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C–H Functionalization

Palladium-Catalyzed Directed C(sp^3)–H Arylation of Saturated Heterocycles at C-3 Using a Concise Optimization Approach

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Abstract: Saturated heterocycles, such as THFs, pyrrolidines, piperidines and THPs, are essential components of many biologically active compounds. Examples of C–H functionalization on these important ring systems remain scarce, especially at unactivated positions. Here we report the development of conditions for the palladium-catalyzed stereoselective C(sp^3)–H arylation at unactivated 3-positions of 5- and 6-membered N- and O-heterocycles with aminoquinoline directing groups. Subtle differences in substrate structures altered their reactivity significantly; and different conditions were required to achieve high yields in each case. Successful conditions were developed using a short empirical optimization approach to cover reaction space with a limited set of variables. Excellent *cis*-selectivity was achieved in all cases, except for the THP substrate where minor *trans*-products were formed through a different palladacyclic intermediate. Here, differences in reactivity and selectivity with other directing groups were examined.

Introduction

Saturated heterocycles, particularly 5- and 6-membered rings containing N or O, are crucial components across a wide range of biologically active compounds, featuring prominently in natural products and pharmaceuticals.[1,2] Extensive synthetic studies have continued across many decades to provide efficient access to substituted heterocyclic derivatives.[3] For medicinal chemistry this has become increasingly relevant, with recent calls for increased saturation and more 3-dimensional characteristics in drug-like and lead-like compounds.[4,5] The concepts of lead-oriented synthesis[4a] and "escape from flatland"[4d] have provided renewed vigor in the study of polar saturated heterocycles.[6] Compounds with reduced aromaticity, low lipophilicity and an increased fraction of sp^3 centers (Fsp^3) have been proposed to afford drug candidates more likely to successfully proceed through all stages of development.[4,5] Reliable synthetic methods that can divergently access saturated heterocyclic frameworks with control over the 3D arrangement of substituents are therefore highly valuable.

Transition metal catalyzed functionalization of unactivated C–H bonds promises to revolutionize the synthesis of complex molecules.[7] For C–C bond formation at sp^3 centers, issues of stereochemistry, the stability of metalated intermediates, and selectivity across often poorly differentiated C–H bonds must be resolved. Recently, selective arylation of C(sp^3)–H bonds has been achieved using directing groups to locate transition metal species and stabilize intermediates.[8–22] Amide-linked directing groups have permitted arylation processes for a variety of substrates, while also making subsequent removal of the directing group possible.[9] In a seminal report in 2005, Daugulis reported the use of 8-aminoquinoline (AQ) amides for C–H arylation at sp^3 centers with aryl iodides, employing catalytic $Pd(OAc)_2$ and stoichiometric AgOAc (Scheme 1, a).[10] Later, Daugulis introduced the 2-(methylthio)aniline group as an effective auxiliary for the arylation of primary C–H bonds, while avoiding bis-arylation, which was a characteristic of the AQ group.[10b] At a similar time, Yu reported the palladium-catalyzed β-C–H arylation of carboxamides employing monodentate directing groups to facilitate functionalization with aryl iodide coupling partners. This weaker coordination mode used finely-tuned, designed ligands.[11] This approach has subsequently been extended to enantioselective variants using enantioenriched ligands.[12]

The last few years has seen the development of alternative strongly coordinating bidentate directing groups for use with palladium catalysts.[13–16] These approaches have extended palladium-catalyzed arylation to a variety of methyl and methylene centers.[9–17] A number of cyclic systems have been investigated, including cyclopropanes[18] and cyclobutanes.[12,19] Furthermore, C–H arylation of amino acid derivatives using both acid[20] and amine,[21,22] linked directing groups have been developed.[23] These reactions with bidentate directing groups are likely to operate through a Pd^{II}/Pd^{IV} catalytic cycle.[10] A concerted metalation-deprotonation is often proposed, invoking an acetate ligand on Pd to assist in breaking the C–H bond and forming a Pd^{II} metallacycle.[24] This intermediate undergoes oxidative addition with an aryl iodide, giving a Pd^{IV} intermediate, followed by reductive elimination to form the new C–C bond.[25] There remain limited examples of successful arylation

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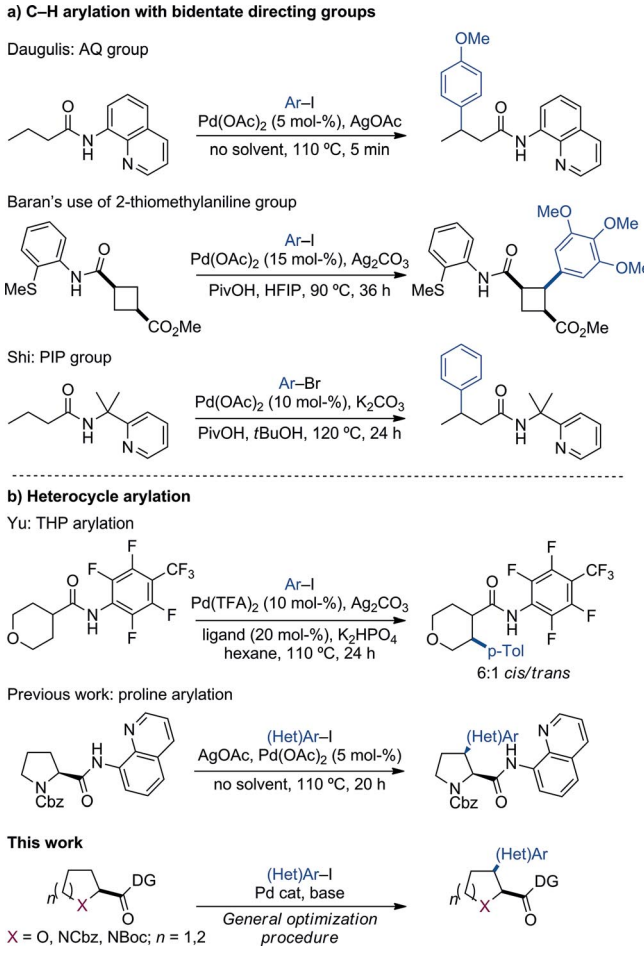


Scheme 1. Directed C(sp^3)–H arylation: acyclic, cyclic and heterocyclic substrates.

using aryl bromides,[13a,26] and of using alkyl halides for C–H alkylation.[10b,27] Examples of the use of Ni[28] and Fe[29] catalysts in C(sp^3)–H arylation have recently been developed.

Notably absent through these extensive works are studies on the catalytic C–H functionalization of saturated heterocycles at unactivated positions (Scheme 1, b).[30–33] Yu has shown a single example of arylation[17a] and alkynylation[34] of a 4-amido-tetrahydropyran derivative, with C–H functionalization occurring at the 3-positions, *beta* to the directing groups. Chen demonstrated a single example of β-C–H alkylation on a 2-piperidinecarboxamide with ethyl iodoacetate, employing the AQ directing group.[27a] We recently published the stereospecific palladium-catalyzed C–H arylation at the 3-position of proline derivatives, starting from *N*-Cbz-protected proline with the AQ directing group.[35,36] During the course of this work Babu reported the arylation of THF derivatives.[37] This limited set of examples is surprising given the importance of saturated heterocycles in biologically active compounds, and the potential for C–H functionalization to provide efficient divergent and iterative synthesis of derivatives, which is essential in the optimization of compounds in drug discovery.

Here, we report the development of C–H arylation protocols for various heterocyclic derivatives using the aminoquinoline directing group (Figure 1). Different arylation conditions are developed for each of the THF, pyrrolidine, piperidine and THP substrates to achieve high yields. We present a comparison of substrate success in these transformations, and provide a condensed optimization approach using only a limited set of reaction conditions. A comparison of directing groups was undertaken on the THP substrate in terms of reactivity and stereoselectivity. Finally, our optimization approach was demonstrated on a carbocyclic and an acyclic aminoquinoline amide to demonstrate the flexibility and applicability of this process, providing comparisons with literature results (Figure 1).

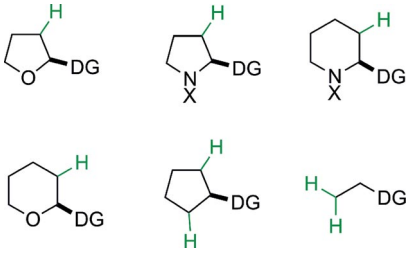


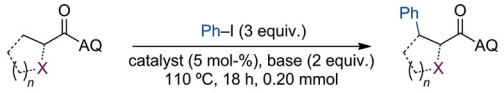
Figure 1. Substrate classes in this study optimized through a concise optimization protocol, posing questions of stereoselectivity or mono vs. bis-arylation (DG = CONHQ, X = Boc, Cbz).

Results and Discussion

Scope of Study and Optimization Protocol

For our study we selected to use Daugulis' bidentate aminoquinoline directing group, which has been shown to be compatible with several substrate classes and varying conditions. Our preliminary investigations indicated that one set of conditions was unlikely to be applicable across the range of substrates of interest; indeed, in our previous study, there was a remarkable variation in reaction outcome even between *N*-Boc- and *N*-Cbz-prolinecarboxamides.[35] In many cases in the literature, extensive optimization is reported for C–H arylation of different AQ-amide substrates, and there are no general conditions. However, it was striking that these final optimized conditions frequently fell within a limited set. We considered that a logical, programmed route to optimization of different substrates would be valuable in expanding access to new heterocyclic derivatives. Consequently, based on examination of the literature and our prior experience we selected a much-reduced set of reaction variables that we considered would cover the relevant reaction space and offer the best chance of success. The resulting optimization process we designed is illustrated in Figure 2.

A number of parameters were maintained constant throughout the optimization process: catalyst loading (5 mol-%), equivalents of base (2 equiv.), iodobenzene (3 equiv.), temperature (110 °C), time (18 h) and scale (0.20 mmol). For efficiency, we limited the optimization to three rounds and 4 new sets of conditions per round, along with selected repeat reactions as control experiments. Initial experiments (round 1) were to establish the viability of the reaction, the preferred Pd source and solvent.[38] One significant decision was to run the reaction un-



	Round 1[a]	Round 2[a,b]	Round 3[c]
1	AgOAc, $Pd(OAc)_2$, toluene	Ag_2CO_3	0.2 M
2	AgOAc, $Pd(TFA)_2$, toluene	Ag_2CO_3, PivOH	0.5 M
3	AgOAc, $Pd(OAc)_2$, *tert*-amyl-OH	K_2CO_3, PivOH	1.0 M
4	AgOAc, $Pd(OAc)_2$, neat	CsOAc	neat

Figure 2. Process and parameters used for optimization of the C–H arylation for each substrate. [a] Reactions were performed at 0.3 M concentration with respect to amide. [b] Using preferred solvent and Pd source from round 1; 1 equiv. Ag_2CO_3, 30 mol-% PivOH. [c] Using preferred solvent, Pd source and base from rounds 1 and 2.

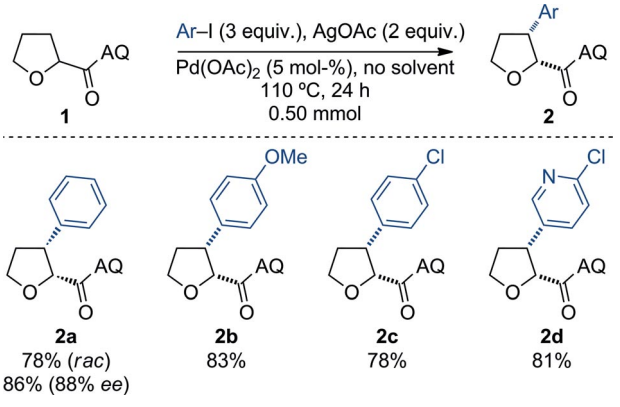
der solvent-free conditions early on. Examples in the literature,[10] as well as our own work,[35] indicated this could be advantageous for challenging substrates, particularly when using AgOAc, but may then offer little scope for further optimization. Next, round 2 would examine halophilic bases, with K, Cs and Ag^I salts featuring prevalently in the literature. Acidic additives (PivOH) were used with Ag_2CO_3 or K_2CO_3, where they appeared most advantageous. For conditions that used a solvent, the concentration of the reaction would then be varied (round 3). Finally, we considered it prudent to allow some flexibility in reaction time or catalyst loading, to generate isolated yields. We anticipated that this study could provide valuable insight into the reactivity of differing substrates, as well as an opportunity for comparison of conditions and directing groups across related substrates.

THF Substrate

Tetrahydrofuran AQ-amide **1** was investigated first through this process (Table 1). Applying round 1 of the optimization process, the solvent-free conditions gave the best result, with a 79 % yield of the desired 3-phenyl-THF **2a** by ^1H NMR spectroscopy (Entry 4). No further improvement was obtained when examining bases (Entries 5–8).

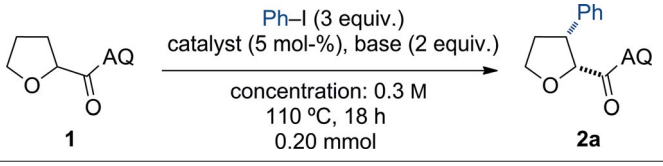
Crucial to our hypothesis was that this result was likely to be a maximum yield for this substrate subject to the imposed constraints (i.e. the AQ directing group with these loadings of base and iodide). To demonstrate this, we progressed a full standard optimization at the same time.[39] By this alternative route we also converged on the same solvent-free conditions, and did not obtain an improved yield.

Encouraged, we ran a small scope with the successful conditions, using a representative range of electron rich, electron poor and heterocyclic aryl iodides (Scheme 2). This was performed using AgOAc as a base with no solvent, but the reaction time was increased to 24 h in an attempt to further conversion. High yields were obtained across the substrates types; the phenyl example **2a** proceeded in 78 % yield, electron rich 4-iodoanisole gave 83 % of the arylated compound **2b** and the *p*-chlorophenyl example **2c** was isolated in a 78 % yield. Additionally, a chloropyridyl substituent could be installed in an excellent yield of 81 %. When using enantiopure **(*R*)-1**, an 88 % *ee* of the phenylated product (–)-**2a** was obtained, suggesting a small degree of racemization of the starting material occurred under these conditions. Notably, only the *cis*-diastereoisomer of the product was observed in all cases.



Scheme 2. Selected scope of aryl iodides compatible with the C–H arylation reaction of THF carboxamide **1**.

Table 1. Optimization of the C–H arylation of THF carboxamide **1**.

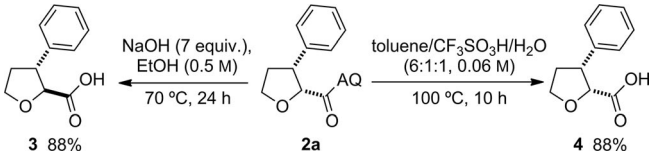


Entry	Round	Varied conditions	Yield **2a** [%][a]	RSM **1** [%][a]
1	1	AgOAc, $Pd(OAc)_2$, toluene	46[b]	54[b]
2	1	AgOAc, $Pd(TFA)_2$, toluene	13	87
3	1	AgOAc, $Pd(OAc)_2$, *tert*-amyl-OH	57	43
4	1	AgOAc, $Pd(OAc)_2$, no solvent	79[b]	21[b]
5[c]	2	Ag_2CO_3, $Pd(OAc)_2$, no solvent	19	81
6[c,d]	2	Ag_2CO_3, PivOH, $Pd(OAc)_2$, no solvent	56	44
7[d]	2	K_2CO_3, PivOH, $Pd(OAc)_2$, no solvent	6	94
8	2	CsOAc, $Pd(OAc)_2$, no solvent	17	83

[a] Yield of product **2a** or recovered starting material **1** determined by ^1H NMR spectroscopy with respect to an internal standard (1,3,5-trimethoxybenzene). [b] Average yield of 2 reactions. [c] 1 equiv. Ag_2CO_3. [d] 30 mol-% PivOH.

During the course of this work Babu reported a related set of conditions for the arylation of THF carboxamide **1**,[37] obtaining a 73 % yield for **2a**, a 62 % yield for **2c** and 56 % yield for **2d**.[40] The optimization process we describe here afforded improved yields with lower catalyst and reagent loadings, based on the examination of reaction concentration as a variable (solvent-free vs. 0.08 M).

The AQ directing group was then removed under two sets of conditions to provide either the *cis* or *trans* isomer selectively (Scheme 3).[41]



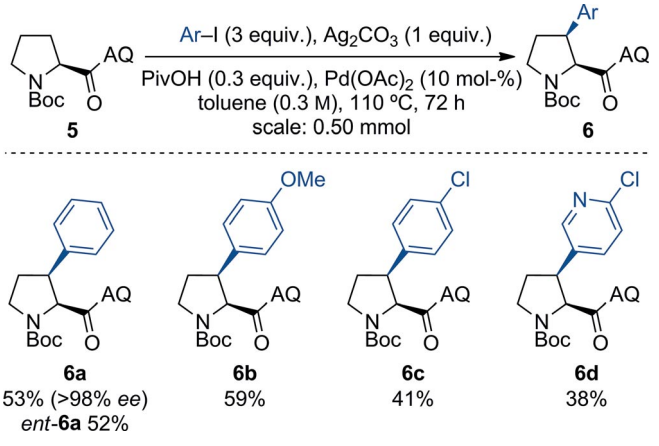
Scheme 3. Selective removal of the 8-aminoquinoline directing group to afford either the *trans*-acid **3** or *cis*-acid **4**.

Hydrolysis and epimerization to the trans-THF acid **3** was observed in 88 % yield, upon treating the THF carboxamide **1** with sodium hydroxide in ethanol at 70 °C for 24 h, with 8-aminoquinoline recovered in 99 %. Alternatively, the *cis*-acid **4** could be isolated in the same yield, when using conditions reported by Babu.[37]

N-Boc Pyrrolidine Substrate

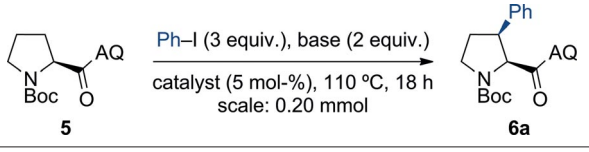
In our previous work on the arylation of *N*-Cbz-proline derivatives we observed significantly reduced reactivity for *N*-Boc-proline AQ-amide **5**.[35] Applying the first round conditions to the *N*-Cbz substrate gave quantitative conversion to the arylated product under the solvent-free conditions, similar to the final conditions developed previously. With the *N*-Boc-pyrrolidine derivative **5** the best yield achieved through round 1 was also under solvent-free conditions, giving a 21 % yield by ^{1}H NMR spectroscopy (Table 2, Entries 1–4), with the majority of the starting material returned unreacted in each case. As the solvent-free conditions were only marginally better than the reaction using $Pd(OAc)_2$ in toluene, we chose to examine conditions using toluene as solvent to provide greater scope for optimization. On examining bases, the Ag_2CO_3 and pivalic acid additive combination was found to be best, providing a 40 % yield by NMR spectroscopy. Varying the concentration of the reaction with these sets of conditions did not improve the yield (Table 2).

For this challenging substrate, additional variables were considered to improve the yield to an acceptable value. Increasing the reaction time to 72 h gave a similar conversion. Increasing the $Pd(OAc)_2$ loading to 10 mol-% at this longer reaction time gave a conversion of 70 %. These conditions were then used to examine the reactivity of the representative scope of aryl iodides (Scheme 4). Pleasingly, all four aryl iodides were compatible in modest to good yields. The phenyl example **6a** was isolated in 53 %, as a single enantiomer, yields ranged from 38 % for the pyridyl example **6d** to 59 % for the *p*-methoxy-



Scheme 4. Selected scope of aryl iodides compatible with the C–H arylation reaction of *N*-Boc-pyrrolidinecarboxamide **5**.

Table 2. Optimization of C–H arylation of *N*-Boc-pyrrolidinecarboxamide **5**.



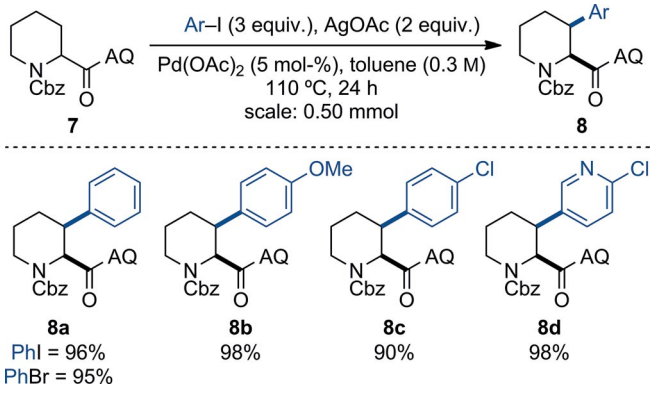
Entry	Round	Varied conditions	Yield **6a** [%][a]	RSM **5** [%][a]
1	1	AgOAc, $Pd(OAc)_2$, toluene (0.3 M)	18[b]	82[b]
2	1	AgOAc, $Pd(TFA)_2$, toluene (0.3 M)	0	100
3	1	AgOAc, $Pd(OAc)_2$, *tert*-amyl-OH (0.3 M)	10	90
4	1	AgOAc, $Pd(OAc)_2$, no solvent	21	79
5[c]	2	Ag_2CO_3, $Pd(OAc)_2$, toluene (0.3 M)	24	76
6[c,d]	2	Ag_2CO_3, PivOH, $Pd(OAc)_2$, toluene (0.3 M)	40[e]	60[e]
7[d]	2	K_2CO_3, PivOH, $Pd(OAc)_2$, toluene (0.3 M)	3	97
8	2	CsOAc, $Pd(OAc)_2$, toluene (0.3 M)	12	88
9[c,d]	3	Ag_2CO_3, PivOH, $Pd(OAc)_2$, toluene (0.2 M)	33	67
10[c,d]	3	Ag_2CO_3, PivOH, $Pd(OAc)_2$, toluene (0.5 M)	33	67
11[c,d]	3	Ag_2CO_3, PivOH, $Pd(OAc)_2$, toluene (1.0 M)	36	64
12[c,d]	3	Ag_2CO_3, PivOH, $Pd(OAc)_2$, no solvent	34	66

[a] Yield of product **6a** or recovered starting material **5** determined by ^{1}H NMR spectroscopy with respect to an internal standard (1,3,5-trimethoxybenzene). [b] Average yield of 3 reactions. [c] 1 equiv. Ag_2CO_3. [d] 30 mol-% PivOH. [e] Average yield of 2 reactions.

phenyl example **6b**. In all cases, single *cis*-diastereoisomers were observed.[42]

N-Cbz-Piperidine: A Highly Reactive Substrate

For *N*-Cbz-piperidinecarboxamide **7** all conditions attempted in the first round of optimization provided quantitative conversion to the 3-phenyl-piperidine **8a** (Table 3, Entries 1–4). This is a remarkable increase in reactivity vs. the five-membered ring derivatives. The conditions using $Pd(OAc)_2$ and toluene (Entry 1) were selected to examine reaction scope due to the increased ease of processing of the crude reaction compared to the reactions without solvent. This gave excellent yields with all examples, ranging from 90 % for the *p*-chlorophenyl example **8c** to 98 % for the *p*-methoxyphenyl **8b** and pyridyl **8d** examples (Scheme 5). In all cases, only the *cis*-configured isomer was observed.[43,44]



Scheme 5. Selected scope of aryl iodides compatible with the C–H arylation reaction of *N*-Cbz-piperidinecarboxamide **7**.

Given the much increased reactivity of this substrate, the first round of optimization was repeated using bromobenzene (Table 3, Entries 5–8). Aryl bromides are generally considerably less expensive than aryl iodides, but have been mostly ineffective in this mode of C–H arylation. On this substrate, the yields were lower than those reactions employing the aryl iodide, but by using AgOAc as a base in neat conditions, the desired 3-phenylpiperidine **8a** was formed in 99 % conversion, which corresponded to a 95 % isolated yield, comparable to using the aryl iodide. However, despite the increased reactivity of this substrate, attempts to use 2-iodotoluene as a coupling partner were unsuccessful, demonstrating the difficulties of using *ortho*-substituted aryl iodides in directed C–H arylation processes.[45]

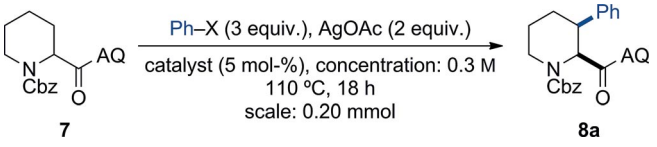
N-Boc Piperidine Substrate

Given the reduced propensity of *N*-Boc-pyrrolidine amide **5** to undergo C–H arylation compared to the *N*-Cbz derivative, we were interested to compare this trend in the piperidine series. Indeed, on subjecting the *N*-Boc-piperidine derivative **9** to round 1 of the optimization, reduced yields were obtained compared with *N*-Cbz-piperidine substrate **7** (Table 4). Only 14 % of 3-phenyl-Boc-piperidine **10a** was obtained with $Pd(TFA)_2$ (Entry 2), but 90 % was obtained with $Pd(OAc)_2$ under solvent-free conditions (Entry 4). For the *N*-Cbz derivative these reaction conditions both gave quantitative conversion to the desired arylated compound, indicating that the Boc group again caused a reduction in reactivity. With the solvent-free conditions significantly better than the others investigated, we took these forward to the base screen. The silver carbonate and pivalic acid additive combination gave the best yield of arylated compound **10a** (Entry 6, 96 % by ^{1}H NMR spectroscopy). This combination of Ag_2CO_3 and pivalic acid has not been previously reported under solvent-free conditions.

These conditions were then used to examine the reaction scope with the same selection of aryl iodides. Good to excellent yields were achieved, ranging from 52 % for the pyridyl example **10d** to 89 % for the *p*-chlorophenyl example **10c** (Scheme 6).

Using 4-iodoanisole in a one gram scale reaction gave an identical yield after 36 h. With this more challenging *N*-Boc-piperidine substrate, a wider selection of aryl iodides was employed to demonstrate functional group tolerance under these relatively forcing conditions. The reaction was successful with 3-iodobenzonitrile as well as *para*-ester and methyl ketone sub-

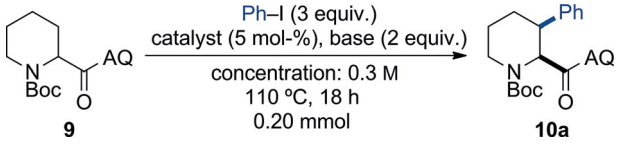
Table 3. Optimization of the C–H arylation of *N*-Cbz-piperidinecarboxamide **7**.



Entry	Round	Varied conditions	Yield **8a** [%][a]	RSM **7** [%][a]
1	1	PhI, $Pd(OAc)_2$, toluene	100[b]	0[b]
2	1	PhI, $Pd(TFA)_2$, toluene	100	0
3	1	PhI, $Pd(OAc)_2$, *tert*-amyl-OH	100	0
4	1	PhI, $Pd(OAc)_2$, no solvent	100	0
5	1	PhBr, $Pd(OAc)_2$, toluene	92[b]	8[b]
6	1	PhBr, $Pd(TFA)_2$, toluene	7	93
7	1	PhBr, $Pd(OAc)_2$, *tert*-amyl-OH	83	17
8	1	PhBr, $Pd(OAc)_2$, no solvent	99	1

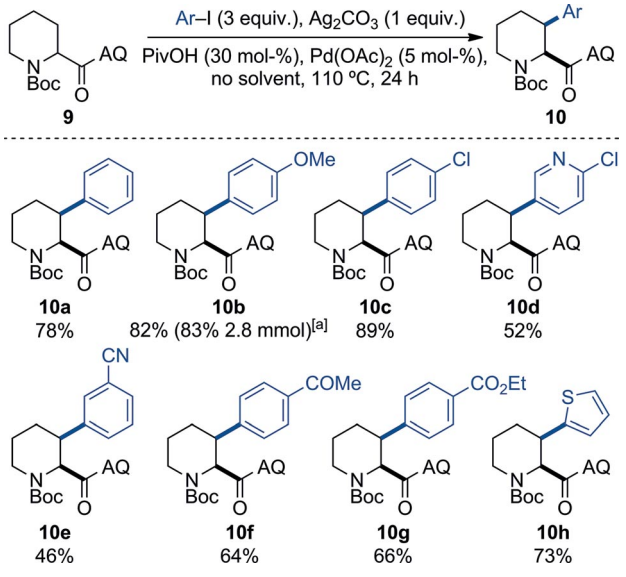
[a] Yield of product **8a** or recovered starting material **7** determined by ^{1}H NMR spectroscopy with respect to an internal standard (1,3,5-trimethoxybenzene). [b] Average yield of 2 reactions.

Table 4. Optimization of the C–H arylation of *N*-Boc-piperidinecarboxamide **9**.



Entry	Round	Varied conditions	Yield **10a** [%][a]	RSM **9** [%][a]
1	1	AgOAc, $Pd(OAc)_2$, toluene	47[b]	50[b]
2	1	AgOAc, $Pd(TFA)_2$, toluene	14	85
3	1	AgOAc, $Pd(OAc)_2$, *tert*-amyl-OH	53	47
4	1	AgOAc, $Pd(OAc)_2$, no solvent	90[b]	10[b]
5[c]	2	Ag_2CO_3, $Pd(OAc)_2$, no solvent	88	12
6[c,d]	2	Ag_2CO_3, PivOH, $Pd(OAc)_2$, no solvent	96	4
7[d]	2	K_2CO_3, PivOH, $Pd(OAc)_2$, no solvent	29	71
8	2	CsOAc, $Pd(OAc)_2$, no solvent	48	52

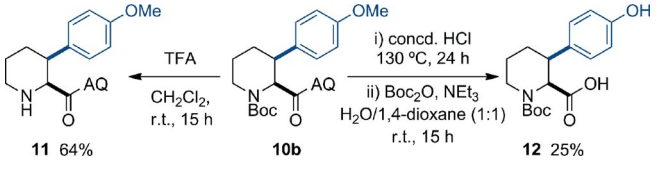
[a] Yield of product **10a** or recovered starting material **9** determined by ^1H NMR spectroscopy with respect to an internal standard (1,3,5-trimethoxybenzene). [b] Average yield of 2 reactions. [c] 1 equiv. Ag_2CO_3. [d] 30 mol-% PivOH.



Scheme 6. Selected scope of aryl iodides compatible with the C–H arylation reaction of *N*-Boc-piperidinecarboxamide **9**. [a] 36 h reaction time.

stituents to give piperidines **10e**–**10g** respectively. In addition, 2-iodothiophene afforded piperidine **10h** in good yield. Again, in all cases, only a single diastereoisomer was observed.[43]

From 3-(4-methoxyphenyl)piperidine derivative **10b** the Boc group could be removed with TFA to give the free amine **11** (Scheme 7). Alternatively, heating in concentrated aqueous HCl gave full deprotection, removing the Boc group, the aminoquinoline directing group, and also converted the anisole to the phenol. Subsequent Boc protection of the resulting amino



Scheme 7. Deprotection of **10b** to form amine **11** or 3-arylpipecolinic acid derivative **12**.

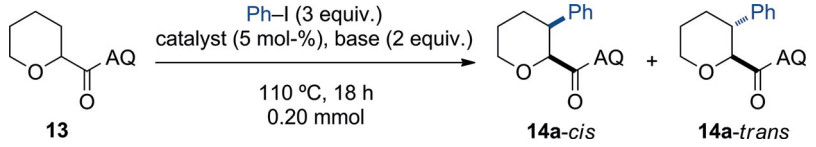
acid afforded pipecolinic acid derivative **12** which constituted an interesting scaffold for further elaboration in multiple directions.

THP Substrate: *cis*/*trans* Selectivity

When tetrahydropyran AQ-carboxamide **13** was subjected to round 1 of optimization, a mixture of 3-phenyl-THP products was observed (**14a**-*cis* and **14a**-*trans*, Table 5). Unlike in the previous cases, the *trans*-configured arylated product was now observed as a minor component under all conditions.[46] The solvent-free conditions showed the most reactivity, but provided low *cis*-*trans* selectivity (Entry 4). The best balance of yield and diastereomeric ratio (*dr*) was observed using *tert*-amyl-OH and $Pd(OAc)_2$ (Entry 3), therefore these conditions were progressed to the next round. On varying the bases, both Ag_2CO_3 (Entry 5) and Ag_2CO_3/PivOH (Entry 6) gave similar results, with 66 % *cis*-**14a** and approximately 11 % *trans*-**14a** under both conditions. The set of conditions without PivOH were taken forward to the concentration screen for reasons of experimental simplicity. In this case, the concentration of the reaction was found to have little effect on yield and *dr* (Entries 9–12).

This substrate provided an interesting opportunity to compare reactivity and selectivity with different directing groups. Therefore, Shi's PIP-amine directing group and the 2-(methylthio)aniline auxiliary were examined and taken through the optimization procedure. However, these gave reduced reactivity and reduced selectivity vs. the aminoquinoline auxiliary (Figure 3; see the Supporting Information for full details). For the PIP-amine tetrahydropyran carboxamide, round 1 of optimization gave the desired arylation with just 14 % *cis* and 4 % *trans* products **15a** as the best conditions [*tert*-amyl-OH, $Pd(OAc)_2$]. These conditions were carried forward to the second round of optimization, where the Ag_2CO_3/PivOH additive combination was found to be the best base/additive mixture, giving 48 % *cis* and 11 % *trans*-configured arylated THP **15a**. The concentration of the reaction was found to have little effect on yield or *dr*. These optimised conditions gave a 34 % isolated yield of **15a** as the *cis*-isomer. Interestingly, the optimized conditions were very similar for **14a** and **15a**. The 2-(methylthio)aniline directing

Table 5. Optimization of the C–H arylation of THP carboxamide **13**.



Entry	Round	Varied conditions	*cis* [%][a]	*trans* [%][a]
1	1	$AgOAc$, $Pd(OAc)_2$, toluene (0.3 M)	38[b]	13[b]
2	1	$AgOAc$, $Pd(TFA)_2$, toluene (0.3 M)	22	3
3	1	$AgOAc$, $Pd(OAc)_2$, *tert*-amyl-OH (0.3 M)	47[b]	11[b]
4	1	$AgOAc$, $Pd(OAc)_2$, no solvent	49	23
5[c]	2	Ag_2CO_3, $Pd(OAc)_2$, *tert*-amyl-OH (0.3 M)	66	13
6[c,d]	2	Ag_2CO_3, PivOH, $Pd(OAc)_2$, *tert*-amyl-OH (0.3 M)	66	11
7[d]	2	K_2CO_3, PivOH, $Pd(OAc)_2$, *tert*-amyl-OH (0.3 M)	24	10
8	2	$CsOAc$, $Pd(OAc)_2$, *tert*-amyl-OH (0.3 M)	32	6
9[c,d]	3	Ag_2CO_3, PivOH, $Pd(OAc)_2$, *tert*-amyl-OH (0.2 M)	65	13
10[c,d]	3	Ag_2CO_3, PivOH, $Pd(OAc)_2$, *tert*-amyl-OH (0.5 M)	62	17
11[c,d]	3	Ag_2CO_3, PivOH, $Pd(OAc)_2$, *tert*-amyl-OH (1.0 M)	62	11
12[c,d]	3	Ag_2CO_3, PivOH, $Pd(OAc)_2$, no solvent	61	16

[a] Yield determined by ^1H NMR spectroscopy with respect to an internal standard (1,3,5-trimethoxybenzene). In all cases, the remainder of the mass balance corresponded to unreacted starting material **13**. [b] Average yield of 2 reactions. [c] 1 equiv. Ag_2CO_3. [d] 30 mol-% PivOH.

group was also examined, but less than 5 % yield of the corresponding product **16a** was observed in all cases. This unbiased comparison, indicated the AQ amide **13** to be most successful in this case, and therefore this derivative was used to exemplify the C–H arylation on the THP ring (Scheme 8).

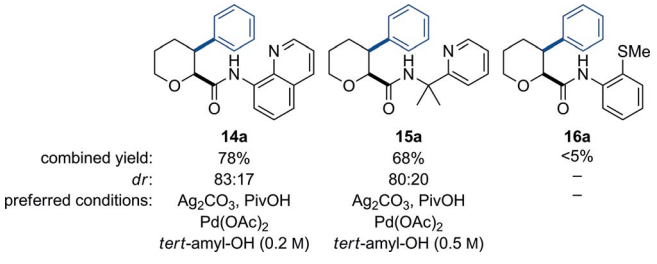
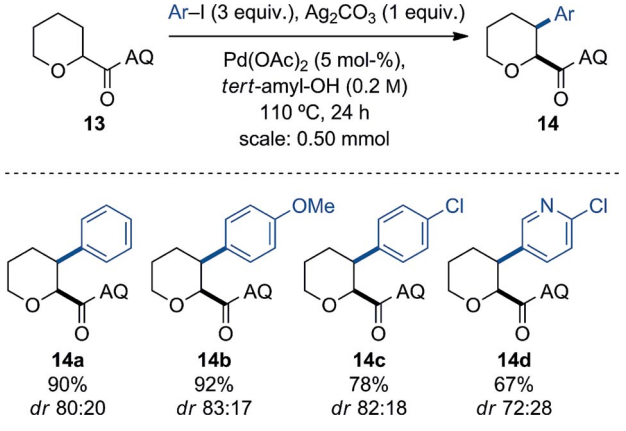


Figure 3. Comparison of optimal yields and product ratios of different directing groups on THP carboxamides, following the standard optimization procedure, yields and diastereomeric ratio (*dr*) quoted as observed in the crude reaction mixture against an internal standard after 18 h reaction time.



Scheme 8. Selected scope of aryl iodides compatible with the C–H arylation reaction of THP carboxamide **11**, yield and *dr* of products on isolation after a 24 h reaction time.

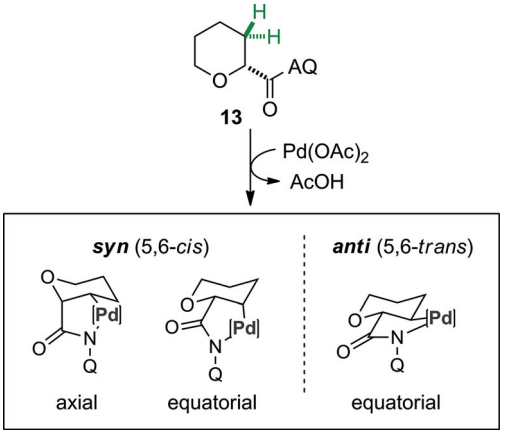
Under the conditions optimized for THP AQ-amide **13** the reaction scope was investigated, with an increased reaction time of 24 h. Good to excellent yields were achieved in all cases. Diastereomeric ratios of between 83:17 and 80:20 were obtained on isolation of phenyl derivatives **14a**–**14c**, with the pyridyl example **14d** giving a 72:28 *dr*.

Stereochemical Outcomes

To provide insight into the origin of the diastereomeric mixture formed from THP **13**, the purified product **14a** (as an 81:19 *cis*/*trans* mixture of diastereoisomers by ^1H NMR) was resubjected to the reaction conditions for 18 h. Identical *dr* (81:19 *cis*/*trans*) was observed on workup. In addition, the reaction of THP **13** with PhI, under the optimized conditions, was stopped after a series of time points, and at each time point the same *dr* was observed.[47] These results indicate that epimerization of the product does not occur under the reaction conditions. We propose that this is a result of both *cis* and *trans*-palladacycles being formed, leading to the two diastereoisomers. These would correspond to three feasible intermediates leading to the *syn* and *anti*-substituted products (Scheme 9).

This is consistent with the outcome observed by Yu on C(sp^3)–H arylation of a 4-amido tetrahydropyran, which afforded a 6:1 *cis*/*trans* mixture, albeit with a different substitution pattern on the heterocycle (Scheme 1, b). Also, Daugulis reported the di-arylation of a cyclohexane AQ-carboxamide, which afforded a 69 % *all-cis* to 13 % *cis-trans* mixture of isomers, using 4-iodoanisole and AgOAc as base under solvent-free conditions.[10b]

By contrast, for the THF and pyrrolidine substrates, the *trans*-5,5-palladacycle would likely be significantly higher in energy, hence the observation that only *cis* diastereoisomers are formed in these cases. Interestingly, both *N*-carbamate piperidine examples (**7** and **9**) gave only the *cis*-diastereoisomers, which is likely due to the strong preference for the ring to adopt conformations with the directing group in an axial position, to minimize A(1,3) strain with the *N*-carbamate group.[48]



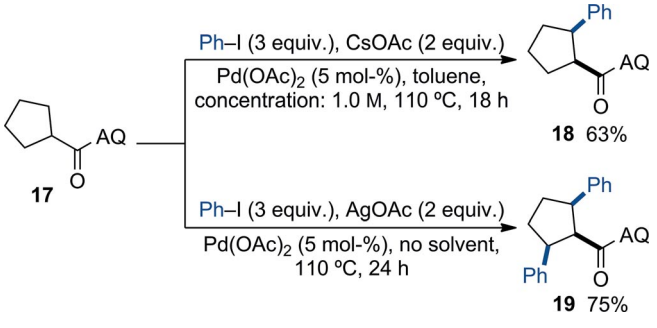
Scheme 9. Viable conformations of the palladacyclic intermediate formed from THP carboxamide **13**.

Cyclopentane and Propionamide Substrates: Selectivity in Mono/Di-Arylation

To further study the applicability of this optimization process, we examined two non-heterocyclic substrates to provide a comparison with previously reported conditions, particularly with substrates that can undergo multiple arylation reactions to probe for selectivity.

Cyclopentanecarboxamide **17** can undergo mono or di-arylation, to provide trifunctionalized cyclopentanes. The best yields of mono β-C–H arylation of cyclopentane carboxylic acid derivatives have been achieved by Daugulis (52 % yield)[10b] and Yu (71 % yield as a 7:1 mono/di mixture).[17a,49] Shi demonstrated di-arylation of cyclopentanecarboxamide **17**, installing two phenyl groups in 51 % yield, as the *all-cis* diastereoisomer, using diarylhyperiodonium salts as coupling partners.[17b]

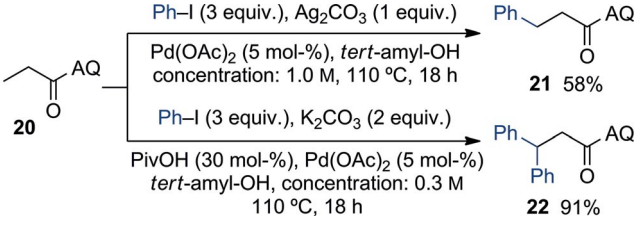
Cyclopentanecarboxamide **17** was subjected to the round 1 of optimization. All reaction conditions gave over 90 % conversion to mixtures of mono and di-arylated products,[50] displaying considerably increased reactivity compared to the five-membered heterocyclic derivatives. The highest mono-selectivity was obtained using toluene with $Pd(OAc)_2$ as catalyst (64 % yield of mono-arylated cyclopentane **18**). These conditions were taken on to the base screen, where CsOAc gave an improvement to 71 % yield. The concentration of the reaction had little effect on the yield, but with a 1.0 M concentration the yield of mono-arylated compound **18** increased to 72 % (corresponding to 63 % isolated yield), with a 24 % yield of di-arylated **19** also observed (Scheme 10).



Scheme 10. Isolated yields for the mono and di-selective β-C–H arylations of cyclopentanecarboxamide **17**.

During the first optimization round, di-arylation of cyclopentanecarboxamide **17** was achieved in 71 % yield under the solvent-free conditions (25 % mono-arylation). Varying the bases did not afford an improved yield. The di-arylated product **19** was isolated in a 75 % yield under these conditions using AgOAc as base with a 24 h reaction time (Scheme 10). This short optimization process enabled selective mono-arylation of the cyclopentane derivative in 63 % yield, or di-arylation in 75 % yield, which provides similar or improved outcomes in comparison to the literature results.

A similar process was performed with propionamide **20** where sequential C–H arylations may occur on the same carbon atom, the second at a more acidic benzylic position. This short optimization process provided conditions for selective mono or bis-arylation, using $Pd(OAc)_2$ and an excess of aryl iodide in both cases.[50] Using Ag_2CO_3 in *tert*-amyl-OH gave mono-selective arylation product **21** in 58 % yield (Scheme 11). On the other hand, using a K_2CO_3/PivOH combination and *tert*-amyl-OH as solvent provided quantitative conversion to bis-arylated product **22** (91 % isolated yield), giving a similar set of conditions to those reported by Zeng. These results compare favorably with those previously reported for this substrate.[51]



Scheme 11. Isolated yields for the mono and bis-selective β-C–H arylations of propionamide **20**.

Conclusions

In conclusion, C–H functionalization can rapidly afford 2,3-substituted heterocycles with stereocontrol. We have developed successful conditions for C–H arylation at the 3-position of THF and pyrrolidine derivatives, and the first examples on piperidine and THP substrates, using AQ carboxamide directing groups at C-2. High yields were achieved with each heterocyclic substrate across a representative collection of aryl iodides. Complete *cis*-selectivity was achieved for the THFs, pyrrolidines, and piperidines. The THP substrate was also *cis*-selective, but the *trans*-configured product was also formed as a minor component. Removal of the aminoquinoline group was demonstrated on the THF substrate, to selectively access either *trans* or *cis*-configured THF carboxylic acids.

The same concise optimization process was adopted across all substrates, using a limited number of variables designed to cover appropriate reaction space. This process afforded successful conditions for each heterocyclic substrate. We have also demonstrated that this short optimization procedure could afford conditions that were selective for either mono-arylation or

di-arylation of cyclopentane and propionamide substrates. We consider this may provide a useful process for developing C–H arylation reactions.

This programmed approach allowed facile comparison of the reactivity of the different substrates. The six-membered rings (piperidine and THP) were considerably more reactive than the corresponding five-membered ring derivatives (pyrrolidine and THF). Interestingly, the *N*-Boc-protected *N*-heterocycles were much less reactive than the analogous *N*-Cbz derivatives for both 5- and 6-membered rings. The reasons for the differences in substrate reactivity are not yet well-explained by current models and require further investigation, which will be reported in due course.

Experimental Section

Supporting Information (see footnote on the first page of this article): All experimental details can be found in the supporting information. This includes experimental procedures, characterization data, copies of ^{1}H and ^{13}C NMR spectra and further details of reaction optimization.

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[39] See supporting information for further details of optimization on THF carboxamide **1** (extended optimization process). There was no advantage of using alternative concentrations, additives or bases, with toluene or *tert*-amyl-OH as solvent, providing confidence in this approach.

[40] Babu and co-workers reported the following conditions: 4 equiv. ArI, 10 mol-% $Pd(OAc)_2$, 2.2 equiv. AgOAc, toluene (0.08 M with respect to the amide), 36 h, 110 °C; see ref. 37.

[41] The stereochemical outcome was assigned on the basis of ^{1}H NMR coupling constants. For the (i) *cis*-configured THF acid **4**: δ = 4.65 (d, J = 7.6 Hz, 1 H, HCC=O); and (ii) *trans*-configured THF acid **3**: δ = 4.56 (d, J = 6.0 Hz, 1 H, HCC=O). See reference 37 for crystal structures and J values for compounds **2a** and **4** indicating stereochemistry.

[42] The stereochemical outcome was assigned on the basis of ^{1}H NMR coupling constants. For example, the *cis*-configured *N*-Boc-3-phenylpyrrolidinecarboxamide **6a** gave the following signal for the C(2)-H: δ = 4.77 (d, J = 8.5 Hz, 1 H, HCC=O). For representative values for *cis* (J = 8.1–8.5 Hz) and *trans* (J = 4.0–6.3 Hz) coupling constants of related *cis* and *trans*-configured *N*-acetyl-3-phenylproline and derivatives, see: J. Y. L. Chung, J. T. Wasicak, W. A. Arnold, C. S. May, A. M. Nadzen, M. W. Holladay, *J. Org. Chem.* **1990**, *55*, 270.

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[50] See supporting information for further details.
[51] The best yields of mono β-C–H arylation of propionamide derivatives have been achieved by Yu (58 % yield) using a monodentate fluoro-aryl amide directing group in a ligand-enabled process.[11a] Chen reported the mono-arylation of *N*-Phth alanine derivatives, using the AQ directing group (91 % yield by ^{1}H NMR spectroscopy).[20e] Zeng demonstrated the bis-arylation of propionamide **20** (91 % yield), using 4-bromoanisole (4 equiv.), 5 mol-% $Pd(TFA)_2$, and a potassium carbonate/pivalic acid combination (3.5 equiv. and 0.5 equiv., respectively) in *tert*-amyl-OH as solvent.[26]

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