc/hexanes) afforded **7j** as a pale yellow solid (0.88 g, 93%): mp 189.0–189.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (s, 1H), 7.98 (d, J=9.2 Hz, 1H), 7.90–7.74 (m, 4H), 7.63 (t, J=8.4 Hz, 1H), 7.43 (s, 1H), 7.39 (d, J=7.6 Hz, 2H), 4.17 (s, 3H); ^{13}C NMR (CD_3CN, 100 MHz) δ 159.6, 146.3, 140.5, 139.5, 135.3, 134.9, 129.9, 129.0, 128.1, 128.0, 127.7, 126.9, 126.3, 125.1, 125.1, 124.4, 121.2, 53.7; Anal. Calcd for $C_{18}H_{13}ClN_2O_3$: C, 63.44; H, 3.85; Cl, 10.40; N, 8.22. Found: C, 63.22; H, 3.68; Cl, 10.33; N, 8.10.

4.1.17. Reductive cyclization, method A: 2-phenyl-1*H*-indole (10a).[33] On the bench top, an Endeavor™ glass liner was charged with (*E*)-**7a**,[8c] (169 mg, 0.750 mmol) and the liner was inserted into an Endeavor™ pressure reactor. To the liner was charged $phen_2Pd(OAc)_2$ {3.28×10^{-3} M solution in DMF [prepared by dissolving $Pd(OAc)_2$ (36.9 mg, 0.164 mmol) and 1,10-phenanthroline (62.0 mg, 0.328 mmol) in DMF (50 mL)], 3.43 mL, 0.011 mmol}, and DMF (2.6 mL). The reactor system was sealed and purged three times with N_2 followed by CO. The system was pressurized with CO (15 psig) and heated at 80 °C for 16 h. The mixture was cooled to rt and filtered through solka flok. The filtrate was concentrated in vacuo. Purification by flash chromatography (1:9 to 1:5 EtOAc/hexanes) afforded **10a** as a white solid (128 mg, 87%): mp 193.4–193.9 °C (lit.[31c] mp 191–192 °C).

4.1.18. Reaction of mixture of isomeric olefins, (10a). Using Method A with 1:1 (*E*/*Z*)-**4a**,[21] (169 mg, 0.750 mmol), $phen_2Pd(OAc)_2$ (3.28×10^{-3} M solution in DMF, 3.43 mL, 0.011 mmol) and DMF (2.6 mL) afforded **10a**, after purification by flash chromatography (1:9 to 1:4 EtOAc/hexanes) as a white solid (126 mg, 86%).

4.1.19. Reductive cyclization, method B: methyl 2-phenyl-1*H*-indole-5-carboxylate (10b).[34] In a nitrogen atmosphere glove box, a PPR® glass liner was charged with **7b** (141 mg, 0.500 mmol) and the liner was inserted into the Parallel Pressure Reactor system. To the liner was charged $Pd(TFA)_2$ (6.02×10^{-3} M solution in DMF, 83 μL, 5.0×10^{-4} mmol), 3,4,7,8-tetramethyl-1,10-phenathroline (1.20×10^{-2} M solution in DMF, 292 μL, 3.5×10^{-3} mmol) and DMF (2.65 mL). The reactor system was sealed and purged three times with N_2 followed by CO. The system was pressurized with CO (15 psig) and heated at 80 °C for 16 h. The mixture was cooled to rt and filtered through solka flok. The filtrate was concentrated in vacuo. Purification by flash chromatography afforded **10b** as a white solid (123 mg, 98%): mp 191.0–191.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.57 (br s, 1H), 8.41 (s, 1H), 7.92 (dd, J=8.6, 1.5 Hz, 1H), 7.69 (dd, J=8.5, 1.1 Hz, 2H), 7.50–7.35 (m, 4H), 6.91 (d, J=1.6 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 167.2, 139.7, 139.5, 131.6, 129.0, 128.2, 127.9, 125.2, 122.54. 122.51, 120.9, 111.2, 99.9, 51.6; Anal. Calcd for $C_{16}H_{13}NO_4$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.14; N, 5.47.

4.1.20. 5-Chloro-2-phenyl-1*H*-indole (10c).[31c] Using Method A with **7c**, (130 mg, 0.500 mmol), $phen_2Pd(OAc)_2$ (7.3×10^{-3} M solution in DMF, 0.70 mL, 5.1×10^{-3} mmol) and DMF (2.3 mL) afforded **10c**, after purification by flash chromatography (1:1 toluene/hexanes) as a white solid (109 mg, 96%): mp 202.9–203.7 °C (lit.[31c] mp 197–198 °C); ^{1}H NMR (d_6-DMSO, 400 MHz) δ 11.27 (br s, 1H), 7.86–7.84 (m, 2H); 7.56 (d, J=2.0 Hz, 1H), 7.49–7.45 (m, 2H), 7.39 (d, J=8.6 Hz, 1H), 7.35–7.31 (m, 1H), 7.08 (dd, J=8.6, 2.1 Hz, 1H), 6.88 (d, J=1.7 Hz, 1H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 139.3, 135.6, 131.7, 129.8, 129.0, 127.8, 125.2, 123.9, 121.4, 119.1, 112.7, 98.4.

4.1.21. 5-Methyl-2-phenyl-1*H*-indole (10d).[35] Using Method B with **7d**, (110 mg, 0.462 mmol), $phen_2Pd(OAc)_2$ (3.6×10^{-3} M solution in DMF, 1.30 mL, 4.7×10^{-3} mmol) and DMF (2.4 mL) afforded **10d**, after purification by flash chromatography (1:3 to 1:1 toluene/hexanes) as an off-white solid (85 mg, 89%): mp 221.8–223.0 °C (lit.[33b] mp 218–219 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (br s, 1H), 7.68–7.66 (m, 2H), 7.47–7.43 (m, 3H), 7.35–7.29 (m, 2H), 7.03 (dd, J=8.2, 1.2 Hz, 1H), 6.77 (d, J=1.4 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.9, 135.2, 132.5, 129.5, 129.5, 129.0, 127.6, 125.0, 124.0, 120.3, 110.5, 99.6, 21.5.

4.1.22. *N*,*N*-Dimethyl-2-phenyl-1*H*-indole-6-amine (10e). Using Method A with **7e** (56 mg, 0.21 mmol), $Pd(TFA)_2$ (3.0×10^{-3} M solution in DMF, 0.690 mL, 2.07×10^{-3} mmol), 3,4,7,8-tetramethyl-1,10-phenathroline (7.1×10^{-3} M solution in DMF, 0.58 mL, 4.1×10^{-3} mmol) and DMF (2.4 mL) afforded **10e**, after purification by flash chromatography (1:4 EtOAc/hexanes) as an off-white solid (30 mg, 61%): mp 190.4–190.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (br s, 1H), 7.63–7.61 (m, 2H), 7.48 (d, J=8.6 Hz, 1H), 7.44–7.40 (m, 2H), 7.29–7.25 (m, 1H), 6.79–6.73 (m, 3H), 2.99 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.4, 138.8, 135.2, 132.7, 128.8, 126.4, 124.2, 120.8, 120.3, 109.1, 98.5, 94.3, 41.2; Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.58; H, 6.85; N, 11.70.

4.1.23. 7-Methoxy-2-phenyl-1*H*-indole (10f). Using Method B with **7f** (100 mg, 0.391 mmol), $Pd(TFA)_2$ (6.0×10^{-3} M solution in DMF, 1.30 mL, 3.91×10^{-3} mmol), 3,4,7,8-tetramethyl-1,10-phenathroline (1.2×10^{-2} M solution in DMF, 0.650 mL, 7.8×10^{-2} mmol), and DMF (1.05 mL) afforded **10f**, after purification by flash chromatography as an off-white solid (16 mg, 18%). Spectral data matched that reported in the literature.[36]

4.1.24. Methyl *N*-(5*H*-[1,3]dioxolo[4,5-*f*]indol-6-ylcarbonyl)glycinate (10g). Using Method A with **7g** (231 mg, 0.750 mmol), $Pd(TFA)_2$ (3.56×10^{-3} M solution in DMF, 2.1 mL, 7.5×10^{-3} mmol), 3,4,7,8-tetramethyl-1,10-phenathroline (7.1×10^{-3} M solution in DMF, 2.1 mL, 1.5×10^{-2} mmol) and DMF (1.8 mL) afforded **10g**, after purification by flash chromatography (1:4 EtOAc/hexanes) as an off-white solid (149 mg, 72%): mp 259.2–261.4 °C; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 11.39 (s, 1H), 8.73 (t, J=5.9 Hz, 1H), 7.06–7.01 (m, 2H), 6.86 (s, 1H), 5.95 (s, 2H), 4.00 (d, J=10.7 Hz, 2H), 3.65 (s, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 170.9, 161.7, 146.4, 143.4, 132.4, 130.0, 121.3, 104.0, 100.8, 99.6, 92.5, 52.1, 41.1; Anal.

Calcd for $C_{13}H_{12}N_2O_5 \cdot \frac{1}{3}H_2O$: C, 55.32; H, 4.52; N, 9.93. Found: C, 55.69; H, 4.38; N, 9.67.

4.1.25. 5-Methoxy-2-(2-methoxypyridin-3-yl)-1*H*-indole (10h). Using Method A with **7h**[37] (215 mg, 0.750 mmol), $phen_2Pd(OAc)_2$ (3.28×10^{-3} M solution in DMF, 3.43 mL, 0.015 mmol) and 2.6 mL DMF at 30 psig CO and 70 °C afforded **10h**, after purification by flash chromatography (1:4 to 1:2 EtOAc/hexanes) as an off-white solid (138 mg, 72%): mp 120.7–121.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.59 (br s, 1H), 8.12 (dd, J=5.8, 1.8 Hz, 1H), 8.09 (dd, J=7.6, 1.9 Hz, 1H), 7.33 (d, J=8.8 Hz, 1H), 7.09 (d, J=2.4 Hz, 1H), 7.02 (dd, J=7.6, 4.8 Hz, 1H), 6.90–6.87 (m, 2H), 4.18 (s, 3H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.0, 154.3, 145.1, 135.6, 134.0, 131.4, 128.4, 117.6, 115.3, 112.9, 111.8, 101.5, 100.0, 55.7, 53.8; Anal. Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.68; H, 5.53; N, 10.90.

4.1.26. Methyl 2-(2-methoxyquinolin-3-yl)-1*H*-indole-5-carboxylate (10i). Using Method B with **7i** (182 mg, 0.50 mmol), $Pd(TFA)_2$ (6.02×10^{-3} M solution in DMF, 83 μL, 5.00×10^{-4} mmol), 3,4,7,8-tetramethyl-1,10-phenathroline (1.20×10^{-2} M solution in DMF, 292 μL, 3.5×10^{-3} mmol) and DMF (2.65 mL) afforded **10i**, after purification by flash chromatography (1:2 EtOAc/hexanes) as an off-white solid (130 mg, 78%): mp 206.2–206.8 °C; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 11.89 (br s, 1H), 8.73 (s, 1H), 8.31 (s, 1H), 7.94 (d, J=8.0 Hz, 1H), 7.84–7.78 (m, 2H), 7.72–7.68 (m, 1H), 7.56 (d, J=8.6 Hz, 1H), 7.52–7.48 (m, 1H), 7.32 (d, J=1.8 Hz, 1H), 4.18 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 167.1, 158.3, 144.7, 139.4, 135.4, 134.2, 129.9, 127.8, 127.7, 126.4, 124.85, 124.83, 123.0, 122.9, 120.9, 116.5, 111.3, 104.7, 53.8, 51.7; Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.28; H, 4.80; N, 8.36.

4.1.27. 3-(5-Chloro-1*H*-indol-2-yl)-2-methoxyquinoline (10j). Using Method A with **7j** (71 mg, 0.21 mmol), $phen_2Pd(OAc)_2$ (3.56×10^{-3} M solution in DMF, 0.58 mL, 2.1×10^{-3} mmol) and 2.4 mL DMF afforded **10j**, after purification by flash chromatography (1:8 EtOAc/hexanes) as an off-white solid (58 mg, 91%): mp 172–174 °C; ^{1}H NMR (d_6-DMSO, 400 MHz) δ 9.71 (br s, 1H), 8.46 (s, 1H), 7.87 (d, J=7.8 Hz, 1H), 7.79 (d, J=7.9 Hz, 1H), 7.67–7.63 (m, 2H), 7.46–7.42 (m, 1H), 7.38 (d, J=8.5 Hz, 1H), 7.17 (d, J=8.2 Hz, 1H), 7.01 (s, 1H), 4.30 (s, 3H); ^{13}C NMR (d_6-DMSO, 100 MHz) δ 158.0, 145.3, 135.4, 134.9, 134.6, 129.7, 129.1, 127.4, 126.9, 125.7, 125.3, 124.8, 122.7, 119.6, 116.0, 112.1, 100.5, 54.0. Anal. Calcd for $C_{18}H_{13}ClN_2O \cdot 0.25H_2O$: C, 69.01; H, 4.34; N, 8.94. Found: C, 69.85; H, 4.27; N, 9.11.

4.1.28. 2-Methyl-6-(trifluoromethoxy)-1*H*-indole (5k).[6a] Using Method A with **4k**[6a] (124 mg, 0.500 mmol), $tm\text{-}phen_2Pd(TFA)_2$ (6.0×10^{-3} M solution in DMF, 0.833 mL, 5.0×10^{-3} mmol), and DMF (2.2 mL) afforded **5k** in 84% assay yield.

4.1.29. 1*H*-Indol-2-yl(phenyl)methanone (10l).[8c,38] Using Method A with **7l**, (253 mg, 1.0 mmol), $phen_2Pd(OAc)_2$ (7.3×10^{-3} M solution in DMF, 1.37 mL, 0.01 mmol) and DMF (3.6 mL) afforded **10l**, after purification by flash chromatography (1:6 EtOAc/hexanes) as a white solid (187 mg, 84%): mp 151.0–151.6 °C (lit.[8c] mp 151–152 °C).

4.1.30. 2-(2-Methoxyquinolin-3-yl)-5-{[4-(methylsulfonyl)piperazine-1-yl]methyl}-1*H*-indol-1-ol (14).[6a] Using Method B with **3** (100 mg, 0.207 mmol), $phen_2Pd(OAc)_2$ (1.55×10^{-3} M solution in toluene, 1.33 mL, 2.07×10^{-3} mmol) and toluene (1.7 mL) afforded **14**, after purification by flash chromatography (1:1 toluene/hexanes) as an off-white solid (20 mg, 20%). Spectral data matched that reported in the literature.[6a]

4.1.31. 4,5-Dimethyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (22).[17] Using Method B with nitrobenzene (43 μL, 0.41 mmol), $phen_2Pd(OAc)_2$ (3.56×10^{-3} M solution in DMF, 1.16 mL, 4.13×10^{-3} mmol), 2,3-dimethylbutadiene (0.5 mL, 4.4 mmol) and DMF (4.3 mL) at 15 psig CO and 70 °C afforded **22** in 29% assay yield.

4.2. Electrochemical measurements

All electrochemical measurements were performed with a Bioanalytical Systems (BAS) Model C-3 electrochemical analyzer and were conducted at room temperature. Experiments were carried out with tetra-*n*-butylammonium hexafluorophosphate (0.45 M solution in DMF) electrolyte which was degassed with nitrogen while in the electrochemical cell. A polished working Pt electrode, a Pt auxiliary electrode, and a Ag/AgCl pseudoreference electrode were used. Potentials were referenced to Fc^+/Fc couple versus Ag/AgCl pseudoreference electrode, which was observed at 0.41 V. Reversible reduction was observed for **7a–f** at a scan rate of 100 mV/s.

4.3. Competition experiments, sample experimental

A PPR® glass liner was charged with **7a** (37.0 mg, 0.164 mmol) and **7e** (44.0 mg, 0.164 mmol). The liner was taken into a nitrogen atmosphere glove box and inserted into the Parallel Pressure Reactor system. To the liner was charged $Pd(TFA)_2$ (6.02×10^{-3} M solution in DMF, 27 μL, 1.6×10^{-4} mmol), 3,4,7,8-tetramethyl-1,10-phenathroline (1.20×10^{-2} M solution in DMF, 96 μL, 1.1×10^{-3} mmol) and DMF (2.9 mL). The reactor system was sealed and purged three times with N_2 followed by CO. The system was pressurized with CO (15 psig) and heated at 80 °C for 1 h. The mixture was cooled to rt and diluted with acetonitrile. HPLC analysis of the amounts of **7a** and **7e** remaining in the reaction were as follows: **7a** (7.9 mg, 0.035 mmol), **7e** (19.9 mg, 0.074 mmol).

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