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

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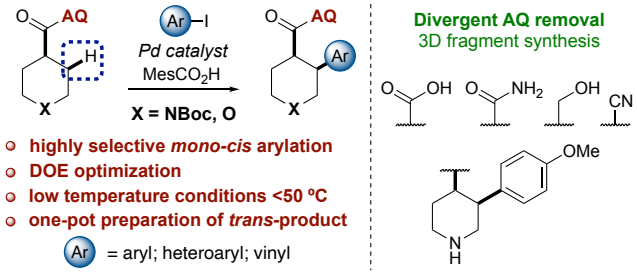
Supporting Information Placeholder



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.

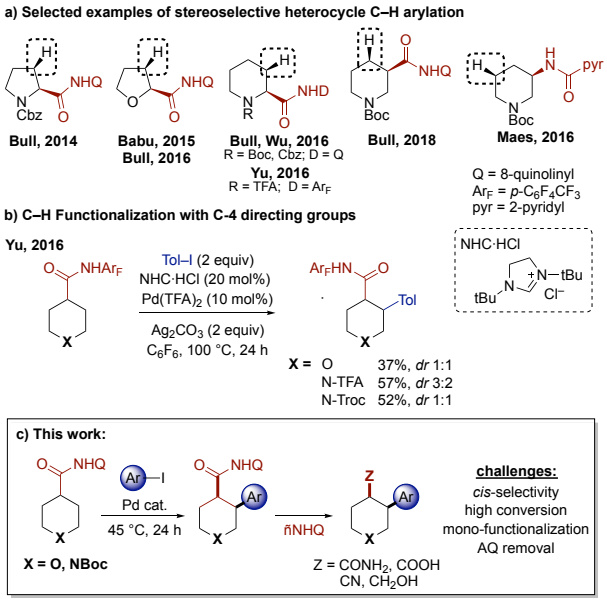
INTRODUCTION

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) aminoquinoline 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.

Figure 1. Directed C(sp^3)–H arylation of saturated heterocycles at unactivated positions.



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 diarylation. Furthermore, these examples have commonly seen low diastereoselectivity. Yu reported early single examples of arylation,[24] and alkynylation[25] on tetrahydropyrans. 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 NHC ligand, with low diastereoselectivity (Figure 1b).[17a] More recently, Yu reported an O-linked C4 directing group with a single example on a tetrahydropyran (2:1 *cis:trans*).[26]

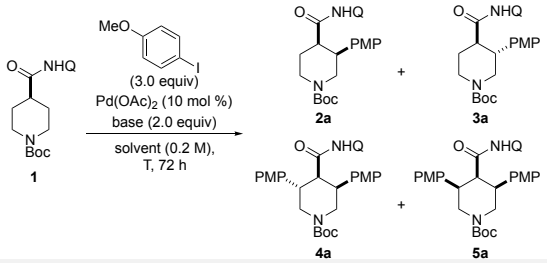
Here we report the stereoselective synthesis of *cis*-3,4-disubstituted piperidines and tetrahydropyrans, by C(3) arylation in the presence of a C(4) aminoquinoline amide directing group (Figure 1c). Notably, using moderate temperatures (45-50 °C) achieved high selectivity for mono-*cis* functionalization on the unbiased C(4)-substituted 6-membered ring. To date, this constitutes the first heterocycle C(sp^3)–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 (isonipecotic acid) derivatives bearing bidentate directing groups.[27] 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.[27] A breakthrough in selectivity was achieved on significantly lowering the temperature. Chen had previously reported monoarylation of cyclopentanes at ambient temperature using chlorinated solvents.[28] Reacting **1** with K_2CO_3 in CH_2Cl_2 gave <5% yield (entry 2) whereas Ag_2CO_3 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.[27] Halogenated aliphatic and aromatic solvents afforded the highest yields of **2a** (entries 3-7), and α,α,α-trifluorotoluene 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).[27]

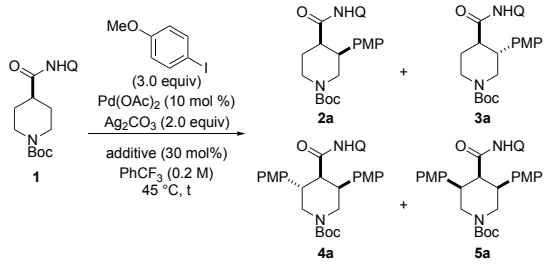
Table 1. Selected optimization for the C–H arylation of piperidine 1.



entry[a]	base	solvent	T (°C)	yield (%)[b]				
				2a	**3a**	**4a**	**5a**	**1**
1[c,d]	K_2CO_3	PhMe[e]	110	18	26	10	24	18
2[d]	K_2CO_3	CH_2Cl_2	25	3	-	-	-	88
3	Ag_2CO_3	CH_2Cl_2	25	33	-	-	-	55
4	Ag_2CO_3	DCE	25	35	-	-	-	48
5	Ag_2CO_3	PhCl	25	31	-	-	-	57
6	Ag_2CO_3	*o*-DCB	25	27	-	-	-	62
7	Ag_2CO_3	$PhCF_3$	25	40	-	-	-	52
8	Ag_2CO_3	$PhCF_3$	45	48	5	4	-	37
9	Ag_2CO_3	$PhCF_3$	65	42	7	8	-	36
10	Ag_2CO_3	$PhCF_3$	85	32	8	13	-	38

[a] Reactions on 0.2 mmol scale. [b] Calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] 24 h reaction time and 5 mol% $Pd(OAc)_2$. [d] 30 mol% PivOH used as additive. [e] 0.3 M concentration of **1.**

Table 2. Additive screen for the C–H arylation of piperidine 1.



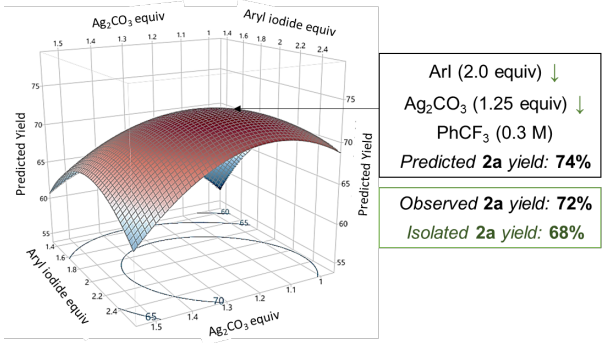
entry[a]	additive	time (h)	yield (%)[b]				
			2a	**3a**	**4a**	**5a**	**1**
1	-	72	48	5	4	-	37
2	PivOH	72	44	5	4	-	38
3	Ad-COOH	72	46	3	3	-	41
4	$(BnO)_2PO_2H$	72	55	12	15	2	14
5	$(PhO)_2PO_2H$	72	31	11	36	21	0
6	MesCOOH	72	45	6	11	20	0
7	MesCOOH	24	57 (53)	10	11	9	9
8[c]	MesCOOH	24	72 (68)	8	9	2	5

[a] Reactions on 0.2 mmol scale. [b] Calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. Isolated yield in parentheses. [c] 2.0 equiv ArI, 1.25 equiv Ag_2CO_3, $PhCF_3$ (0.3 M).

The addition of 30 mol% pivalic acid and adamantane carboxylic acid did not change the reaction profile (entries 1-3). Dibenzylphosphate 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).

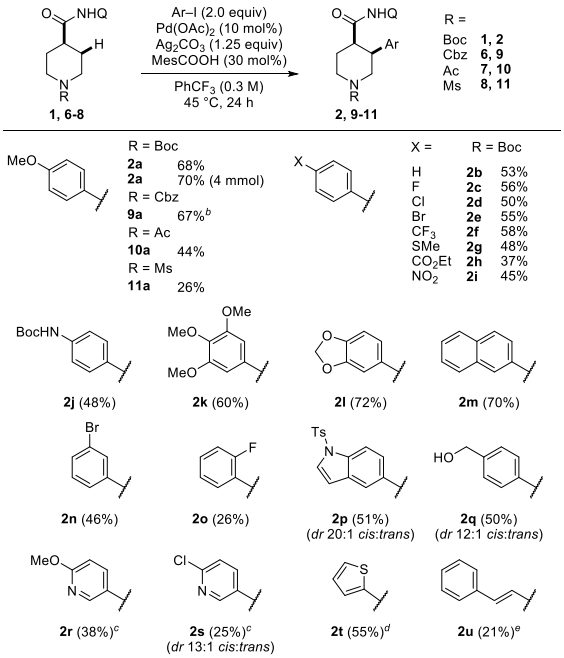
Finally, given the interplay of conditions affecting conversion and side product formation, we further refined the reaction conditions in a Design of Experiment (DoE) study.[27] The workflow involved an initial definitive screening of all reaction parameters apart from catalyst loading. This helped confirm 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, Ag_2CO_3 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.

Figure 2. Plot of predicted yield of 2a *vs* aryl iodide and Ag_2CO_3 equivalents visualized at fixed concentration (0.3 M). DoE study conducted using JMP Pro 14 and a Custom Design Screen.



With the optimized conditions the reaction scope was investigated (Scheme 1). In the presence of 4-iodoanisole, the mono-*cis* 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 (**2j**). *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 aryliodides 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 pyridines 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 styryl 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.[a]

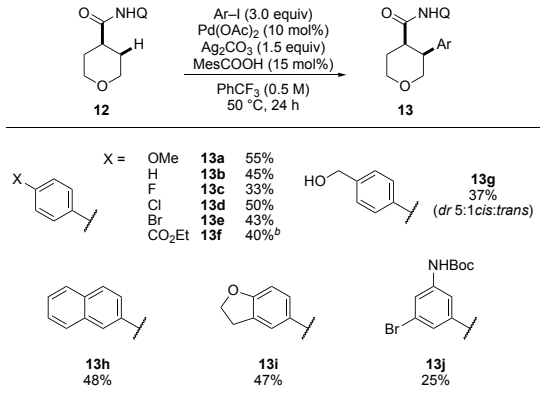


[a] Reactions on 0.4 mmol scale. All products were isolated as cis-diastereomers unless otherwise stated. [b] Product inseparable from unreacted **6**. Yield calculated using 1,3,5-trimethoxybenzene as internal standard. [c] 3.0 equiv ArI and $PhCF_3$ (0.2 M). [d] Represents yield of the *cis*-*trans* di-arylated piperidine. [e] Each of the four possible alkenylation products were isolated: mono-*cis* (21%), mono-*trans* (20%), di-*cis*-*cis* (21%) and di-*cis*-*trans* (19%) alkenylated piperidines. Alkene *E*-geometry preserved in all products.

Minor adaptation of the reaction conditions enabled application to the corresponding tetrahydropyran aminoquinoline 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 Ag_2CO_3 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 electron-rich coupling 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 **2c** 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.[27,29] To test the viability of a direct *trans*-arylation, we examined a second arylation using a different aryl iodide to provide a stereochemical marker (Scheme 3).

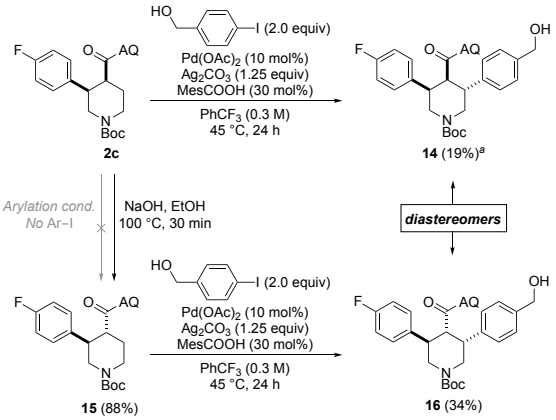
Scheme 2. Scope of aryl iodides for tetrahydropyran C–H arylation.[a]



[a] Reactions on 0.4 mmol scale. All products were isolated as *cis*-diastereomers unless otherwise stated. [b] 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 preparation of the *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 all-equatorial palladacycle, resulting in unfavourable steric interactions of the directing group with the pre-installed aryl group.

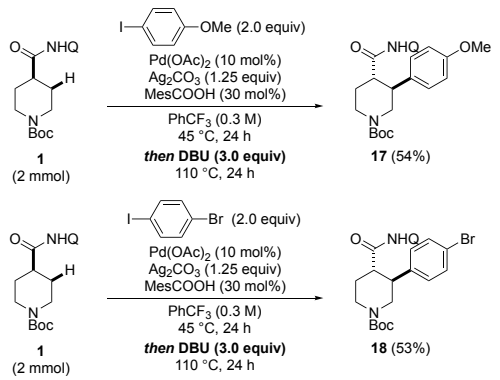
Scheme 3. Diarylation studies investigating the pathways of side-product formation.



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

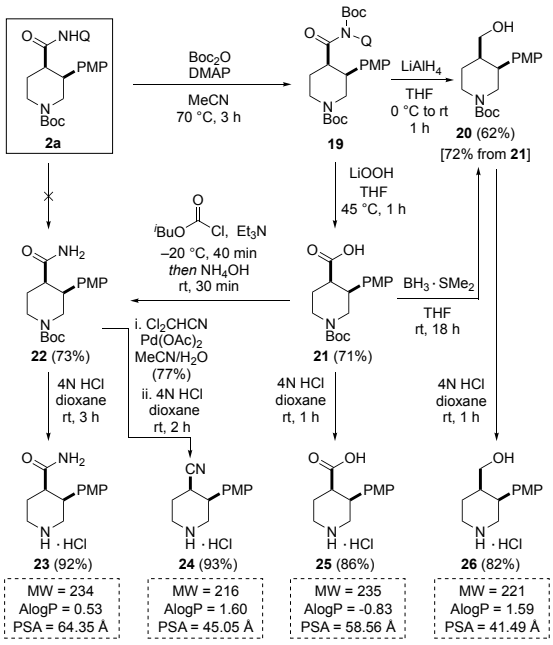
As a direct route to the *trans*-substituted isomers we developed a one-pot arylation-epimerization. Simple addition of DBU to the reaction mixture after the arylation step promoted epimerization of *cis*-arylated products to corresponding *trans*-diastereomers **17** and **18** at 100 ° C (Scheme 4). 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.

Scheme 4. One-pot arylation-epimerization protocol.



Finally, the directing group was removed to unveil polar functionalities and access fragments and building blocks of interest for drug discovery programs (Scheme 5).[30]

Scheme 5. Divergent aminoquinoline removal.[a]



[a] AlogP and Polar Surface Area (PSA) calculated using Llama.[36] Molecular weights corresponding to the free amines.

Boc-activation of amide **2a** and treatment of intermediate **19** with lithium hydrogen peroxide[31] afforded *cis*-carboxylic acid **21** in 71% yield (over 2 steps). Reduction of the same intermediate **19** with $LiAlH_4$ gave alcohol **20** in 62% yield. Alternatively, alcohol **20** could be accessed by reduction of **21** using $BH_3{\cdot}SMe_2$. Acid **21** was converted to primary amide **22** by anhydride formation with isobutyl chloroformate, followed by treatment with aqueous NH_4OH.[32] Notably, conversion of **2a** to the primary amide **22** using IBX[33] or ozonolysis[34] conditions was unsuccessful due to alternative oxidation of the electron-rich PMP substituent. A Pd-catalyzed dehydration of amide **22** gave the corresponding nitrile in 77% yield.[35] Acid-mediated Boc deprotection allowed the isolation of HCl salts **23**–**26** in excellent yields. Starting from 2-3 mmol of **2a**, useful quantities (50-80 mg) of fragment compounds were rapidly synthesized, highlighting the practical applications of this methodology.

CONCLUSION

In summary, we have demonstrated an efficient stereoselective C(3) mono-*cis* functionalization of piperidines and tetrahydropyran bearing a C(4) aminoquinoline 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 aminoquinoline directing group could be removed in a divergent manner. The *N*-Boc protected aminoquinoline 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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