Regio- and Stereoselective Palladium Catalyzed C(sp^3)–H Arylation of Pyrrolidines and Piperidines with C(3) Directing Groups

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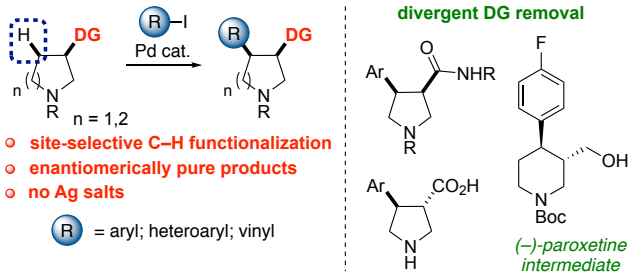
Supporting Information Placeholder



ABSTRACT: The selective synthesis of *cis*-3,4-disubstituted pyrrolidines and piperidines is achieved by a Pd-catalyzed C–H arylation with excellent regio- and stereo-selectivity using an aminoquinoline auxiliary at C(3). The arylation conditions are silver free, use a low catalyst loading, and employ inexpensive K_2CO_3 as a base. Directing group removal is accomplished under new, mild conditions to access amide, acid, ester and alcohol containing fragments and building blocks. This C–H arylation protocol enabled a short and stereocontrolled formal synthesis of (–)-paroxetine.

Saturated nitrogen heterocycles present crucial pharmacophores and structural elements in natural products and pharmaceuticals (Figure 1).[1,2] As such, substituted pyrrolidines and piperidines are highly desirable as building blocks in medicinal chemistry, and as fragments for screening in fragment-based drug discovery.[3] This is complemented by the continuing drive to incorporate more topologically diverse and sp^3-rich structures into pharmaceutical screening libraries.[4] Consequently, enormous synthetic efforts are directed at their synthesis,[5,6] with stereocontrolled methods of particular value.

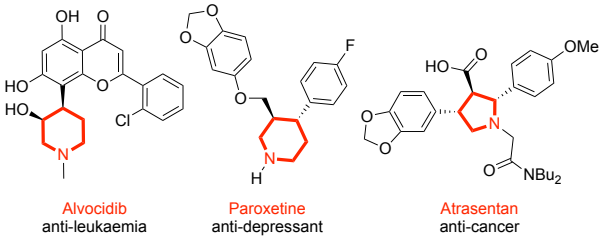


Figure 1. Piperidine and pyrrolidine rings in biologically active compounds.

C–H Functionalization has enormous potential to satisfy the criteria for iterative and divergent synthesis of analogues as required in a medicinal chemistry program.[7] However, there are only limited examples of C–H functionalization on saturated heterocycles, particularly at positions remote from the heteroatom.[8,9,11–18] To date, all examples of directed C–H arylation at unactivated positions of nitrogen-heterocycles use palladium catalysis. We first reported the regio- and stereospecific C(3) arylation of proline derivatives using Daugulis' aminoquinoline amide (AQ)[10] as a directing group (Figure 2).[11,12]

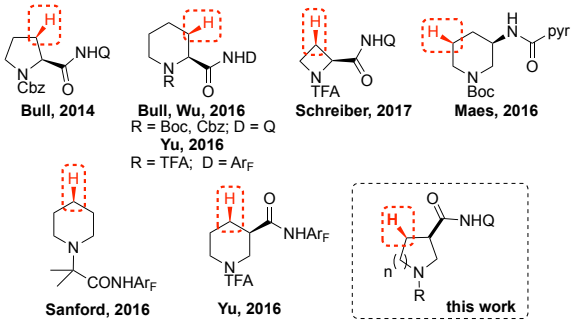


Figure 2. Directed C(sp^3)–H arylation of saturated N-heterocycles at unactivated positions. Q = 8-quinolinyl, Ar_F = *p*-$C_6F_4CF_3$.

We later adapted the conditions to pipecolinic acid derivatives.[13] Wu and Yu independently developed a similar process for C(3) arylation of piperidines,[14,15] and Schreiber reported the directed C(3) arylation of azetidines and pyroglutamic acid derivatives.[16] Maes described the C(5) γ–arylation of 3-aminopiperidine using a picolinamide directing group, via a bridged 5-membered palladacycle.[17] Sanford demonstrated a remarkable remote arylation of bridged heterocycles using an *N*-linked directing

group, which included an example of the C(4) arylation of a piperidine.[18] However, there have been no reported studies on N-heterocycles which pose a regioselectivity question with *beta*-hydrogens in different environments. Yu reported a single example of piperidine arylation with a C(3) directing group, which preferentially gave C(4) arylation as a 1:1 mixture of diastereoisomers, using NHC ligands.[15,19]

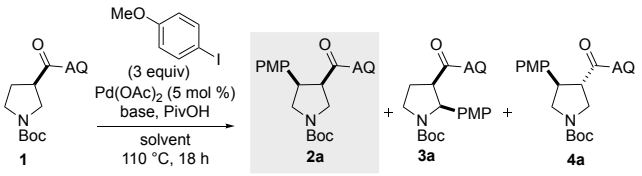
As part of our program on fragment-oriented synthesis, we have targeted substituted N-heterocycles with defined substitution patterns.[11,13] Here we describe the regio- and stereoselective C–H arylation of pyrrolidine and piperidine derivatives at C(4), using a C(3) linked AQ directing group. Conditions were developed that provided high functional group tolerance. Divergent removal of the directing group delivered varied fragments and building blocks suitable for use in medicinal chemistry.

We initially addressed the functionalization of pyrrolidine-3-carboxylic acid which has the potential to undergo C(2) or C(4) arylation, although the C(2) position of pyrrolidines is often considered activated due to the weaker C–H bond. We used the bulky *N*-Boc protecting group alongside a bidentate AQ directing group,[20] expecting the sensitivity of oxidative addition of Pd^{II} to Pd^{IV} to steric hindrance to promote C(4) regioselectivity. Pleasingly, reacting pyrrolidine **1** with 4-iodoanisole, $Pd(OAc)_2$ and AgOAc in toluene gave C–H functionalization preferentially at the unactivated C(4) position (**2a**, 28%) with complete *cis*-selectivity, along with C(2) arylation as the minor product, **3a** (Table 1, entry 1).

The reaction conditions were then adjusted to optimize the yield of **2a** and avoid the use of silver salts.[21] Changing the base to CsOAc gave an improved yield of **2a** (47%), but a significant amount of isomer **3a** was still observed (entry 2), while Cs_2CO_3 was found to promote epimerization of the product to *trans*-substituted **4a** (entry 3). On the other hand, the combination of K_2CO_3 and pivalic acid resulted in improved selectivity for **2a** (entry 4). In the absence of PivOH there was a drop in yield (entry 5). Preformed potassium pivalate resulted in a lower yield and selectivity, and less bulky acids, such as AcOH, were less effective (entries 6, 7). More coordinating solvents, such as *t*-amyl-OH, lowered conversion and increased epimerization (entry 8). On the other hand, α,α,α-trifluorotoluene afforded the desired product in an improved 46% yield with less C(2) functionalization (entry 9). Pleasingly, the base loading could be halved to 1 equiv without affecting the yield (entry 10). Increasing the amount of PivOH to 1 equiv and the reaction concentration to 1 M raised the yield to 71% (entry 11). This enabled isolation of the *cis*-isomer **2a** in 64% yield on a 0.5 mmol scale, and a comparable yield was obtained on a 4 mmol scale by increasing the concentration to 2 M (Scheme 1). Attempts at further improving the conversion led to inferior results, as higher catalyst loading, temperature or reaction time gave a reduction in the recovered material, or increased amounts of epimerization (Table 1, entries 12–14).

Using the optimized conditions (Table 1, entry 11), the scope of the reaction was further investigated (Scheme 1). In all cases, the products (**2** and **9-12**) were isolated exclusively as *cis*-isomers, and with very high C(4) selectivity. Using enantioenriched **(*S*)-1** gave **(+)-2a** with complete retention of enantiomeric excess. This indicates that no racemization of either the starting amide **(*S*)-1** or the arylated derivative **(+)-2a** occurred under our C–H functionalization conditions.

Table 1. Selected optimization for the C–H arylation of *N*-Boc pyrrolidine amide 1.

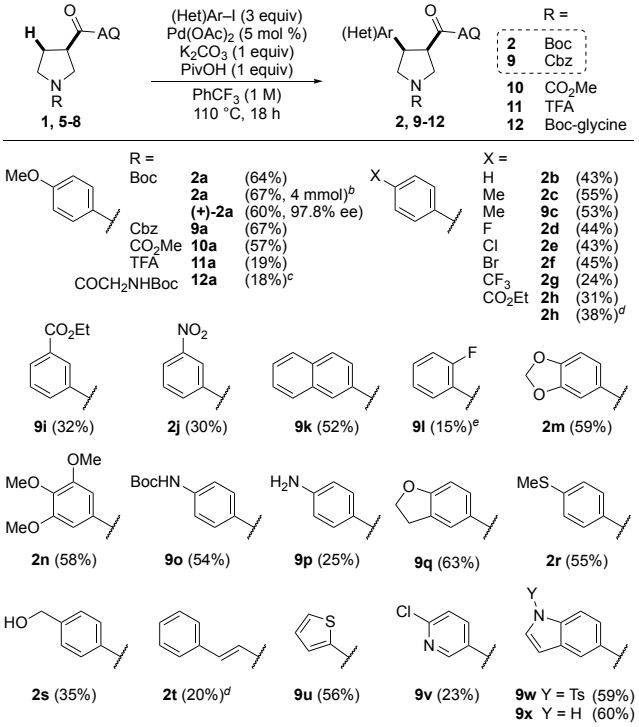


entry[a]	base	equiv PivOH	solvent (concn)	yield (%)[b]			
				1	**2a**	**3a**	**4a**
1	AgOAc	-	PhMe (0.3)	58	28	9	-
2	CsOAc	-	PhMe (0.3)	23	47	11	-
3	Cs_2CO_3	-	PhMe (0.3)	72	3	-	10
4	K_2CO_3	0.3	PhMe (0.3)	53	36	5	-
5	K_2CO_3	-	PhMe (0.3)	59	26	4	-
6	PivOK	-	PhMe (0.3)	50	31	9	-
7[c]	K_2CO_3	0.3	PhMe (0.3)	69	20	2	-
8	K_2CO_3	0.3	*t*-amyl-OH (0.3)	75	11	-	7
9	K_2CO_3	0.3	$PhCF_3$ (0.3)	42	46	6	-
10[d]	K_2CO_3	0.3	$PhCF_3$ (0.3)	36	48	4	-
11[d,e]	**K_2CO_3**	**1.0**	**$PhCF_3$ (1.0)**	**22**	**71 (64)**	**6**	**-**
12[d,f]	K_2CO_3	1.0	$PhCF_3$ (1.0)	15	61	5	-
13[d,g]	K_2CO_3	1.0	$PhCF_3$ (1.0)	20	60	6	5
14[d,h]	K_2CO_3	1.0	$PhCF_3$ (1.0)	24	65	5	5

[a] Conditions: **1** (0.2 mmol), base (2 equiv), solvent (concentration of **1**). [b] Calculated by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. Isolated yield in parentheses. [c] AcOH instead of PivOH. [d] 1 equiv K_2CO_3. [e] 0.5 mmol scale. [f] 10 mol % $Pd(OAc)_2$. [g] 130 °C. [h] 24 h reaction time.

Changing the *N*-protecting group from Boc (**1**) to Cbz (**5**) or methyl carbamate (**6**) gave very similar results with 4-iodoanisole (**9a** and **10a** respectively); Boc and Cbz groups were both used interchangeably to investigate the reaction scope. Trifluoroacetamide (**7**) and *N*-Boc glycine amide (**8**) derivatives were successful but gave lower yields (**11a**, **12a**). Various *para*-substituted aryl iodides were investigated (**2/9b–h**). In general, higher yields were obtained for more electron rich aryl iodides. Halogens were well tolerated, and provided suitable functionality for further reactions (**2d–f**). Using an ester group in the 4-position led to a 31% yield, though the yield could be slightly improved under more forced conditions (**2h**). Aryl iodides with *meta*-electron-withdrawing groups were similarly tolerated (**9i**, **2j**), and the 2-napthyl derivative gave a good yield (**9k**). *ortho*-Substituents were not tolerated: a 2-fluoro-substituted example **9l** was isolated in 15% yield under forced conditions. Electron-rich benzodioxole and trimethoxybenzene functionalities were installed in high yield, as well as *N*-Boc aniline (**2m–n, 9o**). Importantly, groups sensitive to oxidation were successfully installed. Unprotected aniline, dihydrobenzofuran, sulfide and benzyl alcohol functional groups were tolerated (**9p–q**, **2r–s**). Vinylated product **2t** was obtained in 20% yield using *E*-*β*-styryl iodide. Heteroaryl substituents were also successfully installed with 2-iodothiophene and 2-chloro-5-iodopyridine giving 56% and 23% yields respectively (**9u,v**).

Scheme 1. Scope of *N*-protecting groups and aryl iodides for pyrrolidine C–H arylation.[a]

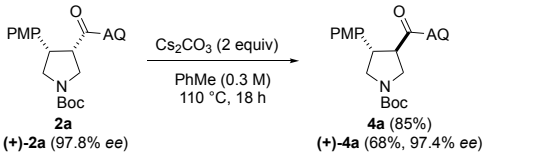


[a] Reactions on 0.5 mmol scale. All products were isolated as *cis*-diastereomers and <5% C2-arylation. [b] 2 M concentration. [c] 5 equiv Ar–I, 48 h. [d] 4 equiv Ar–I, 48 h. [e] 4 equiv Ar–I, 72 h.

Finally, 5-iodoindole derivatives were successful both for *N*-Ts and free *N*-H indoles, affording the arylated products **9w,x** in good yields.

Epimerization of **2a** could be readily promoted to form the *trans*-pyrrolidine derivative **4a** in 85% yield by heating with Cs_2CO_3 in toluene, as suggested by the optimization studies (Scheme 2). Using the enantioenriched product **(+)-2a** gave the *trans*-epimer **(+)-4a** in 68% yield with full retention of *ee*.[22]

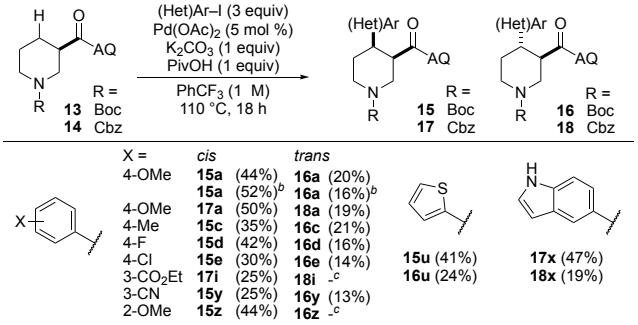
Scheme 2. Epimerization of 2a to *trans*-4a with retention of enantiomeric excess.



The same arylation conditions proved suitable for the corresponding piperidine AQ amides **13** (R = Boc) and **14** (R = Cbz), giving 3,4-disubstituted piperidines (Scheme 3). In this case, a minor *trans*-configured product was isolated directly from the reaction mixture (6:4 to 7:3 *dr*), by SiO_2 flash column chromatography which separated both components. As with the pyrrolidines, *N*-Boc and *N*-Cbz derivatives were similarly successful affording *cis*/*trans* **15**/**16** and **17**/**18** respectively.

Various *para* and *meta*-substituted aryl iodides were successful, with combined yields ranging from 25% to 69% depending on the electronics of the substituents. *p*-Fluoro and *p*-chloro aryl groups were installed in 58% and 44% overall yields, respectively. Interestingly, in this piperidine series the reaction with *ortho*-iodoanisole was successful, affording *cis*-derivative **15z** in 44% yield, where this was unreactive with pyrrolidine substrate **1**. Thiophene and *N*-H indole functionality were introduced in up to 66% combined yield (**15**/**16u**,**x**).

Scheme 3. Scope of *N*-protecting groups and aryl iodides for piperidine C–H arylation.[a]

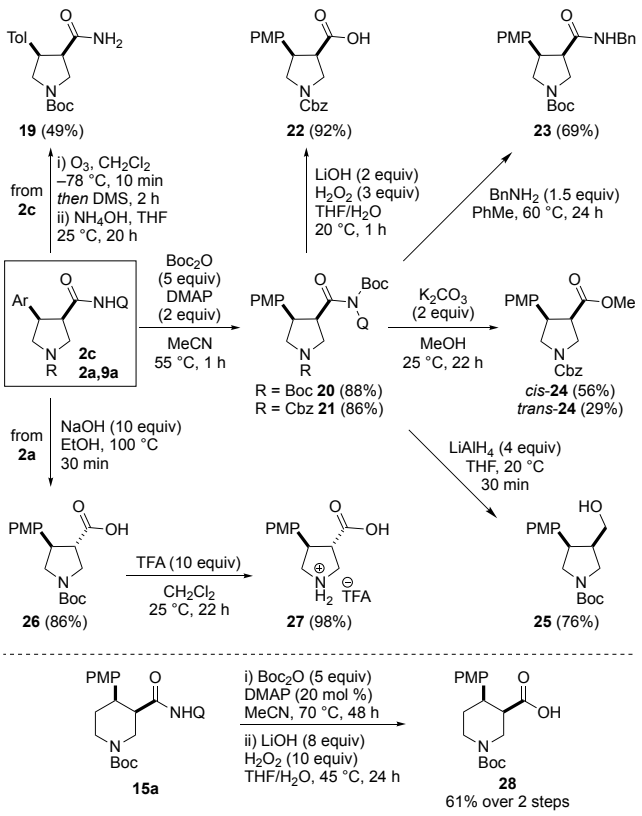


[a] Reactions on 0.5 mmol scale. Isolated yields of single diastereoisomers. [b] Using 3.4 mmol **13**, 2 M concentration. [c] *trans*-Isomer inseparable from recovered **13**/**14**.

Unlike with the pyrrolidines, the presence of the *trans*-piperidine isomer is due to formation of a *trans*-palladacycle.[23] Piperidines **15a** and **16a** were resubjected to the reaction conditions and were recovered without epimerization or further reaction. Attempts to epimerize either *cis*-**15a** or *trans*-**16a** to the other isomer using Cs_2CO_3 gave no reaction. Indeed, epimerization was observed only with *t*-BuOK on **15a** to give the *trans*-epimer (97% isolated yield). Epimerization of enantioenriched **(+)-15d** was also successful using DBU, which afforded **(+)-16d** (see Supporting Information for further discussion). Importantly, this isomerization gave the enantiomer of the *trans* product formed in the arylation reaction [**(–)-16d**], supporting the proposed *trans*-palladacycle.

To access fragments and building-blocks of interest for drug discovery programs it was crucial to remove the directing group, which was accomplished under several conditions (Scheme 4). Using Maulide's ozonolysis protocol and treatment with ammonium hydroxide[24] gave primary amide **19** in 49% yield. However, this strategy was not successful with the more electron rich anisole derivative and the starting material was not recovered. Alternatively, installation of a Boc group to form activated amides **20** and **21** provided various alternative pathways. *cis*-Carboxylic acid **22** was formed in excellent yield as a single diastereomer on hydrolysis with lithium hydrogen peroxide.[25] Secondary amide **23** was obtained in 69% yield by transamidation with benzylamine in toluene as the *cis*-isomer only. Formation of the methyl ester was achieved using K_2CO_3 in MeOH at rt with some epimerization, so both isomers *cis*-**24** (56% yield) and *trans*-**24** (29% yield) were isolated.[26] Reduction of **20** with $LiAlH_4$ gave alcohol **25** as a single *cis*-diastereoisomer in 76% yield, whereas the use of $NaBH_4$ caused epimerization. As a complementary strategy, *trans*-carboxylic acid **26** was obtained directly from the *cis*-carboxamide **2a** by hydrolysis with NaOH. Boc-deprotection gave unnatural amino acid **27** in high yield as the TFA salt. Cleavage of the AQ group from piperidine amide **15a** was accomplished using a similar Boc activation and hydrolysis to give acid **28** in 61% over two steps.

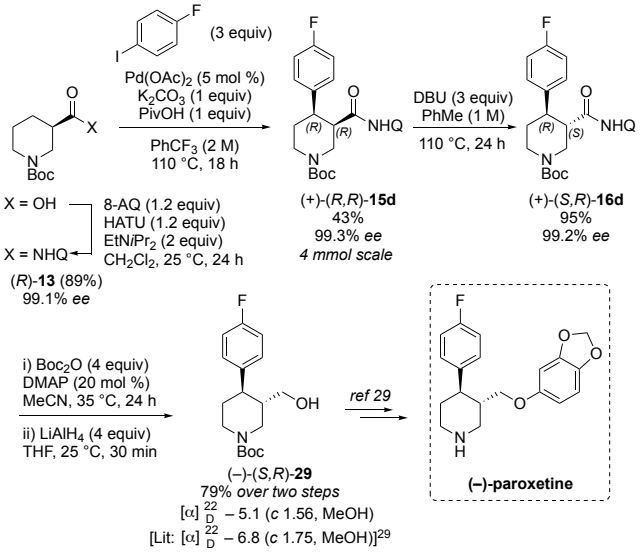
Scheme 4. Divergent removal of AQ directing group.



Finally, piperidine C–H functionalization was applied to the formal stereocontrolled synthesis of blockbuster antidepressant drug (–)-paroxetine (Scheme 5).[2b,27,28] Starting from readily available *N*-Boc (*R*)-nipecotic acid, arylation was performed on 4 mmol scale, affording *cis* arylated product (+)-(*R,R*)-**15d** in >99% *ee* and 43% yield (12% (–)-*trans*-isomer, 99.2% *ee*). Selective C(3) epimerization of the major *cis*-isomer with DBU gave (+)-**16d** with the correct *trans*-stereochemistry. Removal of the aminoquinoline directing groups was achieved by amide activation and reduction with $LiAlH_4$ affording (–)-(*S,R*)-**29** as a single stereoisomer, so completing this formal synthesis of (–)-paroxetine.[29]

In conclusion, we have developed a regio- and stereo-selective palladium catalyzed C(4)–H arylation of pyrrolidine and piperidine derivatives, bearing a C(3) directing group. The conditions are tolerant of varied functionality in the aryl iodide coupling partner. Epimerization can access the *trans*-isomers. New conditions are developed for directing group removal to provide biologically relevant motifs as demonstrated by the stereocontrolled formal synthesis of (–)-paroxetine.

Scheme 5. Stereocontrolled synthesis of antidepressant (–)-paroxetine.



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, HPLC traces, characterization data, and copies of ^{1}H and ^{13}C NMR spectra; detailed optimization tables; NMR studies on product stereochemistry. (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, 57, 10257.

(2) For Figure 1: (a) Zeidner, J. F.; Karp, J. E. *Leuk. Res.* **2015**, *39*, 1312. (b) Bourin, M.; Chue, P.; Guillon, Y. *CNS Drug Rev.* **2001**, *7*, 25. (c) Chiappori, A. A.; Haura, E.; Rodriguez, F. A.; Boulware, D.; Kapoor, R.; Neuger, A. M.; Lush, R.; Padilla, B.; Burton, M.; Williams, C.; Simon, G.; Antonia, S.; Sullivan, D. M.; Bepler, G. *Clin. Cancer Res.* **2008**, *14*, 1464.

(3) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. *Nat. Chem.* **2018**, *10*, 383.

(4) (a) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752. (b) Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem. Int. Ed.* **2012**, *51*, 1114. (c) Murray, C. W.; Rees, D. C. *Angew. Chem. Int. Ed.* **2016**, *55*, 488.

(5) For selected recent advances for the synthesis of pyrrolidine and piperidine rings, see: (a) Wang, Y.; Wen, X.; Cui, X; Zhang, X. P. *J.*

Am. Chem. Soc. **2018**, *140*, 4792. (b) Chen, W.; Ma, L.; Paul, A.; Seidel, D. *Nature Chem.* **2018**, *10*, 165. (c) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan D. W. C. *Science* **2016**, *352*, 1304. (d) Osberger, T. J.; Rogness, D. C.; Kohrt, J. T.; Stepan, A. F.; White, M. C. *Nature* **2016**, *537*, 214. (e) Bhonde, V. R.; O'Neill, B. T.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 1849.

(6) For reviews on functionalization of cyclic amines, see: (a) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. *Chem. Eur. J.*, **2012**, 18, 10092. (b) Seidel, D. *Acc. Chem. Res.* **2015**, *48*, 317.

(7) (a) Godula, K.; Sames, D. Science 2006, 312, 67. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960. (c) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (d) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726. (e) Ping, L.; Chung, D. S.; Bouffard, J.; Lee, S. *Chem. Soc. Rev.* **2017**, *46*, 4299. (f) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *117*. 8754. (g) Larsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287.

(8) For α-C–H functionalization with N-linked directing groups, see: (a) Jain, P.; Verma, P.; Xia, G.; Yu, J.-Q. Nat. Chem. 2016, 9, 140. (b) Schinkel, M.; Wang, L.; Bielefeld, K.; Ackermann, L. *Org. Lett.* **2014**, *16*, 1876. (c) Prokopcová, H.; Bergman, S. D.; Aelvoet, K.; Smout, V.; Herrebout, W.; Van der Veken, B.; Meerpoel, L.; Maes, B. U. W. *Chem. Eur. J.* **2010**, *16*, 13063. (d) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220. (e) Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882.

(9) (a) Sundararaju, B.; Achard, M.; Sharma, G. V. M.; Bruneau, C. *J. Am. Chem. Soc.* **2011**, *133*, 10340. (b) Millet, A.; Larini, P.; Clot, E.; Baudoin, O. *Chem. Sci.* **2013**, *4*, 2241. (c) Zhang, S.-J.; Sun, W.-W.; Cao, P.; Dong, X.-P.; Liu, J.-K.; Wu, B. *J. Org. Chem.* **2016**, *81*, 956. (d) Chen, M.; Liu, F.; Dong, G. *Angew. Chem. Int. Ed.* **2018**, *57*, 3815. (e) Lee, M.; Sanford, M. S. *Org. Lett.* **2017**, *19*, 572.

(10) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

(11) Affron, D. P.; Davis, O. A.; Bull, J. A. *Org. Lett.* **2014**, *16*, 4956.

(12) Also see: a) Feng, R.; Wang, B.; Liu, Y.; Liu, Z.; Zhang, Y. *Eur. J. Org. Chem.* **2015**, *2015*, 142. b) Mondal, B.; Roy, B.; Kazmaier, U. *J. Org. Chem.* **2016**, *81*, 11646.

(13) Affron, D. P.; Bull, J. A. *Eur. J. Org. Chem.* **2016**, *2016*, 139.

(14) Yu, Q.-Y.; Zhong, H.-M.; Sun, W.-W.; Zhang, S.-J.; Cao, P.; Dong, X.-P.; Qin, H.-B.; Liu, J.-K.; Wu, B. *Asian J. Org. Chem.* **2016**, *5*, 608.

(15) Ye, S.; Yang, W.; Coon, T.; Fanning, D.; Neubert, T.; Stamos, D.; Yu, J.-Q. *Chem. Eur. J.* **2016**, *22*, 4748.

(16) (a) Maetani, M.; Zoller, J.; Melillo, B.; Verho, O.; Kato, N.; Pu, J.; Comer, E.; Schreiber, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 11300. (b) Verho, O.; Maetani, M.; Melillo, B.; Zoller, J.; Schreiber, S. L. *Org. Lett.* **2017**, *19*, 4424.

(17) Van Steijvoort, B. F.; Kaval, N.; Kulago, A. A.; Maes, B. U. W. *ACS Catal.* **2016**, *6*, 4486.

(18) (a) Cabrera, P. J.; Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2018**, *140*, 5599. (b) Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. *Nature* **2016**, *531*, 220. (c) For a computational study, see: Dewyer, A. L.; Zimmerman, P. M. *ACS Catal.* **2017**, *7*, 5466.

(19) Yu also demonstrated C(4) arylation of *cis*-2-methyl-3-piperidinecarboxamide, where C(2) was blocked, with high diastereoselectivity (reference 15).

(20) 2-Methylthioaniline amide and the corresponding sulfoxide were tested as directing groups under related and final conditions, but gave <10% conversion.

(21) For related examples of Ag-free Pd-catalyzed C(sp^3)–H arylation, see: (a) Roman, D. S.; Charette, A. B. *Org. Lett.*, **2013**, *15*, 4394. (b) Nadres, E.T; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.*, **2013**, *78*, 9689.

(22) The retention of chiral information confirmed that only one center epimerized. Enantioenriched pyrrolidine (*S*)-**1** was subjected to the same conditions where loss of enantiopurity was observed (78% *ee*). This supports C(3) epimerization in **2a** promoted by the additional *cis*-substituent present.

(23) For trans-palladacycles on 6-membered rings: Yang, X.; Sun, T.-Y.; Rao, Y. *Chem. Eur. J.* **2016**, *22*, 3273.

(24) Berger, M.; Chauhan, R.; Rodrigues, C. A. B.; Maulide, N.; *Chem. Eur. J.* **2016**, *22*, 16805.

(25) (a) Evans, D. A.; Carter, P. H.; Dinsmore, C. J.; Barrow, J. C.; Katz, J. L.; Kung, D. W. *Tetrahedron Lett.* **1997**, *38*, 4535. (b) For example application on AQ removal, see: Feng, Y.; Chen, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 958.

(26) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* **2010**, *12*, 3414.

(27) Barnes; R. D.; Wood-Kaczmar, M. W.; Curzons, A. D.; Lynch, I. R.; Richardson; J. E.; Buxton, P. C. (Beecham Group p.l.c.). Antidepressant crystalline paroxetine hydrochloride hemihydrate. U.S. Patent 4721723, **1986**.

(28) For selected recent synthetic studies towards (–)-paroxetine, see: (a) Chamorro- Arenas, D.; Fuentes, L.; Quintero, L.; Cruz- Gregorio, S.; Höpfl, H.; Sartillo- Piscil, F. *Eur. J. Org. Chem.* **2017**, *2017*, 4104. (b) Kubota, K.; Watanabe, Y.; Hayama, K.; Ito, H. *J. Am. Chem. Soc.* **2016**, *138*, 4338. (c) Wang, Y.-M.; Bruno, N. C.; Placeres, Á. L.; Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 10524. (d) Krautwald, S.; Schafroth, M. A.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2014**, *136*, 3020.

(29) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074.