# Structural Evidence for Aromatic Heterocycle N-O Bond Activation via Oxidative Addition



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**Publication date:**
2023-02-13

**Permanent link:**
https://doi.org/10.3929/ethz-b-000594917



**Originally published in:**
Organometallics 42(3), https://doi.org/10.1021/acs.organomet.2c00533

**Funding acknowledgement:**
184658 - Catalytic synthesis of unprotected amines and heterocycles (SNF)

# Structural Evidence for Aromatic Heterocycle N–O Bond Activation via Oxidative Addition

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### Notes

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**ABSTRACT:** Many methods report the scission of the N–O bonds of aromatic heterocycles and their subsequent functionalization. Oxidative addition is one of the presumed pathways through which aromatic N–O bond activation with transition metals is achieved. We report the first well-defined pathway of (benz)isoxazole's aromatic N–O bond activation through oxidative addition. We also provide control experiments that show that aromatic N–O bonds may be broken by strong inorganic reductants. These results highlight that N–O bonds are susceptible to both reduction and oxidative addition, which has important implications for catalysis. Exploring the reactivity of one of these complexes towards a series or electrophiles led to the discovery of a Staudinger-type β-lactam synthesis upon reaction with a ketene. Finally, we demonstrate that choice of different metal/ligand combinations allows for selective oxidative addition into either C–I bonds or N–O bonds in the presence of the other.

## INTRODUCTION

Medicinal chemistry routinely employs heterocyclic scaffolds, which are found in a large number of marketed pharmaceuticals.[1] Isoxazoles and related heterocycles containing N-X (X = N, O, S) bonds are widely utilized,[1–7] rendering cross-coupling of substrates bearing these scaffolds a particularly important transformation.[3,8–10] There are many examples of reactions in which the N–O bond of isoxazoles, benzisoxazoles or anthranils is functionalized, either under thermal,[11,12] Brønsted basic,[13–15] Lewis acidic[16] or transition-metal catalyzed conditions.[17–19] Isoxazoles are also known to decompose under basic conditions, for example in the Kemp elimination[18] or the Boulton-Katritzky rearrangement.[13,14,20] These transformations provide information on possible decomposition pathways during attempted cross-coupling.

Regarding the activation of the N–O bond of isoxazoles and benzisoxazoles (collectively referred to as (benz)isoxazoles) by oxidative addition to a transition metal, no unambiguous examples have been reported. Ahneman *et al.* reported an example of N–O oxidative addition to an aromatic ring using Pd(0), based on NMR data (Fig. 1a). They used this observation to provide a mechanistic explanation of the observed inhibitory effect of some isoxazoles on the cross-coupling under study.[21] In a later publication, the authors clarified that it was unclear whether the product arising from the Kemp elimination or the isoxazoles themselves were responsible, as performing the experiment using the rearrangement product also causes reaction inhibition.[22] Two examples of aromatic N–O bond activation characterized by single crystal X-ray diffraction (scXRD) exist, with Rh[23] and Pd[24] respectively. Wu *et al.* employ Pd and during their reaction, N–O bond lysis, Pd pre-catalyst ($PdCl_2$) reduction, C–I bond oxidative addition and migratory insertion into norbornene all presumably occur (Fig. 1b). In the report by Yu *et al.* using Rh(III), N–O scission is accompanied by a C–N bond formation

with the ligand (Fig. 1c). It is not clear whether reductive elimination or oxidative addition occurs first.

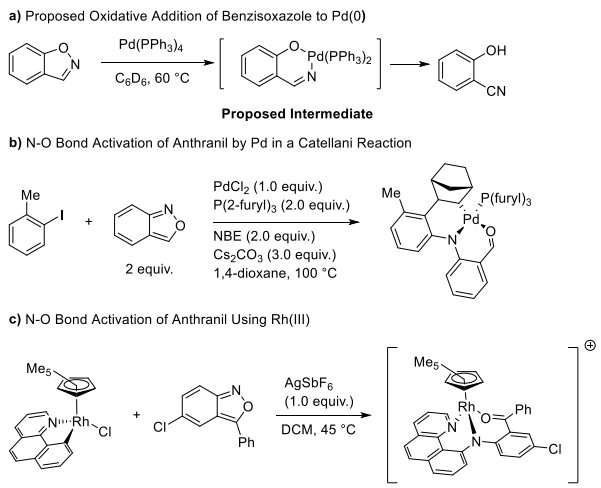


**Figure 1.** Precedent in the transition metal-catalysed aromatic N–O bond activation. **a)** Proposed oxidative addition of $Pd(PPh_3)_4$ to 1,2-benzisoxazole by Ahneman et al. supported by spectroscopic evidence. **b)** Oxidative addition of Pd to anthranil and C–N bond formation in a cascade Catellani reaction by Wu et al. supported by scXRD. **c)** Oxidative addition of Rh to anthranil and C–N bond formation to the cyclometallated ligand by Yu et al. supported by scXRD.

Given our longstanding interest in the reactivity of N–O bonds towards transition metal catalysts,[25–28] as well as the lack of reports unambiguously reporting oxidative addition into N–O bonds of aromatic heterocycles, we were interested in investigating the reactivity of (benz)isoxazoles towards late-transition metals. We focused on Ni in particular, a metal commonly used in numerous catalytic cross-coupling reactions and which has been shown to react with anthranils and other N-O reagents.[29–33] In this work, we provide evidence for the oxidative addition of Ni(0) to (benz)isoxazole N–O bonds. We go on to explore the reactivity of the resulting complexes with electrophiles and provide an example of chemoselective oxidative addition to either C–I or N–O bonds using different combinations of metal/ligand.

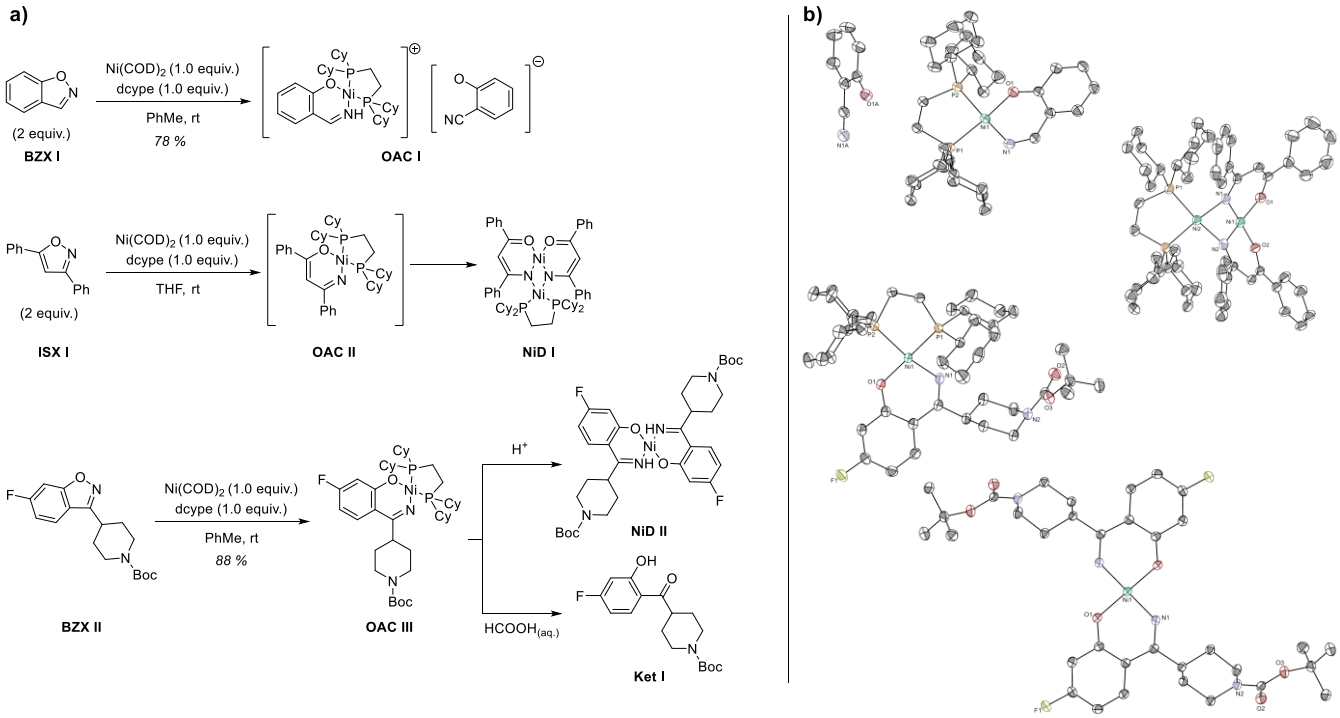


**Figure 2. a)** Reactivity of (dcype)Ni(0) with 1,2-benzisoxazole (**BZX I**), 3,5-diphenylisoxazole (**ISX I**) and *tert*-butyl 4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine-1-carboxylate (**BZX II**), leading to the formation of the corresponding oxidative addition complexes **OAC I**, **OAC II** (transiently) and **OAC III**. **OAC II** leads to the Ni(II) bimetallic complex **NiD I** and **OAC III** is converted to **NiD II** if acidic impurities are present. **b)** Structures of **OAC I**, **NiD I**, **OAC III** and **NiD II** determined using scXRD. Ellipsoids are shown at 50% probability and hydrogen atoms are omitted for clarity. The structure of **Ket I** has also been determined and is presented in the Supporting Information (Section S5). Organometallic reactions without stated yields denote that the shown products are not confidently assigned as major products.

## RESULTS AND DISCUSSION

**Reaction of Ni(0) Complexes with Aromatic N–O Bonds**

There have been reports of – presumably – low valent Ni complexes activating aromatic N–O bonds.[34] To initiate our studies, we chose

the combination of bis(1,5-cyclooctadiene)nickel(0) ($Ni(COD)_2$) and 1,2-bis(dicyclohexylphosphino)ethane (dcype), which we have used in the past to activate challenging bonds such as C–S and C–CN bonds.[35–39] Mixing 1,2-benzisoxazole (**BZX I**) with Ni(0)/dcype (Fig. 2a) resulted in a doublet in $^{31}P\{^1H\}$ NMR and immediate formation of orange crystals. When analyzed using scXRD, they revealed the structure of a cationic complex resulting from N–O oxidative addition and protonation of the Ni(II)-imidate (**OAC I**), with a phenolate (resulting from Kemp rearrangement of **BZX I**) as the counterion (Fig. 2b).

Due to the propensity of **BZX I** to rearrange, the product arising directly from oxidative addition was not isolated. To remedy this, we opted for an alternative substrate. We chose 3,5-diphenylisoxazole (**ISX I**) due to its simplicity and C3 substitution, which should prevent rearrangement to the phenolate. The reaction of **IZX I** with Ni(0)/dcype, results in several new species forming, one of which is a dinickel (II) complex (**NiD I**) thatwas characterized using scXRD (Fig. 2b). We surmise that **NiD I** arises from the disproportionation of the corresponding oxidative addition complex **OAC II**.

Re-evaluating our approach, we identified *tert*-butyl 4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine-1-carboxylate (**BZX II**), a larger analogue which we speculated would slow disproportionation to the dinickel species. We hypothesized that the C3 substituent would prevent Kemp elimination. Moreover, the precursor amine salt 4-(6-fluorobenzo[d]isoxazol-3-yl)piperidin-1-ium chloride is commercially available, which allows easy preparation of **BZX II**. Furthermore, it is a substructure present in several pharmaceuticals,[40,41] making it a representative example of medicinally relevant compounds.

When reacted with Ni(0)/dcype, **BZX II** also showed a characteristic pair of doublets in $^{31}P\{^1H\}$ NMR; crystallization led to the isolation of crystals of the coveted N–O oxidative addition complex (**OAC III**) (Fig. 2b). A mononuclear Ni(II) bearing two substrate molecules (**NiD II**) is formed by protonation of the Ni(II)-imidate as a side-product, only in the presence of small amount of unprotected **BZX II** (see Supporting Information Section S2.2.3 for more details). **NiD II** was also characterized by scXRD (Fig. 2b). Isolation of **OAC III** and subsequent acidic hydrolysis afforded the corresponding ketone (**Ket I**), which we also characterized by scXRD (see Supporting Information Section S5). We consider this to be the first example of an unambiguously characterized oxidative addition to an aromatic N–O bond. Our characterization data include multinuclear solution state NMR ($^1H$, $^{13}C\{^1H\}$, $^{19}F\{^1H\}$, $^{31}P\{^1H\}$), HRMS and scXRD. We could not carry out comparisons of bond lengths or angles of these complexes, as we could not identify any analogous M(II) (M = Ni, Pd, Pt) complexes bearing either dcype and any X-type N and O ligands or imine/phenolate ligands with any neutral phosphines. The most similar complexes in the literature bear neutral imines.[42,43]

**Reactivity of the Ni(II) Complexes with Electrophiles** We probed the reactivity of the oxidative addition complex **OAC III** with various electrophiles (see Supporting Information Section S4). Diphenylketene, which we selected envisioning a sequence of nucleophilic addition and C-X (X = N or O) reductive elimination, instead gave a Ni(II) lactamate (**NiLac I**) which was characterized using scXRD (Fig. 3). We propose that **NiLac I** is the result of a formal [2+2] cycloaddition between the Ni(II)-iminate and the ketene in a Staudinger-type β-lactam synthesis. These types of transformations are known employing Rh[44,45] and Pd[46,47], however to the best of our knowledge, no example involving Ni has been reported. We believe that this transformation follows the generally accepted stepwise mechanism[48] of the Staudinger β-lactam reaction. We propose that the Ni(II) center plays a dual role in this transformation. First, it may aid nucleophilic attack by placing a larger negative charge on the iminate N compared to imines usually employed in the traditional Staudinger synthesis (*N*-sulfonyl, *N*-alkyl or *N*-aryl).[49–51] In the second step, it might act as a Lewis acid activating the imine towards nucleophilic addition with the formed enolate, resulting in **NiLac I**.

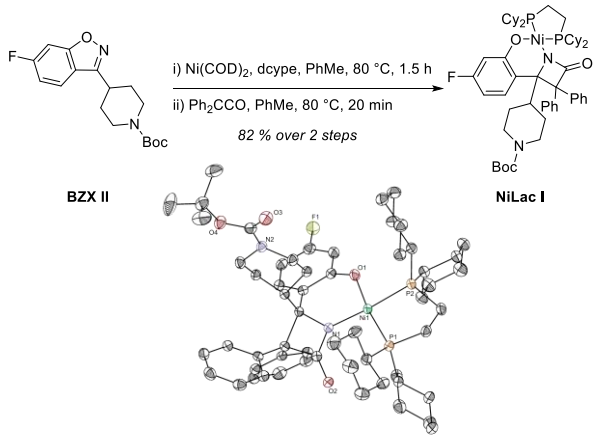


**Figure 3.** Reactivity of *in situ* generated **OAC III** with diphenylketene and structure of the product **NiLac I** determined by scXRD. Ellipsoids are shown at 50% probability and hydrogen atoms are omitted for clarity.

**Oxidative Addition Selectivity** Having established the oxidative addition of Ni(0) to N–O bonds, we must contend with the fact that despite this, cross-coupling of (benz)isoxazoles is still possible.[3,8–10] To elucidate this, we investigated the competition between C($sp^2$)-I and (benz)isoxazole N–O oxidative addition. To this end, we iodinated **BZX II**, obtaining *tert*-butyl 4-(6-fluoro-7-iodobenzo[d]isoxazol-3-yl)piperidine-1-carboxylate (**BZX III**). Reacting **BZX III** with Ni(0)/dcype results in N–O bond activation, yielding the corresponding Ni(II) oxidative addition complex **OAC IV**, similar to the reaction of **BZX II** (Fig. 4). However, when **BZX III** is reacted with Pd(0)/dppf instead, oxidative addition to the C–I bond occurs at room temperature, affording the Pd(II) complex **OAC V** (Fig. 4). Both **OAC IV** and **OAC V** have been characterized by multinuclear solution-state NMR and scXRD. We selected the Pd(0)/dppf system as it is a very common metal/ligand combination for cross coupling in the presence of heterocycles (a SciFinder search for arylation of any benzofused heterocycles bearing a C5 halide returns Pd(0)/$PPh_3$ and Pd(0)/dppf as the most common metal/ligand combinations). The observed chemoselectivity helps

explain why (benz)isoxazoles do not always interfere in the commonly employed palladium-catalyzed cross-couplings, as it is possible to selectively activate aryl halides in the presence of heterocycles which contain N–O bonds.

**Other Metal Complexes and Reducing Agents** To provide additional information on the reactivity of the N–O bond of (benz)isoxazoles towards low-valent metals, we conducted a brief screen of common metal/ligand combinations on **BZX II**, monitoring the formation of **Ket I** by $^{19}F\{^{1}H\}$ NMR after hydrolysis with weak acid. The full results are presented in the Supplementary Information (Section S3.2). In short, we have shown that sufficiently strong reductants ($KC_8$) can break the aromatic N–O bond, whereas milder reductants such as Mn(0) or Zn(0) cannot. This indicates that both oxidative addition and direct electron transfer from reductants can cause the N–O bond to be broken. This also suggests that (benz)isoxazoles may be amenable to cross-electrophile coupling,[29,52] despite the fact that they are not frequently used in such transformations.

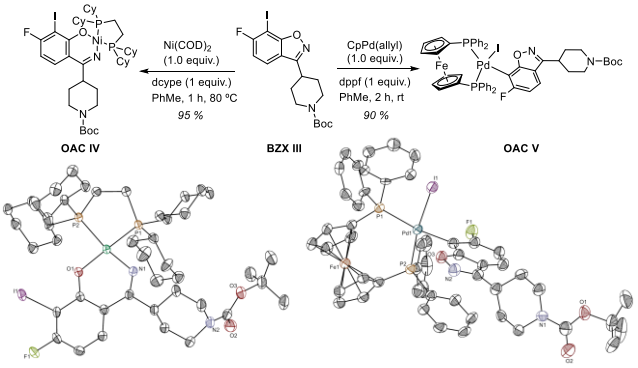


**Figure 4.** Activation of either an aromatic N–O bond or a C–I bond of **BZX III** yielding **OAC IV** or **OAC V** respectively, along with the corresponding structures determined using scXRD. Ellipsoids are shown at 50% probability and hydrogen atoms are omitted for clarity.

## CONCLUSION

In conclusion, we have provided spectroscopic and crystallographic evidence that Ni(0)/dcype can perform oxidative addition into the aromatic N–O bond of (benz)isoxazoles. We have also investigated the reactivity of the resulting Ni(II) complexes with electrophiles and reported a Ni(II)-promoted Staudinger β-lactam synthesis. We showed that oxidative addition to N–O and C–I bonds can be performed orthogonally by employing different combinations of metal and ligand. We posit that this is a plausible explanation for the fact that palladium-catalyzed cross-coupling in the presence of (benz)isoxazoles is sometimes possible.

## EXPERIMENTAL SECTION

Full details regarding the synthesis and characterization of the reported complexes can be found in the Supporting Information, including copies of spectra, along with a link to the Zenodo repository containing files of the processed spectra.

**Synthesis of oxidative addition complex of BZX II (OAC III).** *tert*-butyl 4-(6-fluorobenzo[d]isoxazol-3-yl)piperidine-1-carboxylate (161 mg, 1.00 equiv., 503 µmol) was added to a solution of $Ni(COD)_2$ (138 mg, 1.00 equiv., 502 µmol) and 1,2-bis(dicyclohexylphosphaneyl)ethane (215 mg, 1.02 equiv., 510 µmol) in toluene (5.0 mL). The red-orange solution was heated at 80 °C for 1.5 h. After the reaction mixture was cooled to room temperature, the volatiles were removed under reduced pressure. Washing the obtained orange oil with *tert*-butyl methyl ether (2 × 1 mL) and hexane (3 × 1 mL) afforded the complex **OAC III** (355 mg, 442 µmol, 88 %) as an orange powder. Crystals suitable for single-crystal X-ray diffraction were grown by slow evaporation of a toluene solution.
Other complexes were synthesized using similar procedures.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. The following references are cited in the Supporting Information as they are relevant to the procedures reported therein.[53–60]

Supporting Information (.pdf)

Crystal structures available at the CCDC (.cif)

Machine-readable NMR spectra available on Zenodo at 10.5281/zenodo.7274562 (.jdx)

## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENT

The ETH Zürich is acknowledged for financial support. P. M. acknowledges the Swiss National Science Foundation (SNSF 184658) for funding. We thank the Molecular and Biomolecular Analysis Service (MoBiAS), the X-ray structure service (SMoCC) and the LOC NMR Service at ETH Zürich for technical assistance. We further thank the whole Morandi group for fruitful discussions and critical proofreading of the manuscript.

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