Stereoselective Palladium-Catalyzed C(sp$^3$)–H Mono-Arylation of Piperidines and Tetrahydropyrans with a C(4) Directing Group

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Supporting Information Placeholder

**ABSTRACT:** A selective Pd-catalyzed C(3)–H cis-functionalization of piperidine and tetrahydropyran carboxylic acids is achieved using a C(4) aminoquinoline amide auxiliary. High mono- and cis-selectivity is attained by using mesityl carboxylic acid as an additive. Conditions are developed with significantly lower reaction temperatures (≤50 °C) than other reported heterocycle C(sp$^3$)–H functionalization reactions, which is facilitated by a DoE optimization. A one-pot C–H functionalization-epimerization procedure provides the trans-3,4-disubstituted isomers directly. Divergent aminoquinoline removal is accomplished with the installation of carboxylic acid, alcohol, amide and nitrile functional groups. Overall fragment compounds suitable for screening are generated in 3-4 steps from readily-available heterocyclic carboxylic acids.

**INTRODUCTION**

Saturated N- and O-heterocycles are widespread motifs in natural products and marketed drugs, as well as valuable building blocks in medicinal chemistry.\(^1,2\) Recently, there has been an increased drive to include saturated heterocycles in screening libraries,\(^3\) as well as an empirically observed link between sp$^3$-rich structures and lower attrition rate in drug discovery programs.\(^4\) Small saturated heterocycles are advantageous starting points in fragment-based drug discovery due to their low molecular weight, propensity for H-bonding and potential for 3D growth-vectors along the C(sp$^3$)–H bonds.\(^5,7\) The ability to expediently access any defined substitution pattern would hence be highly desired to elaborate a lead or fragment hit.

Metal-catalyzed C–H functionalization has enormous potential to aid diverse functionalization along C(sp$^3$)–H bonds.\(^8,9\) Regiocontrol remains a challenge in saturated heterocycles, where the C(2) position is considerably more activated than C–H bonds away from the heteroatom.\(^10\) Palladium-catalyzed methods have been developed to allow regio- and stereocontrolled functionalization of the more challenging remote positions by exploiting directing groups (Figure 1a).\(^11,12\) In 2014 we reported the selective C(3) cis-arylation of proline derivatives using an aminoquinoline directing group.\(^13,14\) cis-Functionalization of piperidines and O-heterocycles with C(2) auxiliaries have subsequently been demonstrated,\(^15-17\) as well as other ring sizes.\(^18-20\)

Moving the directing group to the C3-position presents further selectivity requirements. We recently reported the selective C(4) arylation of piperidines and pyrrolidines with a C(3) amidoquinoline amide.\(^21\) Maes reported the use of a C(3) picolinamide/directing group to form 3,5-syn-disubstituted piperidines,\(^22\) and Sanford developed C(4) piperidine functionalization using an N(1)-linked directing group.\(^23\) Notably, many of these reports obtained high levels of diastereoselectivity, often due to local steric requirements or stereospecific mechanistic features, though different, and often forcing reaction conditions were required.
The C–H functionalization of 6-membered heterocycles with C(4) directing groups remains little studied with only a few isolated examples to date. Achieving high conversion with these substrates presents an additional challenge due to the potential for diastereity. Furthermore, these examples have commonly seen low diastereoselectivity. Yu reported early single examples of arylation, and alkynylation on tetrahydropyran. In 2016 Yu developed C(3) arylation of N-heterocycles with a C(4) directing group as part of a broader study using Pd-catalysis with an NHQ ligand, with low diastereoselectivity (Figure 1b). More recently, Yu reported an O-linked C4 directing group with a single example on a tetrahydropyran (2:1 cis:trans).

Here we report the stereoselective synthesis of cis,3,4-disubstituted piperidines and tetrahydropyrans, by C(3) arylation in the presence of a C(4) aminoquinoline amide directing group (Figure 1c). Notably, using moderate temperatures (45-50 °C) achieved high selectivity for mono-cis functionalization on the unbiased C(4)-substituted 6-membered ring. To date, this constitutes the first heterocycle C(sp³)-H functionalization protocol at unactivated positions to not require high temperatures. This method allows generation of attractive fragments for screening as single diastereoisomers.

RESULTS AND DISCUSSION

We first examined N-Boc piperidine 4-carboxylic acid (isonicotinic acid) derivatives bearing bidentate directing groups. Aminoquinoline amide 1 displayed the highest reactivity, and became the focus of our study. However under conditions previously reported for piperidines with a C(3) directing group, a mixture of four arylated products was observed (Table 1, entry 1). These were identified as mono-cis and mono-trans arylated piperidines 2a and 3a, as well as di-cis-trans and di-cis-cis isomers 4a and 5a.

We optimized the reaction conditions aiming to maximize the yield of 2a, with this cis-product offering greater potential for downstream diversification. Initially various bases were investigated at 110 °C. Acetate salts biased the reactivity towards the preferential formation of 2a, albeit in modest yields. A breakthrough in selectivity was achieved on significantly lowering the temperature. Chen had previously reported monoarylation of cyclopentanes at ambient temperature using chlorinated solvents. Reacting 1 with K₂CO₃ in CH₂Cl₂ gave <5% yield (entry 2) whereas Ag₂CO₃ gave 2a exclusively in an encouraging 33% yield over 72 h (entry 3). A range of solvents were screened, including substituted aromatics, alcohols and polar aprotic solvents. Halo-genated aliphatic and aromatic solvents afforded the highest yields of 2a (entries 3-7), and α,ω,α-tri-fluorotoluene gave 40% of the mono-cis arylation exclusively (entry 7). Increasing the temperature in increments of 10 °C led to a peak of 48% yield at 45 °C (entry 8). Above this temperature the overall conversion could not be enhanced. Instead, formation of mono-trans 3a and diarylation to cis-trans 4a was encouraged at the expense of 2a. Having identified the reaction temperature as a crucial factor, we next examined the effect of additives to increase reactivity, aiming to reduce the reaction time (Table 2).

Table 1. Selected optimization for the C–H arylation of piperidine 1.

| entry | base | solvent | T (°C) | yield (%)<sup>b</sup> |
|-------|------|---------|-------|---------------------|
| 1<sup>c,d</sup> | K₂CO₃ | PhMe<sup>e</sup> | 110 | 18 26 10 24 18 |
| 2<sup>d</sup> | K₂CO₃ | CH₂Cl₂ | 25 | 3 - - - 88 |
| 3 | Ag₂CO₃ | CH₂Cl₂ | 25 | 33 - - - 55 |
| 4 | Ag₂CO₃ | DCE | 25 | 35 - - - 48 |
| 5 | Ag₂CO₃ | PhCl | 25 | 31 - - - 57 |
| 6 | Ag₂CO₃ | α-DCB | 25 | 27 - - - 62 |
| 7 | Ag₂CO₃ | PhCF₃ | 25 | 40 - - - 52 |
| 8 | Ag₂CO₃ | PhCF₃ | 45 | 48 5 4 - 37 |
| 9 | Ag₂CO₃ | PhCF₃ | 65 | 42 7 8 - 36 |
| 10 | Ag₂CO₃ | PhCF₃ | 85 | 32 8 13 - 38 |

<sup>a</sup> Reactions on 0.2 mmol scale. <sup>b</sup> Calculated by 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. <sup>c</sup> 24 h reaction time and 5 mol% Pd(OAc)₂. <sup>d</sup> 30 mol% PivOH used as additive. <sup>e</sup> 0.3 M concentration of I.
Table 2. Additive screen for the C–H arylation of piperidine 1.

| entry | additive | time (h) | yield (%) | 2a | 3a | 4a | 5a | 1 |
|-------|----------|----------|-----------|----|----|----|----|---|
| 1     | -        | 72       | 48        | 5  | 4  | -  | 37 |   |
| 2     | PivOH    | 72       | 46        | 3  | 3  | -  | 41 |   |
| 3     | Ad-COOH  | 72       | 55        | 12 | 15 | 2  | 14 |   |
| 4     | (BnO)₂PO₂H | 72    | 31        | 11 | 36 | 21 | 0  |   |
| 5     | (PhO)₂PO₂H | 72   | 45        | 6  | 11 | 20 | 0  |   |
| 6     | MesCOOH  | 24       | 57 (53)   | 10 | 11 | 9  | 9  |   |
| 7     | MesCOOH  | 24       | 72 (68)   | 8  | 9  | 2  | 5  |   |
| 8     | MesCOOH  | 24       | -         | -  | -  | -  | -  |   |

* Reactions on 0.2 mmol scale.  
* Calculated by ¹H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. Isolated yield in parentheses.  
* 2.0 equiv ArI, 1.25 equiv Ag₂CO₃, PhCF₃ (0.3 M).

The addition of 30 mol% pivalic acid and adamantane carboxylic acid did not change the reaction profile (entries 1-3). Dibenzyolphosphate increased conversion, whereas diphenylphosphate and 2-mesitylenecarboxylic acid (MesCOOH) promoted complete consumption of 1 (entries 5-6), which would facilitate purification. Moreover, using MesCOOH, the reaction time could be reduced to 24 h limiting diarylation and providing 2a in 53% isolated yield (entry 7).

Finally, given the interplay of conditions affecting conversion and side product formation, we further refined the reaction conditions in a Design of Experiment (DoE) study. The workflow involved an initial definitive screening of all reaction parameters apart from catalyst loading. This helped confirm the limits of temperature (45 °C) and time (24 h) for a suitable model, as well as demonstrated that the reaction outcome is unaffected by additive loading above 30 mol%. Moreover, aryl iodide loading, Ag₂CO₃ loading and substrate concentration were found to be the main factors affecting yield and selectivity. These parameters were therefore employed in a subsequent custom design screen aimed at maximizing the predicted yield of 2a whilst minimizing diarylation (see Supporting Information for full workflow). Up to 3rd order interactions of these parameters were examined, however, under the set temperature and time conditions no 2nd or higher order interactions were seen. Visualization of 3-dimensional response surfaces of predicted yield against any two of the major factors revealed a defined dome-shaped surface (predicted yield against aryl iodide and base equivalents) with a plateau at 74%. The optimum set of conditions from the plateau gave excellent correlation with the in-situ and isolated yields of 2a (Table 2, entry 8 and Figure 2). Overall, an increased yield and selectivity was achieved at 45 °C along with a reduction in the equivalents of both aryl iodide and silver carbonate base that were required.

With the optimized conditions the reaction scope was investigated (Scheme 1). In the presence of 4-idoanisole, the monocis isomer (2a) was isolated in 68% yield on 0.4 mmol scale, and 70% yield on 4 mmol scale. Changing the N-protecting group from Boc (2) to Cbz (6) gave a similar in-situ yield, although the N-Cbz group led to a more challenging purification. N-Acetyl (7) and N-mesyl (8) derivatives could also be successfully arylated, albeit in lower yields (10a, 11a). Aryl iodides with various electronic requirements were successfully employed in the reaction, affording piperidines 2b-i in good yield as single diastereoisomers. Halogens were well tolerated (2c-e), providing a useful handle for further functionalization. Boc-protected aniline could be installed in 48% yield (2f). meta-Substituted and electron-rich trimethoxybenzene and benzodioxole derivatives gave high yields (2k, 2l), as did 2-naphthyliodide (2m). 3-Bromo- and 2-fluoro-substituted aryl iodides were tolerated (2n, 2o), though the ortho-substitution resulted in a reduced yield. Unprotected benzyl alcohol functionality was compatible with the reaction conditions, providing 2q in 50% yield. Medicinally relevant heterocycles were successfully installed, including N-Ts protected indole (2p), as well as piperidines bearing electron-donating or electron-withdrawing groups (2r, 2s). 2-Iodothiophene exhibited an unusually high reactivity, whereby the monoarylation was observed in only trace amounts and cis-trans diarylated product (2t) was isolated in 55% yield. Similar high reactivity was seen with styrly iodide, leading to an equimolar mixture of all four possible mono- and di-alkenylated piperidines, each isolated in similar yields (19–21%).
Scheme 1. Reaction scope of aryl iodides for C–H arylation of piperidine 1.

![Reaction scope of aryl iodides for C–H arylation of piperidine 1.](image)

- Reactions on 0.4 mmol scale. All products were isolated as cis-diastereomers unless otherwise stated.
- Product inseparable from unreacted 6. Yield calculated using 1,3,5-trimethoxybenzene as internal standard.
- 3.0 equiv ArI and PhCF3 (0.2 M).
- Represents yield of the cis-trans di-arylated piperidine. Each of the four possible alkynylation products were isolated: mono-cis (21%), mono-trans (20%), di-cis-cis (21%) and di-cis-trans (19%) alkynylation piperidines. Alkene E-geometry preserved in all products.

Minor adaptation of the reaction conditions enabled application to the corresponding tetrahydropyran aminooquinoline amides (Scheme 2). After a screen of additives, 2-mesitylene carboxylic acid (MesCOOH) was also identified as best performing in this case, promoting the highest starting material conversion. A brief DoE study revealed an additive loading of 15 mol% to be optimal in the presence of a similar amount of Ag2CO3 as was required with piperidine. A higher loading of aryl iodide could be tolerated and was employed to enhance reactivity, since high cis-selectivity was observed for this system, with a decreased reactivity towards diarylation. Similarly to the piperidine, higher yields were generally observed for electronically coupled partners and halogens were well-tolerated.

Next we addressed the question of how the minor trans-arylated products were formed. Using conditions with elevated temperatures (110 °C) was shown to cause epimerization of cis-arylated products and so reduce dr. On the other hand, resubjecting cis-arylated piperidine 2e to the optimal reaction conditions, in the absence of aryl iodide, gave no cis-to-trans epimerization at the lower temperature. This suggested an alternative route to the trans-diastereoisomer via a minor trans-palladacycle intermediate. To test the viability of a direct trans-arylation, we examined a second arylation using a different aryl iodide to provide a sterechemical marker (Scheme 3).

Scheme 2. Scope of aryl iodides for tetrahydropyran C–H arylation.

![Scope of aryl iodides for tetrahydropyran C–H arylation.](image)

- Reactions on 0.4 mmol scale. All products were isolated as cis-diastereomers unless otherwise stated.
- Isolated as an inseparable 8:1 mixture of mono-cis and di-cis-cis isomers.

From mono-cis 2c, reaction with 4-iodobenzyl alcohol formed both di-cis-trans (14) and di-cis-cis (not shown) isomers to a similar extent (19% 14 and 15% of the cis-cis-isomer). The relative stereochemistry at the carbonyl center was maintained, with 14 arising from a second arylation occurring trans with respect to the directing group, hence proving the potential for the direct trans-arylation. This was further supported by prepara-
- trans-epimer 15 from 2c by treatment with NaOH. Arylation now gave only trans-cis-product 16 as a diastereoisomer of 14, confirming previous assignments. Interestingly the trans-trans-diastereoisomer was not observed in this instance, presumably due to the increased strain in the required equatorial palladacycle, resulting in unfavourable steric interactions of the directing group with the pre-installed aryl group.

Scheme 3. Diarylation studies investigating the pathways of side-product formation.

![Diarylation studies investigating the pathways of side-product formation.](image)

- The di-cis-cis isomer (not shown) was isolated in 15% yield.

As a direct route to the trans-substituted isomers we developed a one-pot arylation-epimerization. Simple addition of DBU to the reaction mixture after the arylation step promoted epimerization of cis-arylated products to corresponding trans-diastereomers 17 and 18 at 100 °C (Scheme 4). A 24 h heating time promoted the majority of the cis-isomer to epimerize, with a 70% conversion of the cis p-methoxyphenyl-substituted piperidine and a 90% conversion of the cis p-bromophenyl substituted substrate, to afford trans products 17 and 18 in 54% and 53% isolated yields, respectively.
Finally, the directing group was removed to unveil polar functionalities and access fragments and building blocks of interest for drug discovery programs (Scheme 5). Molecular weights corresponding to the free amines and calculated using Llama.

Scheme 5. Divergent aminooquinoline removal.\(^a\)

\(^a\) AlogP and Polar Surface Area (PSA) calculated using Llama.

**CONCLUSION**

In summary, we have demonstrated an efficient stereoselective C(3) mono-cis functionalization of pipidines and tetrahydropropyran bearing a C(4) aminooquinoline directing group. As key features, lower reaction temperatures (45–50 °C) were employed, ensuring high stereocontrol, whilst the use of MesCOOH additive achieved high levels of starting material conversion of up to 95%. A DoE study generated reaction conditions that minimized the competing diarylation and epimerization processes resulting in high stereoselectivity and an overall reduction in the amounts of reagents used. Additionally, single mono-trans diastereomers could be directly accessed through a one-pot arylation-epimerization protocol.

Using mild conditions, the aminooquinoline directing group could be removed in a divergent manner. The N-Boc protected aminooquinoline amide intermediate was used to unveil alcohol, carboxylic acid, amide and nitriles functionalities. The obtained products afforded fragments with desirable physicochemical properties for fragment-based drug discovery. Valuable fragments of this defined substitution pattern featuring a polar ring heteroatom, a C(4) polar functional group, and a C(3) aryl group were accessed in only 3-4 high-yielding steps from inexpensive commercial materials.

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