Tetrahedron 64 (2008) 9675–9684

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Palladium-catalyzed synthesis of quinoxaline derivatives

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ARTICLE INFO

Article history:
Received 5 June 2008
Received in revised form 10 July 2008
Accepted 18 July 2008
Available online 24 July 2008

Keywords:
Palladium-catalyzed annulation
Quinoxaline

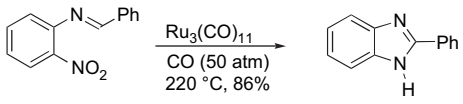
ABSTRACT

A palladium-catalyzed reductive N-heteroannulation of enamines derived from 2-nitrobenzenamines forming mixtures of 1,2-dihydroquinoxalines and 3,4-dihydroquinoxalin-2-ones is described. The reactions are performed using bis(dibenzylideneacetone)palladium(0), 1,3-bis(diphenylphosphino)propane, and 1,10-phenanthroline in DMF under 6 atm of carbon monoxide at 70 °C.

1. Introduction

A variety of heterocyclic compounds have been prepared by transition metal-catalyzed reductive N-heteroannulation of 2-substituted nitrobenzenes.[1] Examples of heterocycles obtained in this fashion include indoles,[2] 2*H*-indazoles,[3] quinolines,[3] 4(1*H*)-quinolones,[4] quinazolines,[5] 4(3*H*)-quinazolinones,[6] pyrrolines,[7] benzimidazoles,[8–10] benzotriazoles,[11] 1,4-dihydro-2*H*-3,1-benzoxazin-2-ones,[12] and 2,1-benzoisoxazole.[3] Palladium has predominantly been used as the catalyst of choice. However, other transition metals, such as iron,[13] manganese,[6b] cobalt,[6b] ruthenium,[14] platinum,[14] selenium,[15] rhodium,[14] and molybdenum[16] have successfully been employed in reductive *N*-heteroannulations of 2-substituted nitrobenzenes.

Cenini et al. have reported a ruthenium-catalyzed reductive N-heteroannulation of intermediately formed 2-nitro-*N*-(phenylmethylene)benzenamines forming 2-substituted benzimidazoles.[9] For example, reaction of 2-nitro-*N*-(phenylmethylene)benzenamine (**1**) with carbon monoxide (50 atm, 220 °C), in the presence of a catalytic amount of triruthenium dodecacarbonyl, gave 2-phenylbenzimidazole (**2**) in 86% yield (Scheme 1). In situ formation of enamines from 2-nitrobenzenamine and aromatic aldehydes or heptanal, using the same catalyst and reaction conditions, also furnished 2-substituted benzimidazoles. Palladium complexes also catalyzed this reaction using aromatic aldehydes but failed using heptanal.[8] In addition to the palladium- and ruthenium-catalyzed reactions, potassium tetracarbonyl-hydridoferrate ($KHFe(CO)_4$) has been reported to mediate the transformation of **1** to **2** in low isolated yield.[17]



1 2

Scheme 1.

In a systematic effort to expand our palladium-catalyzed methodology for the formation of indoles to the synthesis of benzimidazoles and other heterocycles containing two or more nitrogen atoms, we turned our attention to reactions of imines. 2-Nitro-*N*-(4-nitrophenylmethylene)benzenamine (**3**),[18] formed by condensation between 2-nitrobenzenamine and 4-nitrobenzaldehyde, was reacted with carbon monoxide (4 atm, 70 °C) in the presence of a catalytic amount of palladium diacetate and triphenylphosphine (Scheme 2). To our disappointment, 2-(2-nitrophenyl)benzimidazole (**4**) was not observed under the reaction conditions; only recovered imine, and hydrolysis products thereof were isolated. We have previously noted that some substituted 2-nitrostyrenes do not undergo annulation to form indoles under the above conditions, but could be cyclized using a catalytic amount of bis(dibenzylidenacetone)palladium ($Pd(dba)_2$), 1,3-bis(diphenylphosphino)propane (dppp), and 1,10-phenanthroline (phen) in DMF under 6 atm of carbon monoxide at temperatures between 70 and 120 °C.[19,20] However, the latter conditions also failed to produce the expected benzimidazole **4** from **3**.

The failure to produce a 2-substituted benzimidazole was initially thought to be a consequence of the size and/or electronics of

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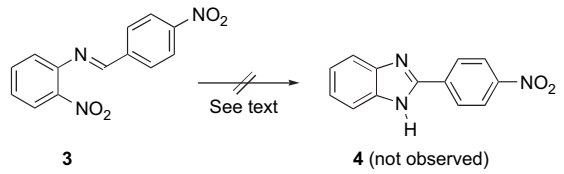
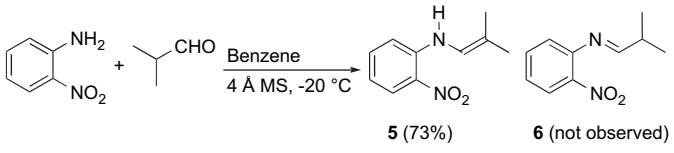
doi:10.1016/j.tet.2008.07.083

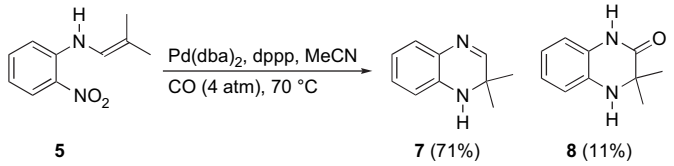


Scheme 2.

the 4-nitrophenyl group. Thus, the formation and cyclization of imines derived from smaller aliphatic aldehydes was examined next. However, reaction of 2-nitrobenzenamine with 2-methylpropanal furnished enamine **5** and not the expected imine **6** (Scheme 3). The enamine **5** was subjected to the N-heteroannulation conditions consisting of $Pd(dba)_2$ (0.07 mol %) and dppp (0.07 mol %) in DMF (~0.1 M) under 4 atm of carbon monoxide with the anticipation of a rapid enamine–imine tautomerization followed by cyclization to give 2-(1-methylethyl)benzimidazole.[21] However, after complete consumption of starting material and purification, two new products, 1,2-dihydroquinoxaline **7** and 3,4-dihydroquinoxalinone **8**, were isolated in place of the expected benzimidazole (Scheme 4).



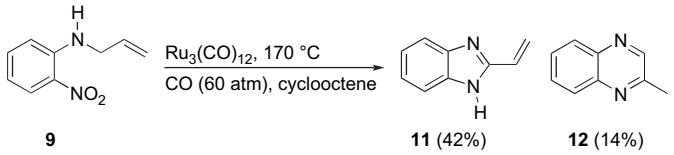
Scheme 3.



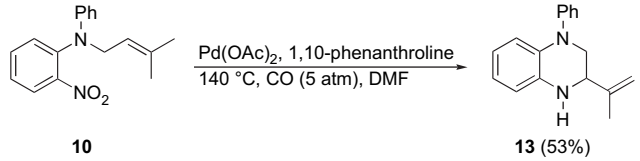
Scheme 4.

Quinoxalines have been isolated in two cases from N-heteroannulations of *N*-(2-propen-1-yl)-2-nitrobenzenamine (**9**)[22] or *N*-phenyl-*N*-(2-methyl-2-propen-1-yl)-2-nitrobenzenamine (**10**)[23] using a triruthenium dodecacarbonyl (7 mol %) or palladium diacetate (60 mol %), respectively (Schemes 5 and 6). 2-Ethenylbenzimidazole **11** was the major product from the ruthenium-catalyzed reaction.

The reaction conditions for the annulation seen in Scheme 4 are significantly milder compared to the ruthenium-catalyzed reaction.



Scheme 5.



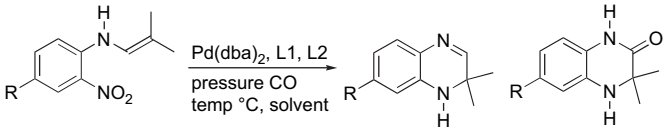
Scheme 6.

In addition, the yield of quinoxaline products is substantially higher. Thus, the scope and limitations of this novel cyclization to give quinoxaline derivatives from 2-nitrobenzenamine-derived enamines were examined and the results are reported herein.[24]

2. Results and discussion

Optimization of the reaction conditions for the synthesis of quinoxalines was examined first. Two different enamines **14** (R=Me) and **15** (R=OMe) were prepared by condensation of commercially available 4-methyl-2-nitrobenzenamine and 4-methoxy-2-nitrobenzenamine with 2-methylpropanal, and used in this optimization (Table 1). The choice of solvent proved to be of importance. For example, reaction of enamine **14** in acetonitrile using the original condition seen in Scheme 4 did, surprisingly, not produce any quinoxaline product even at twice the catalyst load (entry 1). However, simply changing the solvent to DMF gave under the same reaction conditions **16** and **17** in 35% and 21% yield, respectively (entry 2). Raising the reaction temperature to 150 °C and pressure to 6 atm of CO proved detrimental (entry 3). As has been observed previously, a higher yield of products **16** and **17** was realized from **14** when 1,10-phenanthroline monohydrate was added as a co-ligand in addition to dppp (entry 4).[25] Not only was the overall yield higher, but also all starting material was consumed after 2 h. The same effect but to a much higher extent was observed for **15**. For **15**, unsatisfactory yield were obtained both at 70 and 150 °C at 6 atm of CO (entries 5 and 6). However, addition of 1,10-phenanthroline monohydrate gave **18** in high yield and selectivity (entry 7). It is presently unclear why two bidentate ligands are required to obtain an optimum yield. As expected, no reaction occurred in the absence of carbon monoxide (entry 8). The CO pressure did affect both the yield and product distribution using **15**, and a higher ratio of quinoxaline to quinoxalinone (**18** to **19**) was observed at higher CO pressures. Almost no quinoxalinone **19** was isolated at 16 atm of CO (entry 12). Although a higher ratio of

Table 1
Optimization of reaction conditions



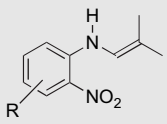
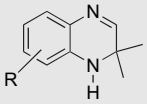
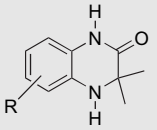
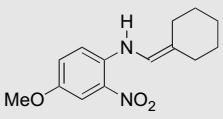
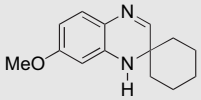
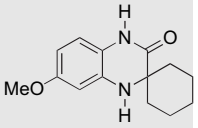
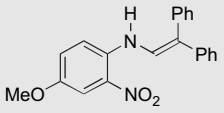
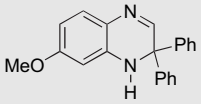
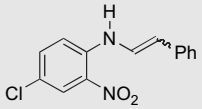
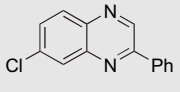
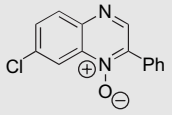
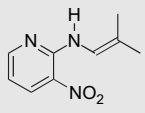
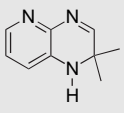
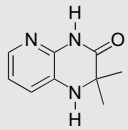
Entry	**14**/**15**	Solvent[a]	L1= dppp[b] (mol %)	L2= phen[c] (mol %)	CO pressure[d] (atm)	Temperature (°C)	Time (h)	Yield **16**:**17** or **18**:**19** (%)
1	**14**	MeCN	13	—	4	70	68	0
2	**14**	DMF	6	—	4	70	120	35:21
3	**14**	DMF	7	—	6	140	60	20:3
4	***14***	*DMF*	*7*	*14*	*6*	*70*	*2*	*50:45*
5	**15**	DMF	9	—	6	70	120	1:6
6	**15**	DMF	8	—	6	150	17	0:13
7	***15***	*DMF*	*6*	*12*	*6*	*70*	*36*	*88:1*
8	**15**	DMF	6	12	No CO	70	18	0
9	**15**	DMF	6	12	2	70	18	60:9
10	**15**	DMF	6	12	4	70	18	83:3
11	**15**	DMF	6	12	8	70	18	88:3
12	**15**	DMF	6	12	16	70	18	99:1
13[e]	**15**	DMF	6	12	6	70	18	60:6
14[e]	**15**	DMF	—	12	6	70	18	50:3

[a] Substrate concentration ~0.1 M for entries 1–6 and ~0.3 M for entries 7–14; ratio $Pd(dba)_2$/L1=~1:1.
[b] dppp=1,3-bis(diphenylphosphino)propane.
[c] phen=1,10-phenanthroline monohydrate.
[d] Initial CO pressure.
[e] $Pd(OAc)_2$ was used as the catalyst in place of $Pd(dba)_2$.

products was obtained at higher pressures, 6 atm was selected as the standard pressure (entry 7) due to the ease of manipulations using simple glass pressure equipment compared to the steel reaction vessel required at pressures above 8 atm. Finally, palladium diacetate could be used as the catalyst, however lower yields were observed (entries 13 and 14).

A variety of enamines were prepared by condensation of substituted 2-nitrobenzenamines with aliphatic aldehydes, usually 2-methylpropanal. The results of the condensation reactions are summarized in Table 2. Most condensation reactions were carried out in benzene or dichloromethane at ambient temperature, under an inert atmosphere, in the presence of 4 Å molecular sieves. The yield of **22** was substantially improved by heating the reaction mixture in a standard microwave oven. In general, the condensation reactions produced the desired enamines in good yields. It should be noted that all enamines prepared underwent noticeable hydrolysis upon standing at ambient temperature for a short period of time. Enamine **22** was particularly unstable and was therefore used immediately after purification in the next step. The low isolated yield of **22** is likely a reflection of its instability. Attempts to generate **22** in situ and immediately submit the compound to the annulation conditions without purification failed to give quinoxaline products.

Table 2
Synthesis of quinoxalines and quinoxalinones

Entry	Enamine[a]	Quinoxaline[b]	Quinoxalinone[b]
			
1	**14** (R=4-Me, 89%)	**16** (50%)	**17** (45%)
2	**15** (R=4-OMe, 94%)	**18** (88%)	**19** (1%)
3	**20** (R=4-Cl, 99%)	**31** (56%)	**32** (16%)
4	**21** (R=5-Cl, 88%)	**33** (29%)	**33** (45%)
5	**22** (R=6-Me, 5%)	**35** (27%)	**34** (42%)
6	**23** (R=3-Me, 36%)	**37** (63%)	**35** (12%)
7	**24** (R=4-COPh, 20%)	**39** (<52%)	
8	**25** (R=4-CO_2Me, 74%)	—	
9	**26** (R=4-NO_2, 77%)	—	
			
10	**27** (88%)	**40** (70%)	**41** (13%)
			
11	**28** (91%)	**42** (69%)	
			
12	**29** (85%)[c]	**43** (25%)	**44** (14%)
			
13	**30** (20%)[d]	**45** (34%)	**46** (6%)

[a] Isolated yield of enamine from the corresponding 2-nitrobenzenamine and aldehyde.
[b] Isolated yield of 1,2-dihydroquinoxaline and 3,4-dihydroquinoxalinone.
[c] As a 6:4 *E*/*Z* mixture.
[d] 21% of an aminal was also isolated.

We were unable to prepare enamines from a 2-nitroaminobenzene and unbranched aliphatic aldehydes such as heptanal by this methodology, again probably a reflection of the sensitivity of the enamines to hydrolysis. In addition to pursuing ring-substituted 2-nitroaminobenzenes, a pyridine-derived enamine was also prepared. Thus, condensation of 2-amino-3-nitropyridine and 2-methylpropanal gave the desired compound **30**, but in low yield. The main product of the reaction was the corresponding aminal formed from two molecules of 2-amino-3-nitropyridine.

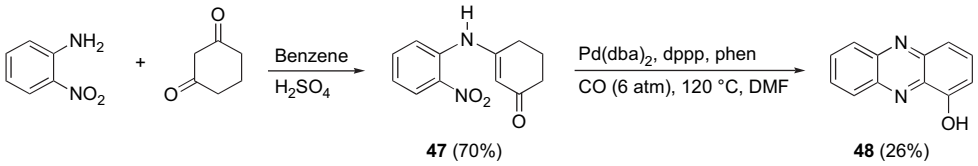
With a variety of enamines available, the N-heteroannulation was examined next. Enamines having an electron-rich aromatic ring gave varying ratios of quinoxaline and quinoxalinone products in all cases examined (Table 2, entries 1–6). The expected spirocyclic products were obtained from enamine **27** (entry 10), and in the case of the diphenyl-substituted enamine **28** only the corresponding quinoxaline **42** was isolated (entry 11). In contrast, enamines having an electron-poor aromatic ring gave lower or no yield of cyclized products. Impure material was obtained from the phenylketo-substituted enamine **24**. The product consisting mainly of the quinoxaline **39** could not be further purified. Although completely consumed during the reaction, both the carbomethoxy- and nitro-substituted enamines (**25** and **26**) did not produce any identifiable products (entries 8 and 9). The fully aromatic quinoxaline **43** and corresponding *N*-oxide **44** were obtained using the mono-phenyl substituted enamine **29**, albeit in lower yields (entry 12). Finally, low yields of products were also obtained from the pyridine-derived enamine **30** (entry 13).

In addition to the enamines described in Table 1, one additional enamine was examined. Condensation of 1,3-cyclohexanedione with 2-nitrobenzenamine gave enamine **47** in 70% isolated yield (Scheme 7). N-heteroannulation of **47** gave the fully aromatic compound **48** in low isolated yield.

The initial hypothesis that imines derived from 2-nitrobenzenamines would undergo palladium-catalyzed reductive N-heteroannulation to afford 2-substituted benzimidazoles, was revisited. Since the condensation reactions between 2-nitrobenzenamines and aldehydes did not furnish any observable amount of imines, the well-documented aza-Wittig reaction between organic azides and aldehydes was examined.[26] In the event, aryl-azide **49** was treated with triphenylphosphine followed by addition of a large excess of 2-methylpropanal affording a deep red reaction mixture. ^{1}H NMR of this mixture was inconclusive with broad unresolved signals. Thus, the crude product was immediately submitted to the annulation conditions, from which three products were obtained, the azide-reduction product, 2-methyl-6-nitrobenzeneamine, the expected 2-(1-methylethyl)-4-methylbenzimidazole **50**, and dihydroquinoxaline **35** (Scheme 8). The benzimidazole was the major product from this reaction and was probably formed by annulation of the imine. This is the first example of a palladium-catalyzed reductive N-heteroannulation forming a benzimidazole from an imine derived from an aliphatic aldehyde.[27]

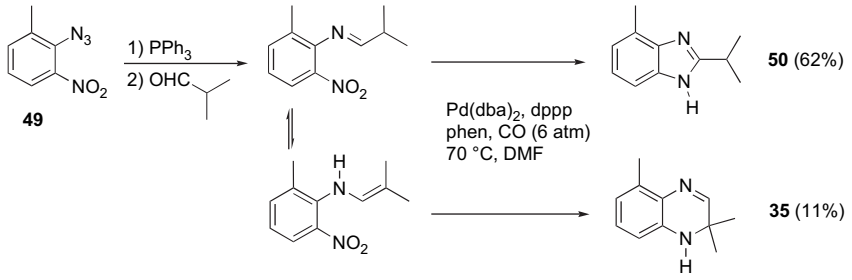
The parent compound, 1-azido-2-nitrobenzene, was reacted in a similar fashion with triphenylphosphine and heptanal followed by annulation (Scheme 9). Three products were again isolated and characterized, 2-hexylbenzimidazole (**51**), 2-pentylquinoxaline (**52**), and 2-pentylquinoxaline-1-oxide (**53**). The latter type of product was also observed using compound **29** (Table 2, entry 12). Considering that mixtures of products were obtained by the aza-Wittig-annulation sequence, this approach to benzimidazoles was not further pursued.

Water in the solvent, or in the carbon monoxide, was initially considered a possible source of the 3,4-dihydroquinoxalinone



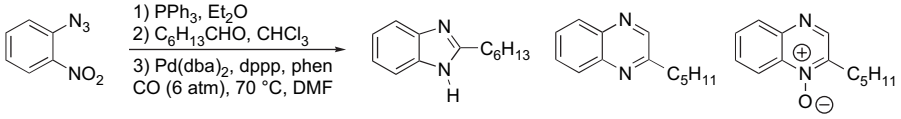
47 (70%) **48** (26%)

Scheme 7.



49 **50** (62%) **35** (11%)

Scheme 8.



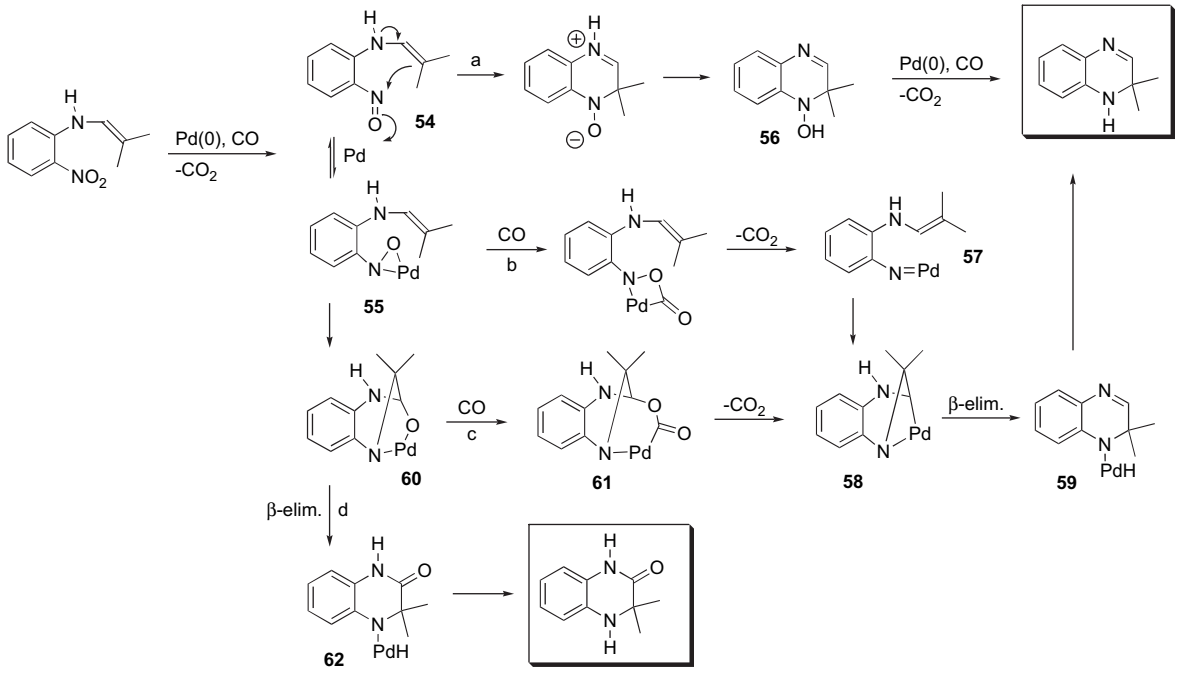
51 (14%) **52** (25%) **53** (8%)

Scheme 9.

oxygen. However, reaction of enamine **5** in a 1:1 DMF–water mixture gave only the 1,2-dihydroquinoxaline **7** in 37% yield in addition to a small amount of starting material. No trace of 3,4-dihydroquinoxalinone **8** was observed by ^{1}NMR of the crude reaction mixture. It should be noted that only hydrolysis of the enamine was observed using water as the solvent.

Oxidation of the 1,2-dihydroquinoxaline to the 3,4-dihydroquinoxalinone was not observed under standard reaction conditions. For example, no trace of oxidation of 1,2-dihydroquinoxaline **21** could be detected after prolonged treatment with the catalytic system. The reverse reaction, i.e., reduction of 3,4-dihydroquinoxalinone to 1,2-dihydroquinoxaline, was also disproved under the same conditions. These results suggest that the 3,4-dihydroquinoxalinone oxygen is derived from the nitro group.

The mechanism of the annulation reaction is presently unclear; however, a few possible sequences of events are outlined in Scheme 10. The true mechanism is most likely more complex. Transition metal-catalyzed deoxygenation of organic nitro-compounds has

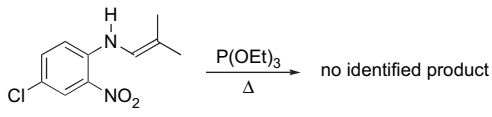


Scheme 10.

been proposed to proceed via the formation of a free or metal-complexed nitrosoarene, in this case compounds **54** and **55**, respectively.[28] The nitrosoarene can undergo cyclization with the adjacent enamine to give an *N*-hydroxy-1,2-dihydroquinoxaline **56** (path a). This intermediate is finally deoxygenated by the catalyst system to give a 1,2-dihydroquinoxaline, a reaction with precedence in literature.[29] A second deoxygenation may occur from the metal-bound nitrosoarenes, affording a free or metal-bound nitrene (**57**, path b). An intramolecular [2+2] cycloaddition between the intermediately formed palladium-bound nitrene **57** and the alkene would furnish the bicyclic compound **58**. Sequential β-hydride elimination, at least formally, to give **59** followed by reductive elimination would again produce a 1,2-dihydroquinoxaline and regenerate the active palladium(0) catalyst. It should be pointed out that no reaction apart from hydrolysis of the enamine was observed in the absence of carbon monoxide. The regioselectivity of the cycloaddition parallels the selectivity observed for intramolecular ketene–alkene cycloadditions of terminally disubstituted alkenes. A related mechanism has been suggested for thermal decompositions of arylamino-substituted Fischer carbene complexes forming quinolines.[30] In addition the formation of a palladium-bound nitrene was suggested for the formation of the tetrahydroquinoxaline seen in Scheme 6.[23]

It is also possible that the enamine inserts into the palladium-bound nitroarene forming a bicyclic complex **60**. Insertion of carbon monoxide forming **61** and deinsertion of carbon dioxide would furnish **58**, the intermediate suggested in path b. Finally, formation of intermediate **62** is possible if insertion of carbon monoxide is slower compared to β-hydride elimination from **60** (path d). Reductive elimination of **62** would then furnish a quinoxalinone. It should be noted that the β-elimination step from **58** and **60** is not a one-step reaction since the hydrogen and the metal cannot achieve a *syn* relationship. The mechanistic picture is supported by the observation that the ratio of 1,2-dihydroquinoxaline to 3,4-dihydro-2-quinoxalinone is significantly increased at higher carbon monoxide pressures (Table 1, entries 7–11), i.e., the rate of deoxygenation is increased (paths b and c).

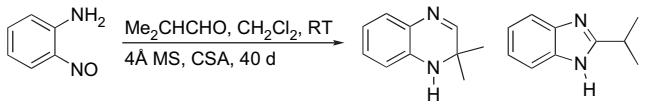
A phosphorus-bound nitrene has been suggested as an intermediate for trialkylphosphite-mediated reductive annulations of 2-nitrostyrenes to give indoles (Cadogan–Sundberg reaction). This type of reducing agent was also examined in this study, however, reaction of **20** with triethylphosphite at 170–180 °C did not furnish any identifiable product (Scheme 11). The absence of quinoxaline product(s) is not so surprising considering the thermal instability of the starting enamines.



20

Scheme 11.

In order to probe into the involvement of a free or a metal-bound 2-nitrosoarene as an intermediate in the annulation reaction, 2-nitrosobenzenamine **63** was prepared according to the procedure reported by Haddadin et al.[31,32] Unfortunately, all attempts to isolate the corresponding 2-nitrosoenamine by condensation with 2-methylpropanal, as described above, failed. Surprisingly, reaction of 2-nitrosobenzenamine with 2-methylpropanal gave dihydroquinoxaline **7** and 2-(1-methylethyl)-benzimidazole (**64**), albeit in very low yields and after prolonged reaction times (Scheme 12). Although the starting material was consumed in the reaction, no other products were identified. It is likely that the dihydroquinoxaline and benzimidazole are formed from the corresponding enamine and imine intermediate, respectively. However, it is unclear how the nitroso-oxygen is lost in the reaction.



63 **7** (5%) **64** (3%)

Scheme 12.

In conclusion, a novel synthesis of functionalized 1,2-dihydroquinoxalines and 3,4-dihydro-2-quinoxalinones has been developed. Some mechanistic insights lending support for nitrosoarene/nitrene intermediates have been presented. Current efforts are focused on the selective synthesis of either 1,2-dihydroquinoxalines or 3,4-dihydro-2-quinoxalinones.

3. Experimental section

3.1. General procedures

NMR spectra were determined in $CDCl_3$ at 270 MHz (^1H NMR) and 67.5 MHz (^{13}C NMR) unless otherwise noted. The chemical shifts are expressed in δ values relative to $(CH_3)_4Si$ (0.00, ^1H and ^{13}C) or $CDCl_3$ (7.26, ^1H and 77.0, ^{13}C) internal standards. ^1H–^1H coupling constants are reported as calculated from spectra; thus, a slight difference in $J_{a,b}$ and $J_{b,a}$ is usually obtained. Results of APT (attached proton test) ^{13}C NMR experiments are shown in parentheses, where relative to $CDCl_3$, (−) denotes CH_3 or CH and (+) denotes CH_2 or C.

Benzene and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Hexanes, acetonitrile, ethyl acetate, and dichloromethane were distilled from calcium hydride. Chemicals prepared according to literature procedures have been referenced the first time they are used; all other reagents were obtained from commercial sources and used as received. Silica gel (200–400 mesh) was used for flash chromatography. Solvents were removed using a rotary evaporator at water aspirator pressure unless otherwise noted.

*3.1.1. 2-Nitro-N-(2-methyl-1-propene-1-yl)benzenamine (**5**)*

To a solution of 2-nitrobenzenamine (502 mg, 3.63 mmol) and 2-methylpropanal (330 μL, 3.64 mmol) dissolved in benzene (10 mL) at −20 °C under argon atmosphere was added 4 Å molecular sieves (4 g); the molecular sieves were activated by heating to 120 °C under vacuum overnight and then stored under argon atmosphere. The reaction was allowed to sit without stirring or agitation at −20 °C for 14 days. The molecular sieves were removed by filtration and rinsed with CH_2Cl_2. The filtrate was concentrated and the crude product was purified by chromatography (hexanes/EtOAc, 95:5) to give **5** (510 mg, 2.65 mmol, 73%) as a red solid. Mp 38–40 °C; ^1H NMR δ 9.64 (br s, 1H), 8.18 (d, J=8.4, 1.5 Hz, 1H), 7.44 (dt, J=8.6, 1.5 Hz, 1H), 7.05 (d, J=8.7 Hz, 1H), 6.70 (dt, J=6.9, 1.2 Hz, 1H), 6.27 (dm, J=8.2, 1.2 Hz, 1H), 1.82 (s, 3H), 1.80 (s, 3H); ^{13}C NMR δ 141.3 (+), 136.0 (−), 131.6 (+), 126.7 (−), 118.4 (+), 118.2 (−), 116.3 (−), 114.1 (−), 22.5 (−), 16.6 (−); IR (neat) 1639 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{12}N_2O_2$ (M^+) 192.0899, found 192.0899.

*3.1.2. 4-Methyl-2-nitro-N-(2-methyl-1-propene-1-yl)-benzenamine (**14**)*

Reaction of 4-methyl-2-nitrobenzenamine (501 mg, 3.29 mmol), 2-methylpropanal (300 μL, 3.3 mmol), and 4 Å molecular sieves (4 g) in benzene (10 mL) at ambient temperature (20 h), as described for **5**, gave after chromatography (hexanes/EtOAc, 95:5), **14** (601 mg, 2.91 mmol, 89%) as a red solid. Mp 53–55 °C; ^1H NMR δ 9.56 (br s, 1H), 7.98 (s, 1H), 7.27 (dd, J=8.6, 2.2 Hz, 1H), 6.96 (d, J=8.9 Hz, 1H),

6.27 (dm, J=9.6 Hz, 1H), 2.28 (s, 3H), 1.81 (s, 3H), 1.79 (s, 3H); ^{13}C NMR δ 139.4 (+), 137.5 (−), 131.1 (+), 126.0 (+), 125.8 (−), 118.4 (−), 117.4 (+), 114.1 (−), 22.4 (−), 19.9 (−), 16.6 (−); IR (neat) 1632 cm^{-1}. Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 64.06; H, 6.84. Found: C, 64.18; H, 6.70.

3.1.3. 4-Methoxy-2-nitro-N-(2-methyl-1-propene-1-yl)-benzenamine (**15**)

4-Methoxy-2-nitrobenzenamine (506 mg, 3.01 mmol) was added to an airless flask under a stream of argon. 2-Methylpropanal (300 μL, 3.29 mmol) was added via syringe. Freshly distilled benzene (10 mL) was then added to the flask. The flask was gently heated with a heat-gun to dissolve the benzenamine. Approximately 5 g of 4 Å molecular sieves (the sieves were activated by heating at 120 °C under vacuum overnight) was added under a stream of argon. The reaction was allowed to sit for 20 h without stirring; a slow color change from yellow to deep purple was observed. The solution was filtered and the molecular sieves were washed with CH_2Cl_2. The solvents were removed from the filtrate at water aspirator pressure. The crude product was purified by column chromatography (hexanes/ethyl acetate, 98:2) to give **15** (635 mg, 2.86 mmol, 95%) as a deep red solid. Mp 57–59 °C; ^{1}H NMR δ 9.61 (d, J=8.2 Hz, 1H), 7.60 (d, J=2.7 Hz, 1H), 7.15 (dd, J=9.4, 3.0 Hz, 1H), 7.02 (d, J=9.4 Hz, 1H), 6.27 (dm, J=9.6 Hz, 1H), 3.81 (s, 3H), 1.81 (s, 3H), 1.79 (s, 3H); ^{13}C NMR δ 150.2 (+), 137.0 (+), 130.6 (+), 127.1 (−), 118.5 (−), 117.5 (+), 115.5 (−), 106.5 (−), 55.6 (−), 22.4 (−), 16.6 (−); IR (neat) 1638, 1520, 1162, 1122 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35. Found: C, 59.18; H, 6.42.

3.1.4. 4-Chloro-2-nitro-N-(2-methyl-1-propene-1-yl)-benzenamine (**20**)

Reaction of 4-chloro-2-nitrobenzenamine (505 mg, 2.93 mmol), 2-methylpropanal (270 μL, 2.9 mmol), and 4 Å molecular sieves (4 g) in benzene (10 mL) at ambient temperature (26 h), as described for **5**, gave without further purification **20** (660 mg, 2.91 mmol, 99%) as a red solid. Mp 109–110 °C; ^{1}H NMR δ 9.58 (d, J=8.2 Hz, 1H), 8.17 (d, J=2.7 Hz, 1H), 7.38 (dd, J=9.2, 2.5 Hz, 1H), 7.01 (d, J=9.1 Hz, 1H), 6.22 (dm, J=9.6, 1.2 Hz, 1H), 1.82 (s, 3H), 1.79 (s, 3H); ^{13}C NMR δ 140.0 (+), 136.2 (−), 131.5 (+), 125.9 (−), 121.2 (+), 119.9 (+), 118.0 (−), 115.7 (−), 22.5 (−), 16.8 (−); IR (neat) 1641 cm^{-1}. Anal. Calcd for $C_{10}H_{11}ClN_2O_2$: C, 52.99; H, 4.89. Found: C, 53.08; H, 4.82.

3.1.5. 5-Chloro-2-nitro-N-(2-methyl-1-propene-1-yl)-benzenamine (**21**)

Reaction of 5-chloro-2-nitrobenzenamine (504 mg, 2.92 mmol), 2-methylpropanal (300 μL, 3.3 mmol), and 4 Å molecular sieves (4 g) in CH_2Cl_2 (15 mL) at ambient temperature (24 h), as described for **5**, gave without further purification, **21** (585 mg, 2.58 mmol, 88%) as a red solid. Mp 99–100 °C; ^{1}H NMR δ 9.60 (br s, 1H), 8.13 (d, J=9.2 Hz, 1H), 7.02 (d, J=2.2 Hz, 1H), 6.66 (dd, J=9.2, 2.2 Hz, 1H), 6.19 (d, J=9.4 Hz, 1H), 1.83 (s, 3H), 1.79 (s, 3H); ^{13}C NMR δ 142.8 (+), 141.8 (+), 130.3 (+), 128.2 (−), 120.5 (+), 117.8 (−), 116.9 (−), 113.8 (−), 22.5 (−), 16.8 (−); IR (neat) 3112, 1570 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{11}ClN_2O_2$ (M^+) 226.0509, found 226.0500.

3.1.6. 6-Methyl-2-nitro-N-(2-methyl-1-propene-1-yl)-benzenamine (**22**)

To a solution of 2-methyl-6-nitrobenzenamine (1.03 g, 6.77 mmol) and 2-methylpropanal (2.00 mL, 22.0 mmol) dissolved in 1,2-dichloroethane (20 mL) in an ACE-Glass threaded pressure tube was added 4 Å molecular sieves until the level of the sieves was just below that of the solvent. The pressure tube was capped tightly with a threaded Teflon plug. The reaction was heated in a standard microwave oven for 30 s and then allowed to cool for 3-5 min. This was repeated until the total heating time reached 15 min. The molecular sieves were removed by filtration and washed with CH_2Cl_2. The filtrate was concentrated and the crude product was purified by chromatography (hexanes/EtOAc, 9:1) to give **22** (71 mg, 0.34 mmol, 5%) as a red paste.[33] ^{1}H NMR δ 8.75 (d, J=5.9 Hz, 1H), 7.95 (d, J=8.6 Hz, 1H), 7.30 (d, J=7.4 Hz, 1H), 6.76 (t, J=7.7 Hz, 1H), 5.98 (d, J=8.4 Hz, 1H), 2.40 (s, 3H), 1.76 (s, 3H), 1.72 (s, 3H); ^{13}C NMR δ 141.5 (+), 138.2 (−), 137.3 (+), 129.4 (+), 124.2 (−), 124.1 (−), 118.5 (−), 114.6 (+), 22.2 (−), 20.9 (−), 16.3 (−); IR (neat) 1634, 1598, 1339 cm^{-1}.

3.1.7. 3-Methyl-2-nitro-N-[(2-methyl)-1-propene-1-yl]-benzenamine (**23**)

Reaction of 3-methyl-2-nitrobenzenamine (500 mg, 3.29 mmol), 2-methylpropanal (500 μL, 5.5 mmol), and 4 Å molecular sieves (15 g) in benzene (20 mL) at ambient temperature (3 days), as described for **5**, gave after chromatography (hexanes), **23** (241 mg, 1.17 mmol, 36%) as a red paste.[33] ^{1}H NMR δ 8.24 (d, J=8.4 Hz, 1H), 7.23 (t, J=7.9 Hz, 1H), 6.84 (d, J=8.6 Hz, 1H), 6.58 (d, J=7.4 Hz, 1H), 6.12 (d, J=9.4 Hz, 1H), 2.49 (s, 3H), 1.78 (s, 3H), 1.73 (s, 3H); ^{13}C NMR δ 140.3 (+), 135.9 (+), 135.5, 133.3 (−), 120.5 (−), 119.4 (−), 116.8 (+), 112.3 (−), 22.5 (−), 21.6 (−), 16.6 (−).

3.1.8. [4-(2-Methylpropenylamino)-3-nitrophenyl]phenyl-methanone (**24**)

Reaction of 3-nitro-4-aminobenzophenone (500 mg, 2.06 mmol), 2-methylpropanal (300 μL, 3.3 mmol), and 4 Å molecular sieves (15 g) in CH_2Cl_2 (40 mL) at ambient temperature (12 days), as described for **5**, gave after chromatography (hexanes/EtOAc, 9:1), **24** (120 mg, 0.41 mmol, 20%) as a red paste.[33] ^{1}H NMR δ 9.96 (d, J=9.4 Hz, 1H), 8.66 (d, J=2.0 Hz, 1H), 8.04 (dd, J=9.1, 2.0 Hz, 1H), 7.75 (dd, J=8.4, 1.5 Hz, 2H), 7.60 (t, 1H), 7.50 (t, 2H), 7.14 (d, J=9.1 Hz, 1H), 6.34 (d, J=9.4 Hz, 1H), 1.86 (s, 3H), 1.84 (s, 3H); ^{13}C NMR δ 193.4 (+), 143.4 (+), 137.4 (+), 136.8 (−), 132.3 (−), 130.7 (−), 130.5 (+), 129.4 (−), 128.5 (−), 125.5 (+), 121.8 (+), 117.6 (−), 114.3 (−), 22.6 (−), 16.9 (−); IR (neat) 1650, 1612, 1209, 1132 cm^{-1}.

3.1.9. Methyl 4-(N-2-methyl-1-propene-1-yl)amino-3-nitro-benzoate (**25**)

Reaction of methyl 4-amino-3-nitrobenzoate (500 mg, 2.55 mmol), 2-methylpropanal (500 μL, 55.1 mmol), camphor sulfonic acid (10 mg), 4 Å molecular sieves (50 g) in CH_2Cl_2 (150 mL) at ambient temperature (11 days), as described for **5**, gave after chromatography (hexanes/EtOAc, 95:5) **25** (470 mg, 1.88 mmol, 74%) as a red solid. Mp 121–124 °C; ^{1}H NMR δ 9.87 (d, J=11.4 Hz, 1H), 8.89 (d, J=2.0 Hz, 1H), 8.05 (dd, J=9.2, 1.5 Hz, 1H), 7.06 (d, J=9.2 Hz, 1H), 6.30 (d, J=9.4 Hz, 1H), 3.91 (s, 3H), 1.85 (s, 3H), 1.82 (s, 3H); ^{13}C NMR δ 165.4 (+), 143.4 (+), 136.1 (−), 131.0 (+), 129.4 (−), 121.2 (+), 118.1 (+), 117.6 (−), 113.9 (−), 52.1 (−), 22.6 (−), 16.8 (−); IR (neat) 1707, 1615, 1523, 1437, 1287, 1217 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{14}N_2O_4$ (M^+) 250.0954, found 250.0960.

3.1.10. 2,4-Dinitro-N-(2-methyl-1-propene-1-yl)benzenamine (**26**)

The same procedure as described for **22** was repeated except that a mixture of 2,4-dinitrobenzenamine (1.00 g, 5.46 mmol), 2-methylpropanal (1.00 mL, 13.9 mmol), and 1,2-dichloroethane (20 mL) was reacted for a total of 15 min. Purification by chromatography (hexanes/EtOAc, 9:1) gave **26** (1.00 g, 4.21 mmol, 77%) as a red solid. Mp 113–115 °C; ^{1}H NMR δ 10.06 (d, J=8.2 Hz, 1H), 9.16 (d, J=2.5 Hz, 1H), 8.27 (dd, J=9.6, 2.7 Hz, 1H), 7.12 (d, J=9.6 Hz, 1H), 6.32 (d, J=9.4 Hz, 1H), 1.88 (s, 3H), 1.85 (s, 3H); ^{13}C NMR δ 143.8 (+), 136.5 (+), 130.0 (−), 129.9 (+), 124.1 (−), 124.0 (+), 117.0 (−), 114.4 (−), 22.5 (−), 16.8 (−); IR (neat) 1590, 1426 cm^{-1}. Anal. Calcd for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67. Found: C, 50.79; H, 4.77.

3.1.11. 4-Methoxy-2-nitro-N-(cyclohexylmethylene)-benzenamine (**27**)

Reaction of 4-methoxy-2-nitrobenzenamine (508 mg, 3.02 mmol), formylcyclohexane (360 μL, 3.2 mmol), and 4 Å molecular sieves

(4 g) in benzene (10 mL), at ambient temperature (2.5 h), as described for **5**, gave without further purification **27** (696 mg, 2.65 mmol, 88%) as a red solid. Mp 46–48 °C; ^{1}H NMR δ 9.68 (br s, 1H), 7.60 (d, J=2.7 Hz, 1H), 7.15 (dd, J=9.4, 3.2 Hz, 1H), 7.05 (d, J=9.2 Hz, 1H), 6.22 (d, J=9.4 Hz, 1H), 3.81 (s, 3H), 2.3–1.5 (m, 10H); ^{13}C NMR δ 150.3 (+), 137.4 (+), 130.6 (+), 127.2 (−), 126.1 (+), 115.6 (−), 115.5 (−), 106.6 (−), 55.7 (−), 33.6 (+), 28.3 (+), 27.5 (+), 26.9 (+), 26.6 (+); IR (neat) 2929, 1517 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}N_2O_3$ (M^+) 262.1317, found 262.1310.

3.1.12. 4-Methoxy-2-nitro-N-(2,2-diphenylethenyl)-benzenamine (**28**)

Reaction of 4-methoxy-2-nitrobenzenamine (304 mg, 1.80 mmol), diphenylethanal (400 μL, 2.3 mmol), 4 Å molecular sieves (15 g) in CH_2Cl_2 (30 mL) at ambient temperature (3 days), as described for **5**, gave after chromatography (hexanes/EtOAc, 9:1) **28** (572 mg, 1.65 mmol, 92%) as a red solid. Mp 152–153 °C; ^{1}H NMR δ 9.93 (d, J=11.6 Hz, 1H), 7.53 (d, J=2.7 Hz, 1H), 7.48–7.05 (m, 13H), 3.74 (s, 3H); ^{13}C NMR δ 151.3 (+), 140.7 (+), 137.4 (+), 135.1 (+), 132.2 (+), 129.7 (−), 129.3 (−), 128.4 (−), 127.9 (−), 126.6 (−), 126.5 (two overlapping peaks; both −), 124.0 (+), 121.6 (−), 115.8 (−), 107.4 (−), 55.8 (−); IR (neat) 3055, 1517 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{19}N_2O_3$ (M+H^+) 347.1390, found 347.1391.

3.1.13. (E)-4-Chloro-2-nitro-N-(2-phenylethen-1-yl)benzenamine (**29-E**) and (Z)-4-chloro-2-nitro-N-(2-phenylethen-1-yl)benzenamine (**29-Z**)

Reaction of 4-chloro-2-nitrobenzenamine (1.00 g, 5.79 mmol), phenylethanal (700 μL, 6.0 mmol), and 4 Å molecular sieves (15 g) in CH_2Cl_2 (35 mL) at ambient temperature (20 h), as described for **5**, gave after solvent removal **29-E** and **29-Z** (1.35 g, 4.99 mmol, 86%, E/Z=6:4, by ^{1}H NMR) as a red solid. The compounds partially decompose/hydrolyze upon column chromatography. Small amount of pure **29-Z** was obtained having the following analytical data: mp 104–106 °C; ^{1}H NMR δ 10.41 (d, J=10.6 Hz, 1H), 8.20 (d, J=2.5 Hz, 1H), 7.5–7.4 (m, 5H), 7.27 (tt, J=6.9, 1.7 Hz, 1H), 7.18 (d, J=9.2 Hz, 1H), 6.64 (dd, J=11.1, 9.4 Hz, 1H), 5.83 (d, J=9.2 Hz, 1H); ^{13}C NMR δ 138.9 (+), 136.3 (−), 135.2 (+), 132.7 (+), 129.1 (−), 127.7 (−), 127.1 (−), 126.1 (−), 122.9 (+), 122.5 (−) 115.8 (−), 111.5 (−); IR (neat) 3317, 1640 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{11}ClN_2O_2$ (M^+) 274.0509, found 274.0513.

Partial data for the E isomer: ^{1}H NMR δ 9.87 (d, J=11.9 Hz, 1H), 9.14 (d, J=2.5 Hz, 1H), 7.6–7.2 (m, 6H), 7.06 (d, J=15.8 Hz, 1H), 6.98 (d, J=11.4 Hz, 1H), 6.16 (d, J=15.6 Hz, 1H).

3.1.14. 3-Nitro-N-[(2-methyl)-1-propen-1-yl]-2-pyridinamine (**30**) and N-(1-(3-nitropyridin-2-ylamino)-2-methylpropyl)-3-nitropyridin-2-amine

Reaction of 2-amino-3-nitropyridine (505 mg, 3.63 mmol), 2-methylpropanal (350 μL, 3.9 mmol), and 4 Å molecular sieves (15 g) in CH_2Cl_2 (35 mL) at ambient temperature (5 days), as described for **5**, gave after chromatography (hexanes/EtOAc, 9:1), in order of elution, **30** (139 mg, 0.72 mmol, 20%) as a red solid and *N*-(1-(3-nitropyridin-2-ylamino)-2-methylpropyl)-3-nitropyridin-2-amine (258 mg, 0.78 mmol, 43%) as a yellow solid. Analytical data for **30**: mp 62–64 °C; ^{1}H NMR δ 9.87 (br s, 1H), 8.5–8.4 (m, 2H), 7.08 (d, J=8.2 Hz, 1H), 6.8–6.6 (m, 1H), 1.84 (s, 3H), 1.82 (s, 3H); ^{13}C NMR δ 155.8 (−), 148.4 (+), 135.4 (−), 127.6 (+), 117.3 (−), 116.8 (+), 112.8 (−), 22.7 (−), 16.8 (−); IR (neat) 2917, 1604 cm^{-1}. Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74. Found: C, 56.06; H, 5.69.

Analytical data for N-(1-(3-nitropyridin-2-ylamino)-2-methylpropyl)-3-nitropyridin-2-amine: mp 101–103 °C; ^{1}H NMR δ 8.81 (d, J=7.9 Hz, 2H), 8.45–8.35 (m, 4H), 6.73–6.67 (m, 2H), 6.29 (quartet, J=7.6 Hz, 1H), 2.63 (octet, J=6.9 Hz, 1H), 1.11 (d, J=6.7 Hz, 6H); ^{13}C NMR δ 155.2 (−), 151.7 (+), 135.1 (−), 128.1 (+), 112.4 (−), 64.2 (−), 32.0 (−), 18.4 (−); IR (neat) 3372, 1600, 1569, 1481, 1443, 1245 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}N_6O_4$ (M^++H^+) 333.1311, found 333.1300.

3.1.15. 1,2-Dihydro-2,2-dimethylquinoxaline[34] (**7**) and 3,4-dihydro-3,3-dimethyl-2-quinoxalinone[35] (**8**)

2-Nitro-*N*-[(2-methyl)-1-propenyl]benzenamine (**5**) (102 mg, 0.53 mmol), $Pd(dba)_2$ (20 mg, 0.035 mmol), 1,3-bis(diphenylphosphino)propane (dppp) (15 mg, 0.036 mmol), and acetonitrile (5 mL) were combined in an ACE-Glass threaded pressure tube fitted with a pressure head. The tube was flushed three times with carbon monoxide and then pressurized to 4 atm. The reaction was heated and stirred at 70 °C under CO (4 atm, 20 h). The reaction mixture was filtered through Celite and washed with CH_2Cl_2. The solvent was removed at reduced pressure and the product was purified by chromatography (hexanes/EtOAc, 7:3) to give **7** (60 mg, 0.375 mmol, 71%) and **8** (10 mg, 0.057 mmol, 11%) as off-white solids. Mp for **7**: 103–104 °C (lit.[34] 107 °C). Mp for **8**: 178–179 °C (lit.[35] 179–181 °C).

3.1.16. 1,2-Dihydro-2,2,7-trimethylquinoxaline (**16**) and 3,4-dihydro-3,3,6-trimethyl-2-quinoxalinone[35] (**17**)

Reaction of **14** (102 mg, 0.49 mmol), $Pd(dba)_2$ (18 mg, 0.031 mmol), dppp (14 mg, 0.034 mmol), and phen (12 mg, 0.067 mmol) in DMF (5 mL) at 70 °C under CO (6 atm, 2 h), as described for **7**, gave after chromatography (hexanes/EtOAc, 7:3) **16** (43 mg, 0.25 mmol, 50%) and **17** (42 mg, 0.22 mmol, 45%) as off-white solids. *Analytical data for* **16**: mp 112–115 °C; ^{1}H NMR δ 7.23 (s, 1H), 7.13 (d, J=7.7 Hz, 1H), 6.53 (d, J=7.7 Hz, 1H), 6.31 (s, 1H), 3.87 (d, J=4.2 Hz, 1H), 2.24 (s, 3H), 1.30 (s, 6H); ^{13}C NMR δ 159.5 (−), 139.0 (+), 136.4 (+), 129.2 (+), 127.4 (−), 119.2 (−), 114.1 (−), 50.3 (+), 27.1 (−), 21.4 (−); IR (neat) 3240, 2964, 1610, 1482, 1453, 1322, 1246 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}N_2$ 174.1157, found 174.1163.

Analytical data for **17**: mp 140–141 °C (lit.[35] mp 140 °C).

3.1.17. 1,2-Dihydro-2,2-dimethyl-7-methoxyquinoxaline (**18**) and 3,4-dihydro-3,3-dimethyl-6-methoxy-2-quinoxalinone[36] (**19**)

Reaction of **15** (200 mg, 0.90 mmol), $Pd(dba)_2$ (31 mg, 0.05 mmol), dppp (22 mg, 0.05 mmol), 1,10-phenanthroline (19 mg, 0.10 mmol) in DMF (3 mL) at 70 °C under CO (6 atm, 36 h), as described for **7**, gave after chromatography (hexanes/EtOAc, 85:15 followed by 6:4) **18** (151 mg, 0.80 mmol, 88%) and **19** (2.0 mg, 0.0097 mmol, 1%) both as off-white solids. *Analytical data for* **18**: mp 65–66 °C; ^{1}H NMR δ 7.20–7.10 (m, 2H), 6.26 (dd, J=8.6, 2.5 Hz, 1H), 6.02 (d, J=2.5 Hz, 1H), 3.85 (s, 1H), 3.74 (s, 3H), 1.30 (s, 6H); ^{13}C NMR δ 160.1 (+), 157.7 (−), 137.8 (+), 128.6 (−), 125.7 (+), 103.4 (−), 98.9 (−), 55.2 (−), 50.1 (+), 27.1 (−); IR (neat) 3362, 3260, 2963, 1619, 1583, 1454, 1249, 1209, 1166, 1035 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}N_2O$ 190.1106, found 190.1103.

Analytical data for **19**: mp 210–213 °C (lit.[36] 200 °C).

3.1.18. 7-Chloro-1,2-dihydro-2,2-dimethylquinoxaline (**31**) and 6-chloro-3,4-dihydro-3,3-dimethyl-2-quinoxalinone[37] (**32**)

Reaction of **20** (100 mg, 0.44 mmol), $Pd(dba)_2$ (17 mg, 0.029 mmol), dppp (12 mg, 0.029 mmol), and phen (12 mg, 0.067 mmol) in DMF (5 mL) at 70 °C under CO (6 atm, 2 h), as described for **7**, gave after chromatography (hexanes/EtOAc, 7:3) in order of elution **31** (48 mg, 0.25 mmol, 56%) and **32** (15 mg, 0.070 mmol, 16%) as off-white solids. Analytical data for **31**: mp 136–138 °C; ^{1}H NMR δ 7.26 (s, 1H), 7.14 (d, J=8.2 Hz, 1H), 6.67 (dd, J=8.4, 2.2 Hz, 1H), 6.48 (d, J=2.2 Hz, 1H), 3.75 (s, 1H), 1.33 (s, 6H); ^{13}C NMR δ 160.3 (−), 137.6 (+), 133.8 (+), 129.9 (+), 128.7 (−), 118.2 (−), 113.3 (−), 50.3 (−), 27.2 (−); IR (neat) 3229, 2972, 1600, 1480, 1451, 1238 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{11}ClN_2$ 194.0611, found 194.0611.

Analytical data for **32**: mp 175–176 °C (lit.[37] 166–170 °C).

*3.1.19. 6-Chloro-1,2-dihydro-2,2-dimethylquinoxaline (**33**) and 7-chloro-3,4-dihydro-3,3-dimethyl-2-quinoxalinone[38] (**34**)*

Reaction of **21** (200 mg, 0.88 mmol), $Pd(dba)_2$ (30 mg, 0.052 mmol), dppp (23 mg, 0.056 mmol), and phen (21 mg, 0.117 mmol) in DMF (10 mL) at 70 °C under CO (6 atm, 5.5 h), as described for **7**, gave after chromatography (hexanes/EtOAc, 8:2) **33** (50 mg, 0.26 mmol, 29%) and **34** (84 mg, 0.40 mmol, 45%) as off-white solids. *Analytical data for **33***: mp 112–114 °C; ^{1}H NMR δ 7.29 (d, J=1.7 Hz, 1H), 7.23 (d, J=2.5 Hz, 1H), 6.96 (dd, J=8.4, 2.2 Hz, 1H), 6.42 (d, J=8.4 Hz, 1H), 3.78 (br s, 1H), 1.31 (s, 6H); ^{13}C NMR δ 161.5 (−), 135.3 (+), 132.1 (+), 128.4 (−), 127.3 (−), 122.5 (+), 114.5 (−), 50.4 (+), 27.0 (−); IR (neat) 3249, 2970, 1600, 1485, 1455 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{11}ClN_2$ 194.0611, found 194.0619.

*3.1.20. 1,2-Dihydro-2,2,5-trimethylquinoxaline (**35**) and 3,4-dihydro-3,3,8-trimethyl-2-quinoxalinone[36] (**36**)*

Reaction of **22** (43 mg, 0.21 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), dppp (7 mg, 0.017 mmol), and phen (7 mg, 0.039 mmol) in DMF (5 mL) at 70 °C under CO (6 atm, 2 h), as described for **7**, gave after chromatography (hexanes/EtOAc, 8:2) **35** (10 mg, 0.057 mmol, 27%) and **36** (17 mg, 0.089 mmol, 42%) as off-white solids. *Analytical data for **35***: mp 79–81 °C; ^{1}H NMR δ 7.29 (s, 1H), 6.91 (t, J=7.7 Hz, 1H), 6.58 (d, J=7.7 Hz, 1H), 6.35 (d, J=7.7 Hz, 1H), 3.65 (br s, 1H), 2.41 (s, 3H), 1.31 (s, 6H); ^{13}C NMR (150 MHz) δ 158.8 (−), 136.5 (+), 135.6 (+), 129.8 (+), 128.1 (−), 119.9 (−), 111.6 (−), 49.5 (+), 26.7 (−), 17.2 (−); IR (neat) 3275, 2960, 1590, 1464, 1289, 1160 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}N_2$ (M^+) 174.1157, found 174.1150.

*Analytical data for **36***: mp 140–141 °C (lit.[36] 140 °C).

*3.1.21. 1,2-Dihydro-2,2,8-trimethylquinoxaline (**37**) and 3,4-dihydro-3,3,5-trimethyl-2-quinoxalinone[38] (**38**)*

Reaction of **23** (228 mg, 1.10 mmol), $Pd(dba)_2$ (38 mg, 0.067 mmol), dppp (27 mg, 0.065 mmol), and phen (24 mg, 0.13 mmol) in DMF (3 mL) at 70 °C under CO (6 atm, 14 h), as described for **7**, gave after chromatography (hexanes/EtOAc, in order 9:1, 8:2, 7:3 and 1:1) in order of elution **37** (120 mg, 0.69 mmol, 63%) and **38** (26 mg, 0.14 mmol, 12%) as off-white solids. *Analytical data for **37***: mp 95–97 °C; ^{1}H NMR δ 7.28 (d, J=2.0 Hz, 1H), 7.14 (d, J=7.9 Hz, 1H), 6.93 (d, J=7.4 Hz, 1H), 6.65 (t, J=7.7 Hz, 1H), 3.53 (br s, 1H), 2.10 (s, 3H), 1.34 (s, 6H); ^{13}C NMR δ 159.7 (−), 134.5 (+), 130.7 (+), 129.8 (−), 125.5 (−), 120.8 (+), 117.3 (−), 50.2 (+), 27.3 (−), 16.0 (−); IR (neat) 2964, 1624, 1600, 1497, 1280, 1082 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{14}N_2$ (M^+) 174.1157, found 174.11150.

*Analytical data for **38***: mp 182–184 °C (lit.[38] 182 °C).

*3.1.22. (3,4-Dihydro-3,3-dimethylquinoxalin-6-yl)phenylmethanone (**39**)*

A mixture of **24** (120 mg, 0.40 mmol), $Pd(dba)_2$ (14 mg, 0.024 mmol), dppp (10 mg, 0.024 mmol), and phen (9 mg, 0.048 mmol) in DMF (5 mL) was reacted as described for **7** at 70 °C under CO (6 atm, 18 h). The reaction mixture was filtered through Celite, the Celite was washed with EtOAc, and the filtrate was concentrated under reduced pressure. After numerous attempts to purify the product by flash chromatography, the yellow solid isolated was tentatively determined to be **39** (56 mg of solid, <0.2 mmol, <52%). ^{1}H NMR δ 7.79 (dd, J=8.4, 1.5 Hz, 2H), 7.57 (t, J=7.4 Hz, 1H), 7.46 (t, J=7.6 Hz, 2H), 7.39 (d, J=1.7 Hz, 1H), 7.30 (d, J=7.9 Hz, 1H), 7.08 (dd, J=7.9, 1.8 Hz, 1H), 7.03 (d, J=1.7 Hz, 1H), 4.08 (br s, 1H), 1.34 (s, 6H); ^{13}C NMR δ 196.4 (+), 163.0 (−), 137.6 (+), 137.5 (+), 136.8 (+), 134.3 (+), 132.2 (−), 129.9 (−), 128.1 (−), 127.1 (−), 120.8 (−), 115.0 (−), 50.5 (+), 27.1 (−).

*3.1.23. 7′-Methoxy-spiro[cyclohexane-1,2′(1′H)quinoxaline] (**40**) and 1′,4′-dihydro-7′-methoxy-spiro[cyclohexane-1,2′(3′H)quinoxalin]3′-one (**41**)[39]*

Reaction of **27** (201 mg, 0.77 mmol), $Pd(dba)_2$ (27 mg, 0.047 mmol), dppp (19 mg, 0.046 mmol), and phen (19 mg, 0.105 mmol) in DMF (10 mL) at 70 °C under CO (6 atm, 4.5 h), as described for **7**, gave after chromatography (hexanes/EtOAc, 7:3) **40** (123 mg, 0.534 mmol, 70%) and **41** (24 mg, 0.097 mmol, 13%) as off-white solids. *Analytical data for **40***: mp 141–142 °C; ^{1}H NMR δ 7.23 (s, 1H), 7.15 (d, J=8.4 Hz, 1H), 6.27 (dd, J=8.4, 2.5 Hz, 1H), 6.08 (d, J=2.7 Hz, 1H), 4.06 (br s, 1H), 3.76 (s, 3H), 1.80–1.30 (m, 10H); ^{13}C NMR δ 160.0 (+), 157.7 (−), 137.7 (+), 128.5 (−), 126.5 (+), 103.4 (−), 99.0 (−), 55.1 (−), 51.4 (+), 34.7 (+), 25.1 (+), 20.3 (+); IR (neat) 3243, 2927, 1612, 1582, 1466, 1308, 1257, 1102 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}N_2O$ 230.1419, found 230.1410.

*Analytical data for **41***: mp 260–263 °C; ^{1}H NMR (DMSO-d_6) δ 9.93 (s, 1H), 6.59 (d, J=8.4 Hz, 1H), 6.52 (d, J=2.5 Hz, 1H), 6.17 (dd, J=8.6, 2.5 Hz, 1H), 5.96 (s, 1H), 3.63 (s, 3H), 1.7–1.4 (m, 10H); ^{13}C NMR (DMSO-d_6) δ 169.5 (+), 155.3 (+), 134.4 (+), 120.0 (+), 116.6 (−), 102.8 (−), 100.3 (−), 55.6 (+), 54.9 (−), 31.4 (+), 25.0 (+), 19.9 (+); IR (neat) 3368, 2929, 1672, 1518, 1259, 1015 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{18}N_2O_2$ 246.1368, found 246.1371.

*3.1.24. 1,2-Dihydro-2,2-diphenyl-7-methoxyquinoxaline (**42**)*

Reaction of **28** (96 mg, 0.28 mmol), $Pd(dba)_2$ (10 mg, 0.017 mmol), dppp (7 mg, 0.017 mmol), and phen (7 mg, 0.039 mmol) in DMF (4 mL) at 70 °C under CO (6 atm, 18 h), as described for **7**, gave after chromatography (hexanes/EtOAc, 8:2) **42** (60 mg, 0.19 mmol, 69%) as a tan solid. Mp 164–166 °C; ^{1}H NMR δ 7.59 (d, J=2.5 Hz, 1H), 7.40–7.25 (m, 10H), 7.19 (d, J=8.7 Hz, 1H), 6.27 (dd, J=8.4, 2.5 Hz, 1H), 6.09 (d, J=2.5 Hz, 1H), 4.43 (br s, 1H), 3.75 (s, 3H); ^{13}C NMR δ 160.5 (+), 153.3 (−), 144.1 (+), 136.5 (+), 129.1 (−), 128.6 (−), 127.6 (−), 127.4 (−), 124.7 (+), 103.8 (−), 98.4 (−), 62.5 (+), 55.2 (−); IR (neat) 3232, 2998, 2930, 1594, 1486, 1293, 1224, 1174, 1033 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{18}N_2O$ 314.1419, found 314.1409.

*3.1.25. 7-Chloro-2-phenylquinoxaline[40] (**43**) and 7-chloro-2-phenylquinoxaline-1-N-oxide (**44**)*

Reaction of **29** (106 mg, 0.39 mmol), $Pd(dba)_2$ (13 mg, 0.023 mmol), dppp (10 mg, 0.024 mmol), and phen (10 mg, 0.055 mmol) in DMF (10 mL) at 70 °C under CO (6 atm, 48 h), as described for **7**, gave after chromatography (hexanes/EtOAc, 9:1) **43** (23 mg, 0.096 mmol, 25%) and **44** (14 mg, 0.055 mmol, 14%) as off-white solids. *Analytical data for **43***: mp 146–148 °C[41] (lit.[42] 130–132 °C).

*Analytical data for **44***: mp 121–123 °C; ^{1}H NMR δ 9.32 (s, 1H), 8.22–8.18 (m, 2H), 8.16 (d, J=2.2 Hz, 1H), 8.06 (d, J=8.9 Hz, 1H), 7.69 (dd, J=8.9, 2.2 Hz, 1H), 7.60–7.56 (m, 3H); ^{13}C NMR (150 MHz) δ 152.6, 143.4, 142.7, 140.1, 136.3, 136.1, 130.6, 130.5, 130.4, 129.2, 128.5, 127.6; IR 1486, 1352, 1310, 1091, 915 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{10}ClN_2O$ ($M+H^+$) 257.0576, found 257.0476.

*3.1.26. 1,2-Dihydro-2,2-dimethylpyrido[2,3-b]pyrazine (**45**) and 1,2-dihydro-2,2-dimethylpyrido[2,3-b]pyrazin-3-one (**46**)*

Reaction of **30** (100 mg, 0.52 mmol), $Pd(dba)_2$ (18 mg, 0.031 mmol), dppp (14 mg, 0.034 mmol), and phen (13 mg, 0.072 mmol) in DMF (5 mL) at 70 °C under CO (6 atm, 6 h), as described for **7**, gave after chromatography (hexanes/EtOAc, 7:3) in order of elution **45** (28 mg, 0.17 mmol, 34%) and **46** (5 mg, 0.028 mmol, 6%) as off-white solids. Analytical data for **45**: mp 131–132 °C; ^{1}H NMR δ 9.28 (s, 1H), 7.57 (dd, J=4.7, 1.5 Hz, 1H), 6.85–6.70 (m, 2H), 4.03 (br s, 1H), 1.81 (s, 6H); ^{13}C NMR δ 157.5 (−), 146.2 (+), 137.5 (−), 131.9 (+), 119.6 (−), 115.2 (−), 80.0 (+), 27.5 (−); IR (neat) 2976, 1674, 1609, 1444, 1343, 1245 cm^{-1}; HRMS (EI, NH_3) calcd for $C_9H_{12}N_3$ ($M+H^+$) 162.1031, found 162.1037.

*Analytical data for **46***: mp 202–205 °C; ^{1}H NMR δ 9.24 (br s, 1H), 7.83 (dd, J=4.9, 1.5 Hz, 1H), 6.94 (dd, J=7.9, 1.5 Hz, 1H), 6.84 (dd, J=7.7, 4.9 Hz, 1H), 3.72 (br s, 1H), 1.45 (s, 6H); ^{13}C NMR δ 171.0 (+), 140.3 (+), 137.9 (−), 128.5 (+), 120.2 (−), 119.1 (−), 56.0 (+), 26.1(−); IR (neat) 3310, 1683, 1558, 1458, 1289 cm^{-1}; HRMS (EI) calcd for $C_9H_{11}N_3O$ 177.0902, found 177.0899.

*3.1.27. 2-(2-Nitrophenylamino)-2-cyclohexen-1-one (**42**)*

2-Nitrobenzenamine (2.00 g, 14.5 mmol), 1,2-cyclohexanedione (1.90 g, 16.9 mmol), benzene (40 mL), and concentrated H_2SO_4 (five drops) were combined in a round-bottomed flask fitted with a Dean–Stark trap and a reflux condenser. The reaction was heated and stirred at reflux for 21 h. The reaction mixture was then concentrated and the crude product was purified by chromatography (hexanes/EtOAc, 9:1, then 8:2) to give **42** (1.07 g, 4.6 mmol, 32%) as an orange solid. Mp 75–77 °C; ^{1}H NMR δ 9.38 (br s, 1H), 8.18 (dd, J=8.7, 1.5 Hz, 1H), 7.43 (ddd, J=8.7, 7.4, 1.7 Hz, 1H), 7.31 (dd, J=8.7, 1.5 Hz, 1H), 6.87–6.77 (m, 2H), 2.65–2.54 (m, 4H), 2.10 (p, J=6.2 Hz, 2H); ^{13}C NMR δ 194.6 (+), 140.6 (+), 135.2 (−), 134.8 (+), 134.6 (+), 129.7 (−), 126.7 (−), 118.1 (−), 116.8 (−), 37.7 (+), 25.0 (+), 22.4 (+); IR (neat) 3294, 2944, 1672, 1571, 1430, 1246, 1155 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.58; H, 5.74; N, 12.28.

*3.1.28. 3-(2-Nitrophenylamino)-2-cyclohexen-1-one (**47**)*[43]

2-Nitrobenzenamine (1.26 g, 8.92 mmol), 1,3-cyclohexanedione (1.00 g, 8.92 mmol), benzene (30 mL), and concentrated H_2SO_4 (five drops) were combined in a round-bottomed flask fitted with a Dean–Stark trap and a reflux condenser. The reaction was heated and stirred at reflux for 22 h. The reaction mixture was then concentrated and the crude product was recrystallized from EtOAc to give **47** (1.45 g, 6.30 mmol, 70%) as a yellow solid.

*3.1.29. 1-Hydroxyphenazine (**48**)*[44]

Reaction of 3-(2-nitrophenylamino)-2-cyclohexen-1-one (**47**) (302 mg, 1.30 mmol), Pd(dba)$_2$ (45 mg, 0.078 mmol), dppp (33 mg, 0.080 mmol), and phen (30 mg, 0.17 mmol) in DMF (4 mL), as described above for **7** (6 atm CO, 120 °C, 22 h), gave after purification by chromatography (hexanes/EtOAc, 8:2, 7:3, 1:1, and EtOAc) **48** (67 mg, 0.34 mmol, 26%) as a brown solid. Mp 155–156 °C (lit.[45] 157–159 °C).

3.1.30. 2-Methyl-6-nitroaminobenzene,[45] *1,2-dihydro-2,2,5-trimethylquinoxaline (**35**), and 4-methyl-2-(1-methylethyl)-benzimidazole (**50**)*[46]

To a solution of 2-azido-3-nitrotoluene (**49**)[47] (1.00 g, 5.61 mmol) dissolved in diethyl ether (anhydrous, 40 mL) was added triphenylphosphine (1.50 g, 5.72 mmol). The mixture was stirred under argon atmosphere at ambient temperature for 1 h. The solvent was removed under reduced pressure and the resulting solid was dissolved in $CHCl_3$ (40 mL) and 2-methylpropanal (7.0 mL, 77.0 mmol) was added. The reaction mixture was stirred at reflux under an argon atmosphere for 6 days. The solvent was removed under reduced pressure to give a crude reaction mixture. Reaction of the crude mixture with Pd(dba)$_2$ (190 mg, 0.33 mmol), dppp (140 mg, 0.34 mmol), and phen (120 mg, 0.66 mmol), in DMF (8 mL), as described for **7** (6 atm CO, 21 h), gave after chromatography (hexanes/EtOAc, in order 9:1, 8:2, 1:1, 3:7, and EtOAc), 2-methyl-6-nitroaminobenzene (71 mg, 0.47 mmol, 8%) as a yellow solid, **35** (106 mg, 0.61 mmol, 11%) as a pale yellow solid, and **50** (603 mg, 3.46 mmol, 62%) as a tan solid.

*3.1.31. 2-Pentylquinoxaline (**52**), 2-pentylquinoxaline-1-oxide (**53**), and 2-hexylbenzimidazole*[44] *(**51**)*

2-Azidonitrobenzene[48] (500 mg, 3.05 mmol) was reacted with first triphenylphosphine (800 mg, 3.05 mmol) in diethyl ether (anhydrous, 20 mL) followed by heptanal (4.0 mL, 29.8 mmol) in $CHCl_3$ (25 mL), as described for reaction of **49** (1 h, then 7 days) to give a crude reaction mixture. Reaction of the crude mixture with Pd(dba)$_2$ (110 mg, 0.19 mmol), dppp (80 mg, 0.19 mmol), and phen (70 mg, 0.39 mmol) in DMF (10 mL), as described for **7** (6 atm CO, 72H), gave after chromatography (hexanes/EtOAc, 8:2, 7:3, 6:4, 1:1, and 3:7) **52** (153 mg, 0.76 mmol, 25%) as a yellow oil, **53** (54 mg, 0.25 mmol, 8%) as an off-white solid, and **51** (84 mg, 0.42 mmol, 14%) as a tan solid. *Analytical data for **52***: ^{1}H NMR δ 8.75 (s, 1H), 8.06 (apparent triplet with further fine splitting, J=9.4 Hz, 2H), 7.76 (dt, J=6.7, 1.7 Hz, 1H) partially overlapping, 7.71 (dt, J=6.9, 1.7 Hz, 1H), 3.02 (t, J=7.7 Hz, 2H), 1.86 (p, J=7.6 Hz, 2H), 1.47–1.32 (m, 4H), 0.91 (t, J=7.0 Hz, 3H); ^{13}C NMR (150 MHz) δ 157.6 (+), 145.7 (−), 142.1 (+), 141.1 (+), 129.8 (−), 129.1 (−), 128.8 (−), 128.7 (−), 36.4 (+), 31.5 (+), 29.1 (+), 22.4 (+), 13.9 (−); IR (neat) 2957, 2927, 2857, 1561, 1492, 1126, 761 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{17}N_2$ (M+H$^+$) 201.1392, found 262.1371.

*Analytical data for **53***: mp 32–34 °C; ^{1}H NMR δ 8.69 (s, 1H), 8.61 (apparent doublet with further fine splitting, J=10.1 Hz, 1H), 8.10 (apparent doublet with further fine splitting, J=9.7 Hz, 1H), 7.81–7.71 (m, 2H), 3.08 (t, J=7.7 Hz, 2H), 1.84 (p, J=7.4 Hz, 2H), 1.48–1.38 (m, 4H), 0.93 (t, J=6.9 Hz, 3H); ^{13}C NMR (150 MHz) δ 146.8 (−), 144.4 (+), 143.0 (+), 137.0 (+), 130.5 (−), 130.0 (−), 129.9 (−), 118.7 (−), 31.7 (+), 28.7 (+), 25.2 (+), 22.3 (+), 13.9 (−); IR (neat) 2957, 2927, 2860, 1579, 1494, 1359, 1302, 766 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{17}N_2O$ (M+H$^+$) 217.1335, found 217.1334.

*3.1.32. 2,2-Dimethyl-1,2-dihydroquinoxaline (**7**) and 2-(1-methylethyl)benzimidazole (**64**)*[44]

Reaction of 2-nitrosoaminobenzene[31,32] (**63**) (326 mg, 2.67 mmol), 2-methylpropanal (440 μL, 4.85 mmol), camphor sulfonic acid (10 mg), 4 Å molecular sieves (30 g) in CH_2Cl_2 (50 mL) at ambient temperature (40 days), as described for **5**, gave after chromatography (hexanes/EtOAc, in order 9:1, 8:2, 6:4, 1:1, and 3:7) in order of elution, **7** (20 mg, 0.12 mmol, 5%) and **64** (13 mg, 0.081 mmol, 3%). *For **64***: mp 220–225 °C (lit.[49] mp 223–225 °C).

Acknowledgements

This work was supported by research grants from the National Science Foundation (CHE 0611096), the National Institute of General Medical Sciences, National Institutes of Health (RO1 GM57416), and the American Chemical Society Petroleum Research Fund (40665-AC1). NSF-EPSCoR (Grant #1002165R) is gratefully acknowledged for the funding of a 600 MHz Varian Inova NMR and a Thermo-Finnegan LTQ-FT Mass Spectrometer and the NMR and MS facilities in the C. Eugene Bennett Department of Chemistry at West Virginia University. J.T. is grateful to OAS (F54111), CONACYT (250099), and COFAA-IPN (9711220214) for financial support during his sabbatical leave in the USA (1997–1998).

Supplementary data

^{1}H NMR, ^{13}C NMR, and IR (for one compound) data for compounds **17**, **19**, **32**, **34**, **36**, **38**, **43**, and **47** previously described but without reported data. Supplemental data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.083.

References and notes

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