Tuning Reactivity in Pd-catalysed C(sp\(^3\))-H Arylations via Directing Group Modifications and Solvent Selection

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Abstract: The palladium-catalysed \(sp^3\) C–H arylation of a selection of saturated amine scaffolds was investigated using substituted picolinamide directing groups. On the bornylamine scaffold, highly selective monoarylation takes place using unsubstituted picolinamide or 3-methylpicolinamide, whereas a double C–H arylation occurs with other substituents present, becoming a significant product with 3-trifluoromethylpicolinamide. DFT calculations were used to help rationalise the effect of directing groups on the C–H palladation steps which were found experimentally to be irreversible. The substituted picolinamide directing groups were also examined on acyclic amine scaffolds and in many cases increased yields and selectivity could be obtained using methylpicolinamides. For a selection of other amine scaffolds, the yield of C–H arylation could be improved significantly using 3-methylpicolinamide as the directing group and/or 3-methylpentan-3-ol as the solvent.

Keywords: Palladium; C–H Activation; Density Functional Calculations; Regioselectivity; Arylation

Introduction

Palladium-mediated C–H functionalisation reactions provide a powerful approach for selective transformation of individual C–H bonds on \(sp^3\)-rich scaffolds.\(^{[1]}\) Given the increasing importance of these compounds in medicinal chemistry,\(^{[2]}\) the ability to selectively introduce novel functionality at particular locations in the molecular framework could provide a highly useful tool in drug development. Building upon pioneering work on the use of stoichiometric quantities of palladium(II) salts to mediate selective reactions of C–H bonds in \(sp^3\)-rich scaffolds\(^{[3]}\) catalytic reactions employing a directing group to coordinate to the palladium(II) catalyst to control the site of reaction have proved to be especially effective.\(^{[4–5]}\) In most cases, the directing group incorporates one or more heteroatoms which can act as ligands for the palladium and deliver it to an adjacent C–H bond. Nitrogen-rich scaffolds are of particular importance in a wide range of chemistry-related fields, so nitrogen-linked directing groups have been the focus of considerable attention.\(^{[5]}\) In 2005 Daugulis introduced the 8-aminoquinoline and picolinamide directing groups,\(^{[5a]}\) and since then a number of nitrogen-linked directing groups for C–H activation have been reported (Figure 1).\(^{[5]}\) Typically, these directing groups deliver the palladium catalyst to a nearby C–H bond via the formation of a 5- or 6-membered palladacycle, though transannular functionalisation reactions have been observed in some cases.\(^{[5a]}\)

Two major drawbacks of many of these reactions are the requirement for excess silver salt in the C–H activation reaction, as well as difficulty in removing the directing group from the product molecule to recover a free amine for use in further synthetic
Manipulation. In recent work we have shown that selective monoarylation of bicyclic amine scaffolds can be achieved efficiently under silver-free conditions using the 2-picolinamide directing group. The picolinamide group can readily be removed under mild reductive conditions using Zn/HCl. We envisaged (Figure 2) that by manipulating the electronic and steric properties of the picolinamide directing group, it should be possible to enhance the efficiency and selectivity of Pd-catalysed C–H functionalisation reactions, as well as potentially enabling C–H functionalisation at different reaction sites within a molecule.

Results and Discussion

We elected to study three different scaffolds which each contain two chemically distinct C–H bonds capable of undergoing C–H activation to yield a 5-membered palladacycle (Figure 2). A wide range of picolinic acids are available commercially and we selected seven examples bearing both electron-donating (Me, MeO) and electron-withdrawing (CF₃) substituents at a variety of positions around the ring, alongside the unsubstituted picolinic acid as a benchmark.

In the case of the bornylamine scaffold, despite the proximity of the methyl C–H bond to the directing group, we had not observed C–H activation taking place at that site during our original study with an unsubstituted picolinamide directing group. Interestingly, in our evaluation of the substituted picolinic acid directing groups, it rapidly became apparent that the substituent on the directing group exerts a significant effect on the reactivity of the methyl group (Table 1). As reported previously, the unsubstituted picolinamide 1a gives an excellent yield of monoarylated product 2a under our optimised reaction conditions, with no trace of methyl C–H activation. The 3-methylpicolinamide 1b also gives the monoarylated product 2b with complete selectivity and with the highest yield. Interestingly, upon changing the position of the methyl substituent to the 4 or 5 positions on the pyridine ring (1c–1d), a novel diarylated compound (3e–3d) was observed as a minor product, perhaps suggesting that the conformational or electronic effects of the substituent are able to facilitate C–H activation on the methyl group, although the C–H activation still evidently occurs preferentially at the CH₃ in both substrates. Introduction of an electron withdrawing CF₃ group at the 3-position (1e) increased the quantity of diarylated product formed, giving almost equal amounts of monoarylated product 2e and diarylated product 3e. The 5-CF₃ derivative 1f gave the lowest overall conversion, with a mixture of monoarylated 2f and diarylated 3f products being generated. The 4- and 5-methoxypicolinamides 1g and 1h gave similar overall yields of product, with small quantities of diarylated product in both cases. As a general rule, high overall yields were obtained with all of the picolinamides bearing the moderately electron-donating methyl group, with the 3-methylpicolinamide giving the highest yield of monoarylated product 2b with no observable formation of the corresponding diarylated compound 3b. The 2,5-difluoromethylpicolinamide 1e provided the largest quantity of diarylated product 3e as well as giving a high overall product yield.

Control experiments (Scheme 1) demonstrated that the C–H insertion step for the initial methylene arylation reaction was not reversible as no deuterium exchange was observed at the methylene unit to give d₂-1a upon heating 1a in the presence of Pd(OAc)₂ and CsOAc in deuterated tert-butanol. Furthermore, the palladated complex 1a-Pd (L=CD₃CN) generated from 1a and Pd(OAc)₂/CsOAc in acetonitrile did not undergo deuteriation upon treatment with either deuterated tert-butanol or deuterated acetic acid. In addition we observed that the monoarylated product 2e...
was not converted into the diarylated product 3e upon resubmission to the reaction conditions. This suggests that the selectivity in the Pd-catalysed C–H arylation is under kinetic control, and hence determined by the energy barriers of the C–H insertion steps. The diarylation product must be formed via two sequential C–H arylation processes without dissociation of the palladium catalyst, as dissociation of the palladium from the monoarylated product 2e seems to be irreversible.

On changing the coupling partner from an aryl iodide to an aryl bromide,[11] the formation of the diarylated product was no longer observed (Scheme 2). Electron withdrawing directing groups gave lower overall yields of the arylation products (2e and 2f) and higher yields were seen with the unsubstituted picolinamide and substrates bearing electron donating groups (2a–2c and 2h). This monoarylation reaction almost certainly provides a better reflection of the inherent reactivity of each directing group in terms of facilitating the catalytic cycle. The improved efficiency of the reaction with 3-methylpicolinamide perhaps reflects conformational effects on the palladium complexation/decomplexation steps which enable better catalytic turnover. More generally, electron-donating substituents on the picolinamide are clearly preferable to electron-withdrawing substituents in terms of reaction efficiency. Again, the 3-methylpicolinamide 1b gave the highest yield of monoarylated product.

To gain further insight into the regioselectivity of the arylation processes, we undertook computational studies of the various possible C–H activation steps. Density functional theory (DFT) calculations were carried out with the M06 functional,[12] using the 6-31 +G(d) basis set for C, H, N, O and F atoms and the

### Table 1. C–H arylation of the bornylamine scaffold using different picolinamide directing groups.

| Directing Group | Yield[a] | Ratio of 2:3[b] |
|-----------------|----------|----------------|
| 1a              | 91%      | >98:2          |
| 1b              | 97%      | >98:2          |
| 1c              | 97%      | 88:12          |
| 1d              | 99%      | 89:11          |
| 1e              | 99%      | 52:48          |
| 1f              | 73%      | 73:27[c]      |
| 1g              | 75%      | 79:21          |
| 1h              | 79%      | 88:12          |

Conditions: 5 mol% Pd(OAc)₂, 4 equiv. CsOAc, 10 mol% CuBr₂, 4 equiv. 4-iodoanisole, tert-amyl alcohol (tAmOH) 1 M, 140°C, 24 h.

[a] Combined isolated yield of a mixture of mono and diarylated products;
[b] Ratio of 2:3 was determined from the crude ¹H NMR spectrum;
[c] Diarylated product 3f was isolated in 17% yield.
LANL2DZ basis set for Pd. All optimised structures were confirmed by the presence of zero or one imaginary frequencies for minima and transition states respectively, and transition states were shown to link the correct minima through IRC calculations. Calculated free energies were corrected to the reaction temperature of 413 K.

Initially, we modelled an adduct 1a (R = H) in which a palladium atom with a bidentate acetate ligand was chelated by the two nitrogens of a deprotonated molecule of 1a (Scheme 3). Transition states for a concerted metalation-deprotonation (CMD) mechanism could then be located for both methylene and methyl groups (IIa and IIIa respectively; Scheme 3 and Table 2). As expected, these calculations indicated that insertion into the methylene group had a much lower energy barrier ($\Delta \Delta G^\ddagger = 18.1$ kJ mol$^{-1}$). A second insertion step was then investigated, starting from the monophenylated adduct VIIa. From this complex, the free energy of activation for insertion into a C–H bond of the methyl group (transition state VIIIa) was found to be considerably lower than that for methyl group activation in the initial complex Ia via transition state IIIa (93.1 kJ mol$^{-1}$ vs. 101.7 kJ mol$^{-1}$). The corresponding calculations were repeated for the remaining picolinamide substrates 1b–1h. The free energy of activation for each of the C–H insertion steps is shown in Table 2.

For all compounds, the free energy of activation for initial CH$_3$ insertion is considerably higher than for CH$_2$ insertion ($\Delta \Delta G^\ddagger$ ranges from 12.9 kJ mol$^{-1}$ to 19.8 kJ mol$^{-1}$), explaining why monoarylation at the CH$_3$ is not observed. In all cases except for 1g, arylation of the CH$_2$ leads to a lowering of the activation energy for a subsequent CH$_3$ insertion, with this effect being most pronounced for substrates 1e and 1f ($\Delta \Delta G^\ddagger = 10.3$ kJ mol$^{-1}$ and 11.0 kJ mol$^{-1}$ respectively) which notably were the substrates which yielded the largest proportion of diarylated product. Given the fact that decomplexation of the monoarylated product 2 from the palladium appears to be irreversible (Scheme 1), the quantity of the diarylated product 3 obtained from each substrate probably reflects the relative rates of the CH$_3$ insertion step and the decomplexation. In the case of substrate 1e, where the largest proportion of diarylated product was observed, the activation energy of the second CH$_3$ insertion step (VIIIe) from the arylated palladium complex VIIe is comparable to that of the initial CH$_3$ insertion (IIe) from complex Ie. In the case of substrates 1a and 1b, the decomplexation of the non arylated product 2 from palladium is presumably much more rapid than C–H insertion into the methyl group so only monoarylated product is formed, even though the C–H insertion into the methyl group has a lower activation energy in the aryalted product.

To discover whether such calculations could be used to predict the selectivity for an untested directing group, we calculated the corresponding energy barriers for reactions of the 3-phenylpicolinamide derivative 1i (Scheme 4). Similar values were obtained for the three C–H insertion processes as in the the methyl derivatives 1c/1d, so we expected that this substrate would provide ~10% of the diarylated product. 3-Phenylpicolinamide was synthesised according to a modified literature procedure$^{[15]}$ and coupled to bornylamine to
In the event, the arylation reaction of \(1\) gave 13% of diarylated product \(3\) alongside 65% of \(2\) (Scheme 4). We can therefore conclude that the calculated energy barriers for the C–H insertion steps can only provide a qualitative guide to the likely reaction outcomes. This is a consequence of the difficulties of accurately modelling the decomplexation step which is in competition with the second C–H insertion reaction. Further work will be required to understand the complexation/decomplexation mechanisms in order to make more accurate predictions of the effect of different directing groups on the C–H insertion selectivity.

We then set out to explore whether these directing group effects could be observed with other substrates. In contrast to the bornylamine framework, most acyclic...
scaffolds show a preference for methyl C–H activation over methylene C–H activation.[8] The unsubstituted picolinamide 4a derived from (1-methylcyclohexyl)methylamine[16] gives a ~3:1 ratio of monoarylated product 5a and diarylated product 6a with the monoarylation occurring exclusively on the methyl group (Table 3). Interestingly, the 3-methylpicolinamide undergoes a more selective reaction with 57% of the monoarylated product 5b being isolated, alongside traces of diarylated compound 6b, with the balance of the material being unreacted starting material. The 4- and 5-methyl derivatives 4c and 4d give similar levels of selectivity with the former giving a high overall yield of arylated products (5c and 6c) which was comparable to the unsubstituted system 4a. On this amine scaffold, the trifluoromethyl derivatives (4e/4f) gave relatively low yields in the arylation reaction, as did the 4-methoxy derivative 4h. The 4-methoxy derivative 4g gave a good overall yield with reasonable selectivity for the monoarylated product. Analysis of the 1H and 13C NMR spectra of 6c and comparison with calculated 1H and 13C NMR shifts using Goodman’s DP4 method[17] allowed us to assign the stereochemistry of the major isomer of 6c as the syn compound (Figure 3).

Unlike the bornylamine scaffold above, resubmission of 5c to the reaction conditions gave a 26% yield of the diarylated compound 6c (Scheme 5), indicating that the monoarylated compound 5c can effectively form a reactive complex with palladium, perhaps because the picolinamide is less hindered than in 2e. In contrast to bornylamine above, arylation of the (1-methylcyclohexyl)methylamine scaffold with aryl bromides was ineffective. Furthermore, the arylation reaction with an aryl iodide could be suppressed by the addition of 30 mol% tetrabutylammonium bromide to the reaction mixture.[18] It seems that the presence of bromide in the reaction mixture may inhibit the C–H activation step, perhaps by outcompeting acetate as a ligand on the intermediate palladium complex. This observation may explain why aryl bromides cannot be used on the (1-methylcyclohexyl)methylamine scaffold as inorganic bromide is likely to be present in aryl bromide reagents. This may also explain why only

Table 3. C–H arylation of the (1-methylcyclohexyl)methylamine scaffold using different picolinamide directing groups.

| Amide | Directing group | Yield[a] | Ratio of 5:6[b] |
|-------|----------------|---------|----------------|
| 4a    |                | 81      | 76:24          |
| 4b    |                | 62      | 83:17          |
| 4c    |                | 86      | 78:22          |
| 4d    |                | 54      | 78:22          |
| 4e    |                | 35      | 82:18          |
| 4f    |                | 57      | 77:23          |
| 4g    |                | 77      | 79:21          |
| 4h    |                | 38      | 62:38          |

[a] Combined isolated yield; [b] Calculated from crude 1H NMR; [c] Compound was only isolated as a mixture with other arylation products.

Figure 3. Stereochemical assignment of diarylated product 6c (Ar = 4-methoxyphenyl) was confirmed via DFT calculation of NMR shifts. The mean absolute error (MAE) between the calculated and observed chemical shifts (for the major isomer) is shown in parentheses.
monoarylation of the bornylamine scaffolds is seen when aryl bromides are employed (Schemes 2 & 4).

Next we explored the effect of the eight different picolinamide directing groups on the flexible open-chain scaffold 2-methylbut-1-ylamine (Table 4).\[^9\] As anticipated, arylation of the methyl group occurs preferentially, followed by a second arylation on the ethyl group. Reaction of the unsubstituted amide 7\(a\) gives 72% yield of monoaryl product 8\(a\) and 21% of the diaryl compound 9\(a\). Complete control over the formation of mono or diarylation products is more challenging in this case, but once again the 3-methylpicolinamide gives the highest levels of selectivity yielding only 5% of diaryl compound 9\(b\) alongside a synthetically useful 73% yield of monoarylated compound 8\(b\). Good selectivity was also observed with the 5-methyl (7\(d\)) and 5-methoxy (7\(h\)) derivatives which both also gave improved yields of the monoaryl derivatives 8\(d\) and 8\(h\) respectively. The 4-methylpicolinamide gave a poor overall yield as well as showing no selectivity in the arylation reaction with equal amounts of 8\(c\) and 9\(c\) being produced. In this latter reaction, it was possible to detect a third product 10\(c\) in which diarylation had taken place on the two methyl groups (Figure 4). Trifluoromethyl picolinamides 7\(e\) and 7\(f\) gave high selectivity for the monoarylated products 8\(e\) and 8\(f\) but in only moderate yield. 4-Methoxypicolinamide 7\(g\) gave a similarly low overall yield but with high selectivity for monoarylation.

As a further example, we explored the arylation of substrates 11\(a/11\)b derived from isobutylamine, in which two equivalent methyl groups are present (Scheme 6).\[^{20}\] Switching from the unsubstituted picolinamide 11\(a\) to the 3-methylpicolinamide 11\(b\) led to a slightly increased selectivity for monoarylation (12\(b\) vs 13\(b\)), albeit with the diarylated compound being the major product in both cases. The overall arylation yield

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**Scheme 5.** Further reactions on the (1-methylcyclohexyl)methylamine scaffold. Arylation of 5\(c\) to give 6\(c\) and attempted arylation of 4\(f\) with PMPBr or PMPI in the presence of Bu\(_4\)NBr. (PMP = para-methoxy phenyl)

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**Table 4.** C–H arylation of the 2-methylbut-1-ylamine scaffold using different picolinamide directing groups.

| Entry | Directing group | Yield\(^a\) | Ratio of 8\(9\)\(^b\) |
|-------|-----------------|-------------|----------------------|
| 7\(a\) |                 | 93          | 88:22 (72%, 21%)     |
| 7\(b\) |                 | 78          | (73\(^{[1]}\), 5%)   |
| 7\(c\) |                 | 52          | (26%, 26\(^{[4]}\))  |
| 7\(d\) |                 | 98          | (87%, 11\(^{[4]}\))  |
| 7\(e\) |                 | 57          | > 95:5 (52\(^{[2]}\), 5%) |
| 7\(f\) |                 | 45          | (41%, 4\(^{[3]}\))   |
| 7\(g\) |                 | 55          | > 98:2               |
| 7\(h\) |                 | 91          | (82\(^{[2]}\), 9%)    |

Conditions: 5 mol% Pd(OAc)\(_2\), 4 equiv. CsOAc, 10 mol% CuBr\(_2\), 4 equiv. 4-iodoanisole, rAmOH 1 M, 140 °C, 24 h.

\(^{[a]}\) Combined isolated yield; yields of each product calculated by \(^1\)H NMR shown in parentheses.

\(^{[b]}\) Ratio of products 8\(9\) determined from crude \(^1\)H NMR; it was not possible to accurately determine this ratio for all reactions;

\(^{[c]}\) Compound was only isolated as a mixture with other arylation products.

\(^{[d]}\) A mixture of two diarylated products was obtained including 10\(c\) (Figure 5); see SI for further details.
The directing group effects in the above reactions are not trivial to fully disentangle, but broadly speaking the methyl-substituted picolinamides appear to be advantageous in terms of improving the selectivity of arylation reactions, and typically leading to slightly higher overall yields of the C–H arylation products than the unsubstituted picolinamide. There was no observable benefit to employing systems with the more electron-donating methoxy group, and the electron-withdrawing trifluoromethyl group generally led to lower-yielding reactions. The arylation reaction of bornylamine with aryl bromides perhaps provides the most useful insight into the inherent efficiency of each directing group for mediating catalytic arylation. This likely involves several effects including the efficiency of complexation to/decomplexation from the palladium catalyst as well as the C–H insertion and arylation steps themselves. Some combinations of directing group and scaffold led to greater promiscuity in the terms of the C–H activation site (1e, 7c), but none of these combinations led to a complete change in the initial reaction site. We envisaged that these insights may prove useful for enhancing the yield of more challenging C–H arylation reactions in which the overall conversion under our previously developed conditions is low. In particular, the 3-methylpicolinamide often provided enhanced yield and selectivity in the C–H arylation reactions, which can potentially be attributed to the steric effect of the methyl group accelerating decomplexation from the monoarylated product. This seems more plausible given that the DFT calculations for the bornylamine scaffold suggest that there is little difference in the activation energies for the C–H insertion steps between 3-methylpicolinamide and the unsubstituted system. With this in mind, we then went onto examine other sp³ C–H arylation reactions to see if improved conditions could be identified.

Reaction of cyclohexyl[21] picolinamide 14a and p-fluorotoluene under our standard conditions led to the formation of the arylated product 15a in 70% yield (Scheme 7). By changing the solvent to 3-methylpentan-3-ol (tHxOH, bp 123 °C),[22] without changing the external temperature, the yield of 15a was increased to 80%. 3-Methylpentan-3-ol is available commercially in reasonably large quantities, but has...
rarely been used as a reaction solvent for C–H activation.\textsuperscript{[23]} Changing the directing group to 3-methylpicolinamide 14\textsuperscript{b} led to a further improvement in reaction yield (91%, 15\textsuperscript{b}). These conditions could also be used to improve the arylation yield of the same substrate with p-anisyl iodide from 68% to 85% (15\textsuperscript{c}/15\textsuperscript{d}).

We also extended the reaction to a small selection of other substrates including cyclohexylmethylamine 16\textsuperscript{[16]} (to give diarylated product 17\textsuperscript{a}, along with small quantities of monoarylated derivative 18\textsuperscript{a}), cycloheptylamine 19 (to give 20)\textsuperscript{[24]} and 4-aminotetrahydropyran 21 (to give 22)\textsuperscript{[25]} In all cases, the combination of 3-methylpicolinamide as the directing group and t\textsubscript{HxOH} as solvent gave an improved yield of the arylation product. In the reaction to form 17\textsuperscript{a} only, the use of Cesium pivalate as base was beneficial.

The selectivity in the arylation of 16\textsuperscript{a} is noteworthy in that the monoarylated product 18\textsuperscript{a} is formed exclusively as the trans isomer, whereas the diarylated product 17\textsuperscript{a} is formed exclusively as the all cis isomer. This can be rationalised (Scheme 8) by assuming that the directing group can more effectively mediate the C–H activation step when it occupies an axial position, giving cis selectivity. Thus, arylation cis to the directing group gives a disubstituted cyclohexane cis-18\textsuperscript{a} with one substituent axial and one equatorial. This effectively lowers the energy of the conformation in which the directing group is axial, promoting a second C–H insertion reaction. In contrast, the formation of trans-18\textsuperscript{a} presumably involves some distortion of the chair in the intermediate Pd complex trans-23. The conformation of trans-18\textsuperscript{a} in which both substituents are equatorial is likely to be overwhelmingly favoured and this will make the molecule more rigid preventing further C–H insertion steps from taking place. It is possible that trans-18\textsuperscript{a} is formed via epimeration of the intermediate palladium complex from cis-23 to trans-23 prior to the arylation reaction with the iodoarene. Similarly, monoarylation of 14 and 21 almost certainly occurs selectively due to the requirement for the directing group to be axial in order for the palladium to reach the C-3 hydrogen atom. In the products 15\textsuperscript{22}, the conformation with both substituents axial is likely to be energetically unfavourable, so no second arylation takes place.

**Conclusion**

In summary, it has been shown that the substituents on the picolinamide directing group can have a significant effect on the yield and selectivity of C–H functionalisation conducted under silver-free conditions. A variety of electron rich and electron poor picolinamides were investigated on a range of amine substrates, with the latter generally leading to lower yielding reactions. Highest yields were obtained with a methylpicolinamide directing group which gave some improvements over the unsubstituted system. Most notably, the use of 3-methylpicolinamide typically led to increased yields of C–H arylation reactions in most cases, and also to reduced quantities of diarylation products. The beneficial effect of this directing group can perhaps tentatively be explained by accelerated decomplexation from the palladium leading to more efficient catalytic turnover, and deceleration of over-arylation reactions due to the increased steric hindrance. Further improvements in reaction yields could often be obtained by performing reactions in 3-methyl-3-pentanol (t\textsubscript{HxOH}) as solvent. These conditions enabled us to obtain synthetically useful yields of arylation products from a range of substrates.\textsuperscript{[16]}

**Experimental Section**

**Preparation of Substrates**

3-Phenylpicolinic acid was prepared using previously reported methods.\textsuperscript{[15,27]} Picolinamides were prepared via HATU (1-[Bis (dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate) coupling or B(OCH\textsubscript{3})\textsubscript{3}-catalysed amidation reactions.\textsuperscript{[28]} Data for 7\textsuperscript{a}\textsuperscript{[29]} 11\textsuperscript{a},\textsuperscript{[30]} 15\textsuperscript{c},\textsuperscript{[21a]} 19\textsuperscript{a}\textsuperscript{[16]} and 20\textsuperscript{a}\textsuperscript{[16]} were in accordance with the literature.

All DFT calculations were carried out using Gaussian 09.\textsuperscript{[31]} The 6–31 + G(d) basis set for elements C, H, N, O, F and the LANL2DZ basis set for Pd were used throughout. Structures were initially optimized in the gas phase using the B3LYP functional, with further optimization using the M06 functional. Structures were confirmed as minima or transition states by the existence of zero or one imaginary vibrational frequencies respectively. Transition states were shown to link with the relevant minima by means of intrinsic reaction coordinate (IRC) calculations. Free energies were calculated at 413 K using the GoodVibes software of Paton and Funes-Ardois.\textsuperscript{[32]} This software uses the approach of Grimme\textsuperscript{[33]} in calculating entropic terms for vibrational frequencies below 100 cm\textsuperscript{−1} using the free-rotor approximation while using the rigid-rotor/harmonic oscillator expression for higher frequency vibrations and employing a damping function to interpolate between the two expressions close to the cutoff frequency. Calculated coordi-
nates for all structures are provided as zipped .xyz files in the supporting information.

**General Procedure for Arylation of Picolinamides.**

A tube was charged with a picolinamide (1 eq), CuBr₂ (10 mol%), Pd(OAc)₂ (5 mol%), CsOAc (4 eq), solvent (CH₂O/H₂O, 1 M) and an aryl iodide or bromide (4 eq). The tube was sealed with a PTFE lined cap and heated to 140°C for 24 hours. The reaction mixture was then cooled and filtered through a pad of Celite®, washing with EtOAc. The filtrate was concentrated in vacuo and the resulting crude residue purified by flash column chromatography.

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Tuning Reactivity in Pd-catalysed C(sp³)-H Arylations via Directing Group Modifications and Solvent Selection

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