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C–H Activation

N-Heterocyclic Carbene Ligand-Enabled C(sp^3)–H Arylation of Piperidine and Tetrahydropyran Derivatives

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Abstract: Pd^{II}-catalyzed C(sp^3)–H arylation of saturated heterocycles with a wide range of aryl iodides is enabled by an N-heterocyclic carbene (NHC) ligand. A C(sp^3)–H insertion step by the Pd^{II}/NHC complex in the absence of ArI is demonstrated experimentally for the first time. Experimental data suggests that the previously established NHC-mediated Pd^0/Pd^{II} catalytic manifold does not operate in this reaction. This transformation provides a new approach for diversifying pharmaceutically relevant piperidine and tetrahydropyran ring systems.

In the past decade, a wide range of Pd^{II}-catalyzed β-C–H functionalizations of aliphatic acids have been developed by using directed C–H activation.[1] Our early studies demonstrated excellent stereocontrol in β-C–H functionalizations by using a chiral oxazoline as the auxiliary.[2] The use of aminoquinoline bidentate directing groups proved to be exceptionally effective for methylene C–H arylation.[3] Towards the ultimate goal of achieving simple and practical β-C–H functionalization reactions, we have developed a number of weakly coordinating directing groups.[4] Although these directing groups are highly efficient for the activation of C(sp^2)–H[4a,c] and primary C(sp^3)–H[4a,b] bonds, poor reactivity in methylene C–H activation has been observed.

Recently, the discovery of a series of pyridine and quinoline ligands has enabled methylene C–H activation using these simple weakly coordinating directing groups.[5] However, the scope and efficiency of this ligand scaffold remain limited. Herein we demonstrate that N-heterocyclic carbenes, as another class of σ-donor ligands,[6] can promote Pd^{II}-catalyzed methylene C–H arylation, thus offering another opportunity for ligand development. Notably, this protocol is compatible with medicinally important piperidines and tetrahydropyrans that are unreactive when using the quinoline ligands.

Piperidine and tetrahydropyran motifs are widespread among drug molecules.[7] An analysis of all launched drugs within the Integrity database shows approximately 320 registered drugs containing saturated piperidines and approximately 130 containing saturated tetrahydropyrans (THPs).[8] When one eliminates natural product-based drugs from the analysis (where the piperidine moiety is derived from biosynthetic processes and carbohydrate-based THP derivatives) the remaining approximately 260 piperidines are mostly derived from simple commodity chemicals: unsubstituted piperidine itself and all regioisomers of piperidone and piperidine carboxylic acids. A similar conclusion can be drawn for the approximately 10 non-carbohydrate derived THP-based drugs.[8] We envisage that directed C–H arylation of readily available piperidine or tetrahydropyran building blocks with a wide range of aryl iodides could rapidly expand the diversity of these molecules. Despite significant progress in sp^3 C–H arylation, arylation of piperidines and tetrahydropyrans at the C3 and C4 positions remains a significant challenge.[9–13] Our recent finding that pyridine- and quinoline-type monodentate σ-donor ligands can significantly accelerate sp^3 C–H functionalization of amide substrates[5] prompted us to investigate whether the readily available NHC ligands could be harnessed to promote C–H arylation through Pd^{II}/Pd^{IV} catalysis. Although a Pd^0/NHC-catalyzed intramolecular enantioselective C(sp^3)–H arylation through Pd^0/Pd^{II} redox has been demonstrated in pioneering studies,[14,15] the feasibility of NHC ligands to promote intermolecular C(sp^3)–H arylation remains to be demonstrated.[16] Thus, the development of NHC-promoted C(sp^3)–H arylation reactions of piperidines and tetrahydropyrans is of fundamental importance to catalysis, in addition to being useful in medicinal chemistry.

Our recent success in developing a number of Pd^{II}-catalyzed C–H arylations of amides enabled by mono-dentate σ-donor ligands led us to focus on the use of Pd^{II} catalysts. Guided by the need for diverse piperidines in medicinal chemistry, we began to develop β-arylation of amide **1a** derived from 2-piperidinecarboxylic acid (Table 1). We found that the reaction of 0.1 mmol of amide **1a** with 2.0 equivalents of aryl iodide **2a** in the presence of 10 mol% of $Pd(TFA)_2$, 20 mol% of commercially available NHC ligand **L1**, and 3.0 equivalents of AgOAc (in 0.5 mL of hexafluorobenzene at 100 °C under air for 24 h) gave exclusively the *cis* diastereoisomer of the desired product in 53% yield (Table 1). In the absence of ligand, only a trace amount of product was detected, thus confirming the signifi-

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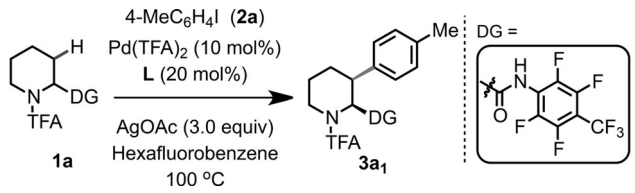
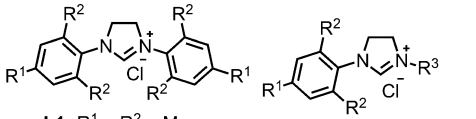
Table 1. Ligand screening.[a,b,c]

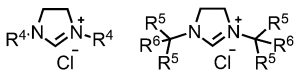


Entry	Ligand	Yield of **3a**$_1$ [%]	Entry	Ligand	Yield of **3a**$_1$ [%]
1	no ligand	<5	9	**L8**	64
2	**L1**	53	10	**L9**	trace
3	**L2**	66	11	**L10**	12
4	**L3**	70	12	**L11**	42
5	**L4**	98	13	**L12**	6
6	**L5**	72	14	**L13**	84
7	**L6**	96	15	**L14**	88
8	**L7**	97			



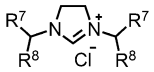
L1: $R^1 = R^2 = Me$
L2: $R^1 = H$, $R^2 = i$Pr

L3: $R^1 = R^2 = Me$, $R^3 = Ad$

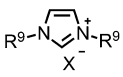


L4: $R^4 = Ad$
L7: $R^4 = t$Bu

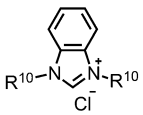
L5: $R^5 = R^6 = n$Pr
L6: $R^5 = Me$, $R^6 = t$Bu



L8: $R^7 = o$-Tol, $R^8 = t$Bu



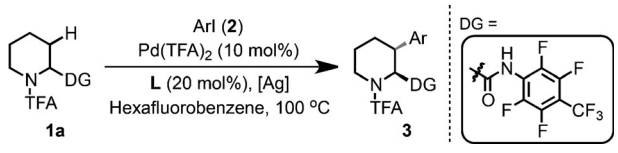
L9: $R^9 = i$Pr, X = Cl
L10: R^9 = Cy, X = Cl
L11: $R^9 = t$Bu, X = Cl
L12: $R^9 = t$Bu, $X = BF_4$
L13: R^9 = Ad, X = Cl

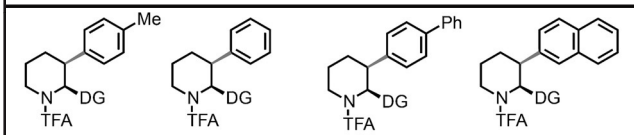


L14: R^{10} = Ad

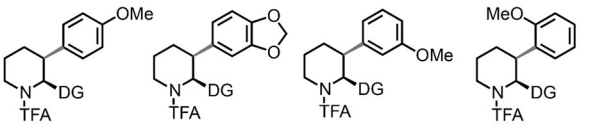
[a] Conditions: **1a** (0.1 mmol), **2a** (2.0 equiv), $Pd(TFA)_2$ (10 mol%), ligand (20 mol%), AgOAc (3.0 equiv), hexafluorobenzene (0.5 mL), 100 °C, under air, 24 h; [b] yields determined by ^{1}H NMR analysis of the crude product with CH_2Br_2 as an internal standard; [c] single *cis*-diastereoisomer was obtained.

Table 2. C(sp^3)–H Arylation.[a,b,c]

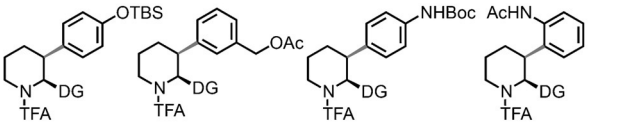




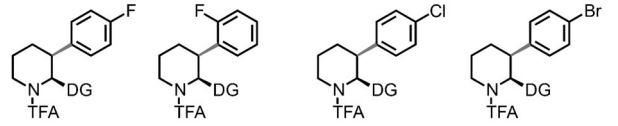
3a$_1$, 98%[a] **3a$_2$**, 92%[a] **3a$_3$**, 90%[a] **3a$_4$**, 91%[a]



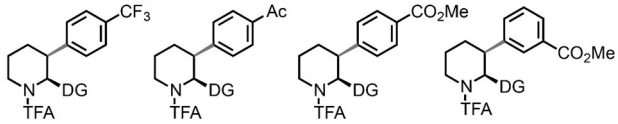
3a$_5$, 98%[a] **3a$_6$**, 88%[a] **3a$_7$**, 92%[d] **3a$_8$**, 83%[d]



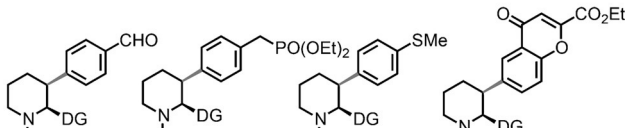
3a$_9$, 90%[d] **3a$_{10}$**, 82%[d] **3a$_{11}$**, 94%[d] **3a$_{12}$**, 70%[d]



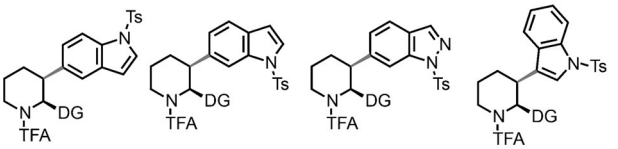
3a$_{13}$, 89%[d] **3a$_{14}$**, 40%[d] **3a$_{15}$**, 84%[d] **3a$_{16}$**, 83%[d]



3a$_{17}$, 79%[d] **3a$_{18}$**, 63%[d] **3a$_{19}$**, 77%[d] **3a$_{20}$**, 93%[d]



3a$_{21}$, 53%[d] **3a$_{22}$**, 73%[d] **3a$_{23}$**, 48%[d] **3a$_{24}$**, 58%[d]



3a$_{25}$, 54%[d] **3a$_{26}$**, 60%[d] **3a$_{27}$**, 48%[d] **3a$_{28}$**, 57%[d]

[a] Conditions (unless otherwise stated): **1a** (0.1 mmol), **2** (2.0 equiv), $Pd(TFA)_2$ (10 mol%), **L4** (20 mol%), AgOAc (3.0 equiv), hexafluorobenzene (0.5 mL), 100 °C, under air, 24 h; [b] yields of isolated product; [c] single *cis*-diastereoisomer was obtained; [d] **2** (3.0 equiv), **L7** (20 mol%), and Ag_2CO_3 (2.0 equiv) were used.

cant impact of NHC ligands on the β-C(sp^3)–H arylation reaction of piperidine amide **1a**. We next performed a systematic screening of 4,5-dihydroimidazolium ligands under these standard conditions. Increasing the steric hindrance on the *N*-aryl ring improved the yield to 66% (**L2**). Replacement of the *N*-aryl group with sterically bulky alkyl groups consistently improved the reaction and afforded excellent yields (**L4**, **L6** and **L7**). The significantly lower yield obtained with **L8** suggests that the tertiary carbon attached to the nitrogen is required. We also examined imidazolium ligands with similar steric environments. The results with **L9**–**L14** showed that imidazolium ligands are inferior to 4,5-dihydroimidazolium ligands for this reaction.

With these optimized reaction conditions in hand, we examined the scope of aryl iodides (Table 2). Arylation of **1a** with a few simple aryl iodides and ligand **L4** gave the expected products **3a**$_{1-4}$ in excellent yields. *Para*-methoxylphenyl iodide and 3,4-methylenedioxyiodobenzene were also effective coupling partners, affording **3a**$_5$ and **3a**$_6$ in 98 and 88% yield, respectively. However, other aryl iodides, especially the *ortho*, or *meta*-substituted aryl iodides, gave moderate yields (ca. 40%) under these initially optimized conditions. We were pleased to

find that the use of the less hindered ligand **L7** significantly improved the yields in these cases (**3a**$_7$, **3a**$_8$). Aryl iodides with different protecting groups [tributylsilyl (TBS), Ac, *tert*-butoxycarbonyl (Boc)] are also compatible with this arylation reaction, using ligand **L7** (**3a**$_{9-12}$). Notably, aryl iodides containing *ortho*-OMe (**3a**$_8$), and *ortho*-NHAc (**3a**$_{12}$) are especially challenging coupling partners in previous studies.[3,4] These results indicate that a better match between substrates and ligands can be achieved by tuning the ligand structures. *Para*-fluoro-, chloro-, and bromophenyliodides were effective coupling partners (**3a**$_{13}$, **3a**$_{15}$, **3a**$_{16}$), whereas *ortho*-fluorophenyl iodide gave the desired product **3a**$_{14}$ in 40% yield. Other strongly electron-withdrawing groups such as CF_3, Ac, COOMe, and CHO were also tolerated (**3a**$_{17-21}$).

Importantly, functionalities such as bromo and CHO are uniquely compatible with these conditions and are more efficiently installed by using this methodology in comparison to more traditional routes that rely on pyridine saturation to generate the piperidine cores. Aryl iodides containing potentially coordinating groups, such as phosphate and thioether, also gave synthetically useful yields (**3a**$_{22}$, **3a**$_{23}$). A limited number of heteroaryl iodides were also successfully coupled with **1a** (**3a**$_{24-28}$) to give heterocycles that are potentially medicinally important.

However, the strongly coordinating pyridinyl, quinolinyl, and pyrazolyl iodides were not compatible with these conditions.

Having established the scope of aryl iodides, we subjected 3- and 4-piperidinecarboxamides **1b** and **1c** to the standard arylation conditions (Table 3). The reactions of these substrates were slower and homocoupling of aryl iodides was observed. Hence, 3 equivalents of aryl iodide was used to improve the yield. The arylated products were obtained in 66 and 57% yields respectively as mixtures of *cis* and *trans* isomers (**3b**, **3c**). Although the directed C–H activation typically favors the *cis*-C–H bond, the *trans*-axial C–H bond in cyclohexane is known be equally reactive due to the conformation.[3] The exclusive regioselectivity observed in **3b** appears to indicate that Pd insertion into the

C–H bonds adjacent to the nitrogen atoms is less favored, which could be due to the known α-effect as the carbon center will be negatively charged during the C–H cleavage step. The use of 2,2,2-trichloroethyl carbonate (Troc) instead of the trifluoroacetyl protecting group did not affect the yield significantly (**3d**). Interestingly, 2-methyl-3-piperidinecarboxamide gave the arylated *trans* isomer **3e** selectively in higher yield. The high *trans* selectivity can be explained by the 1,3-interaction that significantly increases the steric hindrance if the Pd were to insert into the *cis*-axial C–H bond (Figure 1). Arylation of 2-pyrrolidinecarboxamide gave the *cis* isomer **3f** selectively,

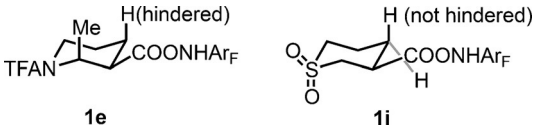
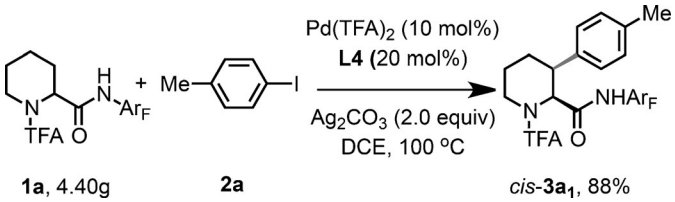


Figure 1. Possible explanation for diastereoselectivity.

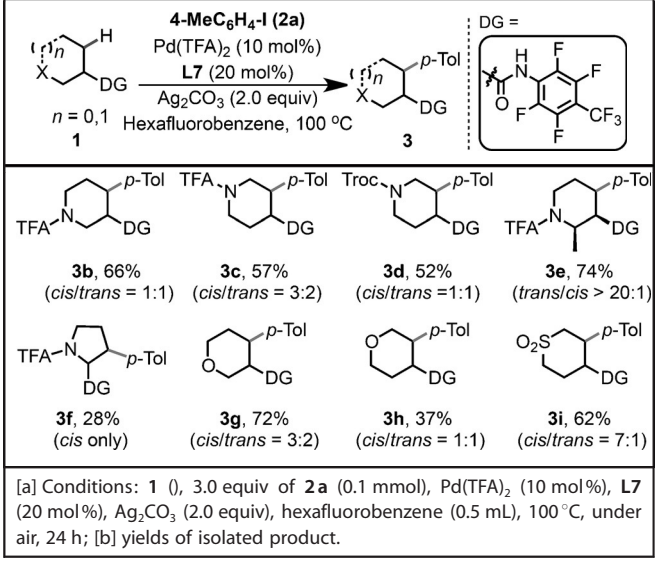
albeit in low yield. This arylation protocol was also extended to the functionalization of tetrahydropyrans. In this case, although arylation of 3-tetrahydropyrancarboxamide **2g** afforded a mixture of the *cis* and *trans* products in 72% yield, 4-tetrahydropyrancarboxamide **2h** was not as reactive, affording the product **3h** in low yield. The lower reactivity of **2h** was most likely due to bidentate coordination from the directing group and the 4-oxygen atom, which was not possible in **2g** due to geometric constraints. Interestingly, arylation of 1,1-dioxohexahydrothiopyran-4-carboxamide **1i** also proceeded to give the desired product **3i** in 62% yield, with the *cis* isomer being the major product. The preference for inserting at the *cis*-axial C–H bonds indicates a strong impact of the large sulfonyl group on the conformation of the six-membered ring (Figure 1).

To demonstrate the scalability of this β-C(sp3)–H arylation reaction, we performed the arylation with 4.4 g of **1a** to form **3a**$_1$ in 84% yield (Scheme 1). Since this reaction is compatible with a wide range of solvents including dichloroethane (DCE), toluene, EtOAc (see the Supporting Information), we chose DCE to perform the gram-scale reaction. Two different protocols were also developed to convert the amide into ester and thioester, respectively, in one-pot reactions (Scheme 2). Treatment with lithium hexamethyl disilazide (LiHMDS) during the

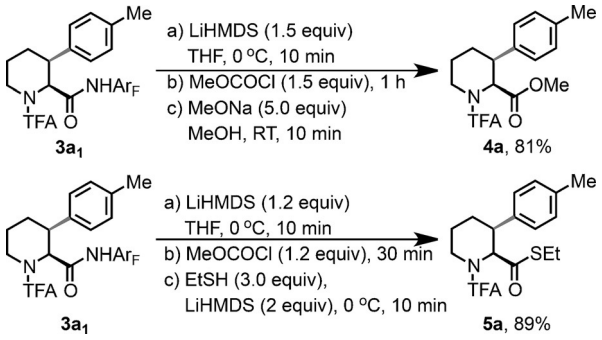


Scheme 1. Gram-scale synthesis.

Table 3. C(sp^3)–H Arylation.[a,b]



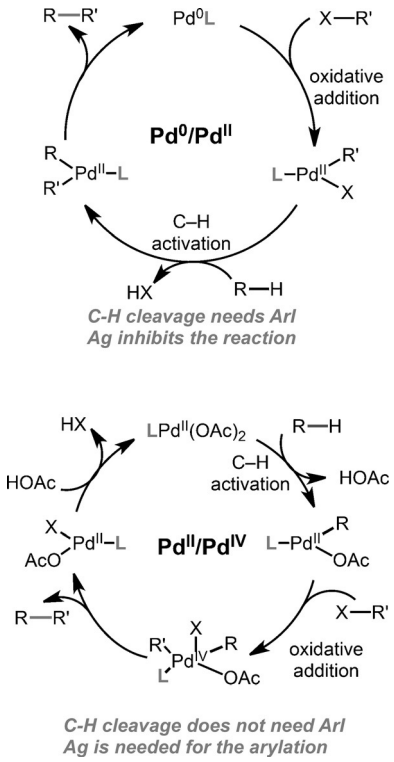
[a] Conditions: **1** (), 3.0 equiv of **2a** (0.1 mmol), $Pd(TFA)_2$ (10 mol%), **L7** (20 mol%), Ag_2CO_3 (2.0 equiv), hexafluorobenzene (0.5 mL), 100 °C, under air, 24 h; [b] yields of isolated product.



Scheme 2. Deprotection of **3a**$_1$.

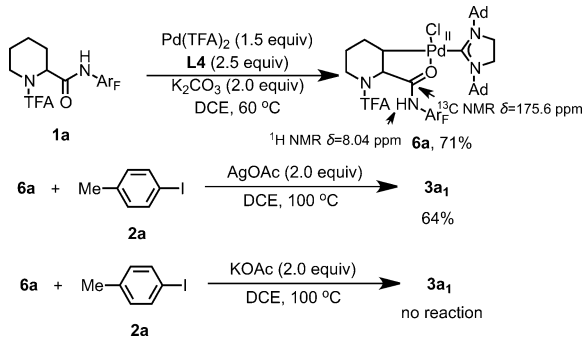
deprotection was carried out for no longer than 10 min to ensure that no epimerization would occur under these conditions.

Although NHC ligands have been employed to promote C–H arylation and alkynylation through Pd^0/Pd^{II} catalysis,[14–16] a number of experimental observations have provided strong evidence against the involvement of oxidative addition of ArI with Pd^0/NHC complex in this case. Although whether the reaction of the C–H insertion intermediate with ArI involves Pd^{IV} has not been fully established in previous studies and is not the subject of this study, we have experimentally shown that the Pd^{II}/NHC complex cleaves the C(sp^3)–H bond in the absence of ArI and the intermediate reacts with ArI subsequently to give the arylated product. Based on these experiments, a Pd^{II}/Pd^{IV} catalytic cycle (Scheme 3) is proposed, as discussed below.



Scheme 3. Comparison of Pd^0/Pd^{II} (top) and Pd^{II}/Pd^{IV} (bottom) catalytic cycles.

Firstly, Ag^I salts are incompatible with Pd^0/Pd^{II} catalysis, as Pd^0 would be oxidized by Ag^I prior to the oxidative addition with ArI in the absence of an efficient phosphine ligand.[14–16] Secondly, we have performed a stepwise stoichiometric arylation reaction of **1a**, which demonstrates that the Pd^{II}/NHC complex inserts into C–H in the absence of ArI to form the alkyl–Pd^{II} intermediate. Although we have not been able to obtain the X-ray structure of the intermediate **6a**, ^{1}H NMR,^{13}C NMR, and mass spectra provided definitive evidence for carbon–Pd bond formation (Scheme 4). Since one of



Scheme 4. Mechanistic investigations.

the most notable differences between Pd^0/Pd^{II} and Pd^{II}/Pd^{IV} catalysis is the order of the C–H insertion step and the reaction with ArI (Scheme 3), the observed C–H insertion in the absence of ArI is consistent with the Pd^{II}/Pd^{IV} pathway. While direct evidence for the involvement of Pd^{II}/Pd^{IV} redox chemistry in C–H arylation reactions is generally lacking in the literature,[18] the Vicente group recently reported the synthesis of a rare Pd^{IV} complex through the stoichiometric reaction of an alkylpalladium(II) species with 2-iodobenzoic acid,[19] supporting the formation of Pd^{IV} by reaction of **6a** with aryl iodide (Scheme 4). Thirdly, a stoichiometric amount of AgOAc is essential for the second step to proceed, in accordance with the previous observation in Pd^{IV} chemistry.[18] Although it is possible that the role of the Ag^I salt might be to abstract the Cl anion from the intermediate **6a**, the lack of reactivity with the preformed complex of Pd^{II} with ligand **L12** bearing BF_4 in the absence of AgOAc suggests that Ag^I is required for the oxidation of Pd^{II} to Pd^{IV} by ArI, as previously documented.[18] Finally, considering that ArBr was used by Kündig and co-workers as the coupling partner in Pd^0/NHC-catalyzed C–H arylation,[14] the lack of reactivity with ArBr in this reaction is also inconsistent with a Pd^0/Pd^{II} catalytic cycle.

In summary, NHC ligands have been found to promote β-C(sp^3)–H insertion by Pd^{II} catalysts for the first time. Experimental data are consistent with a Pd^{II}/NHC complex insertion into C(sp^3)–H bonds followed by subsequent reaction with ArI, which is distinct from the Pd^0/NHC/ArI catalysis. Both C3 and C4 C–H arylation of piperidines and tetrahydropyrans were enabled by NHC ligands. Further optimization of the ligand structure to broaden the scope of heterocycles is underway in our laboratory.

Acknowledgements

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Keywords: arylation · C–H activation · heterocycles · N-heterocyclic carbenes · palladium

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