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Ni(II) catalyzed bromination of aryl C-H bonds

Moumita Bhattacharya¹, David B. Cluff², Siddhartha Das*

Department of Chemistry and Biochemistry, Utah State University, Logan, UT, United States

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1. Introduction

Efficient conversion of aromatic C–H to C–halogen bond provides access to organic halides, which are valuable starting materials in numerous C–C coupling reactions [1]. Presently, halogenation of organic molecules is carried out using X_2 /light [2a,b], Lewis acids (FeCl₂)/X₂ [3a,b], hypervalent iodine reagents/MX (M: Li/Na/K/TMS) [4], X_2 /M (M: Fe) [5] methods. Achieving halogenation of aromatic rings bearing electronwithdrawing groups (EWG) like CF₃ is especially important since incorporation of a CF₃ group in an aromatic ring is widely used to synthesize pharmaceuticals [6]. Selective halogenation of aromatic systems bearing EWG like CF₃ or NO₂ would provide a facile step for subsequent C–C couplings and, therefore, alternative routes for drug synthesis [7a,b].

Among first-row transition metals, Ni(II) has become an appealing alternative for C–C cross coupling. Several groups, most notably those of Chatani, Garg, Shi, and Snieckus, have extensively explored the use of aryl systems bearing various functional groups and $ArB(OH)_2/ArZnX/ArMgX$ (X: halide) reagents [8a–h]. In addition, there has been a report of a Suzuki cross coupling between Ar–X and Ar'B(OH)₂, with Ni(II)CNC (1) (Scheme 1) as the catalyst [9].

However, for activation of the C–H bond, Ni(II) systems have been reported to prefer the thermodynamically favorable C–C coupling during reductive elimination instead of yielding a C-halogen product [10]. An interesting comparison is the use of the 'chelate control' with Pd(II) versus Ni(II); with 2-phenylpyridine, Pd(II)

ABSTRACT

Bromination of unactivated aromatic C–H bonds without directing and/or chelating groups was achieved by employing an air stable N-heterocyclic Ni(II) complex. PhI(OAC)₂ and N-bromosuccinimide have been used as the oxidizing agent and the bromine source, respectively. Yields for bromination are as high as >99%, especially in presence of electron-withdrawing groups like –NO₂ and –CF₃. This is a rare report on C–H bond activation with Ni(II) where, instead of homo C–C coupling, reductive elimination to form C-halogen could be achieved.

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leads to C–H functionalization (insertion of acetate) [11], but for Ni(II), the major product is C–C coupling between two molecules of 2-phenylpyridine (PhPy) [10]. With Ni(II), even when N-bromo-succinimide or N-chlorosuccinimide is used, C–H halogenation is detected only in trace amounts (in these cases a stoichiometric amount of Ni(II) was used).

In Ni(PhPy)₂ system [10], Ni(II) has a near-perfect square planar geometry. However, in a strained system like Ni(II)CNC (See Figure S1(a) and (b) for qualitative MO diagrams), Ni(II) cannot adopt a square planar geometry. The geometry of **1** allows higher orbital overlap between ligand group orbitals (LGOs) and d_{xy} than a square planar geometry; in Ni(II)CNC, LGOs approach Ni(II) along a direction that is in between the x and y axes, not along the axes themselves. This makes the metal centered d_{xy} more destabilized than in a square planar geometry. Also, strong σ -donation from the two NHC ligands in the *xy* plane makes d_{xy} , and especially $d_{x^2-y^2}$ (which experiences direct linear overlap) very destabilized. In the d⁸ Ni(II) system, metal centered d_{xy} and $d_{x^2-y^2}$ have a major contribution to the HOMO and LUMO, respectively. Therefore, we envisioned that Ni(II)CNC, unlike other square planar Ni(II) complexes, would have a significantly high-lying HOMO (with major contribution from d_{xy}) and even a higher-lying LUMO (with major contribution from $d_{x^2-v^2}$). We presumed that (a) the high-lying HOMO (i.e. easier to oxidize) and (b) the CNC ligand's large steric bulk and large percentage buried volume [12] might help Ni(II)CNC to catalyze C-H activation in the presence of an oxidant, and to show subsequent reductive elimination with insertion of a small functional group (thus, avoiding C-C homo-coupling).

This inspired us to investigate Ni(II)CNC (1) in the selective bromination of aryl rings and its functional group tolerance. This opens up the potential for carrying out a "domino reaction", where C-H







^{*} Corresponding author.

¹ Current address: Department of Chemistry, University of Utah, Salt Lake City, UT, USA.

² Current address: Department of Chemistry, UC-Davis, Davis, CA, USA.



Scheme 1. Bromination by Ni(CNC)(1).

halogenation is followed by C–C cross coupling using a single catalyst, in a one-pot reaction. Herein, we report the bromination of C(sp²)–H bonds in biphenyl systems with electron-donating and electron-withdrawing groups by, mainly, the air stable Ni(II)CNC (**1**) and an oxidizing agent. N-bromosuccinimide (NBS) was used as the brominating agent. In some previous studies with a Pd(II) catalyst NBS was used as both the bromine source and the oxidizing agent [**13**]. For Ni(II), it did not afford appreciable bromination in absence of an oxidizing agent under our reaction condition. In addition, we explored the reactivity of some commercially available Ni(II) salts that also showed promising catalytic activity.

2. Experimental

2.1. General

Gas chromatographic analyses were performed on Shimadzu GC-17A GC and QP5000 MS instrument. NMR spectra were recorded on a Jeol 300 MHz spectrometer. The catalyst **1** was synthesized by literature procedure [9].

2.2. Materials

All solvents and substrates were purchased from Sigma Aldrich, Acros Organic, Alfa Aesar, Matrix Scientific and TCI Chemicals and were used as received.

2.3. Standard procedure for catalytic bromination

To 2 mL CF₃COOH (or D₂O), 0.25 mmol substrate, 0.5 mmol oxidizing agent, 0.375 mmol N BS and 5 mol% catalyst were added. The reagents were taken in a specially designed tube (10 mL), were purged with N₂ gas, and sealed; the mixture was stirred for 24 h at room temperature. Next, the volatiles were removed under reduced pressure. The brominated products were analyzed by ¹H NMR spectroscopy and the yields were calculated by GC/MS using dodecane as an internal standard.

3. Results

3.1. Optimization of catalytic conditions

Our hypothesis suggests that **1** is a competent catalyst for functionalization of aromatic C–H bonds. Optimal reaction conditions were determined by varying substrates, solvents, and oxidizing agents. It was found that 5 mol% of pre-catalyst, along with an oxidizing agent and NBS led to the bromination of biphenyl substrates at ambient temperature. KBr was also tested as brominating agent and it was found that the bromide anion was oxidized in the presence of the oxidizing agent to molecular bromine.

Control experiments in the absence of oxidizing agent gave lower yields compared to the reactions carried out in its presence. PhI(OAc)₂ (or, $C_6F_5I(OCOCF_3)_2$) carried out the bromination reactions effectively with electron poor and electron rich substrates respectively. Other oxidizing agents such as benzoquinone, *tert*butylhydroperoxide, di-*tert*-butylperoxide and benzoyl peroxide were not efficient.

Initially, D_2O was used as a solvent since bromination had previously been achieved in aqueous solutions [7]. The bromination could be carried out with limited success (Table S1). However, no bromination occurred regardless of whether the reactions were carried out in CH₃CN or CH₃COOH as solvents. CF₃COOH was found to be the most promising solvent.

3.2. Product analysis

3.2.1. Substituted and unsubstituted mono-phenyl systems

Negligible or no bromination was observed with benzene, PhNO₂, or PhCN. PhNH₂ resulted in dibromination. Significant bromine insertion at the *para* position, both in the presence and absence of Ni(II) catalyst, was observed with PhOMe; tribromination was observed in all these cases. However, the methyl group of PhOMe (expected to undergo bromination if a freely diffusing bromine radical is involved) remained unbrominated in all cases (see below for further investigation with Ph–CH₂–Ph). One challenge with these mono-phenyl units was their low boiling points, which complicated the work-up process. Therefore, we decided to investigate biphenyl systems, which are solid at ambient temperature.

3.2.2. Bromination of unsubstituted biphenyl

The reaction afforded the mono-brominated product in 2.8% and the dibrominated product in 22.5% yield from biphenyl, always at the 4/4'-position(s).

3.2.3. Bromination of substrates with electron-rich aromatic rings

Electron-rich substrates led to brominated iodobenzene (1bromo-4-iodobenzene) as the major product instead of bromination of biphenyl rings, likely from the oxidizing agent, PhI(OAc)₂.

To test this hypothesis, we added 0.25 equivalents of PhI during catalysis. If **1** has a preference for electron-poor rings then addition of PhI would not change the product composition. Indeed we saw no change in the yield of brominated iodobenzene upon addition of PhI. This suggested that the bromination of the PhI(OAc)₂ could be the first step towards the formation of brominated iodobenzene.

As C–F bonds have been shown to be less susceptible to activation compared to C–H bonds, $(C_6F_5)I(OCOCF_3)_2$ was used as the oxidizing agent, to prevent any attack on the oxidant [14]. Consequently, bromination of electron-rich substrates was performed successfully (Table S2).

3.2.4. Bromination of substrates with electron-deficient aromatic rings

PhI(OAc)₂ proved to be rather efficient in supporting bromination of substrates bearing electron-withdrawing groups. The yields varied between 53–>99% and 87–97% selectivity for the aromatic C–H bond at the 4'-position with respect to the electron-deficient ring. Control experiments without PhI(OAc)₂ indicated that NBS in this case functions mostly as the brominating agent; its potential role as an oxidant is not apparent (Table 1). In one case, with a CF₃-substituted biphenyl system (entry V, Table 1), the uncatalyzed reaction also provided a high yield of bromination. However, consistent high yield and high selectivity in bromination was observed only with Ni(II)CNC.

3.2.5. Investigation for involvement of free radicals

Freely diffusing radical-driven reactions are serious concerns in C–H functionalization, especially if regioselectivity is desired [15].

In order to investigate if freely diffusing radicals are playing a role in our reactions, diphenylmethane, which has highly activated benzylic C–H bonds, was used. Freely diffusing radicals would have higher probability to attack the benzylic C–H instead of the

Table 1

Bromination of substrates bearing electron-deficient aromatic rings.^a

Entries	Substrate	Mol% of 1	PhI(OAc) ₂ (mmol)	Product(s)	GC Yield (% age) ^b (o:m:p)
Ι		0 5 0 5	0.5 0 0 0.5		14.2(2:0:98) 3.4(0:0:100) 1.3(0:0:100) 53(2:1:97)
Π		0 5 0 5	0.5 0 0 0.5		13.7(11:0:89) 40(15:0:85) 0.5(16:0:84) >99(12:1:87)
III		0 5 0 5	0.5 0 0 0.5		0.7(17:0:83) 8(23:0:77) 0.5(18:0:82) 59(13:0:87)
IV		0 5 0 5	0.5 0 0 0.5	Br CFa	30.6(11:0:89) 35(5:30:65) 16.5(11:0:89) 77(9:0.02:90.8)
V		0 5 0 5	0.5 0 0 0.5	P Br - CF ₃	78(11:0:89) 16(19:0:81) 11(12:0:88) >99(11:0:89)

^a Catalytic conditions: 0.25 mmol substrate with 0.5 mmol Phl(OAc)₂ and 0.375 mmol NBS in 2 mL CF₃COOH at room temperature for 24 h in a sealed tube under an N₂ atmosphere.

^b Yields are calculated using dodecane as an internal standard.

aromatic C–H bonds. In addition, this substrate would give information about the selectivity of aromatic C–H versus methylene C–H functionalization. Bromination was observed only at the aromatic C–H bonds and not the methylene C–H bonds (yield: 71.5%). Interestingly, similar results were observed in the absence of **1**.

The chiral outcome of bromination of α,β -unsaturated carboxvlic acids (e.g. trans-cinnamic acid) with NBS and PhI(OAc)₂ have been used by Jørgensen et al. and others to disprove the possibility of involvement of free radicals [16] If free radicals are involved, upon decarboxylative bromination from trans isomer, both the cis and trans isomers of the brominated products are expected in appreciable amounts. This was not observed. We performed similar studies, with trans-cinnamic acid, under conditions that are identical to Jørgensen and coworkers, i.e. in CH₃CN:H₂O (2:1) with NBS and PhI(OAc)₂, (a) without and (b) with added catalyst 1, as well as under our catalytic conditions, i.e. in CF₃COOH with NBS and PhI(OAc)₂, (c) without and (d) with added catalyst 1. In all cases, we observed trans-brominated product as the major product (94-97% of the total product); based on ¹H NMR, percentages of the *trans* product (i.e. (*E*)-(2-bromovinyl)benzene) in the total product mixture for conditions (a):94%, (b): 96.5%, (c): 96% and (d): 97%. Consistent with prior mechanistic studies, this indicates that, under our catalytic conditions, involvement and/or appreciable formation of free radicals is unlikely.

We also performed our catalysis of C–H halogenation with 4-nitrobiphenyl (substrate of entry III in Table 1) in presence of TEMPO as a radical trap. TEMPO has been used to probe a radical-based mechanism [17]. If radicals are involved as intermediates, TEMPO quenches the radicals, and thus affects the yield and product ratios of the reaction. TEMPO has been reported to intercept radicals with half-lives as low as 0.2 ns [17]. We did not observe any noticeable effect from TEMPO on catalytic yield and/ or product ratio (catalyst:TEMPO = 1:1).

Complete negation of a pathway involving free radicals is always a challenge in C–H functionalization. However, abovementioned experiments provide very convincing indication of a non-radical pathway. 3.2.6. Impact of bromination on substrates with a directing group

When 2-PhPy was used as the substrate, no significant effect was observed with **1**, unlike the results reported by Sanford and coworkers [13]. Under our catalytic conditions, instead of observing a product from 2-PhPy, bromination of the C–H bonds of iodobenzene was observed.

3.3. Bromination with commercially available Ni(II) salts

Bromination of the aromatic systems with electron-withdrawing groups by commercially available Ni(II) salts was also tested. The motivation was to (a) compare activities (as we did not find any prior studies with Ni(II) salts for bromination under similar conditions) and (b) to investigate whether Ni(II)CNC (1) is generating Ni(II) salts that, in turn, are catalyzing the reaction. Compounds NiBr₂, Ni(OCOCH₃)₂, and Ni(OCOCF₃)₂ were found to brominate the electron-poor aromatic systems with varied yield and selectivity, missing the consistency that we observed with **1** (Tables 1 and 2). For example, for 3-nitro-1, 1'-biphenyl (substrate II, Tables 1 and 2), with 1, the conversion was 99%. NiBr₂ and Ni(OCOCH₃)₂ catalyzed the bromination with rather high yields (\sim 60%) in this case; however for all other substrates the conversion was poor, unlike that with **1**. Ni(OCOCF₃)₂ gave a high yield (75%) only with 3-trifluoromethyl-1,1'-biphenyl (substrate IV, Tables 1 and 2), but not with any other substrate.

4. Discussion

Reductive elimination with Pt(IV), Pd(II), and Ni(II) was proposed to follow different mechanisms: fast dissociation of the anionic functional group for Pt(IV) [18]; concomitant elimination of the C-heteroatom bond with Pd(II) [19]; oxidation to a Ni(III) species with Ni(II) [20a–e]. For Ni(II), reductive elimination involves an intramolecular reaction involving the formation of a four, six, or seven-membered ring as the intermediate. However, when the possibility of intramolecular reductive elimination is removed, C–C bond formation was reported to be favored over C-heteroatom bond formation [13].

Pre-catalyst	^b Yield with I (%)	Yield with II (%)	Yield with III (%)	Yield with IV (%)	Yield with V (%)
NiBr ₂	2.45	60	28.5	17.2	46.4
	1:0:99(o:m:p)	11:0:89(o:m:p)	16:0:84(o:m:p)	13:0:87(o:m:p)	9:0:91(o:m:p)
Ni(OCOCH ₃) ₂	5.7	59	31	42.5	23.3
	3:0:97(o:m:p)	12:0:88(o:m:p)	13:0:87(o:m:p)	11:0:89(o:m:p)	1:0:9(o:m:p)
Ni(OCOCF ₃) ₂	34.2	7.56	3.1	74.8	11.8
	4:0:96(o:m:p)	11:0:89(o:m:p)	14:0:86(o:m:p)	10:0:90(o:m:p)	14:0:86(o:m:p)

Table 2 Catalyses with selected Ni(II) salts.^a

Catalytic condition: 0.25 mmol substrate with 0.5 mmol Phl(OAc)₂ and 0.375 mmol NBS in 2 mL CF₃COOH at 25 °C for 24 h in a sealed tube under an N₂ atmosphere. Yields are calculated using dodecane as an internal standard.

Under our conditions, 1 yields C-halogenated products as the major species from aryl C-H bonds with high selectivity. For substrates bearing benzylic C-H bonds, no halogenation at the benzylic position was observed, even for highly activated benzylic C-H bonds like those of diphenyl methane (Ph-CH₂-Ph). Therefore, involvement of freely diffusing halogen radicals is unlikely. In addition, it is difficult to conceive that a cyclic intermediate involving the metal site is likely. Based on the mass balance performed for entries in Table 1 (for entry I: 70%; II: 90%; III: 90%; IV: 78%; V: 70%), it can be inferred that the C-C coupling process is not dominant. The selective C-H halogenation, specially the preference for electron-deficient rings with 1 is intriguing. In fact, if the substrate does not bear an electron-deficient ring (as in C₆H₅-C₆H₅, C₆H₅- C_6H_4 -OMe), the oxidant PhI(OAc)₂ undergoes halogenation instead. These observations are indicative of the involvement of the electron-deficient ring through, perhaps, weak coordination to Ni(II) and by utilizing the filled, low-lying d_z^2 orbital on Ni(II) to drive the functionalization at the ring distant from the functional group (See Figure S1(b) for MO diagram).

For 2-PhPy, a strongly coordinating directing group does not yield any functionalization or C-C coupling. We investigated whether pyridine is functioning as an inhibitor, as was reported by Sanford for a Pd(II) catalyst [19]. With 3-nitrobiphenyl (Table 1, entry II), when pyridine was added, no change in the product mixture or the yield was observed. Future work in our laboratory will focus on understanding the mechanistic details of the process reported herein.

5. Conclusion

In summary, we have investigated the potential of Ni(II)CNC (1) and several commercially available Ni(II) salts as catalysts to brominate aryl C-H bonds of biphenyl systems at room temperature using water and CF₃COOH as solvents, PhI(OAc)₂ as the oxidizing agent and NBS as the bromine source. The bromination reactions were found to be effective for both electron-withdrawing and electron-donating substituents, when CF₃COOH was the solvent. High yields and selectivity towards C-halogenation with 1 were observed especially with electron-deficient substrates. Further studies to look into the reaction mechanism and further exploration of the reactivity will be the future direction. The work presents a new direction for C-H functionalization. instead of homo C-C coupling, with easily accessible Ni(II) catalysts.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ica.2014.08.012.

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