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NHC-Pd(II) Catalyzed Methylene C(sp³)-H Arylation of Piperidines and Tetrahydropyrans

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Abstract

Pd(II)-catalyzed C(sp³)-H arylation of saturated heterocycles with a wide range of aryl iodides has been achieved using a *N*-heterocyclic carbene (NHC) ligand, thus demonstrating the compatibility of carbene ligands in a Pd(II)/Pd(IV) catalytic manifold. This arylation method provides a new approach towards further diversifying pharmaceutically relevant piperidine and tetrahydropyran ring systems.

In the past decade, a wide range of Pd(II)-catalyzed β -C-H functionalization reactions of aliphatic acids have been developed using directed C-H activation.¹ Our early studies demonstrated excellent stereocontrol in β -C-H functionalizations using a chiral oxazoline as the auxiliary.² The use of amino-quinoline bisdentate directing groups has proven 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 While these directing groups are highly efficient for the activation of C(sp²)-H^{4a,c,e,f} and primary C(sp³)-H^{4b,4d} 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

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

simple weakly coordinating directing groups.⁵ Herein we demonstrate that *N*-heterocyclic carbenes, as another class of σ -donor ligands,⁶ can promote Pd(II)-catalyzed methylene C–H arylation. Notably, this protocol is compatible with medicinally important piperidines and tetrahydropyrans.

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 (THP's). When one eliminates natural product-based drugs from the analysis (where the piperidine moiety derives from biosynthetic processes and carbohydrate based THP derivatives) the remaining ~260 piperidines are mostly derived from simple commodity chemicals: un-substituted piperidine itself and all regioisomers of piperidone and piperidine carboxylic acids.⁸ 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 wide range of aryl iodides could rapidly expand the diversity of these molecules. Despite the significant progress in sp^3 C–H arylation, arylation of piperidines and tetrahydropyrans at the C-3 and C-4 remains a significant challenge.^{9–13}

Our recent finding that pyridine and quinoline ligand type mono-dentate σ -donor ligands can significantly accelerate sp^3 C–H functionalization of amide substrates⁵ prompted us to investigate whether the readily available NHC ligands could be harnessed to promote C–H arylation via Pd(II)/Pd(IV) catalysis. Although a Pd(0)/NHC-catalyzed intramolecular enantioselective C(sp^3)–H arylation via 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 a NHC-promoted C(sp^3)–H arylation reaction 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 reacting 0.1 mmol of amide **1a** with 2.0 equiv 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 equiv 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 trace amount of product was detected, thus confirming the significant impact of NHC-ligands on the β -C(sp^3)–H arylation reaction of piperidine amide **1a**. The beneficial effects of Ag(I) salts is also inconsistent with a Pd(0)/Pd(II) redox chemistry, but is consistent with a Pd(II)/Pd(IV) catalytic cycle.^{3,4} We next performed a systematic screen of 4,5-dihydroimidazolium ligands using these standard conditions. Increasing the steric hindrance on the *N*-aryl ring improved the yield to 66% (**L2**). Replacement of the *N*-aryl with sterically bulky alkyl groups consistently improves the reaction and affords excellent yields with **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

environment. The results with **L9–L14** show 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 using **L4** gave the expected products in excellent yields (**3a1–4**). Para-methoxyphenyl iodide and 3,4-methylenedioxyiodobenzene are also effective coupling partners affording **3a5** and **3a6** in 98 and 88% yield respectively. However, other aryl iodides, especially the ortho, or meta-substituted aryl iodides (**3a7, 3a8**), gave moderate yields (~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 (**3a7, 3a8**). Aryl-iodides with different protecting groups (TBS, Ac, Boc) are also compatible with this arylation reaction using ligand **L7** (**3a9–12**). Notably, aryl iodides containing *ortho*-OMe (**3a8**), and *ortho*-NHAc (**3a12**) are especially challenging coupling partners in previous studies.^{3,4} These results indicate a better match between substrates and ligands can be achieved by tuning the ligand structures. Para-fluoro-, chloro- and bromo-phenyliodides are effective coupling partners (**3a13, 3a15, 3a16**) while ortho-fluoro-phenyl iodide gave the desired product **3a14** in 40% yield. Other strongly electron-withdrawing groups CF₃, -Ac, -COOMe, and -CHO are also tolerated (**3a17–21**). Bromo, COOMe and CHO are highly useful functional groups for synthetic elaborations. Aryl iodides containing potentially coordinating groups such as phosphate and thioether also afforded synthetically useful yields (**3a22, 3a23**). A limited number of heteroaryl iodides are also successfully coupled with **1a** (**3a24–28**) to give heterocycles that are potentially medically important. However, the strongly coordinating pyridinyl, quinolinyl and pyrazolyl iodides are not compatible with current 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 arylated products were obtained in 66 and 57% yields respectively as mixtures of *cis* and *trans* isomers (**3b, 3c**). The exclusive regioselectivity observed in **3b** appears to indicate that Pd insertion into 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 Troc instead of 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, albeit in low yield. This arylation protocol is also extended to the functionalization of tetrahydropyrans. While, arylation of 3-tetrahydropyrancarboxamide **2g** afforded a mixture of the *cis* and *trans* products in 72% yield, 4-tetrahydropyrancarboxamide **2h** is not as reactive affording the products in low yield (**3h**). The lower reactivity of **2h** is most likely due to bidentate coordination from the directing group and the 4-oxygen atom which is not possible in **2g** due to geometric constraints. Interestingly, arylation of 1,1-dioxohexahydrothiopyran-4-carboxamide **1i** also proceeded to give the desired product in 62% yield, with the *cis* isomer being the major product (**3i**). The preference for inserting in

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 robustness of this β -C(sp³)–H arylation reaction, we performed the arylation of **1a** on gram scale to form **3a₁** in 84% yield (Scheme 1). Since this reaction is compatible with a wide range of solvents including DCE (ClCH₂CH₂Cl), toluene, EtOAc (see SI), we chose the less expensive solvent DCE to perform the gram scale reaction. Two different protocols are also developed to convert the amide into ester and thioester respectively in one-pot (Scheme 2).

In summary, NHC ligands were found to promote arylation of β -C(sp³)–H bonds of saturated heterocycles via Pd(II)/Pd(IV) catalysis. Both C-3 and C-4 C–H arylation of piperidines and tetrahydropyrans are enabled by NHC ligands. Further optimization of the ligand structure to broaden the scope of heterocycles is under way in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Examples of synthetic piperidine and tetrahydropyran drugs

Figure 2.
Possible Explanation for Diastereoselectivity

Scheme 1.
Gram-Scale Synthesis

Scheme 2.
Deprotection

Table 1

Ligand Screening^{a,b,c},

Entry	Ligand	Yield (%) 3a₁	Entry	Ligand	Yield (%) 3a₁
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: R¹ = R² = Me
L2: R¹ = H, R² = ⁱPr
L3: R¹ = R² = Me, R³ = Ad
L4: R⁴ = Ad
L5: R⁵ = R⁶ = ⁿPr
L6: R⁵ = Me, R⁶ = ⁱBu
L7: R⁴ = ⁱBu
L8: R⁷ = *o*-Tol, R⁸ = ⁱBu
L9: R⁹ = ⁱPr, X = Cl
L10: R⁹ = Cy, X = Cl
L11: R⁹ = ⁱBu, X = Cl
L12: R⁹ = ⁱBu, X = BF₄⁻
L13: R⁹ = Ad, X = Cl
L14: R¹⁰ = Ad

^a Conditions: 0.1 mmol of **1a**, 2.0 equiv of **2a**, 10 mol% of Pd(TFA)₂, 20 mol% of ligand, 3.0 equiv of AgOAc, 0.5 mL of hexafluorobenzene, 100 °C, under air, 24 h.

^b The yield was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as an internal standard.

^c Single *cis*-diastereoisomer was obtained.

Table 2

C(sp³)-H Arylation^{a,b,c}

^a Conditions: 0.1 mmol of 1a, 2.0 equiv of 2, 10 mol% of Pd(TFA)₂, 20 mol% of L4, 3.0 equiv of AgOAc, 0.5 mL of hexafluorobenzene, 100 °C, under air, 24 h.

^b Isolated yields.

^c Single *cis*-diastereoisomer was obtained.

^d 3.0 equiv of 2 was used, L7 was used, 2.0 equiv of Ag₂CO₃ was used.

Table 3

C(sp³)-H Arylation^{a,b}

^a Conditions: 0.1 mmol of **1**, 3.0 equiv of **2a**, 10 mol% of Pd(TFA)₂, 20 mol% of **L7**, 2.0 equiv of Ag₂CO₃, 0.5 mL of hexafluorobenzene, 100 °C, under air, 24 h.

^b Isolated yields.