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Nickel-Catalyzed Regioselective C-H Bond mono- and bis-Nitration of Aryl Oxazolines with *tert*-Butyl Nitrite as Nitro Source

Li Wan,[a,b] Kai Qiao,[a] Xin Yuan,[a] Ming-Wei Zheng,[a] Bing-Bing Fan,[a] Zhe Chen Di,[a] Dong Zhang,[a] Zheng Fang,[a] and Kai Guo*[a,b,c]

[a] College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, Nanjing 211816, P. R. China Fax: (+86)-25-5813-9926; phone: (+86)-25-5813-9926; e-mail: guok@njtech.edu.cn
[b] Jiangsu National Synergetic Innovation Center for Advanced Materials (SICAM), Nanjing 211816, P. R. China
[c] State Key Laboratory of Materials-Oriented Chemical Engineering, Nanjing Tech University, Nanjing 210009, P. R. China

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Abstract. An efficient and regioselectivenickel-catalyzed remote C-H nitration of 2-aryl oxazoline amides using the non-corrosive TBN as nitro source has been developed. The protocol makes use of inexpensive nickel salts as catalysts and delivers the corresponding products in excellent yields. Notably, bis-nitration products were obtained by simply increasing the amount of *tert*-butyl nitrite. This reaction proceeds in air and features excellent functional group compatibility, broad substrate scope and is suitable for gram-scale synthesis.

Keywords: nickel, nitration, oxazoline, amide, SET

Introduction

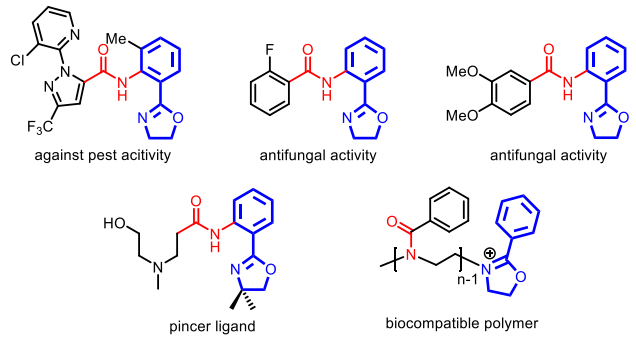


Figure 1. Representative application of molecules containing aryl oxazoline and amide functionalities.

Substituted aryl oxazolines are not only present in numerous natural products, pharmaceuticals, functional materials and ligands,[1] but can also be used as directing groups in a number of synthetic reactions,[2] thus their synthesis has attracted tremendous interest within the chemical community (Figure 1). Moreover, oxazolines are readily accessible and can be converted into many other valuable compounds such as *N*-(2-Aminoethyl)acylamides, 4,5-dihydro-1,3-oxazin-6-ones and β-amidoaldehydes.[3] As a consequence, new methodologies for further functionalization of readily accessible aryl oxazolines are potentially important developments in organic synthesis. Transition metal catalyzed C-H functionalization reactions have been recognized as straightforward and robust methods for the formation of carbon-carbon and carbon-heteroatom bonds.[4] These methodologies enable the direct introduction of complex functional groups into an assortment of organic molecules in an environmentally benign manner. C-H bond functionalization is an attractive alternative to classical cross-coupling reactions (which usually require organohalides and organometallic reagents) due to the abundance and relatively low cost of various hydrocarbons.[5] However, the majority of procedures reported thus far predominantly employ rhodium, ruthenium, iridium and palladium as catalysts. The use of a more economic and inexpensive metal in C-H bond functionalization reactions is therefore greatly desired.

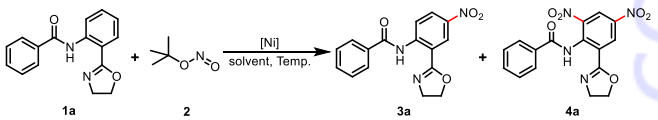
In consideration of the attractive features associated with naturally abundant 3d transition metals, recent efforts towards C-H functionalization have focused on the utilization of inexpensive base-metal catalysts.[6] In particular, nickel salts have emerged as effective catalysts for direct C-H bond functionalizations.[7] Since the pioneering work of Daugulis et al.,[8] bidentate chelation-assisted C-H functionalizations using 8-aminoquinoline as an auxiliary have provided a powerful tool for the synthesis of a diverse range of molecules.[9] While substantial progress has been made in the area of directing group assisted functionalization to C(sp^2)-H and C(sp^3)-H bonds, current studies in the field typically focus on C-H transformations on quinoline frameworks. Stahl et al. first reported the copper catalyzed remote C5-selective chlorination of 8-amidoquinolines via a single-electron-transfer (SET) pathway.[10] Subsequently, multiple transition metal-catalyzed C-H bond functionalizations at the C5 or C7 position of quinoline have been reported by various groups.[11] However, efficient C-H functionalizations of the remote and unactivated C-H bonds of 2-aryl oxazolines remain rare.

Nitroarenes have been widely employed as key intermediates for the preparation of a variety of dyes, plastics, explosives, pharmaceuticals and natural products.[12] Generally, a mixed acid system (HNO_3/H_2SO_4) and N_2O_5 are used as nitrating reagents in the classical electrophilic nitration reaction.[13] Unfortunately, due to the harsh reaction conditions, these simple and efficient procedures often suffer from poor regioselectivity, limited functional group tolerance and over-nitration. To overcome these problems, the metal-free nitrating reagent *tert*-butyl nitrite (TBN) has been utilized as a precursor for the generation of NO_2 in many nitration protocols involving aromatic compounds.[11g, 14] Therefore, the nitration of 2-aryl oxazolines using TBN as an NO_2 source is of great interest. To the best of our knowledge, the Ni-catalyzed regioselective nitration of 2-aryl oxazolines via remote C-H functionalization is not well-developed and still represents a great challenge. Herein, we disclose the first example of a Ni-catalyzed nitration of 2-aryl oxazolines at geometrically inaccessible C-H bonds.

Results and Discussion

Initially, 2-aryl oxazoline bearing benzamide **1a** was chosen as the model substrate for the optimization of reaction parameters (Table 1). To our delight, excellent conversion of **1a** was achieved when the reaction was carried out at 80 °C for 16 h in the presence of a catalytic amount of NiI_2 (10 mol%) under an air atmosphere and using PhCl as a solvent. The corresponding nitrated products, **3a** and **4a**, were isolated in 47% and 42% yield respectively (Table 1, entry 1). To improve the selectivity of mono- and bis-nitration, different nickel catalysts were examined. As the results listed in Table 1, $Ni(acac)_2$ was found to possess the highest catalytic activity compared to other catalysts, giving the mono-nitration product **3a** in 86% yield (Table 1, entry 9). The molecular structure of **3a** was unambiguously confirmed by single crystal X-ray diffraction (Figure 2). This finding is interesting since it enables the nitration to take place at the remote C-H bond that is inaccessible using conventional methods. A number of solvents such as DCE, CH_3CN, DMF, EtOH, AcOH and THF were examined, and the results showed that none of them could match the efficacy of PhCl (Table 1, entries10-15). Moreover, temperatures lower or higher than 80 °C resulted in reduced yields of **3a** (Table 1, entries 16 and 17). It should be noted that a slightly lower yield (82%) of **3a** was obtained when the loading of $Ni(acac)_2$ was reduced to 1 mol% (Table 1, entry 19). This result indicates that $Ni(acac)_2$ is highly effective for the mono-nitration of **1a**. After establishing an efficient synthesis of **3a**, our attention turned to the preferential formation of **4a**. According to our previous results, a higher yield of the bis-nitration product **4a** was obtained when employing NiI_2 as a catalyst or DCE as a solvent. Thus, the reaction was carried out using a combination of NiI_2 and DCE. To our delight, the yield of **4a** increased to 53% when using 10 mol% NiI_2 as a catalyst and DCE as a solvent (Table 1, entry 20). Surprisingly, **4a** was obtained in 81% yield when 6 equiv of TBN was employed (Table 1, entry 21). An elevated temperature appears to be detrimental to the selectivity of the bis-nitration (Table 1, entry 22). For comparison, the bis-nitration reaction was carried out in the presence of 10 mol% $Ni(acac)_2$, and with 6 equiv TBN in DCE or PhCl solvent at 80 °C (Table 1, entries 23 and 24). As expected, the selectivity of the bis-nitration under these reaction conditions was significantly lower than the optimal conditions. Clearly, NiI_2 exhibits higher catalytic activity when the phenyl ring is substituted with a strong electron-withdrawing group. This may be due to the chelating ability of NiI_2 with the nitorgen atoms of the amide and oxazoline groups being strogner than that of $Ni(acac)_2$.

Table 1. Optimization of the Reaction Conditions[a]



Entry	Catalyst (% mol)	TBN (equiv)	Temp (°C)	Solvent	Yield (%, **3a+4a**)[b]
1	NiI_2 (10)	3	80	PhCl	47 + 42
2	$Ni(COD)_2$ (10)	3	80	PhCl	78 + 5
3	$NiCl_2$ (10)	3	80	PhCl	72 + 4
4	$Ni(OTf)_2$ (10)	3	80	PhCl	79 + 6
5	$NiCl_2$ (10)	3	80	PhCl	71 + 5
6	$NiBr_2$ (10)	3	80	PhCl	64 + 15
7	$Ni(OAc)_2$ (10)	3	80	PhCl	52 + 29
8	$Ni(NO_3)_2$ (10)	3	80	PhCl	53 + 33
9	$Ni(acac)_2$(10)	3	80	PhCl	86 + 4
10	$Ni(acac)_2$ (10)	3	80	DCE	67 + 19

11	$Ni(acac)_2$ (10)	3	80	CH_3CN	32 + 14
12	$Ni(acac)_2$ (10)	3	80	DMF	trace
13	$Ni(acac)_2$(10)	3	80	EtOH	trace
14	$Ni(acac)_2$ (10)	3	80	AcOH	3 + 25
15	$Ni(acac)_2$ (10)	3	80	THF	trace
16	$Ni(acac)_2$ (10)	3	60	PhCl	71 + 4
17	$Ni(acac)_2$ (10)	3	100	PhCl	63 + 11
18	$Ni(acac)_2$ (5)	3	80	PhCl	84 + 5
19	$Ni(acac)_2$ (1)	3	80	PhCl	82 + 3
20	NiI_2 (10)	3	80	DCE	32 + 53
21	NiI_2 (10)	6	80	DCE	3 + 81
22	NiI_2 (10)	6	100	DCE	10 + 71
23	$Ni(acac)_2$ (10)	6	80	DCE	33+51
24	$Ni(acac)_2$ (10)	6	80	PhCl	62+24

[a] *Reaction conditions*: **1a** (0.2 mmol), TBN, nickel catalyst, solvent (2.0 mL), stirred under air for 16 h in a sealed tube.
[b] Isolated yield.

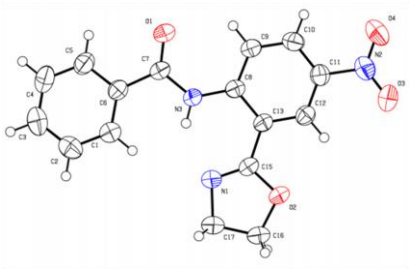
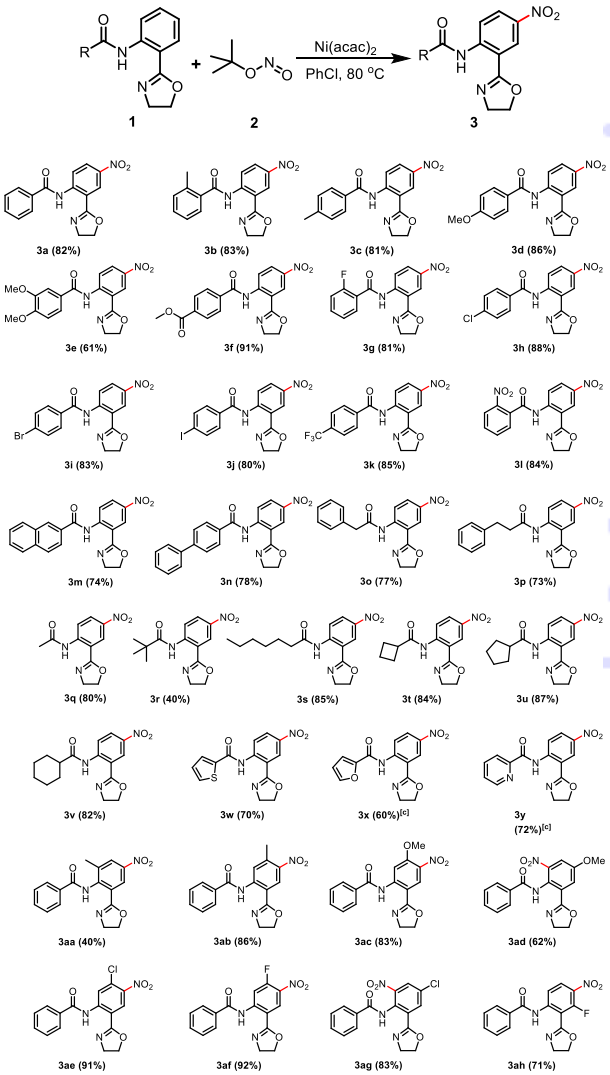


Figure2. X-ray structure of **3a**.

With the optimized reaction conditions in hand, we first probed the versatility of the site-selective, remote C-H functionalization with regards to a series of diversely substituted carboxamides. As shown in Table 2, aromatic amides bearing a variety of substituted groups, including electron-donating groups (Me, MeO) and electron-withdrawing gruops (F, Cl, Br, I, CF_3, NO_2, Ph) on the benzene ring, exhibited high reactivity with TBN under the optimal reaction conditions. The desired products (**3b-3n**) were obtained in good to excellent yields. It is noteworthy that substrates **1e** and **1g** possess antifungal activity and that their nitration products **3e** and **3g**, may be able to be converted into molecules bearing higher bioactivities. Moreover, a wide range of alkyl substituted carboxamides performed well and furnished the corresponding products in satisfactory yields (**3o-3q**, **3s-3v**), with the exception of *tert*-butyl amide (**3r**). The significantly reduced yield of **3r** can be attributed to the *tert*-butyl group preventing the nickel catalyst from coordinating to the amide and oxazoline groups due to steric effects.[11g, 11i] Indeed, the less sterically demanding substituents such as cyclobutyl, cyclopentyl and cyclohexyl, all provided their corresponding mono-nitration products in good yields (**3t-3v**). Furthermore, the reaction scope is broad, with heterocyclic amides such as 2-furan, 2-thiofuran and 2-pyridine, all being amenable to the reaction conditions giving their nitrated products in high yields (**3w-3y**). In addition, the influence of substituents on the phenyl ring of the 2-aryl oxazolines was also explored. Notably, the presence of electron-donating or electron-withdrawing halogen substituents on the phenyl ring did not significantly affect the nitration reaction, irrespective of their position. Except for **3aa**, products **3ab-3ah** were obtained with excellent yields. Interestingly, the nitration also proceeded smoothly at the C6 position when the C4 position was blocked by a methoxy or chloride group (**3ad** and **3ag**, respectively).

Table 2. Substrate scope for the preparation of mono-nitrated products[a,b]



[a] *Reaction conditions*: **1** (0.2 mmol), TBN (3.0 equiv), $Ni(acac)_2$ (1 mol%), PhCl (2.0 mL), stirred under air for 16 h in a sealed tube.
[b] Isolated yield.
[c] The catalyst loading of $Ni(acac)_2$ was 10 mol%.

Next, the substrate generality for the formation of the bis-nitration products **4** was investigated. The results listed in Table 3 show that this methodology is amenable to a number of substrates bearing aromatic amides, aliphatic amides and heterocyclic amides. Various substituents, including electron-donating groups or electron-withdrawing halides, were well

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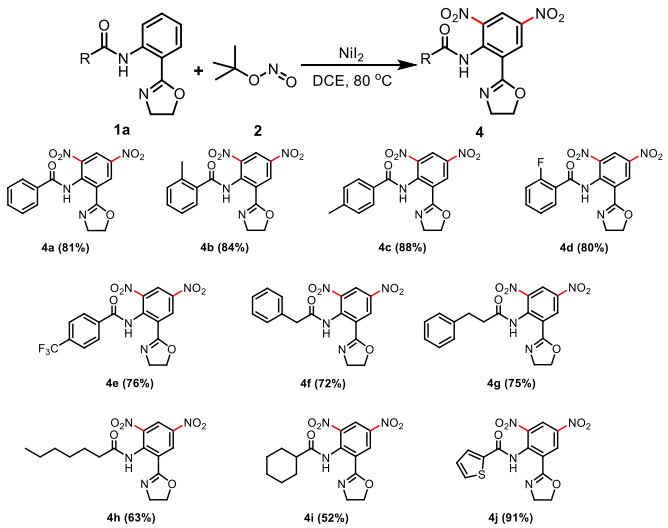
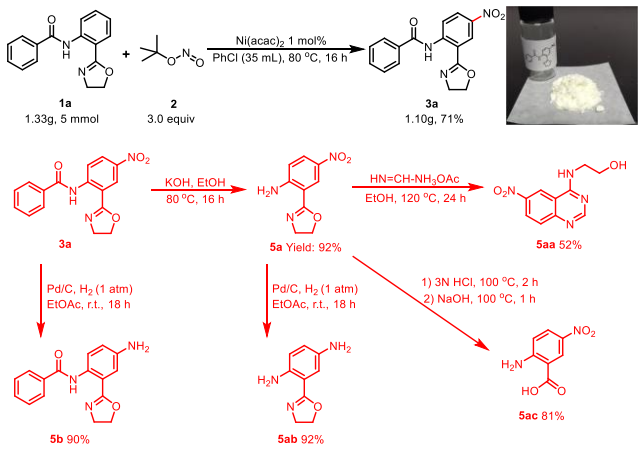
tolerated (**4b**-**4e**). Remarkably, the bis-nitration reaction conditions were also suitable for a carboxamide derived from thiofuran, delivering the desired product in 91% yield (**4j**). As a further demonstration of the synthetic expediency of this methodology, a gram-scale reaction was conducted with **1a** (1.33g, 5.0 mmol) and TBN (3.0 equiv) under the standard reaction conditions (Scheme 1). We are pleased to discover that product **3a** could be obtained in 71% isolated yield with a catalyst loading of 1 mol%. The amide bond could be easily cleaved by treating **3a** with NaOH in refluxing ethanol to give the 2-aryl oxazoline derivative **5a** in 92% yield. Additionally, the nitro group in **3a** and **5a** could be conveniently reduced to the resepctive free amines **5b** and **5ab** under a hydrogen atmosphere (Scheme 1). Moreover, oxazoline **5a** could be further manipulated. As illustrated in Scheme 1, quinazolinone **5aa** and a benzoic acid compound **5ac** bearing both nitro and amine groups, could be prepared in just a few steps.

Table 3. Substrate scope for the preparation of bis-nitrated products[a,b]

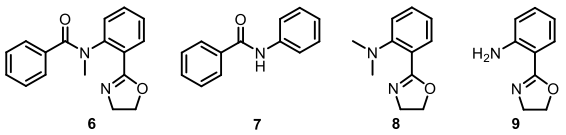


[a] *Reaction conditions*: **1** (0.2 mmol), TBN (6.0 equiv), NiI_2 (10 mol%), DCE (2.0 mL), stirred under air for 16 h in a sealed tube.
[b] Isolated yield.



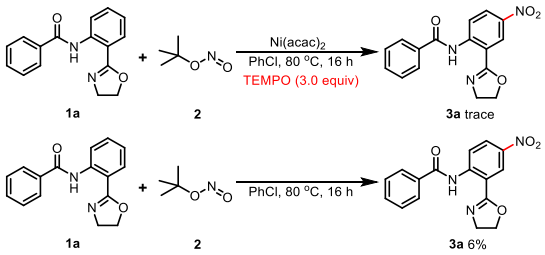
Scheme 1. Gram-scale synthesis and transformation of **3a**.

It is important to note that chelation with the amide and oxazoline functionalities is essential for this reaction. For example, *N*-methy-substituted amide **6** and *N*-phenylbenzamide **7** failed to undergo reaction (Scheme 2). Thus, these results indicate that the secondary amide and oxazoline groups in the substrate are essential requirements for successful nitration. Additionally, the nitration reaction also failed with the electron-rich 2-aryl oxazoline **8** and its derivative **9**. Based on these observations, electrophilic substitutions such as those based on a Friedel-Crafts type mechanism, can be excluded in this nitration reaction.

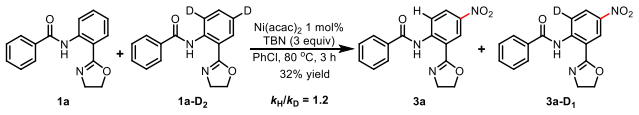


Scheme 2. Ineffective substrates for the nitration reaction

To shed some light on the mechanism, several control experiments were carried out (Scheme 3). The addition of 3 equiv of TEMPO completely suppressed the formation of **3a**, suggesting the involvement of a single electron transfer (SET) pathway. Moreover, treatment of **1a** with TBN in the absence of any nickel catalyst afforded **3a** in only 6% yield, showing that the nickel catalyst is essential for the high-yielding synthesis of **3a**. Additionally, a kinetic isotope effect (KIE) was observed in an intermolecular competition experiment (Scheme 4). A 1:1 mixture of **1a** and the deuterium labelled substrate **1a-D₂** were subjected to the optimized reaction conditions over 3h. The k_H/k_D ratio of **1a** was determined to be 1.2. Such a low KIE implies that remote C-H bond cleavage is not the rate-determining step.



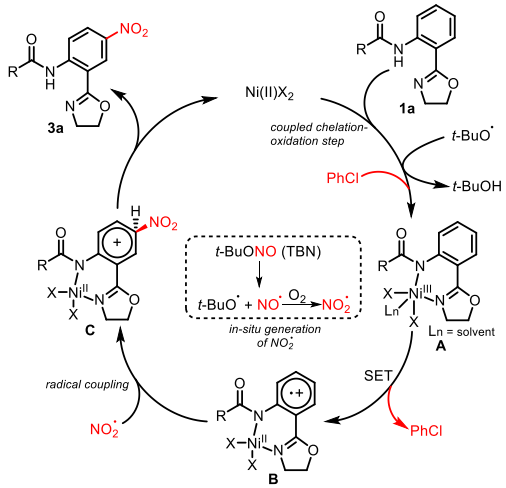
Scheme3. Control experiments.



Scheme 4. Kinetic isotope effect experiment.

According to the experimental results and the literature,[11f, 11g, 11i] a plausible mechanistic pathway for the formation of **3a** has been proposed (Scheme 5). Initially, coordination of **1a** with Ni(II) forms a chelated complex that is subsequently oxidized to the Ni(III) intermediate **A** (most likely stabilized by PhCl)[15] via the *tert*-butoxy radical generated from TBN. Then, an intermolecular SET between the 2-aryl oxazoline moiety and the highly oxidative Ni(III) centre generates the cationic radical/Ni(II) species **B**, with PhCl dissociating from the nickel centre. Next, $NO_2^{\cdot}$ is generated *in-situ* from TBN with O_2 under thermal conditions and reacts with **B** to deliver intermediate **C**. Complex **C** undergoes a concerted proton transfer/demetallation step to provide the nitration product **3a** and regenerate the Ni(II) catalyst which can take part in the next catalytic cycle.

The mechanism of the bis-nitration reaction is likely similar to that described for the formation of the mono-nitration product above. Based on our observations and the experimental data, the bis-nitration product is formed from the mono-nitration product. Due to the presence of an additional nitro group on the benzene ring of mono-nitration product, the coordinating ability of the nitrogen atoms in the amide bond and the oxazoline group is weakened. Under these conditions, the coordinating ability of NiI_2 is better than that of $Ni(acac)_2$ allowing for the ready formation of the bis-nitration product when this catalyst is used. In the experiments, DCE provided the best solubility for the mono-nitration products compared to all other investigated solvents, including PhCl. Hence, the use of DCE may promote the formation of the bis-nitration product from the mono-nitration product because of increased solubility of the mono-nitrated intermediate.



Scheme 5. Plausible mechanism.

Conclusion

In conclusion, we have developed an efficient and convenient C-H bond nitration of 2-aryl oxazoline amides using the inexpensive $Ni(acac)_2$ as a catalyst and TBN as a nitro source. Moreover, bis-nitration products were obtained by simply increasing the amount of TBN. This optimized protocol possesses several advantages over traditional nitration procedures as it avoids the use of highly corrosive H_2SO_4 and HNO_3 as reagents. Generally, the reaction system shows high functional group tolerance, can be easily scaled up and has good regioselectivity.

Experimental Section

General procedure for the mono-nitration of aryl oxazolines

In a 35 mL tube, the corresponding aryl oxazolines**1** (0.2 mmol, 1.0 eq), $Ni(acac)_2$ (0.02 mmol, 1 mol%), TBN (0.6 mmol, 3.0 eq) and 2 mL PhCl were added under air. The tube was sealed and the resulting solution was heated in a 80 °C oil bath with vigorous stirring for 16 h. Then the reaction mixture was cooled to room temperature. The mixture was poured into water (10 mL) and extracted with ethyl acetate (20 mL × 3), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under vacuum. The residue was purified by flash chromatography using CH_2Cl_2/*n*-hexene (2:1) as eluent to afford the products.

General procedure for the bis-nitration of aryl oxazolines

In a 35 mL tube, the corresponding aryl oxazolines 1a (0.2 mmol, 1.0 eq), NiI_2 (0.2 mmol, 10 mol%), TBN (1.2 mmol, 6.0 eq) and 2 mL DCE were added under air. The tube was sealed and the resulting solution was heated in a 80 °C oil bath with vigorous stirring for 16 h. Then the reaction mixture was cooled to room temperature. The mixture was poured into water (10 mL) and extracted with ethyl acetate (20 mL × 3), the combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under vacuum. The residue was purified by flash chromatography using CH_2Cl_2/*n*-hexene (2:1) as eluent to afford the products.

Acknowledgements

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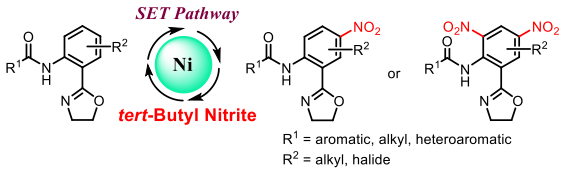
FULL PAPER

Nickel-Catalyzed Regioselective C-H Bond mono- and bis-Nitration of Aryl Oxazolines with *tert*-Butyl Nitrite as Nitro Source



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