Synthesis W. Wertjes et al. Special Topic

A Divergent Nickel-Catalyzed Synthesis of Quinazolinediones and Benzoxazinone Imines

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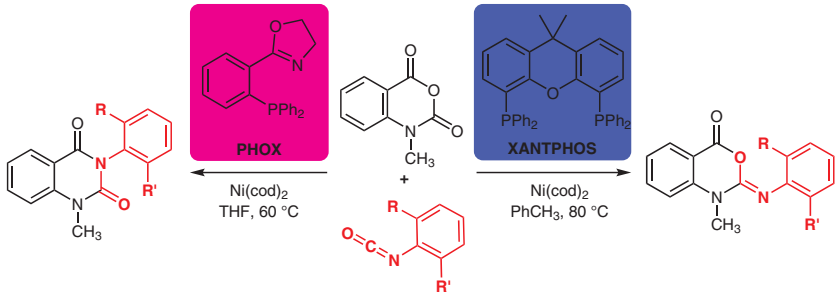

Dedicated to Prof. Scott Denmark on his birthday.

Published as part of the Special Section dedicated to Scott E. Denmark on the occasion of his 65th birthday

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Abstract During exploration of the nickel(0)-catalyzed reaction of isocyanates and isatoic anhydrides, it was found that changes in the substitution pattern of the isocyanate led to constitutionally isomeric quinazolinediones [quinazoline-2,4(1*H*,3*H*)-diones] or benzoxazinone imines [2-imino-1,2-dihydro-4*H*-3,1-benzoxazin-4-ones]. Ligand and solvent screening experiments allowed for identification of conditions that could lead to each constitutional isomer in good to excellent levels of selectivity and yield. Comprehensive characterization of the previously poorly characterized benzoxazinone imines is also provided.

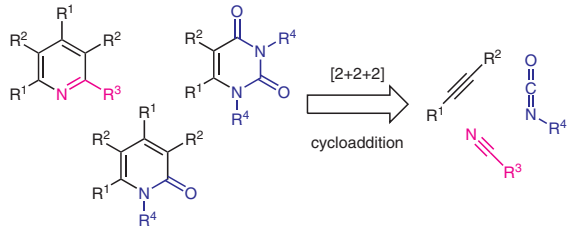
Key words quinazolinedione, benzoxazinone, nickel, cycloaddition

Transition-metal-catalyzed [2+2+2] cycloadditions are a powerful strategy for construction of complex aromatic rings starting from simple and readily available precursors.[1] Although much early work focused on alkynes as 2π-components, the reactivity of nitriles was soon realized, allowing for access to pyridines.[2] Continuing exploration of heteroatom containing 2π components slowly gained momentum, allowing for the synthesis of a wide range of nitrogen-containing heterocycles. At present, the scope of the reaction includes isocyanates, carbodiimides, and sulfur-containing heterocumulenes[3] as competent substrates.

The synthesis of common heterocycles such as pyridines, pyridones, pyrimidinediones, and their conjugated analogues has been explored with a variety of metal precursors including cobalt, iridium, nickel, rhodium, ruthenium, and iron among others (Table 1).[6–18] In some cases, achiral examples have been realized (yellow), while in others chiral ligands (green) have made possible the synthesis of axially chiral heterocycles with high levels of selectivity.[4] However, clearly gaps still remain (red).

Early studies defined the scope and potential of this chemistry, more recent work has set the stage for the synthesis of more complex nitrogen-containing heterocycles. For example, Matsubara and co-workers first demonstrated that isatoic anhydrides can serve as highly functionalized 4π-components, allowing access to quinolones followed by the work of Yang and co workers on the synthesis of indoles in high yields using simple nickel(0) catalysts.[5]

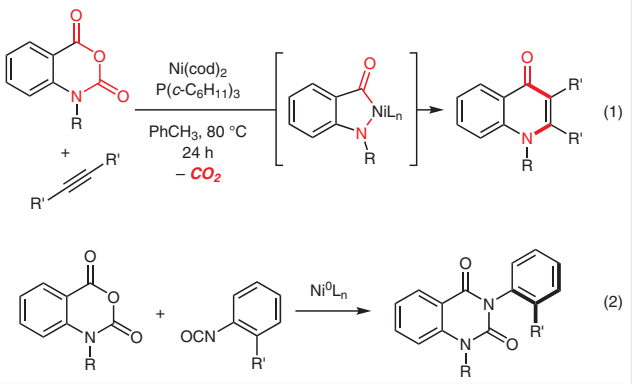
Table 1 References to Metal-Catalyzed [2+2+2] Heterocycle Synthesis



	Pyridines	Pyridones	Pyrimidinediones
Co	ref. 6	ref. 7	
Ir	ref. 8	ref. 9	
Ni	ref. 10	ref. 11	ref. 12
Rh	ref. 13	ref. 14	ref. 15
Ru	ref. 16	ref. 17	
Fe	ref. 18		

Recently, we faced the challenge of preparing an axially chiral quinazolinedione as part of an ongoing drug discovery program.[19] Inspired by examples of the synthesis of closely related pyridones via metal-catalyzed cycloadditions (Scheme 1, eq. 1), we wondered if a similar disconnec-

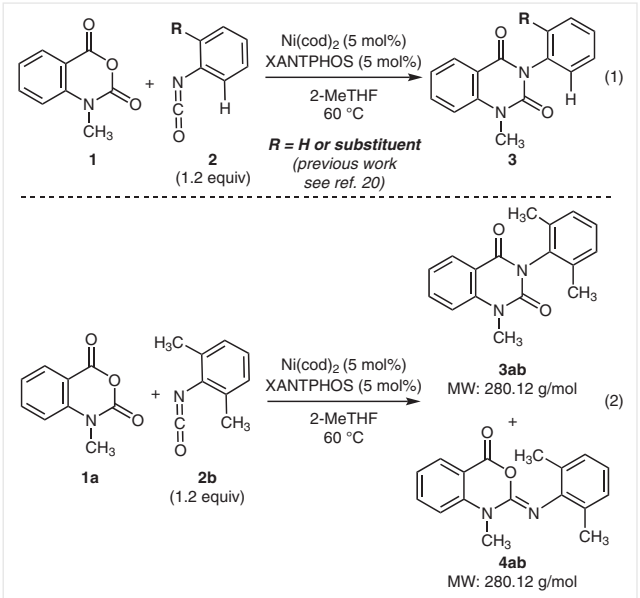
tion could be employed to construct quinazolinediones through a catalytic cycloaddition between an isatoic anhydride and an isocyanate (Scheme 1, eq. 2).



Scheme 1 Proposed Ni-catalyzed synthesis of quinazolinediones

In an earlier communication we described the successful demonstration of this transformation using the Ni(0)–XANTPHOS catalyst system (Scheme 2, eq. 1).[20] The reaction performed well in the case of alkyl isocyanates as well as *ortho*- and unsubstituted aryl isocyanates. We next wanted to explore the reactions of *ortho*,*ortho*-disubstituted aryl isocyanates, since the resulting *ortho*,*ortho*-disubstituted *N*-aryl-quinazolinediones would be of interest due to their known biological activity.[21] Based on the good to excellent yields we had obtained with a range of aryl isocyanates, we did not anticipate significant challenges when moving to these more hindered substrates. But addition of a second *ortho*-substituent to the aryl isocyanate altered the reaction outcome in an unexpected manner. As reported herein, further investigations of impurities formed in those studies led to the discovery of a divergent, ligand-controlled synthesis of two distinct heterocycles, quinazolinediones and benzoxazinone imines, starting from a single set of starting materials.

In initial experiments with isatoic anhydride (**1a**) and 2,6-dimethylphenyl isocyanate (**2b**) under the standard conditions using bis(cycloocta-1,5-diene)nickel(0) [Ni(cod)$_2$] and XANTPHOS, we obtained a small amount of the desired product **3ab** (Scheme 2, eq. 2). Significant amounts of a second compound were also formed. LC-HRMS revealed that this byproduct had an identical elemental composition to the desired product. This byproduct was isolated and its structure was probed by various spectroscopic techniques. ^{1}H and ^{13}C NMR spectroscopy and IR spectroscopy revealed only subtle differences between **3ab** and the unknown ^{1}H-^{13}C HMBC spectra showed identical C–H connectivity in the two products. ^{1}H-^{15}N HMBC spectra revealed a substantial chemical shift difference was observed between the two products (δ = 164.7 vs 196.9), but this did not allow for unambiguous identification of the unknown structure.



Scheme 2 Ni(0)-catalyzed reactions of isocyanates and isatoic anhydrides

Upon consideration of the reaction mechanism, we hypothesized that due to steric constraints, it was possible that insertion could occur across the distal C=O bond of the isocyanate rather than the hindered C=N bond. The resulting product would be a benzoxazinone imine. Based on a review of the literature,[22] the formation of this heterocycle did not seem unreasonable, but further study was needed to confirm this hypothesis due to the dearth of existent structural information on benzoxazinone imines. Growth of single crystals for X-ray diffraction analysis finally secured identification of this new product as a constitutional isomer of the desired quinazolinedione, the benzoxazinone imine **4ab** (Figure 1).[23]

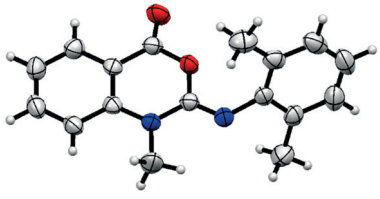
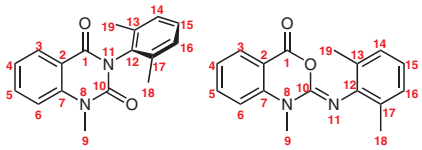


Figure 1 ORTEP diagram (50% ellipsoid probability) of benzoxazinone imine **4ab**

The X-ray structure revealed several interesting features of this heterocycle. It presents a *Z*-imine with the *N*-aryl group forming a dihedral of 76.1° with the main ring system. The C=N bond is 1.260(2) Å, and the ester group is distorted with an O–C–O angle of 127.8(2)°. With the structure confirmed, we completed NMR assignments for **3ab** and **4ab** as shown in Table 2.

Table 2 ^{13}C and ^{15}N NMR Data for **3ab** and **4ab**

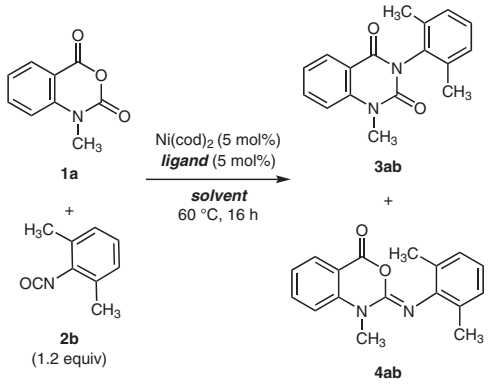


3ab **4ab**

Position	δ_C	δ_N	δ_C	δ_N
1	160.5		157.7	
2	114.8		109.7	
3	128.0		129.5	
4	123.0		121.8	
5	135.8		137.4	
6	115.0		114.0	
7	141.0		143.4	
8		114.2		96.3
9	30.7		32.5	
10	149.4		140.9	
11		164.7		196.9
12	134.4		143.3	
13, 17	135.3		128.3	
14, 16	128.1		127.4	
15	128.2		122.3	
18, 19	17.2		18.0	

With the identity of the constitutional isomer confirmed, we next attempted to identify orthogonal reaction conditions that would lead to selective formation of the benzoxazinone and quinazolinedione products. Work by Belmont and co-workers has demonstrated the potential of ligand control over cyclization of amides in a rhodium-catalyzed reaction, producing related heterocyclic constitutional isomers.[24] Ligand and solvent screening in the reaction between **1a** and **2b** (Table 3)[25] showed that XANTPHOS was unique in its ability to generate significant amounts of the benzoxazinone **4ab**, particularly in non-polar solvents such as toluene (entry 1). Closely related ligands, including DPEPhos and other large bite angle bis-phosphines,[26] gave lower reactivity and favored formation of quinazolinedione **3ab** when compared to XANTPHOS (entries 2–8). The highest selectivity was observed with P,N chelating ligands such as DPPEpy[27] and PHOX[28] which gave complete selectivity for formation of **3ab** (entries 9 and 10). In contrast to the results observed with XANTPHOS, solvent choice appeared to have little effect on conversion or selectivity with P,N ligands and THF was selected for further development.

Table 3 Ligand Screening for Formation of **3ab** and **4ab**

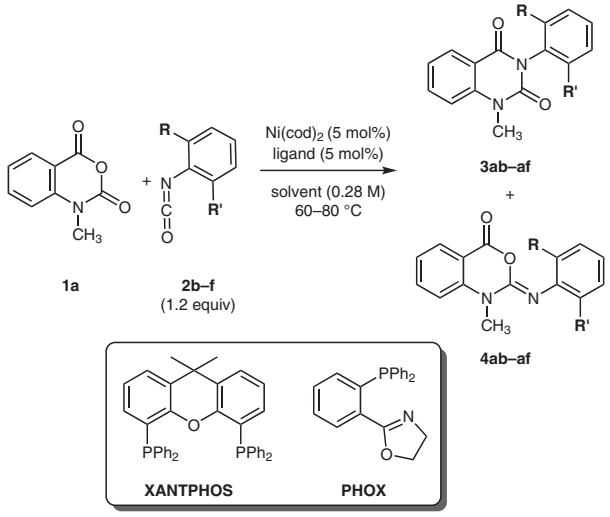


Entry	Ligand	Solvent	Conv. (%)[a]	Ratio[a] **3ab**/**4ab**
1	XANTPHOS	$PhCH_3$	93	44:56
2	DPEPhos	2-MeTHF	14	50:50
3	DPPE	2-MeTHF	1	67:33
4	DPPP	2-MeTHF	18	98:2
5	DPPB	2-MeTHF	7	94:6
6	DPPF	2-MeTHF	16	75:25
7	BISBI	2-MeTHF	29	92:8
8	DBFPhos	2-MeTHF	9	94:6
9	DPPEpy	2-MeTHF	>99	>99:1
10	PHOX	THF	>99	>99:1

[a] Calculated based on HPLC area percent of **1a**, **3ab**, and **4ab** adjusted for UV response factors.

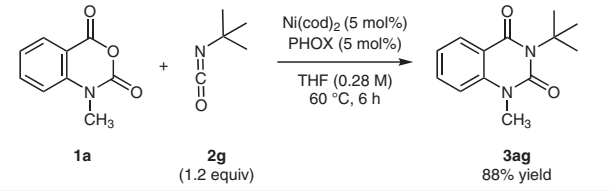
After a brief examination of reaction temperature, we arrived at conditions which could provide the desired quinazolinedione or benzoxazinone in moderate to excellent yields (Table 4). Use of the achiral PHOX ligand provided high levels of selectivity for the quinazolinediones **3** (entries 1–5) while XANTPHOS was optimal for synthesis of the benzoxazinones **4** (entries 6–10). In the case of the Ni(0)-XANTPHOS-catalyzed process, selectivity was significantly lower than with the PHOX ligand but appeared to improve as the steric demands of the isocyanate increased (entry 10). The hindered *tert*-butyl isocyanate (**2g**) yielded quinazolinedione **3ag** in high yield using the PHOX ligand (Scheme 3); however, no reaction of **1a** and **2g** was observed with XANTPHOS.

Table 4 Reaction Scope for Formation of **3** and **4**



Entry	2	Conv.[a] (%) [Ratio 3/4]	Yield[b] (%)	
			3	4
1	Me, Me (**2b**)	>99[c] [>99:1]	83 (**3ab**)	–
2	Et, Et (**2c**)	>99[c] [>99:1]	91 (**3ac**)	–
3	*i*-Pr, *i*-Pr (**2d**)	>99[c] [>99:1]	87 (**3ad**)	–
4	Me, *i*-Pr (**2e**)	95[c] [>99:1]	96 (**3ae**)	–
5	Me, *t*-Bu (**2f**)	87[c] [>99:1]	76 (**3af**)	–
6	Me, Me (**2b**)	90[d] [25:75]	15 (**3ab**)	53 (**4ab**)
7	Et, Et (**2c**)	88[d] [50:50]	37 (**3ac**)	56 (**4ac**)
8	*i*-Pr, *i*-Pr (**2d**)	84[d] [33:67]	20 (**3ad**)	46 (**4ad**)
9	Me, *i*-Pr (**2e**)	73[d] [33:67]	13 (**3ae**)	52 (**4ae**)
10	Me, *t*-Bu (**2f**)	91[d] [1:99]	–	80 (**4af**)

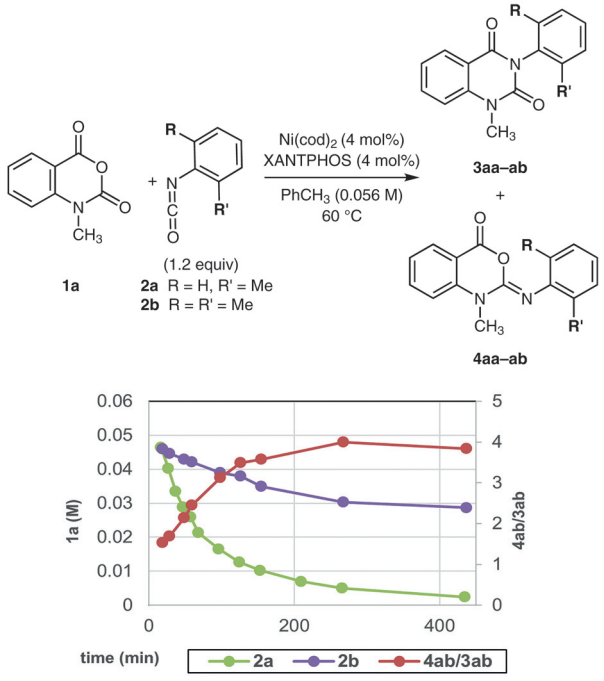
[a] Based on HPLC area percent of **3** and **4**.
[b] Based on isolated material.
[c] PHOX, THF, 60 °C, 4 h.
[d] XANTPHOS, toluene, 80 °C, 4 h.



Scheme 3 Reaction of isatoic anhydride with *tert*-butyl isocyanate

Consideration of the series of compounds as a whole revealed some systematic differences between heterocycles **3** and **4**, consistent with previous observations from the literature.[29] All benzoxazinones **4** were significantly less polar than the corresponding quinazolinediones **3**, allowing for easy separation by chromatography. UV-VIS spectroscopy revealed a clear and systematic bathochromic shift between **3** and **4**. IR spectroscopy showed that **3** had a clear band at ~1720 cm^{-1}, while **4** exhibited a distinctive band at higher frequency (~1765 cm^{-1}). Finally, several significant differences were observed in the NMR spectra, namely the ^{15}N chemical shift for N-11 (δ = ~165 vs ~197 for **3** vs **4**, respectively) and the ^{13}C chemical shift for C-10 (δ = ~150 vs ~141 for **3** vs **4**, respectively). MS analysis did not provide a consistent method for differentiating between the two constitutional isomers. Only in the cases of the more sterically hindered benzoxazinones **4ac**–**4af**, MS/MS facilitated identification of the structure due to the loss of CO_2 in the major molecular fragment.

We monitored the progress of the reaction using HPLC analysis with two substrates to probe for differences which might explain formation of the different heterocycles (Scheme 4). In the presence the Ni(0)–XANTPHOS complex, the reaction of mono-*ortho*-substituted isocyanate **2a** was found to be significantly faster than that of di-*ortho*-substituted isocyanate **2b** (compare green and purple trace). None of benzoxazinone **4aa** derived from mono-*ortho*-substituted isocyanate **2a** was detected at any point during the reaction.



Scheme 4 Kinetic analysis of the reactions of **2a** and **2b**

In contrast, under identical reaction conditions, the disubstituted isocyanate **2b** exhibited stalling that was coincident with a shift in the product selectivity towards **4ab** (red trace). Initial selectivity between **4ab** and **3ab** was nearly 1:1 but shifted to 4:1 by the time the reaction had stalled at ~50% conversion after 3 h. This could signify a change in the resting state of the nickel catalyst or it could

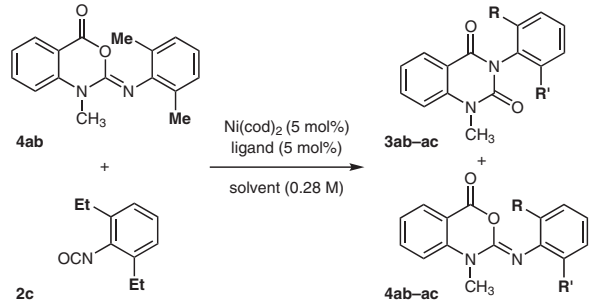
suggest an equilibrium between **3** and **4**. Investigation of this reaction mixture by ^{31}P NMR did show a change in the catalyst resting state from Ni(XANTPHOS)$_2$[30] to a new, unidentified signal coincident with the reaction stalling. This new species appeared to be catalytically inactive since addition of fresh substrates did not lead to any additional product formation or change in product selectivity.

To test whether the formation of **3** and **4** is reversible in the Ni(0)–XANTPHOS catalyzed reaction, a series of experiments was designed in which benzoxazinone **4ab** was resubjected to the reaction conditions. Earlier studies demonstrated that benzoxazinones were the kinetic products of the reaction between anthranilic acids and isocyanates.[31] The benzoxazinones could then be converted into the thermodynamically favored quinazolinediones by prolonged heating in the presence of a Brønsted acid through a process similar to the Chapman rearrangement.[32] Control experiments in this system revealed that equilibration between **4** and **3** did not occur upon heating alone or in the presence of Ni(cod)$_2$ or ligand individually. However, in the presence of ligated nickel complexes, reversibility was observed under mild conditions (Table 5). Benzoxazinone **4ab** was completely converted into quinazolinedione **3ab** in less than 1 h in the presence of both the Ni(0)–PHOX and Ni(0)–XANTPHOS catalysts (entries 1 and 2). Although this result seems at odds with the high selectivity for the benzoxazinones **4** observed with the Ni(0)–XANTPHOS complex, catalyst decomposition during the actual reaction may prevent full equilibration to **3**, consistent with the results of the ^{31}P NMR monitoring of the reaction (*vide supra*).

To gain additional insights into the equilibration mechanism, we repeated the experiments in the presence of isocyanate **2c** to probe for the formation of cross-over products (entries 3 and 4). With the Ni(0)–PHOX catalyst, less than 1% of the isomeric cross-over products derived from incorporation of **2c** were observed. In contrast significant amounts of **3ac**/**4ac** were formed using the XANTPHOS catalyst in the presence of **2c**.

Considering these results a mechanism can be proposed for the reaction to rationalize formation of the benzoxazinones (Scheme 5). The pre-formed Ni(XANTPHOS)$_2$ complex ***i*** is the catalyst resting state and undergoes dissociative ligand exchange to give the isocyanate-bound complex ***ii*** and free XANTPHOS. This species ***ii*** is then in equilibrium with two other catalytic intermediates ***iii*** and ***iv***. For unhindered isocyanates, binding of a second molecule of isocyanate leads to the inactive, off-cycle intermediate ***iii***. Alternatively, binding of isatoic anhydride leads to the productive complex ***iv***. This complex ***iv*** can then undergo insertion in the acyl C–O bond of the isatoic anhydride with release of carbon dioxide to give complex ***v***. The nickel(II) center in ***v*** can bind to either the distal C=O or the proximal C=N bond, depending on the steric demands of the aryl group. The

Table 5 Equilibration Studies on **4ab**

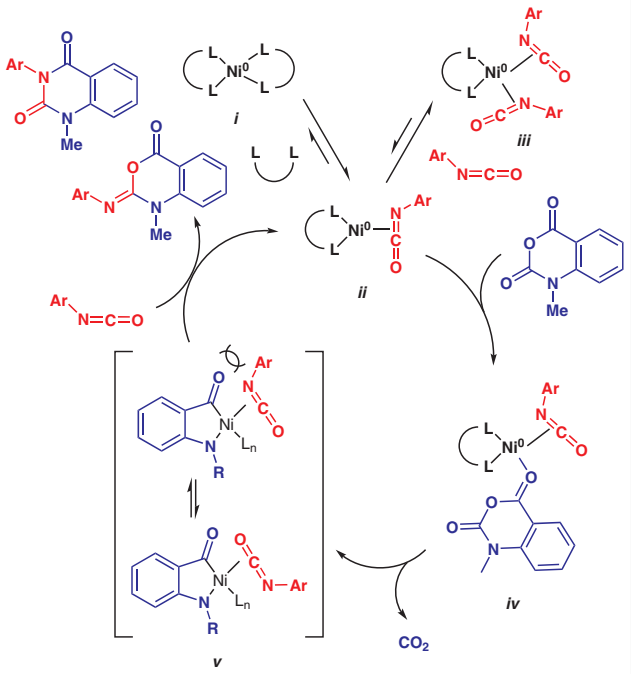


Entry	Method[a]	Additive	**3ab** (%)[b]	**4ab** (%)[b]	**3ac** (%)[b]	**4ac** (%)[b]
1	A	none	100	0	0	0
2	B	none	100	0	0	0
3	A	+ **2c** (1.2 equiv)	99.4	0	0.4	0.2
4	B	+ **2c** (1.2 equiv)	54.6	7.5	27.5	10.4

[a] Method A: PHOX, THF, 60 °C, 1 h; B: XANTPHOS, toluene, 80 °C, 1 h.
[b] Reported values are HPLC area percent.

product determining step likely arises from this isocyanate-bound intermediate ***v*** in the final insertion and reductive elimination. This final reductive elimination is reversible, allowing for equilibration between the benzoxazinone imine and quinazolinedione isomers. Matsubara and coworkers have ascribed selectivity in the nickel(0)-catalyzed reaction of unsymmetrical alkynes and isatoic anhydrides[5c] to minimization of steric interactions in related intermediates prior to reductive elimination.[33] The fact that formation of the benzoxazinone imine, which requires insertion into the distal C=O bond of the isocyanate, is sensitive to the steric demands of the pendant aryl group is consistent with this computational analysis.

In conclusion, we have discovered a novel and divergent method for synthesis of quinazolinediones or benzoxazinone imines starting from readily available isatoic anhydrides and *ortho*-disubstituted aryl isocyanates. Ligand choice in this nickel(0)-catalyzed reaction is critical and XANTPHOS was shown to be unique in its ability to form the benzoxazinone imine. Switching to the PHOX ligand allowed for synthesis of the constitutionally isomeric quinazolinediones in excellent yields and selectivities. Although we are unable at this point to completely rationalize this intriguing change in selectivity, this work demonstrates the utility of iterative rounds of reaction screening to develop truly general processes and highlights the opportunities that a 'failed' reaction can present for new discoveries.



Scheme 5 Proposed reaction mechanism

Required reagents, chemicals, and solvents were purchased from commercial vendors and used without additional purification. 1-Methyl-3,1-benzoxazine-2,4-dione (**1a**) was crystallized prior to use as follows: The crude material was slurried in DMAc (5 mL/g) and heated to 60 °C to generate a solution. To this was slowly added water (2.5 mL/g). The resulting slurry was allowed to cool to r.t. and age for several hours before filtration, washing twice with 2 mL/g water and then drying under an N_2/vacuum sweep overnight. The crude, commercial material could be used for the reaction, but led to lower yields. Anhydrous, degassed solvents were used for all reactions. The presence of BHT as inhibitor was not found to be detrimental to reactivity or selectivity. All reactions were prepared and performed in an inert atmosphere glovebox.

2-Isopropyl-6-methylphenyl Isocyanate (2e)

The 2-isopropyl-6-methylaniline (5.0 g, 33.5 mmol, 1.0 equiv) and Me_3N (4.7 mL, 33.5 mmol, 1.0 equiv) were dissolved in EtOAc (50 mL) and cooled in an ice bath. To this was added a solution of triphosgene (4.6 g, 15.1 mmol, 0.45 equiv) in EtOAc (50 mL) via a dropping funnel over 10 min. The bath was then removed and the thick suspension was stirred at r.t. for 1 h. The mixture was then filtered through Celite and the cake washed with EtOAc. The combined organics were washed with water (100 mL) and 0.2 M pH 8 sodium phosphate buffer (2 × 100 mL) (a mildly basic buffer wash is required to decompose residual triphosgene which can inhibit the reaction) and then dried (Na_2SO_4), filtered, and concentrated to give **2e** (4.78 g, 82%, 95 wt% by NMR) as a tan oil. The isocyanate was of acceptable quality to be used without further purification.

IR (toluene): 2293, 2270 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.12 (m, 3 H), 3.25 (sept, *J* = 7.0 Hz, 1 H), 2.36 (s, 3 H), 1.26 (d, *J* = 7.0 Hz, 6 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 142.7, 133.4, 130.0, 127.8, 125.7, 124.2, 123.6, 29.4, 22.8, 18.9.

3-(2,6-Dimethylphenyl)-1-methylquinazoline-2,4(1*H*,3*H*)-dione (3ab); Typical Procedure 1 (TP1)

$Ni(cod)_2$ (40 mg, 0.141 mmol, 0.05 equiv) and PHOX (47 mg, 0.141 mmol, 0.05 equiv) were combined and dissolved in THF (5 mL). The mixture was stirred for 10 min to give a dark green solution. This solution was then added to a suspension of **1a** (0.5 g, 2.82 mmol, 1.0 equiv) and 2,6-dimethylphenyl isocyanate (**2b**; 0.476 mL, 3.38 mmol, 1.2 equiv) in THF (5 mL). The vial was capped and heated to 60 °C for 4 h, or until full conversion was observed by HPLC analysis. Concentration of the resulting brown solution followed by direct purification by chromatography (silica gel) gave **3ab** (0.65 g, 83%) as a white crystalline solid; R_f = 0.50 (hexanes/EtOAc 7:3); mp 183 °C (DSC).

IR (solid state): 1719, 1707, 1660, 1606, 1499, 1480, 1448, 1424, 1380, 1344, 1329, 1316, 1262, 1189, 1170, 1146, 1113 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 7.6 Hz, 1 H), 7.77 (t, *J* = 7.3 Hz, 1 H), 7.29 (m, 3 H), 7.19 (d, *J* = 7.2 Hz, 2 H), 3.68 (s, 3 H), 2.13 (s, 6 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 161.0, 150.1, 141.1, 135.4, 135.3, 134.0, 129.4, 128.8, 128.5, 123.0, 115.7, 113.7, 30.9, 17.7.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_2$: 281.1285; found: 281.1290.

UV (MeCN): λ = 223, 246, 314 nm.

3-(2,6-Diethylphenyl)-1-methylquinazoline-2,4(1*H*,3*H*)-dione (3ac)

Following TP1: $Ni(cod)_2$ (40 mg, 0.141 mmol, 0.05 equiv), PHOX (47 mg, 0.141 mmol, 0.05 equiv), **1a** (0.5 g, 2.82 mmol, 1.0 equiv), and 2,6-diethylphenyl isocyanate (**2c**; 0.585 mL, 3.38 mmol, 1.2 equiv) were combined in THF (10 mL) and heated to 60 °C for 4 h before direct purification by chromatography (silica gel) to yield **3ac** (0.79 g, 91%) as a white crystalline solid; R_f = 0.61 (hexanes/EtOAc 7:3); mp 135 °C (DSC).

IR (solid state): 1710, 1660, 1604, 1482, 1460, 1421, 1378, 1324, 1313, 1290, 1259, 1184, 1162, 1142, 1116 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (dd, *J* = 8.2, 1.5 Hz, 1 H), 7.76 (dt, *J* = 7.6, 1.5 Hz, 1 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.32 (m, 2 H), 7.25 (m, 2 H), 3.86 (s, 3 H), 2.42 (q, *J* = 7.6 Hz, 4 H), 1.16 (t, *J* = 7.6 Hz, 6 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 161.5, 150.6, 141.1, 140.7, 135.4, 132.8, 129.5, 129.1, 126.4, 123.0, 115.7, 113.7, 30.9, 24.0, 13.8.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_2$: 309.1598; found: 309.1602.

UV (MeCN): λ = 223, 246, 313 nm.

3-(2,6-Diisopropylphenyl)-1-methylquinazoline-2,4(1*H*,3*H*)-dione (3ad)

Following TP1: $Ni(cod)_2$ (40 mg, 0.141 mmol, 0.05 equiv), PHOX (47 mg, 0.141 mmol, 0.05 equiv), **1a** (0.5 g, 2.82 mmol, 1.0 equiv), and 2,6-diisopropylphenyl isocyanate (**2d**; 0.72 mL, 3.38 mmol, 1.2 equiv) were combined in THF (10 mL) and heated to 60 °C for 4 h before direct purification by chromatography (silica gel) to yield **3ad** (0.82 g, 87%) as a white crystalline solid; R_f = 0.71 (hexanes/EtOAc 7:3); mp 195 °C (DSC).

IR (solid state): 1712, 1661, 1606, 1480, 1465, 1420, 1376, 1364, 1340, 1322, 1308, 1290, 1258, 1184, 1163, 1144, 1116 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (dd, *J* = 8.4, 1.5 Hz, 1 H), 7.76 (dt, *J* = 7.3, 1.5 Hz, 1 H), 7.44 (t, *J* = 7.9 Hz, 1 H), 7.31 (m, 4 H), 3.67 (s, 3 H), 2.66 (sept, *J* = 6.7 Hz, 2 H), 1.18 (d, *J* = 6.8 Hz, 6 H), 1.16 (d, *J* = 6.8 Hz, 6 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 161.7, 150.8, 145.5, 141.1, 135.4, 131.0, 129.6, 129.5, 124.0, 123.0, 115.7, 113.7, 31.0, 29.0, 24.0, 23.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{25}N_2O_2$: 337.1911; found: 337.1916.

UV (MeCN): λ = 221, 246, 314 nm.

3-(2-Isopropyl-6-methylphenyl)-1-methylquinazoline-2,4(1*H*,3*H*)-dione (3ae)

Following TP1: $Ni(cod)_2$ (40 mg, 0.141 mmol, 0.05 equiv), PHOX (47 mg, 0.141 mmol, 0.05 equiv), **1a** (0.5 g, 2.82 mmol, 1.0 equiv), and 2-isopropyl-6-methylphenyl isocyanate (**2e**; 0.61 mL, 3.38 mmol, 1.2 equiv) were combined in THF (10 mL) and heated to 60 °C for 4 h before direct purification by chromatography (silica gel) to yield **3ae** (832 g, 96%) as a white crystalline solid; R_f = 0.56 (hexanes/EtOAc 7:3); mp 143 °C (DSC).

IR (solid state): 1715, 1701, 1658, 1610, 1479, 1422, 1378, 1344, 1325, 1313, 1293, 1261, 1185, 1171, 1161, 1145, 1126 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.9 Hz, 1 H), 7.74 (t, *J* = 7.4 Hz, 1 H), 7.35 (m, 4 H), 7.19 (d, *J* = 7.0 Hz, 1 H), 3.68 (s, 3 H), 2.72 (sept, *J* = 6.7 Hz, 1 H), 2.14 (s, 3 H), 1.21 (d, *J* = 6.7 Hz, 3 H), 1.19 (d, *J* = 6.7 Hz, 3 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 161.3, 150.4, 145.8, 141.0, 135.3, 135.0, 132.5, 129.3, 129.0, 128.2, 124.0, 122.9, 115.6, 113.7, 30.8, 28.6, 23.8, 23.7, 17.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{21}N_2O_2$: 309.1598; found: 309.1603.

UV (MeCN): λ = 221, 245, 315 nm.

3-(2-*tert*-Butyl-6-methylphenyl)-1-methylquinazoline-2,4(1*H*,3*H*)-dione (3af)

Following TP1: $Ni(cod)_2$ (40 mg, 0.141 mmol, 0.05 equiv), PHOX (47 mg, 0.141 mmol, 0.05 equiv), **1a** (0.5 g, 2.82 mmol, 1.0 equiv), and 2-*tert*-butyl-6-methylphenyl isocyanate (**2f**; 0.64 g, 3.38 mmol, 1.2 equiv) were combined in THF (10 mL) and heated to 60 °C for 4 h before direct purification by chromatography (silica gel) to yield **3af** (0.69 g, 76%) as a white crystalline solid; R_f = 0.62 (hexanes/EtOAc 7:3); mp 156 °C (DSC).

IR (solid state): 1703, 1658, 1608, 1483, 1452, 1425, 1378, 1325, 1312, 1294, 1260, 1178, 1151, 1138, 1118 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (dd, *J* = 8.2, 1.8 Hz, 1 H), 7.75 (dt, *J* = 8.5, 1.5 Hz, 1 H), 7.46 (d, *J* = 8.2 Hz, 1 H), 7.31 (m, 3 H), 7.20 (d, *J* = 8.2 Hz, 1 H), 3.67 (s, 3 H), 2.03 (s, 3 H), 1.27 (s, 9 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 162.2, 151.0, 146.5, 140.9, 136.4, 135.4, 132.8, 129.4, 129.0, 128.8, 126.9, 123.0, 115.9, 113.7, 36.0, 31.9, 30.9, 18.2.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}N_2O_2$: 323.1754; found: 323.1755.

UV (MeCN): λ = 220, 247, 316 nm.

3-*tert*-Butyl-1-methylquinazoline-2,4(1*H*,3*H*)-dione (3ag)

Following TP1: $Ni(cod)_2$ (81 mg, 0.282 mmol, 0.05 equiv), PHOX (94 mg, 0.141 mmol, 0.05 equiv), **1a** (1.0 g, 5.64 mmol, 1.0 equiv), and *tert*-butyl isocyanate (**2f**; 0.78 mL, 6.77 mmol, 1.2 equiv) were combined in THF (10 mL) and heated to 60 °C for 6 h before direct purification by chromatography (silica gel) to yield **3ag** (1.16 g, 89%) as a white crystalline solid; R_f = 0.88 (hexanes/EtOAc 7:3); mp 108 °C (DSC).

IR (solid state): 1700, 1652, 1606, 1497, 1481, 1464, 1418, 1394, 1365, 1344, 1323, 1276, 1253, 1234, 1191, 1168, 1146, 1118 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.6 Hz, 1 H), 7.60 (t, *J* = 7.6 Hz, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 7.10 (d, *J* = 8.2 Hz, 1 H), 3.50 (s, 3 H), 1.76 (s, 9 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 163.7, 151.7, 140.1, 134.2, 128.3, 122.3, 118.2, 113.0, 62.0, 30.6, 29.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}N_2O_2$: 233.1285; found: 233.1287.

UV (MeCN): λ = 222, 247, 315 nm.

(*Z*)-2-[(2,6-Dimethylphenyl)imino]-1-methyl-1,2-dihydro-4*H*-3,1-benzoxazin-4-one (4ab); Typical Procedure 2 (TP2)

$Ni(cod)_2$ (162 mg, 0.564 mmol, 0.05 equiv) and XANTPHOS (334 mg, 0.564 mmol, 0.05 equiv) were combined and dissolved in toluene (20 mL). The mixture was stirred for 10 min to give a bright orange solution. This solution was then added to a suspension of **1a** (2.0 g, 11.3 mmol, 1.0 equiv) and 2,6-dimethylphenyl isocyanate (**2b**; 1.9 mL, 13.5 mmol, 1.2 equiv) in toluene (10 mL). The flask was capped with a septum and needle vent and heated to 80 °C for 4 h, or until full conversion was observed by HPLC analysis. Concentration of the resulting brown solution followed by direct purification by chromatography (silica gel) gave **4ab** (1.67 g, 53%) as a white crystalline solid; R_f = 0.70 (hexanes/EtOAc 7:3); mp 165 °C (DSC).

IR (solid state): 1764, 1667, 1607, 1589, 1492, 1467, 1421, 1368, 1339, 1323, 1271, 1254, 1241, 1210, 1170, 1148, 1125 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.3 Hz, 1 H), 7.7 (t, *J* = 8.2 Hz, 1 H), 7.14 (m, 2 H), 7.04 (m, 2 H), 6.90 (t, *J* = 7.3 Hz, 1 H), 3.72 (s, 3 H), 2.15 (s, 6 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 157.9, 143.7, 142.7, 140.7, 137.2, 130.7, 128.6, 127.7, 122.9, 121.9, 113.0, 110.2, 32.6, 18.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_2O_2$: 281.1285; found: 281.1289.

UV (MeCN): λ = 233, 264, 343 nm.

(*Z*)-2-[(2,6-Diethylphenyl)imino]-1-methyl-1,2-dihydro-4*H*-3,1-benzoxazin-4-one (4ac)

Following TP2: $Ni(cod)_2$ (81 mg, 0.282 mmol, 0.05 equiv), XANTPHOS (167 mg, 0.282 mmol, 0.05 equiv), **1a** (1.0 g, 5.7 mmol, 1.0 equiv), and 2,6-diethylphenyl isocyanate (**2c**; 1.2 mL, 6.8 mmol, 1.2 equiv) in toluene (20 mL) were heated to 80 °C for 4 h before purification by chromatography (silica gel) to yield **4ac** (975 mg, 56%) as a white crystalline solid; R_f = 0.78 (hexanes/EtOAc 7:3); mp 127 °C (DSC).

IR (solid state): 1760, 1668, 1606, 1589, 1483, 1454, 1414, 1368, 1335, 1320, 1269, 1245, 1199, 1164, 1145, 1124 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.9 Hz, 1 H), 7.71 (t, *J* = 8.2 Hz, 1 H), 7.14 (m, 2 H), 7.07 (m, 2 H), 7.00 (m, 1 H), 3.71 (s, 3 H), 2.49 (q, *J* = 7.6 Hz, 4 H), 1.17 (t, *J* = 7.6 Hz, 6 H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 157.9, 143.7, 141.6, 140.9, 137.2, 134.2, 130.7, 125.8, 123.2, 121.8, 113.0, 110.2, 32.5, 24.9, 14.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{21}N_2O_2$: 309.1598; found: 309.1603.

UV (MeCN): λ = 233, 264, 344 nm.

(*Z*)-2-[(2,6-Diisopropylphenyl)imino]-1-methyl-1,2-dihydro-4*H*-3,1-benzoxazin-4-one (4ad)

Following TP2: 81 mg $Ni(cod)_2$ (0.282 mmol, 0.05 equiv), XANTPHOS (167 mg, 0.282 mmol, 0.05 equiv), **1a** (1.0 g, 5.7 mmol, 1.0 equiv), and 2,6-diisopropylphenyl isocyanate (**2d**; 1.4 mL, 6.8 mmol, 1.2 equiv) in

toluene (20 mL) were heated to 90 °C for 4 h before purification by chromatography (silica gel) to yield **4ad** (867 mg, 46%) as a white crystalline solid; R_f = 0.82 (hexanes/EtOAc 7:3); mp 146 °C (DSC).

IR (solid state): 1765, 1665, 1606, 1587, 1484, 1457, 1376, 1358, 1339, 1320, 1270, 1246, 1194, 1173, 1146, 1124 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.0 Hz, 1 H), 7.72 (t, *J* = 8.2 Hz, 1 H), 7.13 (m, 4 H), 7.07 (m, 1 H), 3.73 (s, 3 H), 2.94 (sept, *J* = 6.7 Hz, 2 H), 1.20 (d, *J* = 6.7 Hz, 12 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 157.8, 143.8, 140.3, 140.2, 138.8, 137.2, 130.7, 123.5, 122.9, 121.8, 113.0, 110.2, 32.5, 28.7, 23.3.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{25}N_2O_2$: 337.1911; found: 337.1913.

UV (MeCN): λ = 233, 264, 345 nm.

(*Z*)-2-[(2-Isopropyl-6-methylphenyl)imino]-1-methyl-1,2-dihydro-4*H*-3,1-benzoxazin-4-one (4ae)

Following TP2: $Ni(cod)_2$ (81 mg, 0.282 mmol, 0.05 equiv), XANTPHOS (167 mg, 0.282 mmol, 0.05 equiv), **1a** (1.0 g, 5.7 mmol, 1.0 equiv), and 2-isopropyl-6-methylphenyl isocyanate (**2e**; 1.22 mL, 6.76 mmol, 1.2 equiv) in toluene (20 mL) were heated to 80 °C for 4 h before purification by chromatography (silica gel) to yield **4ae** (905 mg, 52%) as a white crystalline solid; R_f = 0.76 (hexanes/EtOAc 7:3); mp 118 °C (DSC).

IR (solid state): 1756, 1667, 1607, 1558, 1486, 1473, 1460, 1440, 1420, 1369, 1333, 1320, 1268, 1242, 1198, 1163, 1145, 1123 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.6 Hz, 1 H), 7.72 (t, *J* = 7.9 Hz, 1 H), 7.14 (m, 3 H), 7.04 (d, *J* = 7.3 Hz, 1 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 3.72 (s, 3 H), 3.01 (sept, *J* = 7.3 Hz, 1 H), 2.14 (s, 3 H), 1.20 (d, *J* = 6.7 Hz, 6 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 157.9, 143.7, 141.5, 140.6, 139.1, 137.2, 130.7, 128.4, 127.6, 123.2, 123.0, 121.8, 113.0, 110.2, 32.6, 28.6, 23.2, 18.5.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_2$: 309.1598; found: 309.1599.

UV (MeCN): λ = 231, 266, 342 nm.

(*Z*)-2-[(2-*tert*-Butyl-6-methylphenyl)imino]-1-methyl-1,2-dihydro-4*H*-3,1-benzoxazin-4-one (4af)

Following TP2: $Ni(cod)_2$ (40 mg, 0.141 mmol, 0.05 equiv), XANTPHOS (84 mg, 0.141 mmol, 0.05 equiv), **1a** (0.5 g, 2.82 mmol, 1.0 equiv), and 2-*tert*-butyl-6-methylphenyl isocyanate (**2f**; 0.64 g, 3.38 mmol, 1.2 equiv) in toluene (10 mL) were heated to 80 °C for 4 h before purification by chromatography (silica gel) to yield **4af** (724 mg, 80%) as a white crystalline solid; R_f = 0.76 (hexanes/EtOAc 7:3); mp 173 °C (DSC).

IR (solid state): 1761, 1659, 1607, 1583, 1508, 1482, 1471, 1455, 1426, 1368, 1336, 1319, 1301, 1268, 1243, 1213, 1184, 1169, 1145, 1125 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.9 Hz, 1 H), 7.71 (t, *J* = 8.3 Hz, 1 H), 7.22 (d, *J* = 7.9 Hz, 1 H), 7.14 (m, 2 H), 7.07 (d, *J* = 7.3 Hz, 1 H), 6.93 (t, *J* = 7.6 Hz, 1 H), 3.75 (s, 3 H), 2.11 (s, 3 H), 1.36 (s, 9 H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 157.8, 143.7, 142.4, 140.3, 140.1, 137.2, 130.7, 128.9, 128.4, 124.0, 122.7, 121.8, 113.0, 110.1, 35.0, 32.4, 30.1, 18.6.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{23}N_2O_2$: 323.1754; found: 323.1758.

UV (MeCN): λ = 233, 265, 347 nm.

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Supporting Information

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