Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 11483–11498

Scope and selectivity in palladium-catalyzed directed C–H bond halogenation reactions

Dipannita Kalyani, Allison R. Dick, Waseem Q. Anani and Melanie S. Sanford*

University of Michigan, Department of Chemistry, 930 N. University Ave., Ann Arbor, MI 48109, USA

Received 13 May 2006; revised 17 June 2006; accepted 21 June 2006
Available online 20 July 2006

Abstract—Palladium-catalyzed ligand directed C–H activation/halogenation reactions have been extensively explored. Both the nature of the directing group and the substitution pattern on the arene ring of the substrate lead to different reactivity profiles, and often different and complementary products, in the presence and absence of the catalyst.

1. Introduction

Halogenated organic compounds are important components of a variety of biologically active molecules and pharmaceutical agents.[1] Aryl, vinyl, and benzylic halides also serve as important precursors to organolithium[2] and Grignard reagents.[3] Aryl halides have been employed as substrates for nucleophilic aromatic substitution[4] and for benzyne generation.[5] Additionally, both aryl[6,7] and vinyl[8] halides have found widespread utility as substrates for a variety of cross-coupling reactions. As a result of the diverse potential applications of organic halides, the development of new regioselective, chemoselective, and functional group tolerant approaches to the synthesis of these molecules remains an important challenge.

Our group has recently developed several palladium-catalyzed methods for the chelate-directed oxidative functionalization of C–H bonds using hypervalent iodine(III) reagents as terminal oxidants. For example, the reaction of diverse organic substrates with $PhI(OAc)_2$[9a–d] or $[Ph_2I]BF_4$[9e,f] in conjunction with a Pd^{II} catalyst leads to the ligand-directed conversion of sp^2 and sp^3 C–H bonds to C–O and C–C bonds, respectively. These results suggested the possibility of an analogous Pd-catalyzed transformation for the direct conversion of C–H bonds to C–X (X=Cl, Br, I) bonds using electrophilic halogenating reagents such as $PhICl_2$. We envisioned that such a reaction would provide the desired products with complete regioselectivity and without the requirement for electron-rich substrates or strong acids/bases. These features would impart a significant advantage over many commonly used methods (e.g., electrophilic aromatic substitution (EAS),[10,11] directed *ortho*-lithiation (DoL),[12] and the addition of X_2 or HX to alkynes[13]) for the construction of certain classes of aryl and vinyl halides.

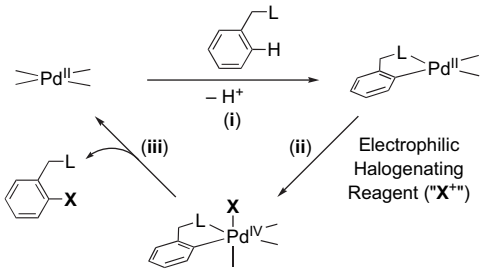
A key step in the proposed palladium-catalyzed directed C–H activation/halogenation reactions would require carbon–halogen bond-forming reductive elimination from a palladium center. This transformation is well known to be challenging from Pd^{II} (and most other metal complexes) because its microscopic reverse—the oxidative addition of aryl/vinyl/alkyl halides to Pd^0—is highly thermodynamically favored relative to the desired reductive elimination reaction. For example, Roy and Hartwig have shown that K_{eq} for direct reductive elimination of haloarenes from Pd^{II} ranges from $\sim 10^{-5}$ (for Ar–I) to $\sim 10^{-2}$ (for Ar–Cl).[14] As a result, the desired reaction is not amenable to catalysis via a traditional $Pd^{II/0}$ catalytic cycle. However, recent work from our group has shown that reductive elimination reactions from Pd^{IV} have very different electronic requirements than those from Pd^{II},[15] indicating that the desired carbon–halogen coupling could be facile from this oxidation state. A number of literature reports further supported the potential viability of this approach; for example, van Koten and Elsevier have both directly observed transient Pd^{IV} intermediates in the oxidation of Pd^{II} complexes with molecular halogen or $PhICl_2$.[16a,b,h] In addition, several groups have reported stoichiometric C–X coupling upon treatment of palladium(II)-aryl/alkyl complexes with oxidants such as X_2, $CuCl_2$, mixtures of peroxides and halide salts, or $PhICl_2$.[17] Furthermore, both oxypalladation and aminopalladation of alkenes at Pd^{II} have been terminated by C–X coupling under oxidizing reactions conditions.[16,17]

Based on this precedent, we felt that Pd-catalyzed C–H bond halogenation could potentially proceed by a catalytic cycle involving (i) ligand-directed C–H activation at a Pd^{II} center,[18] (ii) oxidation of the resulting palladacycle to

* Corresponding author. Tel.: +1 734 615 0451; e-mail: mssanfor@umich.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.06.075

Pd^{IV}, and (iii) carbon–halogen bond-forming reductive elimination to form the desired product and regenerate the catalyst (Scheme 1). Importantly, a similar cycle was proposed in early work by Fahey, who demonstrated the palladium-catalyzed *ortho*-chlorination of azobenzene with Cl_2.[19] More recent preliminary communications from our group[9d,g,h] and later from Yu and co-workers[20a,b] have established that such Pd-catalyzed C–H activation/oxidative halogenation reactions can be general and practical methods for organic synthesis. Herein, we present a full account of our efforts in the development and exploration of these transformations. The scope and limitations of these reactions with respect to directing group and functional group tolerance are discussed in detail, and general trends that dictate the reactivity of diverse arene substrates in these transformations are identified.



Scheme 1. Proposed catalytic cycle for directed C–H bond halogenation.

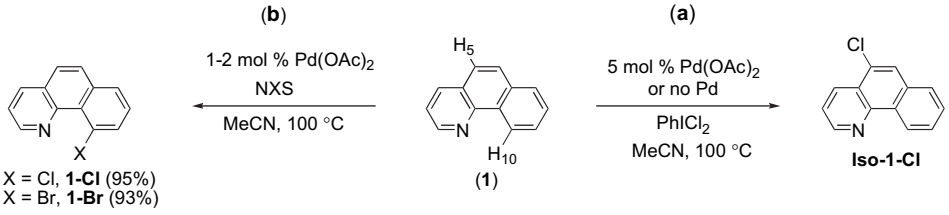
2. Results and discussion

Our initial studies focused on the palladium-catalyzed reaction of benzo[*h*]quinoline (**1**) with $PhICl_2$ (Eq. 1a). By analogy to reactions with the related iodine(III) oxidant $PhI(OAc)_2$,[9a–d] we expected to observe the selective conversion of C–H_{10} to a C–Cl bond. However, interestingly, the treatment of **1** with $PhICl_2$ in MeCN or AcOH afforded exclusive chlorination at the 5-position (~38% conversion by GC), both in the presence and the absence of Pd catalyst (Eq. 1a).

Palladium-catalyzed directed bromination of **1** was also possible using *N*-bromosuccinimide as a terminal oxidant.[9d] Analogous to NCS, reaction of **1** with NBS (1 mol % of $Pd(OAc)_2$, 1.1 equiv NBS, MeCN, 100 °C, 1.5 days) afforded a single product, where bromination occurred exclusively at the 10-position (**1-Br**) (Eq. 1b).[9d] In the absence of palladium, a mixture of isomeric mono-brominated products was obtained. Interestingly, $CuBr_2$ was also an effective oxidant for the Pd-catalyzed transformation, and afforded complete conversion to **1-Br** (as measured by ^1H NMR spectroscopy) in the presence of $Pd(OAc)_2$. In contrast, other brominating reagents (e.g., Br_2, $Br_2/PhI(OAc)_2$) provided complex mixtures of isomeric brominated products.

Attempts to carry out analogous iodination reactions of benzo[*h*]quinoline with NIS or $I_2/PhI(OAc)_2$[20a] were generally unsuccessful. Under all conditions screened for this transformation, only traces of unidentified isomers of iodinated product were obtained, with starting material remaining largely unconsumed. Because of the rigid planar nature of this substrate and the location of the C–H_{10} bond in a sterically congested portion of the molecule, steric constraints may prevent incorporation of the large iodine atom during these Pd-catalyzed reactions.

With optimal parameters for the chlorination and bromination of **1** in hand, we next focused our attention on the Pd-catalyzed halogenation of other organic substrates. Initial experimentation revealed that there was no universal set of reaction conditions for these transformations, and that varying the solvent (typically between MeCN and AcOH), temperature (ranging from 100 to 120 °C), and the oxidant



(1)

This initial result suggested that $PhICl_2$ was too reactive, leading to a faster rate of uncatalyzed backbone halogenation relative to chelate-directed C–H activation. As a result, we next examined a variety of alternative electrophilic halogenating reagents, anticipating that some might afford more competitive relative rates of the catalyzed to the uncatalyzed reaction. We were delighted to find that commercially available and inexpensive *N*-chlorosuccinimide provided the desired chlorination product **1-Cl** as a single regioisomer in 95% isolated yield (Eq. 1b) under standard reaction conditions (2 mol % of $Pd(OAc)_2$, 1.1 equiv NCS, MeCN, 100 °C, 3 days).[9d] In addition, further screening of oxidants revealed that $CuCl_2$ (in MeCN) and Chloramine-T (in AcOH) afforded comparable GC yields of **1-Cl** (81% and 85%, respectively) in much shorter times (~12 h). Notably, the control reaction of **1** with Chloramine-T (in the absence of Pd catalyst) provided mixtures of regioisomeric monochlorinated products, while the analogous controls with NCS and $CuCl_2$ returned unreacted starting material.

(between NXS and CuX_2) was necessary in order to obtain the optimal conditions for each substrate. Additionally, substrates with different substitution patterns on the aryl ring and with different directing groups showed dramatically different reactivities. In general, the substrates could be divided into four types based on their reactivity in the presence and absence of palladium as follows: (i) substrates for which the Pd-catalyzed reaction results in chelate-directed halogenation, while the control (without Pd catalyst) affords no halogenated products (*type 1*), (ii) substrates for which the Pd-catalyzed and control reactions afford different halogenated products (*type 2*), (iii) substrates for which the

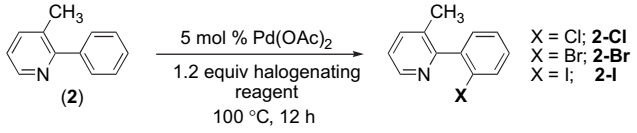
catalyzed and the uncatalyzed reactions afford the same product or mixtures of products (*type 3*), and (iv) substrates for which the similarity/difference in reactivity between the Pd-catalyzed and control reactions is dictated by the nature of the oxidant (*type 4*). A detailed discussion of each of these types of substrates follows below.

2.1. Type 1 substrates

The palladium-catalyzed halogenation of 3-methyl-2-phenylpyridine (**2**) was studied using a variety of electrophilic halogenating reagents in AcOH and MeCN (Table 1). Under all of the conditions examined, **2** exemplified a *type 1* substrate, affording <5% halogenated products in the absence of palladium catalyst. In contrast, in the presence of $Pd(OAc)_2$, most of the reagents screened afforded significant quantities of the *ortho*-halogenated products **2-Cl**, **2-Br**, or **2-I**. In general, the *N*-halosuccinimides proved to be superior oxidants, providing the highest isolated yields of **2-Cl** (65%), **2-Br** (56%), and **2-I** (79%).

Among the other oxidants examined, a number of notable observations were made. For example, unlike with benzo[*h*]-quinoline, the reaction of **2** with $PhICl_2$ afforded <5% of a mono-halogenated product in the absence of the catalyst. This is likely due to the low inherent reactivity of the relatively electron-deficient arene moiety of **2** toward electrophilic aromatic substitution. In the presence of the Pd catalyst, this iodine(III) reagent afforded the desired product **2-Cl**, albeit in only 32% GC yield (Table 1, entry 5). The low yield of this transformation can most likely be attributed to the instability of $PhICl_2$ at the elevated temperatures (100 °C) utilized for these transformations.[21]

Table 1. Palladium-catalyzed reaction of **2** with diverse electrophilic halogenating reagents



Entry	Halogenating reagent	Product	GC yield in AcOH (isolated) (%)	GC yield in MeCN (isolated) (%)
1	NCS	**2-Cl**	60 (65)[b]	56
2	$Pb(OAc)_4$/LiCl[c]	**2-Cl**	63	51
3	Chloramine-T	**2-Cl**	56	36
4	$K_2Cr_2O_7$/LiCl[c]	**2-Cl**	42	0
5	$PhICl_2$	**2-Cl**	32	15
6	$CuCl_2$	**2-Cl**	21[a]	30[a]
7	NBS	**2-Br**	53 (56)[b]	44
8	Br_2/$PhI(OAc)_2$	**2-Br**	39	24
9	$Pb(OAc)_4$/LiBr[c]	**2-Br**	32	42
10	$K_2Cr_2O_7$/LiBr[c]	**2-Br**	15	8
11	Br_2	**2-Br**	0	26
12	$CuBr_2$	**2-Br**	0[a]	15[a]
13	NIS	**2-I**	64	87 (79)
14	I_2/$PhI(OAc)_2$	**2-I**	64	71
15	$K_2Cr_2O_7$/LiI[c]	**2-I**	44	0
16	$Pb(OAc)_4$/LiI[c]	**2-I**	37	0
17	I_2	**2-I**	0	40

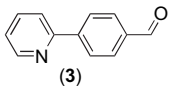
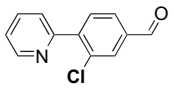
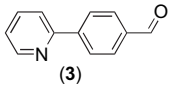
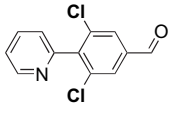
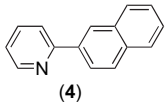
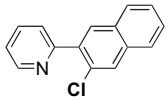
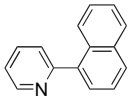
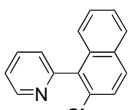
[a] Halogenating reagent (2.4 equiv).
[b] Isolated yields from reactions carried out at 120 °C.
[c] LiX (2 equiv).

Interestingly, neither Br_2 nor I_2 afforded substantial quantities of halogenated products (Table 1, entries 11 and 17, respectively), despite the fact that these reagents are highly effective for the stoichiometric halogenation of Pd^{II} alkyl,[16f] aryl,[16c,19] and vinyl[16a] species. This may be due to the decreased reactivity and/or solubility of PdX_2 (presumably formed in situ from the reaction of $Pd(OAc)_2$ with X_2) in these reactions.[20a] In contrast, $CuCl_2$ was an effective reagent for transforming **2** to **2-Cl** in 30% GC yield under standard conditions (Table 1, entry 6). This result is particularly remarkable because $CuCl_2$ could potentially be utilized in catalytic quantities with readily available and inexpensive dioxygen as the ultimate terminal oxidant.[22]

A number of other *type 1* substrates were identified, and the results of their Pd-catalyzed reactions with *N*-halosuccinimides are summarized in Tables 2–4. As discussed above, all these substrates afforded <5% of halogenated products in the absence of palladium. In general, the *type 1* substrates contain electron-withdrawing directing groups such as pyridines, oxime ethers, isoxazolines, quinolines, and tetrazoles; furthermore, the arene ring that undergoes halogenation is typically electron neutral or electron deficient (containing substituents such as halides, esters, enolizable oxime ethers, ketones, and aldehydes). Notably, substrates containing such structural motifs possess a wide range of potential applications. For example, isoxazolines serve as useful precursors to β-amino acids,[23] while pyridines and tetrazoles are important components of diverse drug molecules.[24] Tetrazole derivatives can also be used as trigger explosives and serve as components of mixed propellants.[24] In addition, the brominated 2-phenylpyridine derivatives are readily transformed into ligands that can be used to form a variety of late transition metal complexes.[15,25]

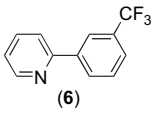
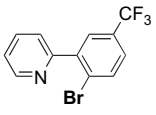
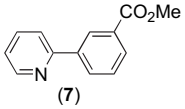
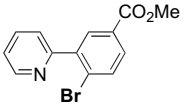
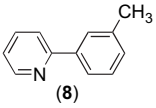
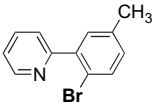
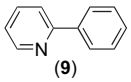
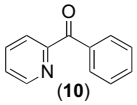
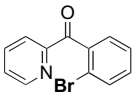
Importantly, all of these transformations (and those described throughout this paper) are completely tolerant of ambient air and moisture and were typically conducted on

Table 2. Palladium-catalyzed chlorination of *type 1* substrates[a]

Entry	Starting material	Major product	Product #, yield (%)
1	 (3)	 Cl	**3-Cl**, 57
2	 (3)	 Cl Cl	**3-Cl_2**, 72[b]
3	 (4)	 Cl	**4-Cl**, 82
4	 (5)	 Cl	**5-Cl**, 70

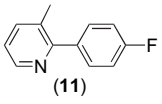
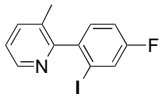
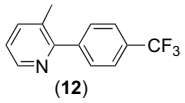
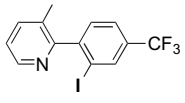
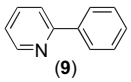
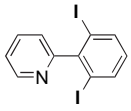
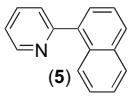
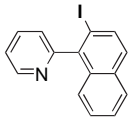
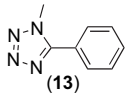
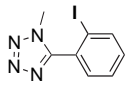
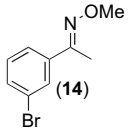
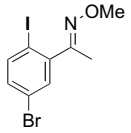
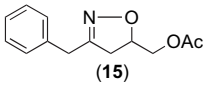
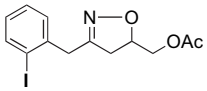
[a] Conditions: 5 mol % $Pd(OAc)_2$, 1.1–1.2 equiv NCS, 100–120 °C, 12 h, MeCN or AcOH.
[b] NCS (2.5 equiv).

Table 3. Palladium-catalyzed bromination of *type 1* substrates[a]

Entry	Starting material	Major product	Product #, yield (%)
1	 (**6**)		**6-Br**, 63
2	 (**7**)		**7-Br**, 70
3	 (**8**)		**8-Br**, 51
4	 (**9**)		**9-Br**, 63
5	 (**10**)		**10-Br**, 56

[a] Conditions: 5 mol % $Pd(OAc)_2$, 1.2–2.0 equiv NBS, 100–120 °C, 12 h, MeCN or AcOH.

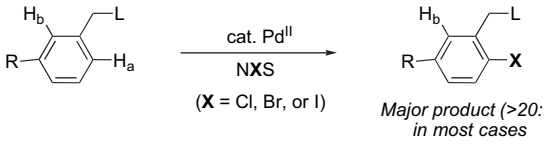
Table 4. Palladium-catalyzed iodination of *type 1* substrates[a]

Entry	Starting material	Major product	Product #, yield (%)
1	 (**11**)		**11-I**, 70
2	 (**12**)		**12-I**, 78
3	 (**9**)		**9-I_2**, 41
4	 (**5**)		**5-I**, 60[b]
5	 (**13**)		**13-I**, 41
6	 (**14**)		**14-I**, 57
7	 (**15**)		**15-I**, 54

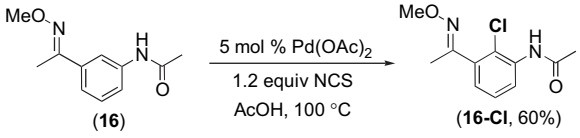
[a] Conditions: 5 mol % $Pd(OAc)_2$, 1.05–2.1 equiv NIS, 100–120 °C, 12 h, MeCN or AcOH.
[b] NIS (3.0 equiv).

the bench-top using commercial solvents and reagents. Furthermore, the safe and inexpensive nature of these transformations makes them easily scalable, and relatively large-scale reactions (11–82 mmol) typically afforded comparable yields to those carried out with 0.5–1.5 mmol of material. This is exemplified by substrate **8** (Table 3), for which the reactions performed at 17 mmol and 1.4 mmol scales afforded the product **8-Br** in nearly identical 51% isolated yield. In addition, the use of 1 mol % catalyst afforded comparable yields in similar reaction times to 5 mol % $Pd(OAc)_2$; for example, **2-Cl**, **2-Br**, and **2-I** were obtained in 71%, 54%, and 90% GC yields, respectively, after 12 h with 1 mol % Pd. Further reduction of the catalyst load (to 0.5 mol %) typically resulted in some (~20%) diminishment in yield. The easy and practical scale up along with the low catalyst loadings should make these halogenation reactions very attractive for diverse applications.

In *meta*-substituted arene substrates bearing two chemically inequivalent *ortho*-C–H bonds, the less hindered position was usually halogenated with high selectivity (Eq. 2).[9b] Both electron-deficient (Table 3, entries 1 and 2) and electron-rich arenes (Table 3, entry 3) exhibited a comparable preference for halogenation at the less congested position. Further, the site selectivity of these reactions was general for different directing groups. For example, the reaction of oxime ether **14** resulted in halogenation *para* to the *meta*-substituent (Table 4, entry 6). In napthyl substituted substrates **4** and **5**, the less sterically congested 3′ *ortho*-C–H bond was selectively halogenated, despite the fact that the 1′ position is more nucleophilic. This sensitivity to the steric environment of the arene ring appears to be general for a wide variety of Pd-catalyzed C–H activation/functionalization reactions.[9a,b,f] However, the *meta*-substituted oxime ether **16** (Eq. 3), which possesses three potential sites for directed C–H activation, presents an interesting exception. In contrast to the substrates discussed above, **16** underwent chlorination with extremely high (>20:1) selectivity for the more hindered 2-position of the arene. This may be the result of the cooperative coordination of both the amide and the oxime directing groups to the Pd-center during the C–H activation step of this reaction.[26] Notably, **16** is not technically a *type 1* substrate, as reaction with NCS in the absence of palladium afforded a complex mixture of isomeric chlorinated products.



(2)

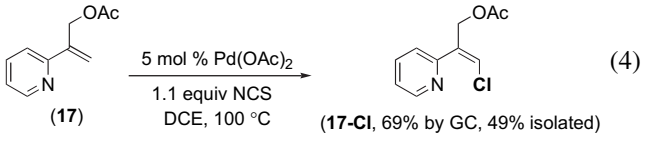


(3)

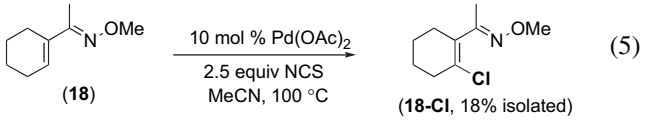
C–H activation/halogenation reactions of substrates containing two readily accessible, chemically equivalent C–H bonds generally led to modest yields of the mono-halogenated products due to competitive formation of the

corresponding difunctionalized compounds (e.g., see Table 2, entry 1). Tuning the stoichiometry of the oxidant in these systems allowed for the formation of dihalogenated products in good yields (e.g., Table 2, entry 2). Several approaches can be taken to attenuate the extent of dihalogenation in these systems if it is not desired. For example, as discussed above, the incorporation of a *meta*-substituent generally decreased the formation of dihalogenated side-products by reducing the rate of a second C–H activation at the more sterically hindered site. Additionally, dihalogenation could be minimized in phenylpyridine derivatives by placing a substituent at the 3-position of the pyridine moiety (e.g., substrate **2** in Table 1). The degree of dihalogenation in these systems decreases with increasing size of the halogen on the arene counterpart. This is illustrated by the fact that ~35% of the difunctionalized products were formed when **2-Cl** and **2-Br** were subjected to forcing reaction conditions (5 mol % $Pd(OAc)_2$, 2 equiv NXS, AcOH, 120 °C), while only traces (<5%) of the diiodinated product were observed in the analogous reaction of **2-I** with NIS. In these systems, the unfavorable steric interactions between the *ortho*-halogen of the mono-functionalized arene and the 3-substituent on the pyridine ring make it difficult to achieve coplanarity between the aryl rings, which is necessary for the second C–H activation/functionalization to occur.[27]

Preliminary results indicate that alkene derivatives can also act as *type 1* substrates in C–H bond halogenation reactions. For example, alkenyl pyridine **17** underwent $Pd(OAc)_2$-catalyzed reaction with NCS to afford the chlorinated product **17-Cl** in reasonable yield (69% by GC, 49% isolated) and with high stereochemical integrity (Eq. 4). Importantly, this product possesses a well-defined olefin geometry, presumably resulting from the selective functionalization of the alkene C–H bond proximal to the pyridine moiety.[28] Such stereochemically pure alkenes serve as important starting materials for many applications, including cross-coupling,[8] carbenoid transfer, and cycloaddition reactions.[29,30] Other alkenes, such as oxime ether **18** also reacted to form directed halogenation products (Eq. 5); however, in this case, the product was obtained in low yield under our standard reaction conditions. Ongoing work aims to optimize reaction conditions for the halogenation of this important class of substrates and to further probe the mechanisms of these transformations.[22e]



(4)



(5)

2.2. Type 2 substrates

Type 2 substrates undergo clean mono-halogenation both in the presence and absence of the Pd catalyst. However, in these cases there is a mismatch in the products favored by the catalyzed reaction versus by electrophilic aromatic substitution; therefore, the products obtained with Pd are different from and complementary to those obtained in the control reactions. Oxime ether substrate **19** exemplifies this class of substrates. The arene ring of **19** is activated at the 3-position toward traditional electrophilic aromatic substitution due to the electron-donating methoxy substituent, and, as a result, control reactions with NXS in AcOH cleanly afforded the 3-substituted products *iso*-**19-Cl**, *iso*-**19-Br**, and *iso*-**19-I** (Table 5, entry 1). However, in the presence of 5 mol % $Pd(OAc)_2$, the catalyzed reaction out-competed EAS such that the *ortho*-halogenated products **19-Cl**, **19-Br**, and **19-I** were formed exclusively, in yields ranging from 46% to 72% (Table 5, entry 1).

Similar results were observed in analogous substrates with different directing groups; for example, 3-methyl-2-(4-methoxyphenyl)pyridine (**20**) afforded **20-Cl** in 76% isolated yield in the Pd-catalyzed reaction, while only *iso*-**20-Cl** was obtained in the control (Table 5, entry 2). Substrate **23**, which contains methoxy substitution on the ring of the pyridine directing group, also showed comparable behavior. In the absence of Pd, a mixture of regioisomeric products was obtained, with Cl incorporated *ortho* (*iso*-**23-Cla**) and *para* (*iso*-**23-Clb**) to the methoxy substituent on the electron-rich pyridine ring. However, in the presence of 20 mol % $Pd(OAc)_2$, the directed chlorination product **23-Cl** was obtained cleanly in 71% yield (Table 5, entry 5).[31]

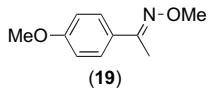
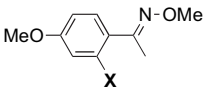
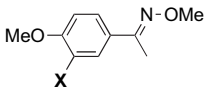
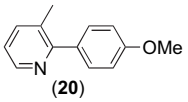
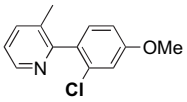
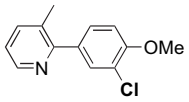
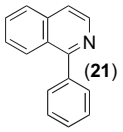
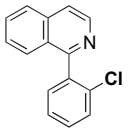
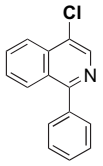
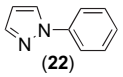
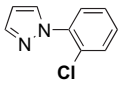
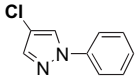
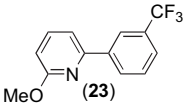
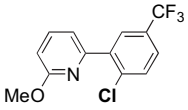
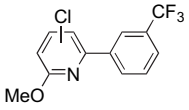
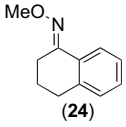
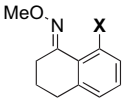
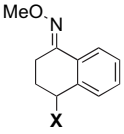
Other substrates that fall into *type 2* are those containing heterocyclic directing groups such as pyrazole and isoquinoline (Table 5, entries 3 and 4). Without added palladium, these substrates underwent chlorination on the heterocyclic ring; however, in the presence of 5 mol % $Pd(OAc)_2$, Pd-catalyzed directed C–H activation/chlorination out-competed EAS, and the *ortho*-chlorinated products **21-Cl** and **22-Cl** were obtained in 53% and 58% isolated yields, respectively.

A final example of a *type 2* substrate is oxime ether **24**. The 2° benzylic position of **24** is highly activated toward benzylic halogenation with NCS or NBS, and, in the absence of Pd catalyst, the benzylic halides *iso*-**24-Cl** and *iso*-**24-Br** were obtained as the major products (albeit in modest yields—Table 5, entry 6). However, in the Pd-catalyzed process, chelate-directed halogenation was fast relative to benzylic oxidation, and the haloarenes **24-Cl** and **24-Br** were obtained in 88% and 62% isolated yields, respectively.

2.3. Type 3 substrates

Type 3 substrates consist of compounds that favor the same product or mixtures of products both in the presence and absence of palladium. Hence, unless otherwise noted the use of a palladium catalyst offers no significant advantage in terms of the yield, purity or selectivity of reactions with these *type 3* substrates. Substrates such as **28–30**, containing highly electron-donating arene substituents (e.g., NMe_2, OMe) at the position *meta*- to the directing group, are representative members of this type. In these compounds, both the catalyzed and the uncatalyzed processes afforded halogenation

Table 5. Palladium-catalyzed halogenation of *type 2* substrates[a,b]

Entry	Starting material	Major product with Pd catalyst	Product #, yield (%)	Major product without Pd catalyst	Product #, yield (%)
1	 (**19**)		**19-Cl**, 58 **19-Br**, 72 **19-I**, 46		*iso*-**19-Cl**, 53 *iso*-**19-Br**, 69 *iso*-**19-I**, 47
2	 (**20**)		**20-Cl**, 76		*iso*-**20-Cl**, 95
3	 (**21**)		**21-Cl**, 53		*iso*-**21-Cl**, 56
4	 (**22**)		**22-Cl**, 58		*iso*-**22-Cl**, 83
5	 (**23**)		**23-Cl**, 71		*iso*-**23-Cl**, 82[c]
6	 (**24**)		**24-Cl**, 88 **24-Br**, 62		*iso*-**24-Cl**, 39 *iso*-**24-Br**, 29

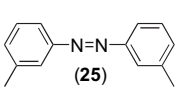
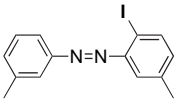
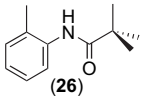
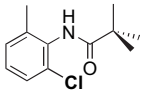
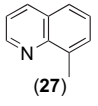
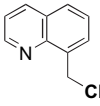
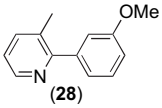
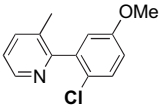
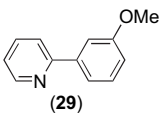
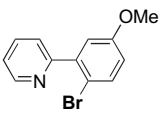
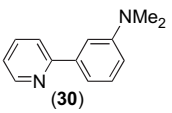
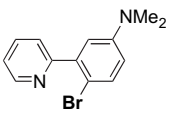
[a] Conditions without Pd: 1–2 equiv NXS, 100–120 °C, 12 h, MeCN or AcOH.
[b] Conditions with Pd: 5 mol % $Pd(OAc)_2$, 1–1.5 equiv NXS, 100–120 °C, 12 h, MeCN or AcOH.
[c] $Pd(OAc)_2$ (20 mol %).

para to the substituent. Hence, the use of a palladium catalyst was not necessary to obtain the 'chelate-directed' *ortho*-halogenated products **28-Cl**, **29-Br**, and **30-Br** in high yields (Table 6, entries 4–6).

Azobenzene **25** also falls under *type 3* as both the catalyzed and the uncatalyzed reactions afford the *ortho*-iodinated product as the major product. However, in this case, the use of palladium affords the desired chelate-directed product in higher yields because the reaction in the absence of palladium affords a 4:1 mixture of isomeric iodinated products. Similarly, reaction of pivalamide **26** with NCS afforded significant quantities of the *ortho*-chlorinated product **26-Cl** with or without palladium. However, in this case, the catalyzed reaction provided **26-Cl** in higher yield and selectivity, as it suppressed formation of a dichlorinated side-product, which was produced in ~50% yield in the control reaction. Thus for substrates **25** and **26**, the addition of Pd would be advantageous for applications where high material throughput and facile isolation/purification steps are necessary.

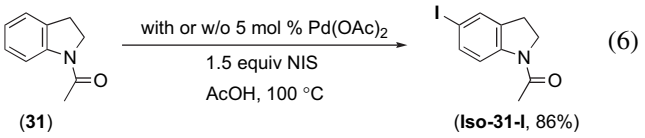
The indoline and the oxazolidinone substrates **31** and **32** are examples of *type 3* substrates in which EAS predominates, and the 'chelate-directed' product is not favored in either the Pd-catalyzed or the control reactions. For example, **31** and **32** reacted with NIS to afford the *para*-iodinated products *iso*-**31-I** and *iso*-**32-I**, respectively, in both the presence and absence of Pd (Eqs. 6 and 7). When analogous reactions were conducted with NCS and NBS, mixtures of

Table 6. Palladium-catalyzed halogenation of *type 3* substrates[a]

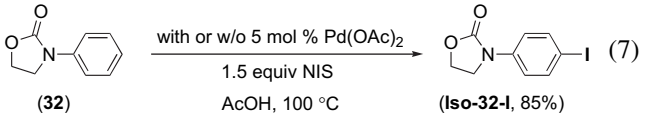
Entry	Starting material	Major product with and without Pd catalyst	Product #, yield (%)
1	 (**25**)		**25-I**, 41
2	 (**26**)		**26-Cl**, 67
3	 (**27**)		**27-Cl**, 86[b]
4	 (**28**)		**28-Br**, 95
5	 (**29**)		**29-Br**, 94
6	 (**30**)		**30-Br**, 99[c]

[a] Conditions: 1–1.2 equiv NXS, 100–120 °C, 12 h, MeCN or AcOH.
[b] $CuCl_2$ (4.0 equiv) with 5 mol % $Pd(OAc)_2$.
[c] 25 °C.

mono-halogenated compounds were formed; however, the addition of 5 mol % $Pd(OAc)_2$ did not alter the ratio of these compounds.



(6)



(7)

Type 3 substrates are not limited to those undergoing arene C–H functionalization. For example, 8-methylquinoline (**27**) reacts with NCS to afford the benzylic chloride **27-Cl** with or without palladium. However, interestingly, with $CuCl_2$ as the oxidant, this product is formed only in the Pd-catalyzed transformation, and not in the control. Hence, **27** represents a *type 3* substrate with NCS while it is a *type 1* substrate with $CuCl_2$.[32]

2.4. Type 4 substrates

Type 4 substrates are those in which there is a delicate balance between the catalyzed and uncatalyzed processes, such that the nature of the oxidant dictates which product predominates. In general, the chlorination of *type 4* substrates with NCS was most amenable to palladium catalysis, and they typically reacted to form different major monochlorinated products in Pd-catalyzed versus control reactions. In contrast, reactions of these substrates with NIS generally afforded identical results with and without Pd.

This *type 4* behavior is clearly illustrated by the reactivity profile of pyrrolidinone substrate **33**. As shown in Table 7, the control reaction with NCS afforded a ~1:1 mixture of *ortho* and *para*-chlorinated products (**33-Cl** and *iso*-**33-Cl**, respectively), while the *ortho*-chlorinated product **33-Cl** predominated in the Pd-catalyzed reaction. In contrast, the reaction of **33** with NBS provided a mixture of *ortho* and *para* brominated products **33-Br** and *iso*-**33-Br** both in the presence and absence of palladium. Finally, the reaction of **33** with NIS afforded exclusively the *para*-iodinated product *iso*-**33-I** in both the catalyzed and the uncatalyzed reactions.

Similarly, control reactions of pyrrolidinones **34**, **35**, and **36** as well as the acetanilide **37** with NCS afforded a mixture of chlorinated products, while the analogous Pd-catalyzed reactions afforded **34-Cl**, **35-Cl**, **36-Cl**, and **37-Cl** cleanly in 58%, 77%, 81%, and 70% isolated yields, respectively, along with only traces of the undesired isomeric products. Again, the corresponding bromination reactions of **33**, **34**, and **35** afforded approximately 3:1–4:1 mixture of regioisomeric brominated products both in the presence and absence of palladium.

The reactivity of *type 4* substrates represents a competition between the palladium-catalyzed reaction and uncatalyzed electrophilic aromatic substitution. The results in Table 7 clearly demonstrate that changing the oxidant changes the relative rates of these two competing processes, and current efforts in our group aim to delineate the effect of the oxidants on the relative contributions of the catalyzed versus the non-catalyzed pathways.

3. Conclusions

In summary, we have reported a full exploration of the palladium-catalyzed chelate-directed chlorination, bromination, and iodination of arenes using *N*-halosuccinimides as terminal oxidants. In addition, preliminary results reported herein demonstrate that the halogenation of alkene and benzylic sp^3 C–H bonds can also be achieved using this methodology. These reactions were generally tolerant toward a variety of functional groups and showed wide scope with respect to directing groups. Furthermore, the reactivity trends of the various compounds greatly depended on the substitution pattern/electronics of the substrate as well as the ligand abilities of the directing group. Hence, the products obtained from these reactions are often different from and highly complementary to those obtained via traditional methods, such as electrophilic aromatic substitution and benzylic halogenation. The broad scope and often orthogonal nature of these Pd-catalyzed halogenation reactions should make them a valuable synthetic tool for accessing a more diverse array of halogenated organic molecules.

4. Experimental

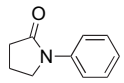
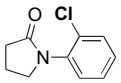
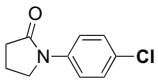
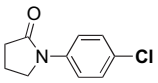
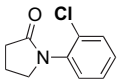
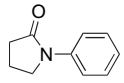
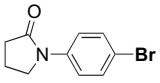
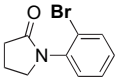
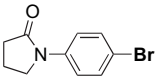
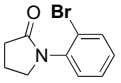
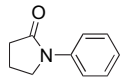
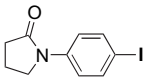
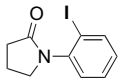
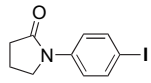
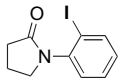
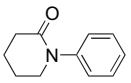
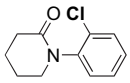
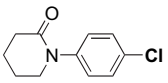
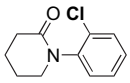
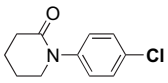
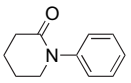
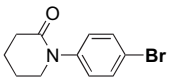
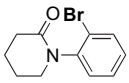
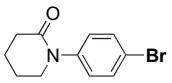
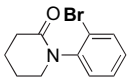
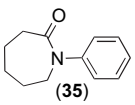
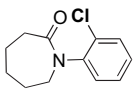
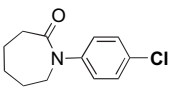
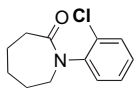
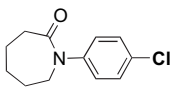
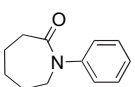
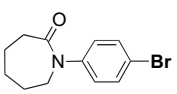
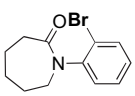
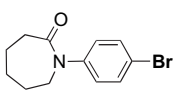
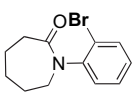
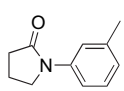
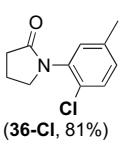
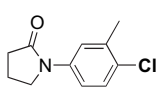
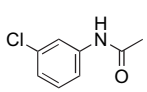
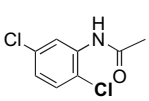
4.1. General

All reactions were performed with magnetic stirring in scintillation vials or thick-walled glass pressure-resistant vessels sealed with a Teflon bushing. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation and then at ca. 10 mTorr (vacuum pump). Flash chromatography was performed on EM Science silica gel 60 (0.040–0.063 mm particle size, 230–400 mesh) and thin layer chromatography was performed on Merck TLC plates pre-coated with silica gel 60 F254.

4.2. Materials

Pyridine substrates **5**, **12**, **21**, **23**, and **29** were prepared by Suzuki coupling of the corresponding arylboronic acid with 2-bromo-3-picoline, 2-bromopyridine, or 1-chloroisoquinoline.[33] Substrate **30** was prepared in two steps by (i) Suzuki coupling of 3-aminophenylboronic acid with 2-bromopyridine followed by (ii) methylation of the amine using NaH and MeI. Substrates **7** and **8** were prepared by Stille coupling of 2-tributylpyridyltin with the corresponding aryl bromides.[34] Oxime substrates **16**, **18**, **19**, and **24** were prepared as previously reported,[9c] and tetrazole[35] and azobenzene[36] substrates **13** and **25** were prepared according to the literature procedures. Substrate **17** was prepared in two steps from 2-picoline.[37,38] Amide substrate **34** was synthesized via arylation of δ-valerolactam.[39] The remainder of the substrates were obtained from commercial sources (typically Acros Organics, Aldrich, or Lancaster) and were used without further purification. $Pd(OAc)_2$ was obtained from Pressure Chemical and used as received. NCS and NBS were obtained

Table 7. Palladium-catalyzed halogenation of *type 4* substrates[a]

Entry	Starting material	Oxidant	Major product with Pd catalyst	Minor product with Pd catalyst	Major product without Pd catalyst	Minor product without Pd catalyst
1	 (**33**)	NCS	 (**33-Cl**, 77%)	 (*Iso*-**33-Cl**, <5%)	 (*Iso*-**33-Cl**, 50%)[b]	 (**33-Cl**, 50%)[b]
2	 (**33**)	NBS	 (*Iso*-**33-Br**, 75%)[b]	 (**33-Br**, 17%)[b]	 (*Iso*-**33-Br**, 73%)[b]	 (**33-Br**, 19%)[b]
3	 (**33**)	NIS	 (*Iso*-**33-I**, 80%)	 (**33-I**, <5%)	 (*Iso*-**33-I**, 80%)	 (**33-I**, <5%)
4	 (**34**)	NCS	 (**34-Cl**, 57%)	 (*Iso*-**34-Cl**, <5%)	 (**34-Cl**, 45%)[b]	 (*Iso*-**34-Cl**, 41%)[b]
5	 (**34**)	NBS	 (*Iso*-**34-Br**, 63%)	 (**34-Br**, 37%)	 (*Iso*-**34-Br**, 81%)[b]	 (**34-Br**, 19%)[b]
6	 (**35**)	NCS	 (**35-Cl**, 77%)	 (*Iso*-**35-Cl**, <5%)	 (**35-Cl**, 41%)[b]	 (**35-Cl**, 28%)[b]
7	 (**35**)	NBS	 (*Iso*-**35-Br**, 60%)[b]	 (**35-Br**, 40%)[b]	 (*Iso*-**35-Br**, 77%)[b]	 (**35-Br**, 23%)[b]
8	 (**36**)	NCS	 (**36-Cl**, 81%)	 (*Iso*-**36-Cl**, <5%)	Complex mixture of products	
9	 (**37**)	NCS	 (**37-Cl**, 70%)	(*Iso*-**37-Cl**, 17%)	(**37-Cl**, 43%)	(*Iso*-**37-Cl**, 39%)

[a] NXS (1.5–1.8 equiv), 100 °C, 12 h, AcOH.
[b] Uncorrected yields as determined by GC and GC–MS.

from Acros, while NIS was obtained from Oakwood Products, and all were used without further purification. Solvents were obtained from Fisher Chemical and used as received. The synthesis of some substrates and characterization of the corresponding halogenated products (**1-Cl**, **1-Br**, **2-Cl**, **2-Br**, **2-I**, **3-Cl**, **3-Cl_2**, **4-Cl**, **6-Br**, **10-Br**, **11-I**, **14-I**, **15-I**, **20-Cl**, **20**-*iso*-**Cl**, **21-Cl**, **28-Cl**, **35-Cl**, and **36-Cl**) has been reported previously in preliminary communications of this work.[9d,g]

4.3. Instrumentation

NMR spectra were obtained on a Varian Inova 500 (499.90 MHz for ^{1}H; 125.70 MHz for ^{13}C), a Varian Inova 400 (399.96 MHz for ^{1}H; 100.57 MHz for ^{13}C; 376.34 MHz for ^{19}F), or a Varian Mercury 300 (300.07 MHz for ^{1}H NMR, 75.45 MHz for ^{13}C; 282.35 MHz for ^{19}F) spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublets of doublets (ddd), doublet of triplets (dt), triplet (t), triplet of doublets (td), triplet of triplets (tt), quartet (q), quintet (quin), multiplet (m), and broad resonance (br). IR spectra were obtained on a Perkin–Elmer Spectrum BX FT-IR spectrometer. Melting points were determined with a Mel-Temp 3.0, a Laboratory Devices Inc, USA instrument and are uncorrected. HRMS data were obtained on a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer. Gas chromatography

was performed on a Shimadzu GC-17A equipped with a Restek Rtx©-5 column (15 m, 0.25 mm ID, 0.25 μm df) and a FID detector. GC yields are reported as corrected GC yields based on a calibration curve against naphthalene as an internal standard. Typical errors associated with GC yields are approximately ±5%. GC–MS analysis was performed on a Shimadzu GCMS QP-5000 equipped with a Restek Rtx©-5 column (30 m, 0.25 mm ID, 0.25 μm df). Reactions with $CuCl_2$ were not conducive to GC analysis directly from the crude reaction mixture because a large amount of the desired product remained coordinated to the copper. To correct for this, pyridine was added to each crude reaction mixture (1/2 the total volume of the reaction for small-scale screenings) to liberate the product prior to GC analysis.

4.4. General procedures

Procedure A. Substrate, oxidant, and $Pd(OAc)_2$ were combined in a 20 mL vial or a larger pressure vessel. Solvent was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 °C (unless otherwise noted) for 12 h. The solvent was removed under vacuum, and the resulting residues were purified by chromatography on silica gel.

Procedure B. Substrate, oxidant, and $Pd(OAc)_2$ were combined in a 20 mL vial. Solvent was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 °C (unless otherwise noted) for 12 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL). An aqueous solution of Na_2CO_3 (10 mL) was then added dropwise to this mixture until the effervescence ceased. The organic and aqueous layers were separated. The aqueous layer was washed with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was then purified by chromatography on silica gel.

Procedure C. Substrate, oxidant, and $Pd(OAc)_2$ were combined in a 20 mL vial. Solvent was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 °C (unless otherwise noted) for 12 h. The solvent was removed under vacuum. The crude residue was dissolved in CH_2Cl_2 (15 mL) and washed with $NaHCO_3$ (1×15 mL). The aqueous layer was washed with CH_2Cl_2 (2×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated. The resulting oil was purified by chromatography on silica gel.

Procedure D. A solution of the oxidant in the reaction solvent was added slowly with stirring to a solution of the substrate in the same solvent. The resulting mixture was stirred at room temperature for 1 h, then the solvent was evaporated. The crude residue was extracted between CH_2Cl_2 and H_2O to remove the succinimide by-product. The organic layer was washed with brine, filtered, and concentrated to afford the product.

Procedure E. The substrate and CuX_2 were dissolved in MeCN and heated to 120 °C for 12 h. After evaporation of the solvent, the resulting material was taken up in CH_2Cl_2 and washed several times with an equal volume of a solution of 5% pyridine in water, until the aqueous layer was no longer a bright blue color. The organic layer was then washed with brine, dried with $MgSO_4$, filtered, and condensed to give the crude product, liberated from most of the copper oxidant.

Procedure F. Substrate, oxidant, and $Pd(OAc)_2$ were combined in a 20 mL vial. Solvent was added, the vial was sealed with a Teflon lined cap, and the mixture was heated at 100 °C for 12 h. The solvent was removed under vacuum. The crude residue was dissolved in CH_2Cl_2 (15 mL) and washed with a solution of 5% pyridine in water (3×15 mL) followed by washing with brine (1×15 mL). The combined organic layers were dried over $MgSO_4$, filtered, and then concentrated. The resulting oil was purified by chromatography on silica gel.

4.4.1. 5-Chlorobenzo[*h*]quinoline (*iso*-1-Cl). Procedure A was followed, utilizing substrate **1** (215.5 mg, 1.2 mmol, 1 equiv), $PhICl_2$ (404.0 mg, 1.5 mmol, 1.3 equiv), and MeCN (10 mL) with no Pd needed. The product was isolated as an off-white solid (R_f=0.21 in 95% hexanes/5% EtOAc, mp=113.6–115.0 °C). Analytically pure material was isolated by further purification by HPLC (98% hexanes/2% EtOAc, 20 mL/min, Waters μ-porasil 19.1 mm). Isolated yield was not determined due to difficulties in purification, but was ~38% by uncorrected GC ratios of the crude reaction mixture. Regiochemistry was assigned by analogy to *iso*-**1**-**Br** (see below). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.26 (dt, *J*=8.0, 1.0 Hz, 1H), 9.05 (dd, *J*=4.5, 1.5 Hz, 1H), 8.65 (dd, *J*=8.5, 1.5 Hz, 1H), 7.94 (s, 1H), 7.85–7.83 (m, 1H), 7.76–7.69 (multiple peaks, 2H), 7.64 (dd, *J*=8.5, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5, 147.1, 133.2, 133.1, 130.7, 129.1, 129.0, 127.5, 127.3, 127.2, 124.9, 122.4 (two peaks are coincidentally overlapping). HRMS EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_8ClN$: 213.0345. Found: 213.0350.

4.4.2. 5-Bromobenzo[*h*]quinoline (*iso*-1-Br). Procedure E was followed, utilizing substrate **1** (1.0968 g, 6.1 mmol, 1 equiv), $CuBr_2$ (3.3578 g, 15.0 mmol, 2.5 equiv), and MeCN (50 mL). The crude residue was purified by column chromatography on silica gel (R_f=0.21 in 95% hexanes/5% EtOAc) and was isolated as a white solid (382.4 mg, 24% yield, mp=108.3–110.8 °C) contaminated with ~10% of an unidentified impurity by ^{1}H NMR. This was removed by further purification by preparative TLC (Whatman PK6F Silica gel, 60 Å, 500 μm thickness), eluting with 20% EtOAc in hexanes. Regiochemistry was confirmed by synthesis of an authentic sample of the 6-Br isomer[40] and comparison of the NMR spectral data to *iso*-**1**-**Br** (see below). For the **5**-**Br** isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.26 (dt, *J*=8.0, 0.5 Hz, 1H), 9.01 (dd, *J*=4.0, 2.0 Hz, 1H), 8.60 (dd, *J*=8.5, 1.5 Hz, 1H), 8.15 (s, 1H), 7.83–7.81 (m, 1H), 7.77–7.74 (m, 1H), 7.72–7.68 (m, 1H), 7.62 (dd, *J*=8.5, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5, 147.0, 135.9, 133.8, 131.2, 131.1, 129.1, 127.7, 127.2, 125.9, 125.0, 122.7, 119.7. HRMS EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_8BrN$: 256.9840. Found: 256.9838. For the **6**-**Br** isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.36–9.33 (m, 1H), 9.01 (dd, *J*=4.0, 2.0 Hz, 1H), 8.36–8.33 (m, 1H), 8.10 (dd, *J*=8.0, 2.0 Hz, 1H), 8.06 (s, 1H), 7.83–7.79 (multiple peaks, 2H), 7.54 (1H, dd, *J*=8.0, 4.5 Hz, 1H).

4.4.3. 2-(2-Chloronapthalen-1-yl)pyridine (5-Cl). Procedure A was followed, utilizing substrate **5** (100 mg, 0.487 mmol, 1 equiv), NCS (72 mg, 0.536 mmol, 1.1 equiv), $Pd(OAc)_2$ (5.5 mg, 0.024 mmol, 5 mol %), and CH_3CN (4.0 mL). Product **5-Cl** was isolated as a yellow solid (81 mg, 70% yield, mp=85.7–86.4 °C, R_f=0.11 in 95% toluene/5% EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 8.80–8.79 (m, 1H), 8.03–7.97 (multiple peaks, 3H), 7.77 (d, J=8.9 Hz, 1H), 7.58–7.49 (multiple peaks, 3H), 7.43 (d, J=7.9 Hz, 1H), 7.26 (d, J=8.5 Hz, 1H). ^{13}C NMR (100 MHz): δ 157.4, 150.6, 137.6, 137.3, 134.2, 133.1, 131.0, 130.7, 129.0, 128.1, 127.8, 127.1, 126.7, 126.6, 123.7. HRMS EI (m/z): [M^+] calcd for $C_{15}H_{10}ClN$, 239.0502. Found: 239.0499.

4.4.4. Methyl 4-bromo-3-(pyridin-2-yl)benzoate (7-Br). Procedure A was followed at 120 °C, utilizing substrate **7** (2.357 g, 11 mmol, 1 equiv), NBS (3.952 g, 22 mmol, 2 equiv), $Pd(OAc)_2$ (120.5 mg, 0.54 mmol, 5 mol %), and HOAc (200 mL). The crude residue was purified by chromatography on silica gel (R_f=0.04 in 90% hexanes/10% EtOAc). Material that was pure by GC was isolated as a yellow oil, which solidified upon standing (2.263 g, 70% yield). Analytically pure material (a white solid, mp=68.0–69.2 °C) was obtained after a second column. ^1H NMR (500 MHz, $CDCl_3$): δ 8.72 (ddd, J=5.0, 2.0, 1.0 Hz, 1H), 8.17 (d, J=2.0 Hz, 1H), 7.89 (dd, J=8.5, 2.0 Hz, 1H), 7.77 (td, J=8.0, 2.0 Hz, 1H), 7.74 (d, J=8.5 Hz, 1H), 7.58 (dt, J=8.0, 1.0 Hz, 1H), 7.31 (ddd, J=7.5, 5.0, 1.0 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 157.6, 149.7, 141.6, 136.1, 133.7, 132.5, 130.5, 129.7, 127.3, 124.7, 122.9, 52.4. IR (KBr): 1734, 1260, 753 cm^{-1}. Anal. Calcd for $C_{13}H_{10}BrNO_2$: C, 53.45; H, 3.45; N, 4.79. Found: C, 53.18; H, 3.40; N, 4.71.

4.4.5. 2-(2-Bromo-5-methylphenyl)pyridine (8-Br). Procedure A was followed at 120 °C, utilizing substrate **8** (201 mg, 1.20 mmol, 1 equiv), NBS (254 mg, 1.40 mmol, 1.2 equiv), $Pd(OAc)_2$ (13.3 mg, 0.06 mmol, 5 mol %), and CH_3CN (7.7 mL). Product **8-Br** was isolated as a clear oil (151 mg, 51% yield, R_f=0.10 in 95% hexanes/5% EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J=4.9 Hz, 1H), 7.75 (td, J=7.6, 1.8 Hz, 1H), 7.61 (d, J=7.9 Hz, 1H), 7.54 (d, J=8.1 Hz, 1H), 7.36 (d, J=2.3 Hz, 1H), 7.29 (ddd, J=7.5, 4.9, 1.2 Hz, 1H), 7.07 (dd, J=8.1, 2.3 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 149.3, 140.8, 137.5, 135.7, 132.9, 132.1, 130.5, 124.8, 122.3, 118.3, 20.8. Anal. Calcd for $C_{12}H_{10}BrN$: C, 58.09; H, 4.06; N, 5.65. Found: C, 57.90; H, 3.90; N, 5.49.

4.4.6. 2-(2-Bromophenyl)pyridine (9-Br). Procedure A was followed at 120 °C, utilizing substrate **9** (2.17 g, 14.0 mmol, 1 equiv), NBS (2.99 g, 16.8 mmol, 1.2 equiv), $Pd(OAc)_2$ (156 mg, 0.70 mmol), and CH_3CN (200 mL). Product **9-Br** was isolated as a yellow oil (2.07 g, 63% yield, R_f=0.05 in 95% hexanes/5% EtOAc). ^1H NMR (500 MHz, $CDCl_3$): δ 8.72 (ddd, J=5.0, 1.5, 1.0 Hz, 1H), 7.77 (td, J=8.0, 2.0 Hz, 1H), 7.68 (dd, J=8.0, 1.5 Hz, 1H), 7.61 (dt, J=8.0, 1.0 Hz, 1H), 7.54 (dd, J=7.5, 1.5 Hz, 1H), 7.41 (dt, J=7.5, 1.5 Hz, 1H), 7.30 (ddd, J=7.5, 5.0, 1.0 Hz, 1H), 7.27–7.24 (m (obscured by solvent), 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 149.5, 141.3, 135.9, 133.3, 131.5, 129.8, 127.6, 124.8, 122.5, 121.8. HRMS EI (m/z): [$M]^+$ calcd for $C_{11}H_8BrN$: 232.9840. Found: 232.9839.

4.4.7. 2-(2-Iodo-5-(trifluoromethyl)phenyl)-3-methylpyridine (12-I). Procedure B was followed, utilizing substrate **12** (150 mg, 0.633 mmol, 1 equiv), NIS (171 mg, 0.759 mmol, 1.2 equiv), $Pd(OAc)_2$ (7.1 mg, 0.032 mmol, 5 mol %), and CH_3CN (5.3 mL). Product **12-I** was isolated as a light yellow viscous oil with gradient elution from 100% CH_2Cl_2 to 95% CH_2Cl_2/5% EtOAc (179 mg, 78% yield, R_f=0.22 in CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J=3.6 Hz, 1H), 8.19 (s, 1H), 7.71 (d, J=6.0 Hz, 1H), 7.64 (d, J=6.4 Hz, 1H), 7.38 (d, J=6.4 Hz, 1H), 7.30 (dd, J=6.2, 3.8 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 148.9, 146.8, 138.1, 135.8 (q, J_{CF}=4.4 Hz), 131.4 (q, J_{CF}=33 Hz), 131.1, 129.5, 125.2 (q, J_{CF}=3.6 Hz), 123.5, 122.8 (q, J_{CF}=272 Hz), 97.5, 18.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.7 (s). Anal. Calcd for $C_{13}H_9F_3IN$: C, 43.00; H, 2.50; N, 3.86. Found: C, 43.41; H, 2.57; N, 3.86.

4.4.8. 2-(2,6-Diiodophenyl)pyridine (9-I_2). Procedure A was followed, utilizing substrate **9** (150 mg, 0.966 mmol, 1 equiv), NIS (457 mg, 2.03 mmol, 2.1 equiv), $Pd(OAc)_2$ (10.8 mg, 0.048 mmol, 5 mol %), and AcOH (8.1 mL). Product **9-I_2** was isolated as a light brown solid (162 mg, 41% yield, mp=122.7–124.2 °C, R_f=0.29 in 90% hexanes/10% EtOAc). ^1H NMR (500 MHz, $CDCl_3$): δ 8.76 (d, J=4.5 Hz, 1H), 7.93 (d, J=8 Hz, 2H), 7.83 (t, J=8 Hz, 1H), 7.36 (m, 1H), 7.26 (d, J=8 Hz, 1H), 6.75 (t, J=8 Hz, 1H). ^{13}C NMR (100 MHz): δ 164.2, 149.2, 148.2, 139.0, 136.6, 131.1, 124.1, 123.2, 96.9. Anal. Calcd for $C_{11}H_7I_2N$: C, 32.46; H, 1.73; N, 3.44. Found: C, 32.71; H, 1.66; N, 3.50.

4.4.9. 2-(8-Iodonapthalen-1-yl)pyridine (5-I). Procedure A was followed, utilizing substrate **5** (100 mg, 0.487 mmol, 1 equiv), NIS (329 mg, 1.46 mmol, 3.0 equiv), $Pd(OAc)_2$ (5.5 mg, 0.024 mmol, 5 mol %), and CH_3CN (4.0 mL). Product **5-I** was isolated as a yellow solid (97 mg, 60% yield, mp=85.9–87.0 °C, R_f=0.19 in 97.5% toluene/2.5% EtOAc). ^1H NMR (400 MHz, acetone-d_6): δ 8.78 (ddd, J=4.9, 1.8, 1.0 Hz, 1H), 8.03–7.97 (multiple peaks, 3H), 7.77 (d, J=8.9 Hz, 1H), 7.58–7.49 (multiple peaks, 2H), 7.44–7.42 (multiple peaks, 2H), 7.26 (d, J=8.5 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 161.8, 150.5, 144.4, 137.5, 136.3, 133.9, 131.1, 130.6, 129.0, 127.9, 127.4, 127.1, 126.3, 123.9, 97.1. HRMS EI (m/z): [M^+] calcd for $C_{15}H_{10}IN$, 330.9858. Found: 330.9857.

4.4.10. 5-(2-Iodophenyl)-1-methyl-1*H*-tetrazole (13-I). Procedure A was followed, utilizing substrate **13** (150 mg, 0.936 mmol, 1 equiv), NIS (442 mg, 1.97 mmol, 2.1 equiv), $Pd(OAc)_2$ (20.9 mg, 0.094 mmol, 10 mol %), and AcOH (7.8 mL). Product **13-I** was isolated as a viscous milky white oil (111 mg, 41% yield, R_f=0.23 in 98.5% toluene/1.5% MeCN). The calibrated GC yield (against naphthalene as the internal standard) of the reaction was 41%. Note: the sample obtained from column chromatography was contaminated with approximately 50% of the starting material. Samples for HRMS, NMR analysis, and calibrated GC yields were obtained after further purification by HPLC (95% hexanes/5% EtOAc, 20 mL/min, Waters μ-porasil 19.1 mm). Mp=71.8–72.7 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, J=7.8, 1.0 Hz, 1H), 7.73 (dd, J=7.8, 1.4 Hz, 1H), 7.46 (td, J=7.8, 1.6 Hz, 1H), 7.16 (td, J=7.8,

1.5 Hz, 1H), 4.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 140.7, 132.4, 131.2, 131.1, 128.2, 95.6, 39.7. HRMS EI (*m*/*z*): [M$^+$] calcd for $C_8H_7IN_4$, 285.9715. Found: 285.9720.

4.4.11. *N*-(2-Chloro-3-(1-(methoxyimino)ethyl)phenyl)-acetamide (16-Cl). Procedure C was followed, utilizing substrate **16** (150 mg, 0.727 mmol, 1 equiv), NCS (116 mg, 0.872 mmol, 1.2 equiv), $Pd(OAc)_2$ (16.3 mg, 0.072 mmol, 10 mol %), and AcOH (6.1 mL). Product **16-Cl** was isolated as a light yellow solid as a 4:1 mixture of oxime isomers (105 mg, 60% yield, mp=123.9–125.3 °C, R_f=0.20 in 70% hexanes/30% EtOAc). *Major oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J*=8.1 Hz, 1H), 7.64 (br s, 1H), 7.24 (t, *J*=7.8 Hz, 1H), 7.02 (d, *J*=7.5 Hz, 1H), 3.94 (s, 3H), 2.21 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz): δ 168.2, 155.4, 137.2, 135.0, 128.4, 127.5, 125.0, 121.7, 61.9, 24.9, 16.3. *Minor oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J*=7.9 Hz, 1H), 7.67 (br s, 1H), 7.31 (t, *J*=7.7 Hz, 1H), 6.85 (d, *J*=7.7 Hz, 1H), 3.80 (s, 3H), 2.24 (s, 3H), 2.15 (s, 3H). IR (KBr): 1654 cm^{-1}. HRMS EI (*m*/*z*): [M$^+$] calcd for $C_{11}H_{13}ClN_2O_2$, 240.0666. Found: 240.0662. The reaction in the absence of palladium showed a complex mixture of isomeric chlorinated products by GC analysis.

4.4.12. (*E*)-3-Chloro-2-(pyridin-2-yl)allyl acetate (17-Cl). Procedure C was followed, utilizing substrate **17** (107.8 mg, 0.61 mmol, 1 equiv), NCS (88.6 mg, 0.66 mmol, 1.1 equiv), $Pd(OAc)_2$ (6.6 mg, 0.029 mmol, 5 mol %), and 1,2-dichloroethane (10 mL). GC analysis of the crude reaction mixture afforded a calibrated yield of 69%. Product **17-Cl** was isolated as a tan oil (71.2 mg, contaminated with 12% of an inseparable dichlorinated product, 49% yield, R_f=0.04 in 90% hexanes/10% EtOAc). Samples for HRMS, NMR analysis, and calibrated GC yields were obtained after further purification by HPLC (90% hexanes/10% EtOAc, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (ddd, *J*=4.5, 2.0, 1.0 Hz, 1H), 7.73 (td, *J*=7.5, 2.0 Hz, 1H), 7.68 (dt, *J*=8.0, 1.0 Hz, 1H), 7.24 (ddd, *J*=7.0, 5.0, 1.5 Hz, 1H), 6.65 (t, *J*= 1.5 Hz, 1H), 5.09 (s, 2H), 2.01 (s, 3H). NOE: Irradiation of olefinic proton (at 6.65 ppm) produces a 1% enhancement of the methylene at 5.09 ppm and a trace enhancement of the methyl at 2.01 ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 153.5, 149.6, 136.9, 136.1, 125.1, 123.1, 120.7, 65.6, 21.0. IR (thin film): 1743, 1226 cm^{-1}. HRMS EI (*m*/*z*): [M]$^+$ calcd for $C_{10}H_{10}ClNO_2$: 211.0400. Found: 211.0399.

4.4.13. 1-(2-Chlorocyclohex-1-enyl)ethanone *O*-methyl oxime (18-Cl). Procedure C was followed, utilizing substrate **18** (103.7 mg, 0.68 mmol, 1 equiv), NCS (226.0 mg, 1.7 mmol, 2.5 equiv), $Pd(OAc)_2$ (15.1 mg, 0.067 mmol, 10 mol %), and MeCN (10 mL). The product **18-Cl** was isolated as a colorless oil (23.1 mg, 18% yield, R_f=0.08 in 98% hexanes/2% EtOAc). The low isolated yield appears to be the result of incomplete conversion as well as the volatility of the product. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 3H), 2.40–2.36 (m, 2H), 2.27–2.23 (m, 2H), 1.98 (s, 3H), 1.76–1.71 (m, 2H), 1.69–1.64 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 131.9, 130.6, 61.7, 33.9, 30.2, 23.6, 22.1, 14.7. IR (thin film): 1722, 1435, 1052 cm^{-1}. HRMS EI (*m*/*z*): [M]$^+$ calcd for $C_9H_{14}ClNO$: 187.0764. Found: 187.0760.

4.4.14. (*E*)-1-(2-Chloro-4-methoxyphenyl)ethanone *O*-methyl oxime (19-Cl). Procedure A was followed, utilizing substrate **19** (100 mg, 0.558 mmol, 1 equiv), NCS (81.9 mg, 0.614 mmol, 1.1 equiv), $Pd(OAc)_2$ (6.2 mg, 0.028 mmol, 5 mol %), and AcOH (4.6 mL). Product **19-Cl** was isolated as a clear oil as a 3:1 mixture of oxime *E*/*Z* isomers (69 mg, 58% yield, R_f=0.20 in 55% hexanes/45% CH_2Cl_2). *Major oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J*=8.8 Hz, 1H), 6.94 (d, *J*=2.5 Hz, 1H), 6.81 (dd, *J*=8.8, 2.5 Hz, 1H), 3.99 (s, 3H), 3.82 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 155.8, 133.4, 130.9, 129.3, 115.3, 112.8, 61.8, 55.6, 16.5. *Minor oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J*=8.5 Hz, 1H), 6.96 (d, *J*=2.5 Hz, 1H), 6.84 (dd, *J*=8.5, 2.5 Hz, 1H), 3.99 (s, 3H), 3.83 (s, 3H), 2.20 (s, 3H). HRMS EI (*m*/*z*): [M$^+$] calcd for $C_{10}H_{12}ClNO_2$, 213.0557. Found: 213.0563.

4.4.15. (*E*)-1-(3-Chloro-4-methoxyphenyl)ethanone *O*-methyl oxime (*iso*-19-Cl). Procedure A was followed, utilizing substrate **19** (100 mg, 0.558 mmol, 1 equiv), NCS (89.4 mg, 0.669 mmol, 1.2 equiv), and AcOH (4.6 mL). Product *iso*-**19-Cl** was isolated as a white solid as a single oxime isomer (62 mg, 53% yield, mp=60.2–61.6 °C, R_f=0.25 in 60% hexanes/40% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J*=2.0 Hz, 1H), 7.50 (dd, *J*=8.8, 2.4 Hz, 1H), 6.90 (d, *J*=8.4 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 152.9, 130.0, 127.8, 125.4, 114.0, 111.5, 61.9, 56.2, 12.3. HRMS EI (*m*/*z*): [M$^+$] calcd for $C_{10}H_{12}ClNO_2$, 213.0557. Found: 213.0562.

4.4.16. (*E*)-1-(2-Bromo-4-methoxyphenyl)ethanone *O*-methyl oxime (19-Br). Procedure A was followed, utilizing substrate **19** (100 mg, 0.558 mmol, 1 equiv), NBS (109 mg, 0.614 mmol, 1.1 equiv), $Pd(OAc)_2$ (6.2 mg, 0.028 mmol, 5 mol %), and AcOH (4.6 mL). Product **19-Br** was isolated as a clear oil as a 3:1 mixture of oxime *E*/*Z* isomers (105 mg, 72% yield, R_f=0.30 in 55% hexanes/45% CH_2Cl_2). *Major oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J*=8.8 Hz, 1H), 7.12 (d, *J*=2.8 Hz, 1H), 6.85 (dd, *J*=8.4, 2.8 Hz, 1H), 3.97 (s, 3H), 3.80 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 156.7, 131.3, 130.9, 122.2, 118.3, 113.3, 61.8, 55.6, 16.7. HRMS EI (*m*/*z*): [M$^+$] calcd for $C_{10}H_{12}BrNO_2$, 257.0051. Found: 257.0056. *Minor oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J*=2.3 Hz, 1H), 7.00 (d, *J*=8.6 Hz, 1H), 6.87 (dd, *J*=8.6, 2.3 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 2.15 (s, 3H). HRMS EI (*m*/*z*): [M$^+$] calcd for $C_{10}H_{12}BrNO_2$, 257.0051. Found: 257.0057.

4.4.17. (*E*)-1-(3-Bromo-4-methoxyphenyl)ethanone *O*-methyl oxime (*iso*-19-Br). Procedure A was followed, utilizing substrate **19** (100 mg, 0.558 mmol, 1 equiv), NBS (119 mg, 0.669 mmol, 1.2 equiv), and AcOH (4.6 mL). Product *iso*-**19-Br** was isolated as a white solid as a single oxime isomer (99 mg, 69% yield, mp=70.2–71.1 °C, R_f= 0.30 in 55% hexanes/45% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J*=2.4 Hz, 1H), 7.55 (dd, *J*=8.4, 2.4 Hz, 1H), 6.87 (d, *J*=8.8 Hz, 1H), 3.98 (s, 3H), 3.91 (s, 3H), 2.17

(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 152.9, 130.9, 130.4, 126.2, 111.7, 111.4, 61.9, 56.3, 12.3. HRMS EI (*m*/*z*): [M^+] calcd for $C_{10}H_{12}BrNO_2$, 257.0051. Found: 257.0056.

4.4.18. (*E*)-1-(2-Iodo-4-methoxyphenyl)ethanone *O*-methyl oxime (19-I). Procedure A was followed, utilizing substrate **19** (100 mg, 0.558 mmol, 1 equiv), NIS (151 mg, 0.669 mmol, 1.2 equiv), $Pd(OAc)_2$ (6.2 mg, 0.028 mmol, 5 mol %), and AcOH (4.6 mL). Product **19-I** was isolated as a clear oil as a 3:1 mixture of oxime *E*/*Z* isomers (78 mg, 46% yield, R_f=0.29 in 55% hexanes/45% CH_2Cl_2). *Major oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J*=2.4 Hz, 1H), 7.15 (d, *J*=8.4 Hz, 1H), 6.89 (dd, *J*=8.8, 2.8 Hz, 1H), 3.98 (s, 3H), 3.79 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 158.2, 135.2, 129.9, 124.7, 114.1, 96.0, 61.8, 55.6, 16.9. *Minor oxime isomer*: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J*=2.2 Hz, 1H), 6.94 (d, *J*=8.4 Hz, 1H), 6.92 (dd, *J*=8.4, 2.1 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.14 (s, 3H). HRMS EI (*m*/*z*): [M^+] calcd for $C_{10}H_{12}INO_2$, 304.9913. Found: 304.9909.

4.4.19. (*E*)-1-(3-Iodo-4-methoxyphenyl)ethanone *O*-methyl oxime (*iso*-19-I). Procedure A was followed, utilizing substrate **19** (100 mg, 0.558 mmol, 1 equiv), NIS (151 mg, 0.669 mmol, 1.2 equiv), and AcOH (4.6 mL). Product *iso*-**19-I** was isolated as a light yellow solid as a single oxime isomer (81 mg, 47% yield, mp=65.0–66.4 °C, R_f=0.29 in 55% hexanes/45% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J*=2.4 Hz, 1H), 7.59 (dd, *J*=8.4, 2.4 Hz, 1H), 6.79 (d, *J*=8.8 Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 152.8, 137.0, 131.0, 127.3, 110.3, 86.0, 61.9, 56.4, 12.4. HRMS EI (*m*/*z*): [M^+] calcd for $C_{10}H_{12}INO_2$, 304.9913. Found: 304.9916.

4.4.20. 4-Chloro-1-phenylisoquinoline (*iso*-21-Cl). Procedure A was followed, utilizing substrate **21** (100 mg, 0.487 mmol, 1 equiv), NCS (130 mg, 0.974 mmol, 2.0 equiv), and AcOH (4.0 mL). Product *iso*-**21-Cl** was isolated as a white solid (66 mg, 56% yield, mp=129.7–130.3 °C, R_f=0.29 in 90% hexanes/10% CH_2Cl_2). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.65 (s, 1H), 8.28 (d, *J*=8.4 Hz, 1H), 8.13 (d, *J*=8.4 Hz, 1H), 7.94 (dt, *J*=6.8, 1.2 Hz, 1H), 7.74 (dt, *J*=6.8, 1.2 Hz, 1H), 7.70–7.68 (multiple peaks, 2H), 7.58–7.53 (multiple peaks, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 160.5, 141.7, 139.9, 134.7, 132.3, 130.8, 129.6, 129.3, 129.1, 128.7, 128.2, 127.6, 124.1. Anal. Calcd for $C_{15}H_{10}ClN$: C, 75.16; H, 4.21; N, 5.84. Found: C, 74.48; H, 4.19; N, 5.65.

4.4.21. 1-(2-Chlorophenyl)-1*H*-pyrazole (22-Cl). Procedure B was followed, utilizing substrate **22** (150 mg, 1.04 mmol, 1 equiv), NCS (146 mg, 1.09 mmol, 1.05 equiv), $Pd(OAc)_2$ (23.3 mg, 0.104 mmol, 10 mol %), and AcOH (8.7 mL). Product **22-Cl** was isolated as a clear oil (108 mg, 58% yield, R_f=0.12 in 60% hexanes/40% CH_2Cl_2). The calibrated GC yield (against naphthalene as the internal standard) of the reaction was 72%. Note: the sample obtained from column chromatography was contaminated with approximately 13% of the starting material. Samples for microanalysis were obtained after further purification by HPLC (98% hexanes/2% EtOAc, 20 mL/min, Waters μ-porasil 19.1 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J*=3.2 Hz, 1H), 7.75 (s, 1H), 7.58 (dd, *J*=10.4, 2.0 Hz, 1H), 7.52 (dd, *J*=10.2, 2.6 Hz, 1H), 7.42–7.30 (multiple peaks, 2H), 6.48 (t, *J*=2.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 131.3, 130.6, 128.9, 128.3, 127.8, 127.6, 106.6. Two carbon resonances are coincidently overlapping. HRMS EI (*m*/*z*): [M^+] calcd for $C_9H_7ClN_2$, 178.0298. Found: 178.0299.

4.4.22. 1-(2-Chlorophenyl)-1*H*-pyrazole (*iso*-22-Cl). Procedure B was followed, utilizing substrate **22** (150 mg, 1.04 mmol, 1 equiv), NCS (146 mg, 1.09 mmol, 1.05 equiv), and AcOH (8.7 mL). Product *iso*-**22-Cl** was isolated as a clear oil (154 mg, 83% yield, mp=72.5–74.3 °C, R_f=0.26 in 70% hexanes/30% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.64–7.62 (multiple peaks, 3H), 7.45 (t, *J*=7.4 Hz, 2H), 7.31(tt, *J*=7.4, 1.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 139.4, 129.5, 126.9, 124.8, 118.9, 112.3. HRMS EI (*m*/*z*): [M^+] calcd for $C_9H_7ClN_2$, 178.0298. Found: 178.0297.

4.4.23. 2-(2-Chloro-5-(trifluoromethyl)phenyl)-6-methoxypyridine (23-Cl). Procedure B was followed, utilizing substrate **23** (100 mg, 0.395 mmol, 1 equiv), NCS (58 mg, 0.434 mmol, 1.1 equiv), $Pd(OAc)_2$ (17.7 mg, 0.079 mmol, 20 mol %), and AcOH (3.3 mL). Product **23-Cl** was isolated as a clear oil (81 mg, 71% yield, R_f=0.35 in 98% hexanes/2% EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.01–7.98 (m, 1H), 7.83 (dd, *J*=8.1, 7.2 Hz, 1H), 7.82–7.75 (multiple peaks, 2H), 7.37 (dd, *J*=10.0, 0.8 Hz, 1H), 6.86 (dd, *J*=11.0, 1.2 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 164.8, 153.4, 140.8, 140.1, 137.1, 132.3, 129.9 (q, J_{CF}=32.2 Hz), 129.3 (q, J_{CF}=4.05 Hz), 127.2 (q, J_{CF}=3.7 Hz), 124.9 (q, J_{CF}=272 Hz), 118.5, 111.4, 53.8. ^{19}F NMR (282 MHz, acetone-d_6): δ –63.1 (s) Anal. Calcd for $C_{13}H_9ClF_3NO$: C, 54.28; H, 3.15; N, 4.87. Found: C, 54.37; H, 3.01; N, 4.80.

4.4.24. 3-Chloro-2-methoxy-6-(3-(trifluoromethyl)-phenyl)pyridine and 3-chloro-6-methoxy-2-(3-(trifluoromethyl)phenyl)pyridine (*iso*-23-Cla) and (*iso*-23-Clb). Procedure B was followed, utilizing substrate **23** (100 mg, 0.395 mmol, 1 equiv), NCS (58 mg, 0.434 mmol, 1.1 equiv), and AcOH (3.3 mL). GC analysis of the crude reaction mixture showed 3:1 mixture of regioisomeric mono-chlorinated products. Isomer *iso*-**23-Cla** was isolated as a clear oil (36 mg, 32% yield, R_f=0.18 in 98% hexanes/2% toluene). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.44 (s, 1H), 8.40 (d, *J*=7.7 Hz, 1H), 7.90 (d, *J*=7.9 Hz, 1H), 7.79–7.73 (multiple peaks, 2H), 7.68 (d, *J*=8.0 Hz, 1H), 4.12 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 159.74, 151.80, 140.43, 139.86, 131.55 (q, J_{CF}=32 Hz), 131.17, 130.70, 125.37 (q, J_{CF}=271 Hz), 126.57 (q, J_{CF}=3.8 Hz), 124.03 (q, J_{CF}=3.8 Hz), 118.28, 115.13, 54.59. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.72 (s). HRMS EI (*m*/*z*): [M^+] calcd for $C_{13}H_9ClF_3NO$, 287.0325. Found: 287.0318. Isomer *iso*-**23-Clb** was isolated as a clear oil (57 mg, 50% yield, R_f=0.13 in 98% hexanes/2% toluene). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12–8.09 (multiple peaks, 2H), 7.73–7.64 (multiple peaks, 2H), 7.59 (t, *J*=7.7 Hz, 1H), 6.85 (d, *J*=8.7 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 151.8, 142.2, 140.1, 134.2, 130.8 (q, J_{CF}=32 Hz), 129.1, 126.9 (q, J_{CF}=3.7 Hz), 126.3

(q, J_{CF}=3.6 Hz), 125.3 (q, J_{CF}=271 Hz), 122.3, 112.8, 54.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.6 (s). HRMS EI (*m/z*): [M^+] calcd for $C_{13}H_9ClF_3NO$, 287.0325. Found: 287.0316.

4.4.25. (*E*)-8-Chloro-3,4-dihydronaphthalen-1(2*H*)-one *O*-methyl oxime (24-Cl). Procedure A was followed, utilizing substrate **24** (150 mg, 0.856 mmol, 1 equiv), NCS (120 mg, 0.899 mmol, 1.05 equiv), $Pd(OAc)_2$ (9.6 mg, 0.043 mmol, 5 mol %), and AcOH (7 mL). Product **24-Cl** was isolated as a clear oil (179 mg, 88% yield, R_f=0.3 in 75% hexanes/25% CH_2Cl_2). ^{1}H NMR (300 MHz, acetone-d_6): δ 7.32 (dd, J=7.8, 1.5 Hz, 1H), 7.23–7.13 (multiple peaks, 2H), 3.96 (s, 3H), 2.72 (t, J=6.6 Hz, 2H), 2.65 (t, J=6.0 Hz, 2H), 1.76–1.67 (m, 2H). ^{13}C NMR (75 MHz, acetone-d_6): δ 152.9, 144.8, 132.3, 130.3, 129.8, 129.7, 127.4, 62.3, 31.3, 25.3, 21.7. Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. Found: C, 63.05; H, 5.83; N, 6.70.

4.4.26. (*E*)-4-Chloro-3,4-dihydronaphthalen-1(2*H*)-one *O*-methyl oxime (*iso*-24-Cl). Procedure A was followed, utilizing substrate **24** (150 mg, 0.856 mmol, 1 equiv), NCS (120 mg, 0.899 mmol, 1.05 equiv), and CH_3CN (7 mL). Product *iso*-**24-Cl** was isolated as a clear oil (70 mg, 39% yield, R_f=0.3 in 75% hexanes/25% CH_2Cl_2). Note: product *iso*-**24-Cl** was isolated in higher yield (66%) from the analogous reaction in AcOH; however, the isolated product from this reaction was contaminated with traces of isomeric chlorinated impurities. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.98 (d, J=7.6 Hz, 1H), 7.33 (t, J=6.4 Hz, 1H), 7.25–7.22 (m, 2H), 5.63 (t, J=2.8 Hz, 1H), 4.02 (s, 3H), 3.26–3.17 (m, 1H), 2.80–2.76 (m, 1H), 2.30–2.15 (multiple peaks, 2H). ^{13}C NMR (100 MHz, acetone-d_6): δ 151.7, 138.3, 130.4, 129.8, 128.6, 127.3, 125.0, 62.8, 47.9, 30.7, 24.4. Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. Found: C, 63.11; H, 5.88; N, 6.68.

4.4.27. (*E*)-4-Bromo-3,4-dihydronaphthalen-1(2*H*)-one *O*-methyl oxime (*iso*-24-Br). Procedure A was followed, utilizing substrate **24** (150 mg, 0.856 mmol, 1 equiv), NBS (160 mg, 0.899 mmol, 1.05 equiv), and AcOH (7.1 mL). Product *iso*-**24-Br** was isolated as a clear oil (64 mg, 29% yield, R_f=0.3 in 80% hexanes/20% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J=7.8 Hz, 1H), 7.30–7.14 (multiple peaks, 3H), 5.63 (t, J=2.7 Hz, 1H), 4.06 (s, 3H), 3.34–3.27 (m, 1H), 2.76 (app d, J=16 Hz, 1H), 2.32–2.24 (m, 1H), 2.19–2.08 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.5, 137.1, 129.5, 128.9, 127.7, 126.5, 124.5, 62.7, 37.9, 30.6, 25.3. HRMS EI (*m/z*): [M^+] calcd for $C_{11}H_{12}BrNO$, 253.0102. Found: 253.0106.

4.4.28. (*E*)-1-(2-Iodo-5-methylphenyl)-2-*m*-tolyldiazene (25-I). Procedure A was followed, utilizing substrate **25** (100 mg, 0.475 mmol, 1 equiv), NIS (160 mg, 0.713 mmol, 1.5 equiv), $Pd(OAc)_2$ (5.3 mg, 0.024 mmol, 5 mol %), and AcOH (4.0 mL). Product **25-I** was isolated as an orange solid (65 mg, 41% yield, mp=64.6–66.0 °C, R_f=0.20 in 98% hexanes/2% CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J=8.0 Hz, 1H), 7.81–7.79 (multiple peaks, 2H), 7.45–7.39 (multiple peaks, 2H), 7.32 (d, J=7.2 Hz, 1H), 7.01 (dd, J=8.0, 2.4 Hz, 1H), 2.48 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 151.1, 139.4, 139.1, 139.0, 133.1, 132.3, 128.9, 123.9, 120.8, 117.8, 98.4, 21.4, 20.9. HRMS EI (*m/z*): [M^+] calcd for $C_{14}H_{13}IN_2$, 336.0123. Found: 336.0123. The reaction in the absence of palladium showed a 4:1 mixture of isomeric iodinated products.

4.4.29. *N*-(2-Chloro-6-methylphenyl)pivalamide (26-Cl). Procedure A was followed, utilizing substrate **26** (150 mg, 0.784 mmol, 1 equiv), NCS (126 mg, 0.941 mmol, 1.2 equiv), $Pd(OAc)_2$ (8.8 mg, 0.039 mmol, 5 mol %), and AcOH (6.5 mL). Product **26-Cl** was isolated as a white solid (118 mg, 67% yield, mp=158.4–160.0 °C, R_f=0.20 in 80% hexanes/20% EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.31 (br s, 1H), 7.28 (dd, J=7.4, 2.4 Hz, 1H), 7.21–7.14 (multiple peaks, 2H), 2.22 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, acetone-d_6): δ 176.9, 139.9, 135.4, 133.5, 129.7, 128.6, 127.7, 39.9, 27.9, 18.8. IR (KBr): 1654 cm^{-1}. Anal. Calcd for $C_{12}H_{16}ClNO$: C, 63.85; H, 7.14; N, 6.21. Found: C, 63.71; H, 7.30; N, 5.84.

4.4.30. 8-Chloromethylquinoline (27-Cl). Procedure F was followed, utilizing substrate **27** (110 mg, 0.768 mmol, 1 equiv), $CuCl_2$ (413 mg, 3.07 mmol, 4.0 equiv), $Pd(OAc)_2$ (8.6 mg, 0.038 mmol, 5 mol %), and CH_2Cl_2 (6.4 mL). Product **27-Cl** was isolated as a yellow solid (118 mg, 86% yield, R_f=0.21 in 95% hexanes/5% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.98 (dd, J=4.2, 1.8 Hz, 1H), 8.16 (dd, J=8.3, 1.8 Hz, 1H), 7.79–7.87 (multiple peaks, 2H), 7.53 (t, J=7.1 Hz, 1H), 7.44 (dd, J=8.3, 4.2 Hz, 1H), 5.34 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.3, 146.1, 136.6, 135.8, 130.3, 128.9, 128.5, 126.5, 121.7, 42.6. Anal. Calcd for $C_{10}H_8ClN$: C, 32.46; H, 1.73; N, 3.44. Found: C, 32.71; H, 1.66; N, 3.50.

4.4.31. 2-(2-Bromo-5-methoxyphenyl)pyridine (29-Br). Procedure A was followed, utilizing substrate **29** (2.879 g, 16 mmol, 1 equiv), NBS (2.770 g, 16 mmol, 1 equiv), and MeCN (200 mL). Product **29-Br** was isolated as a yellow-orange oil (3.861 g, 94% yield, R_f=0.18 in 80%, hexanes/20% EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (ddd, J=5.0, 1.5, 1.0 Hz, 1H), 7.77 (td, J=7.5, 2.0 Hz, 1H), 7.61 (d, J=7.5 Hz, 1H), 7.54 (d, J=9.0 Hz, 1H), 7.31 (ddd, J=7.5, 5.0, 1.5 Hz, 1H), 7.09 (d, J=3.0 Hz, 1H), 6.83 (dd, J=8.5, 3.0 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 158.2, 149.4, 142.0, 135.9, 134.0, 124.8, 122.5, 116.4, 116.3, 112.2, 55.6. IR (thin film): 1584, 1563, 1460 cm^{-1}. Anal. Calcd for $C_{12}H_{10}BrNO$: C, 54.57; H, 3.82; N, 5.30. Found: C, 54.60; H, 3.95; N, 5.36.

4.4.32. 2-(2-Bromo-5-dimethylaminophenyl)pyridine (30-Br). Procedure D was followed utilizing a solution of NBS (1.971 g, 11 mmol, 1 equiv, in 100 mL MeCN) and a solution of substrate **30** (2.180 g, 11 mmol, 1 equiv, in 50 mL MeCN). Product **30-Br** was isolated as a yellow oil (3.005 g, 99% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (ddd, J=5.0, 2.0, 1.0 Hz, 1H), 7.75 (td, J=8.0, 2.0 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.46 (d, J=9.0 Hz, 1H), 7.29 (ddd, J=7.5, 5.0, 1.0 Hz, 1H), 6.86 (d, J=3.0 Hz, 1H), 6.63 (dd, J=9.0, 3.0 Hz, 1H), 2.96 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 149.7, 149.1, 141.1, 135.6, 133.3, 124.7, 122.1, 115.0, 113.9, 107.5, 40.4. Anal. Calcd for $C_{13}H_{13}BrN_2$: C, 56.34; H, 4.73; N, 10.11. Found: C, 56.60; H, 4.78; N, 9.97.

4.4.33. 1-(5-Iodoindolin-1-yl)ethanone (*iso*-31-I). *Procedure with palladium catalyst*: Procedure A was followed, utilizing substrate **31** (100 mg, 0.620 mmol, 1 equiv), NIS (209 mg, 0.930 mmol, 1.5 equiv), $Pd(OAc)_2$ (6.9 mg, 0.031 mmol, 5 mol %), and AcOH (5.2 mL). Product *iso*-**31-I** was isolated as a creamy white solid (154 mg, 86% yield, mp=139.6–140.2 °C, R_f=0.18 in 60% hexanes/40% EtOAc). *Procedure without palladium catalyst*: Procedure A was followed, utilizing substrate **31** (100 mg, 0.620 mmol, 1 equiv), NIS (209 mg, 0.930 mmol, 1.5 equiv), and AcOH (5.2 mL). Product *iso*-**31-I** was isolated as a creamy white solid (154 mg, 86% yield, mp=139.6–140.2 °C, R_f=0.18 in 60% hexanes/40% EtOAc). The products with and without Pd were identical by GC and ^{1}H NMR analysis. ^{1}H NMR (400 MHz, acetone-d_6): δ 7.94 (d, J=8.4 Hz, 1H), 7.52 (s, 1H), 7.47 (d, J=8.4 Hz, 1H), 4.16 (t, J=8.8 Hz, 2H), 3.19 (t, J=8.4 Hz, 2H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 169.4, 144.4, 136.7, 135.9, 134.4, 119.1, 85.9, 49.4, 28.2, 24.2. IR (KBr): 1654, 1475 cm^{-1}. Anal. Calcd for $C_{10}H_{10}INO$: C, 41.83; H, 3.51; N, 4.88. Found: C, 42.00; H, 3.58; N, 4.78.

4.4.34. 3-(4-Iodophenyl)oxazolidin-2-one (*iso*-32-I). Procedure A was followed, utilizing substrate **32** (150 mg, 0.920 mmol, 1 equiv), NIS (248 mg, 1.10 mmol, 1.2 equiv), $Pd(OAc)_2$ (10.3 mg, 0.043 mmol, 5 mol %), and AcOH (7.7 mL). Product *iso*-**32-I** was isolated as a white solid (226 mg, 85% yield, mp=163.6–163.9 °C, R_f=0.25 in 70% hexanes/30% EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J=9 Hz, 2H), 7.46 (d, J=9 Hz, 2H), 4.52–4.48 (m, 2H), 4.14–4.10 (m, 2H). ^{13}C NMR (100 MHz, acetone-d_6): δ 154.8, 139.1, 137.6, 119.9, 85.8, 61.4, 44.3. IR (KBr): 1726, 1416 cm^{-1}. HRMS EI (m/z): [M$^+$] calcd for $C_9H_8INO_2$, 288.9600. Found: 288.9606.

4.4.35. 1-(2-Chlorophenyl)pyrrolidin-2-one (33-Cl). Procedure C was followed, utilizing substrate **33** (209 mg, 1.29 mmol, 1 equiv), NCS (208 mg, 1.55 mmol, 1.2 equiv), $Pd(OAc)_2$ (14.5 mg, 0.064 mmol, 5 mol %), and AcOH (8.4 mL). Product **33-Cl** was isolated as an off-white solid (197 mg, 77% yield, mp=40.9–42.4 °C, R_f=0.30 in 60% hexanes/40% EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.51 (d, J=7.3 Hz, 1H), 7.39–7.32 (multiple peaks, 3H), 3.77 (t, J=6.92 Hz, 2H), 2.43 (t, J=7.2 Hz, 2H), 2.22 (q, J=6.9 Hz, 2H). ^{13}C NMR (100 MHz, acetone-d_6): δ 174.7, 138.2, 132.9, 130.9, 130.8, 129.8, 128.7, 50.5, 31.4, 19.9. IR (KBr): 1698 cm^{-1}. HRMS EI (m/z): [M$^+$] calcd for $C_{10}H_{10}ClNO$, 195.0451. Found: 195.0450.

4.4.36. 1-(4-Chlorophenyl)pyrrolidin-2-one (*iso*-33-Cl). Procedure C was followed, utilizing substrate **33** (203 mg, 1.26 mmol, 1 equiv), NCS (202 mg, 1.51 mmol, 1.5 equiv), and AcOH (8.1 mL). Product *iso*-**33-Cl** was isolated as a white solid (142 mg, 58% yield, mp=95.5–96.6 °C, R_f=0.44 in 60% hexanes/40% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J=9.2 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 3.84 (t, J=7.2 Hz, 2H), 2.62 (t, J=8 Hz, 2H), 2.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 137.9, 129.4, 128.7, 120.8, 48.6, 32.6, 17.8. IR (KBr): 1679 cm^{-1}. HRMS EI (m/z): [M$^+$] calcd for $C_{10}H_{10}ClNO$, 195.0451. Found: 195.0445.

4.4.37. 1-(4-Bromophenyl)pyrrolidin-2-one (*iso*-33-Br). Procedure A was followed, utilizing substrate **33** (150 mg, 0.930 mmol, 1 equiv), NBS (199 mg, 1.12 mmol, 1.2 equiv), $Pd(OAc)_2$ (10.4 mg, 0.046 mmol, 5 mol %), and AcOH (7.7 mL). Product *iso*-**33-Br** was isolated as a white solid (156 mg, 70% yield, R_f=0.30 in 60% hexanes/40% EtOAc). The NMR data were identical to that reported previously for this compound.[41]

4.4.38. 1-(4-Iodophenyl)pyrrolidin-2-one (*iso*-33-I). *Procedure with palladium catalyst*: Procedure A was followed, utilizing substrate **33** (100 mg, 0.620 mmol, 1 equiv), NIS (209 mg, 0.930 mmol, 1.5 equiv), $Pd(OAc)_2$ (6.9 mg, 0.031 mmol, 5 mol %), and AcOH (5.2 mL). Product *iso*-**33-I** was isolated as a light yellow solid (141 mg, 80% yield, mp=140.0–141.6 °C, R_f=0.28 in 60% hexanes/40% EtOAc). *Procedure without palladium catalyst*: Procedure A was followed, utilizing substrate **33** (100 mg, 0.620 mmol, 1 equiv), NIS (209 mg, 0.930 mmol, 1.5 equiv), and AcOH (5.2 mL). Product *iso*-**33-I** was isolated as a light yellow solid (141 mg, 80% yield, mp=140.0–141.6 °C, R_f=0.28 in 60% hexanes/40% EtOAc). The products with and without Pd were identical by GC and ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H), 3.81 (t, J=7.2 Hz, 2H), 2.59 (t, J=8.1 Hz, 2H), 2.19–2.11 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 139.1, 137.7, 121.5, 87.9, 48.4, 32.7, 17.8. IR (KBr): 1684 cm^{-1}. Anal. Calcd for $C_{10}H_{10}INO$: C, 41.83; H, 3.51; N, 4.88. Found: C, 41.82; H, 3.62; N, 4.71.

4.4.39. 1-(2-Chlorophenyl)piperidin-2-one (34-Cl). Procedure C was followed, utilizing substrate **34** (100 mg, 0.571 mmol, 1 equiv), NCS (114 mg, 0.856 mmol, 1.5 equiv), $Pd(OAc)_2$ (6.39 mg, 0.028 mmol, 0.05 mol equiv), and AcOH (8.4 mL). Product **34-Cl** was isolated as an off-white solid (68.0 mg, 57% yield, mp=55.9–56.9 °C, R_f=0.18 in 90% CH_2Cl_2/10% EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (dd, J=7.6, 1.3 Hz, 1H), 7.32 (td, J=7.5, 1.5 Hz, 1H), 7.29–7.25 (multiple peaks, 2H), 3.60 (m, 1H), 3.49 (m, 1H), 2.64–2.52 (multiple peaks, 2H), 2.02–1.93 (multiple peaks, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 140.6, 132.2, 130.4, 129.4, 128.9, 127.9, 50.9, 32.5, 23.4, 21.4. IR (KBr): 2921, 1652 cm^{-1}. HRMS EI (m/z): [M+Na$^+$] calcd for $C_{11}H_{12}ClNO$, 232.0505. Found: 232.0505.

4.4.40. *N*-(2,5-Dichlorophenyl)acetamide (37-Cl). Procedure A was followed, utilizing substrate **37** (150 mg, 0.884 mmol, 1 equiv), NCS (212 mg, 1.59 mmol, 1.8 equiv), $Pd(OAc)_2$ (9.90 mg, 0.044 mmol, 5 mol %), and AcOH (7.4 mL). Product **37-Cl** was isolated as a white solid (126 mg, 70% yield, mp=133.4–133.9 °C, R_f=0.28 in 80% hexanes/20% EtOAc). ^{1}H NMR (400 MHz, acetone-d_6): δ 8.74 (br s, 1H), 8.35 (d, J=2.4 Hz, 1H), 7.44 (d, J=8.4 Hz, 1H), 7.14 (dd, J=8.4, 2.4 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 169.7, 137.6, 133.3, 131.3, 125.3, 123.l, 122.8, 24.3. IR (KBr): 1666 cm^{-1}. HRMS EI (m/z): [M$^+$] calcd for $C_8H_7Cl_2NO$, 202.9905. Found: 202.9896.

4.4.41. *N*-(3,4-Dichlorophenyl)acetamide (*iso*-37-Cl). Procedure A was followed, utilizing substrate **37** (150 mg, 0.884 mmol, 1 equiv), NCS (142 mg, 1.06 mmol,

1.2 equiv), and AcOH (7.4 mL). Product **37-Cl** was isolated as a white solid (77 mg, 43% yield, mp=133.4–133.9 °C, R_f=0.28 in 80% hexanes/20% EtOAc). The NMR data were identical to that reported above for the reaction with palladium. The product *iso*-**37-Cl** was isolated as a white solid (70 mg, 39% yield, mp=121.9–123.3 °C, R_f=0.24 in 60% hexanes/40% EtOAc).^{1}H NMR (400 MHz, acetone-d_6): δ 7.78 (br s, 1H), 7.73 (d, J=1.8 Hz, 1H), 7.35–7.29 (multiple peaks, 2H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 137.3, 132.7, 130.4, 127.5, 121.6, 119.1, 24.5. IR (KBr): 1665 cm^{-1}. HRMS EI (m/z): [M$^+$] calcd for $C_8H_7Cl_2NO$, 202.9905. Found: 202.9904.

Acknowledgements

We thank the NIH NIGMS (RO1–GM073836-01), the University of Michigan, the Camille and Henry Dreyfus Foundation, and the Arnold and Mabel Beckman Foundation for support of this work. Additional unrestricted support from Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, and Merck Research Laboratories is also gratefully acknowledged. Additionally, A.R.D. thanks Eli Lilly for a graduate fellowship, and W.Q.A. is grateful for a Margaret and Henry Sokol undergraduate summer research fellowship. We also thank Kami Hull for valuable assistance with spectral data analysis.

References and notes

1. Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937–1944.
2. Sotomayor, N.; Lete, E. *Curr. Org. Chem.* **2003**, *7*, 275–300.
3. *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Dekker: New York, NY, 1996.
4. Crampton, M. R. *Organic Reaction Mechanisms*; Knipe, A. C., Watts, W. E., Eds.; Wiley: New York, NY, 2003; pp 275–286.
5. Levin, R. H. *Reactive Intermediates*; 1985; Vol. 3, pp 1–18.
6. (a) *Metal Catalyzed Cross Coupling Reactions*; Dieterich, F., Stang, P. J., Eds.; Wiley-VCH: New York, NY, 1998; (b) Prim, D.; Campagne, J.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041–2075; (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364; (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449; (e) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428–2439.
7. (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470; (b) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *102*, 1006–1019; (c) Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley Interscience: New York, NY, 2002; pp 1051–1096; (d) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146; (e) Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley Interscience: New York, NY, 2002; pp 1097–1106.
8. (a) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* **1995**, *27*, 127–160; (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695; (c) *Metal Catalyzed Cross Coupling Reactions*; Dieterich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.
9. (a) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141–1144; (b) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149–4152; (c) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543; (d) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301; (e) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *178*, 4972–4973; (f) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331; (g) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523–2526; (h) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134–7135.
10. (a) Taylor, R. *Electrophilic Aromatic Substitution*; Wiley: New York, NY, 1990; (b) De la Mare, P. B. *Electrophilic Halogenation*; Cambridge University: Cambridge, 1976; Chapter 5; (c) Merkushev, E. B. *Synthesis* **1988**, 923–937.
11. (a) Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* **2005**, 2837–2842 and references therein; (b) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770–15776; (c) Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Lett.* **2003**, *32*, 932–933; (d) Firouzabadi, H.; Iranpoor, N.; Shiri, M. *Tetrahedron Lett.* **2003**, *44*, 8781–8785; (e) Vyas, P. V.; Bhatt, A. K.; Ramachandraiah, G.; Bedekar, A. V. *Tetrahedron Lett.* **2003**, *44*, 4085–4088; (f) Lee, K.; Cho, H. K.; Song, C. *Bull. Korean Chem. Soc.* **2002**, *23*, 773–775; (g) Iskra, J.; Stavber, S.; Zupan, M. *Synthesis* **2004**, *11*, 1869–1873; (h) Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501–4504; (i) Tamhankar, B. V.; Desai, U. V.; Mane, R. B.; Wadgaonkar, P. P.; Bedekar, A. V. *Synth. Commun.* **2001**, *31*, 2021–2027; (j) Roche, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2000**, *41*, 2083–2085; (k) Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Synlett* **2004**, 461–464; (l) Evans, P. A.; Brandt, T. A. *J. Org. Chem.* **1997**, *62*, 5321–5326.
12. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.
13. Shimizu, M.; Toyoda, T.; Baba, T. *Synlett* **2005**, 2516–2518.
14. Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533–1541 and references therein.
15. Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973.
16. (a) van Belzen, R.; Elsevier, C. J.; Dedieu, A.; Veldman, N.; Spek, A. L. *Organometallics* **2003**, *22*, 722–736; (b) Alsters, P. L.; Engel, P. F.; Hogerheide, M. P.; Copijn, M.; Spek, A. L.; van Koten, G. *Organometallics* **1993**, *12*, 1831–1844; (c) Kubota, M.; Boegeman, S. C.; Keil, R. N.; Webb, C. G. *Organometallics* **1989**, *8*, 1616–1620; (d) Bäckvall, J. *Acc. Chem. Res.* **1983**, *16*, 335–342; (e) Bäckvall, J. *Tetrahedron Lett.* **1977**, *18*, 467–468; (f) Wong, P. K.; Stille, J. K. *J. Organomet. Chem.* **1974**, *70*, 121–132; (g) Alsters, P. L.; Boersma, J.; van Koten, G. *Organometallics* **1993**, *12*, 1629–1638; (h) Lagunas, M.-C.; Gossage, R. A.; Spek, A. L.; van Koten, G. *Organometallics* **1998**, *17*, 731–741.
17. (a) Lei, A.; Lu, X.; Liu, G. *Tetrahedron Lett.* **2004**, *45*, 1785–1788; (b) Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618–5621; (c) El-Qisairi, A. K.; Qaseer, H. A.; Katsigras, G.; Lorenzi, P.; Trivedi, U.; Tracz, S.; Hartman, A.; Miller, J. A.; Henry, P. M. *Org. Lett.* **2003**, *5*, 439–441; (d) Zhu, G.; Lu, X. *J. Organomet. Chem.* **1996**, *508*, 83–90.
18. (a) Newkome, G. R.; Puckett, W. E.; Gupta, V. K.; Kiefer, G. E. *Chem. Rev.* **1986**, *86*, 451–489; (b) Ryabov, A. D. *Synthesis* **1985**, 233–252; (c) Dunina, V. V.; Zalevskaya, O. A.; Potapov, V. M. *Russ. Chem. Rev.* **1988**, *57*, 434–473; (d)

Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272–3273.
19. Fahey, D. R. *J. Organomet. Chem.* **1971**, *27*, 283–292.
20. (a) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112–2115; (b) Chen, X.; Hao, X.-S.; GoodHue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791.
21. Togo, H.; Sakuratani, K. *Synlett* **2002**, 1966–1975.
22. For some recent representative examples, see: (a) Balija, A. M.; Stowers, K. J.; Schultz, M. J.; Sigman, M. S. *Org. Lett.* **2006**, *8*, 1121–1124; (b) Gligorich, K. M.; Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2794–2795; (c) Schultz, M. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 1460–1461; (d) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 12996–12997; (e) A reviewer has suggested that the alkene halogenation reactions could proceed by a Wacker-type mechanism rather than by C–H activation/halogenation. This possibility is currently under investigation in our laboratories.
23. Fuller, A. A.; Chen, B.; Minter, A. R. *J. Am. Chem. Soc.* **2005**, *127*, 5376–5383.
24. Voitekhovich, S. V.; Gaponik, P. N.; Koldobskii, G. I. *Russ. J. Org. Chem.* **2005**, *41*, 1565–1582.
25. (a) Chassot, L.; Müller, E.; von Zelewsky, A. *Inorg. Chem.* **1984**, *23*, 4249–4253; (b) Jolliet, P.; Gianini, M.; von Zelewsky, A.; Bernardinelli, G.; Stoeckli-Evans, H. *Inorg. Chem.* **1996**, *35*, 4883–4888.
26. Interestingly, such high selectivity for the functionalization of the more sterically hindered C–H bond was previously observed only with OH as a *meta*-substituent (see Ref. 10a) suggesting that the –OH and –NH functionalities might be playing a role in imparting this selectivity.
27. (a) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579–2581 and references therein; (b) Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **1998**, *62*, 2604–2610.
28. For other examples of the directed C–H activation/functionalization of alkenes, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 5604–5605; (b) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826–834; (c) Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371–5372.
29. (a) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1–120; (b) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137–165.
30. (a) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911–935; (b) Doyle, M. P.; Ren, T. *Prog. Inorg. Chem.* **2001**, *49*, 113–168.
31. Palladium (20 mol %) was required for this substrate to avoid the formation of the uncatalyzed products.
32. Substrates containing unactivated sp^3 substrates did not afford the products of directed halogenation under our standard reaction conditions in the presence of a variety of different halogenating reagents. Ongoing efforts aim to develop methods for the halogenation of this class of substrates.
33. Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028.
34. Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348.
35. Stoyanov, V. M.; El'chaninov, M. M.; Pozharskii, A. F. *Chem. Heterocycl.* **1991**, *27*, 1140–1144.
36. Kaifer, A.; Gustowski, D. A.; Echegoyen, L.; Gatto, V. J.; Schultz, R. A.; Cleary, T. P.; Morgan, C. R.; Goli, D. M.; Rios, A. M.; Gokel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 1958–1965.
37. Newkome, G. R.; Theriot, K. J.; Cheskin, B. K.; Evans, D. W.; Baker, G. R. *Organometallics* **1990**, *9*, 1375–1379.
38. Guanti, G.; Narisano, E.; Riva, R. *Tetrahedron: Asymmetry* **1997**, *8*, 2175–2187.
39. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043–6048.
40. O' Murchu, C. *Synthesis* **1989**, *11*, 880–882.
41. Lucas-Lopez, C.; Patterson, S.; Blum, T.; Straight, A. F.; Toth, J.; Slawin, A. M. Z.; Mitchison, T. J.; Sellers, J. R.; Westwood, N. J. *Eur. J. Org. Chem.* **2005**, 1736–1740.