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Palladium-catalyzed picolinamide-directed iodination of remote *ortho*-C−H bonds of arenes: Synthesis of tetrahydroquinolines

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Full Research Paper

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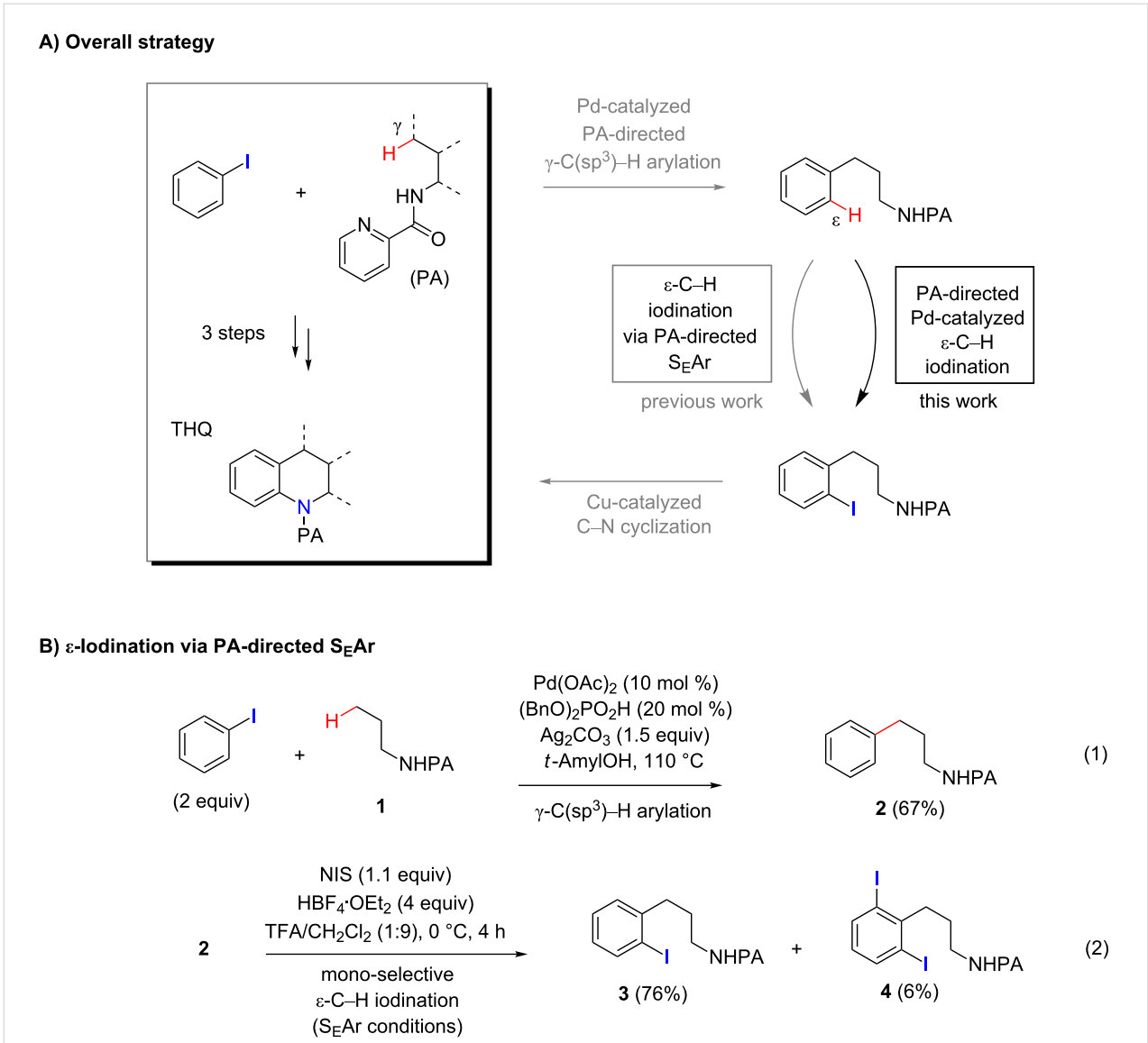
Abstract

A new palladium-catalyzed picolinamide (PA)-directed *ortho*-iodination reaction of ε-C(sp^2)−H bonds of γ-arylpropylamine substrates is reported. This reaction proceeds selectively with a variety of γ-arylpropylamines bearing strongly electron-donating or withdrawing substituents, complementing our previously reported PA-directed electrophilic aromatic substitution approach to this transformation. As demonstrated herein, a three step sequence of Pd-catalyzed γ-C(sp^3)−H arylation, Pd-catalyzed ε-C(sp^2)−H iodination, and Cu-catalyzed C−N cyclization enables a streamlined synthesis of tetrahydroquinolines bearing diverse substitution patterns.

Introduction

Tetrahydroquinoline (THQ) is an important *N*-heterocyclic scaffold found in many natural products and pharmaceutical agents [1,2]. Efficient and generally applicable methods for the synthesis of THQs with complex substitution patterns are still in great demand [3-7]. Recently, we reported a synthetic strategy for THQs based on picolinamide (PA)-directed sequential C−H functionalization reactions starting from readily accessible aryl iodide and alkylamine precursors (Scheme 1) [8]. Alkylpicolinamides were first subjected to Pd-catalyzed γ-C(sp^3)−H arylation with aryl iodides to form γ-arylpropylpicolinamides [9-20]. These γ-arylpropylpicolinamides were then selectively iodinated at the remote ε-C(sp^2)−H position via a rarely precedented PA-directed electrophilic aromatic substitution (S_EAr) reaction (Scheme 1, reaction 2) [21,22]. Copper-catalyzed intramolecular C−N cyclization of these *ortho*-iodinated intermediates provided PA-coupled THQ products in good yields.



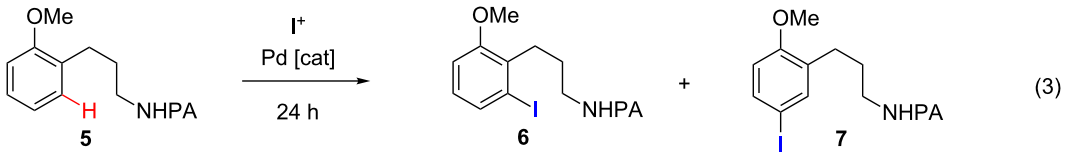
Scheme 1: New synthetic strategy for THQs via PA-directed C−H functionalization.

Although ε-C−H iodination via directed S_EAr proceeds with excellent yield and mono-selectivity for many γ-arylpropylpicolinamides, the scope of these PA-directed S_EAr reactions is limited to arenes bearing moderate electron-donating or withdrawing groups. Arene substrates bearing strongly electron-donating substituents typically gave substantial amounts of undesired iodinated side products via competing innate S_EAr processes, and arene substrates bearing strongly electron-withdrawing substituents were often unreactive. Herein, we report our development of a Pd-catalyzed PA-directed iodination reaction of ε-C(sp^2)−H bonds of γ-arylpropylpicolinamides. This Pd-catalyzed reaction is complementary in scope to the directed S_EAr iodination approach and allows for the efficient synthesis of a broad range of THQs with diverse substitution patterns.

Results and Discussion

Methods for metal-catalyzed halogenation of *ortho* C−H bonds at the more remote ε position are scarce, in contrast to the large number of *ortho* C−H halogenation reactions of arenes effected by more proximal directing groups [23-33]. Fundamentally, it is challenging to achieve efficient reactions through kinetically unfavorable seven-membered palladacycle intermediates. Furthermore, the electrophilic reagents used for C–H halogenation can often react with arenes through undirected S_EAr pathways, which need to be suppressed for regioselectivity. To address this issue upfront, we commenced our study of Pd-catalyzed ε-C−H halogenation with 3-arylpropylpicolinamide **5** bearing a strongly electron-donating OMe group (Table 1, see Supporting Information File 1 for the preparation of **5**). Iodina-

Table 1: Optimization of Pd-catalyzed *ortho* C−H iodination of **5**.[a]



entry	reagents (equiv)	solvent	temperature (°C)	yield (%)[b] 6	7
1	NIS (1.5), $HBF_4{\cdot}EtO_2$ (4.0)	T/D[c]	0	<2	68
2	NIS (1.5)	T/D	0	<2	82
3	$Pd(OAc)_2$ (10 mol %), NIS (1.5)	chlorobenzene	110	<2	74
4	$Pd(OAc)_2$ (10 mol %), NaI (1.5), $NaIO_3$ (1.5), $K_2S_2O_8$ (2.0)	*n*-BuOH	110	<2	<2
5	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $K_2S_2O_8$ (2)	DMF	110	<2	60
6	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0)	DMF	110	43	25
7	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0), K_2CO_3 (1.0)	DMF	110	14	11
8	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0), $KHCO_3$ (2.0)	DMF	110	45	12
9	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0), $KHCO_3$ (1.0)	DMF	110	75 (72)[d]	9 (5)[d]
10	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0), Na_2CO_3 (1.0)	DMF	110	80	8
11	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0), $KHCO_3$ (1.0)	dichloroethane	110	16	58
12	$Pd(OAc)_2$ (10 mol %), I_2 (2.0), $PhI(OAc)_2$ (2.0), $KHCO_3$ (1.0)	dioxane	110	13	65
13	I_2 (2.0), $PhI(OAc)_2$ (2.0), $KHCO_3$ (1.0)	DMF	110	<2	64

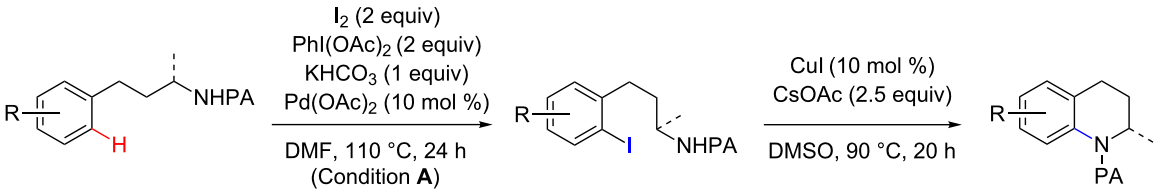
[a]All screening reactions were carried out in a 10 mL glass vial on a 0.2 mmol scale: [b]Yields are based on ^1H NMR analysis of the reaction mixture using CH_2Br_2 as internal standard; [c]T/D: TFA (T)/CH_2Cl_2 (D); [d]isolated yield.

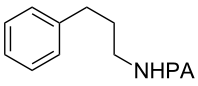
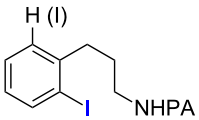
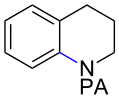
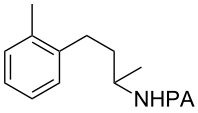
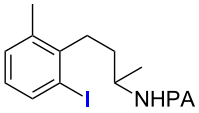
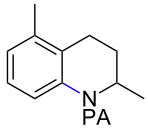
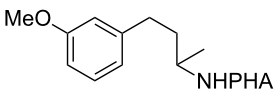
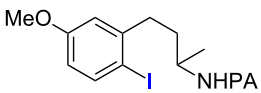
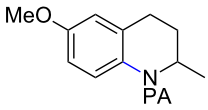
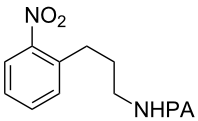
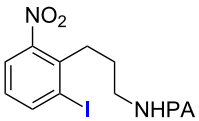
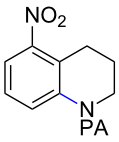
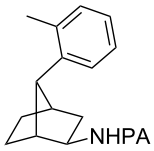
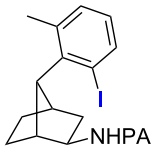
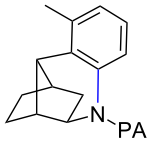
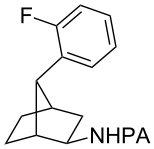
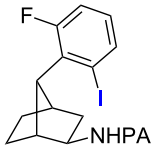
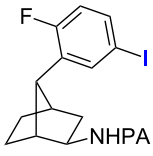
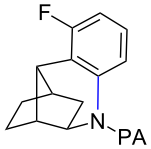
tion of **5** under our previous S_EAr protocol gave undirected iodination product **7** as the major product; only a trace amount of *ortho*-iodination product **6** was detected (Table 1, entries 1 and 2). Iodination of **5** under a variety of Pd-catalyzed oxidative conditions gave either low conversion or poor regioselectivity (Table 1, entries 3–5). To our delight, the use of a combination of 2 equiv of I_2 and 2 equiv of $PhI(OAc)_2$ in DMF at 110 °C gave the desired product **6** in good yield and moderate selectivity. Similar conditions were reported by Yu to effect the Pd-catalyzed NHTf-directed iodination of δ-C(sp^2)−H bonds of β-phenylethyl triflamides [33]. IOAc generated in situ is believed to be the active iodinating species. DMF was found to be the best solvent for this reaction (Table 1, entry 9 vs 11 and 12). Moreover, we found that the choice of alkali carbonate base was important: replacing K_2CO_3 with $KHCO_3$ or Na_2CO_3 gave notably improved yields and ortho selectivity (Table 1, entries 9 and 10) [34,35]. By analogy with similar Pd-catalyzed directed C–H halogenation reactions, we speculate that the catalytic cycle follows a sequence of C−H palladation, oxidative addition and reductive elimination [36,37].

With the best conditions in hand (Table 1, entries 9 and 10), we then examined the substrate scope of this Pd-catalyzed iodination of γ-arylpropylpicolinamides (Table 2). The γ-arylpropylpicolinamides were prepared from the corresponding *N*-alkylpicolinamides and aryl iodides under our $(BnO)_2PO_2H$-promoted Pd-catalyzed γ-C(sp^3)−H arylation conditions (see Supporting Information File 1 for details). The substrate scope was chosen to complement the S_EAr method, which is notably incompatible with NO_2, F and OMe substituents. In contrast to the mono-selectivity of the directed S_EAr approach (reaction 2, Scheme 1), iodination of γ-phenylpropylpicolinamide **2** bearing two equivalent *ortho* C−H bonds under Pd-catalyzed conditions A gave a mixture of mono-iodinated **3** and *ortho* diiodinated product **4**. However, no *para*-iodinated side product was formed. With 4 equiv of $PhI(OAc)_2/I_2$ and 1 equiv of $KHCO_3$, **4** can be formed as the major product in 69% yield.

Arenes bearing *meta*-substituents (e.g., **12**) were selectively iodinated at the less hindered *ortho* position. Pd-catalyzed iodination of substrate **15** bearing a strongly electron-withdrawing

Table 2: Substrate scope of Pd-catalyzed ε-C−H iodination and Cu-catalyzed C−N cyclization to form THQs[a].



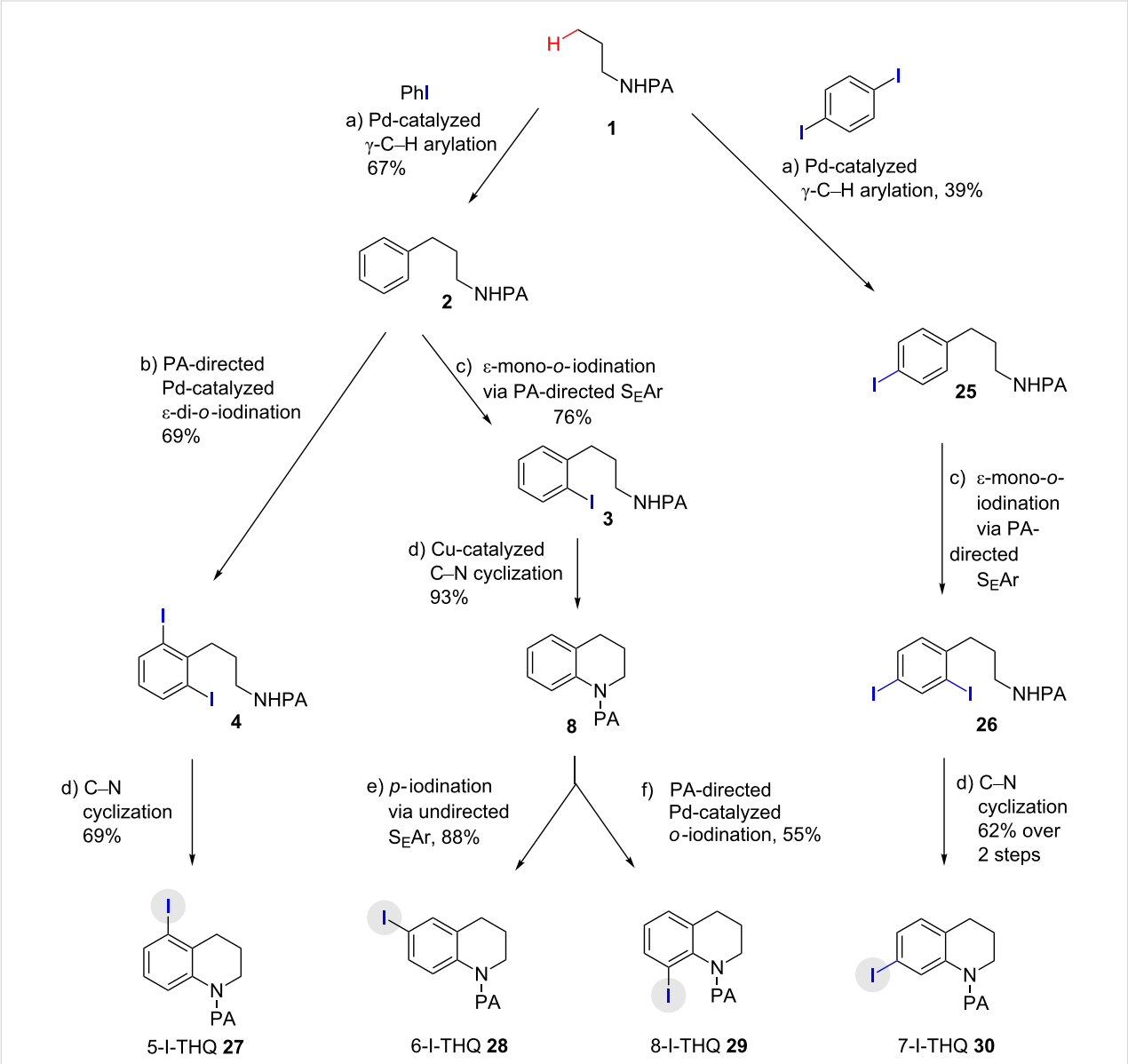
C–H arylation[b]	iodination		C–N cyclization
	Pd catalyzed	directed S_EAr	
 **2** (67%)	 **3** (mono-I, 47%) + **4** (di-I, 25%)[c]	**3** (76%) + **4** (6%)	 **8** (93%)
 **9** (81%)	 **10** (75%)	**10** (60%) (*o*/*x* = 5:3)[c]	 **11** (96%)
 **12** (81%)	 **13** (68%)	**13** (50%) (*o*/*x* = 5:4)[c]	 **14** (94%)
 **15** (28%)	 **16** (68%)	NR	 **17** (47%)
 **18** (60%)	 **19** (56%)	**19** (20%) (*o*/*x* = 1:4)[c]	 **20** (85%)
 **21** (95%)	 **22** (53% or 85%[d])	 **23** (90%) X-ray	 **24** (78%)

[a]Yields are based on isolated product on a 0.2 mmol scale; [b]see reaction 1 in Scheme 1B for conditions for Pd-catalyzed C−H arylation; [c]di: *ortho*-diiodinated isomer, *x*: mixture of other iodinated isomers; [d]conditions B: I_2 (2 equiv), $PhI(OAc)_2$ (2 equiv), $Pd(OAc)_2$ (10 mol %), Na_2CO_3 (1 equiv), DMF, 110 °C, 24 h.

NO_2 group also proceeded smoothly to give **16**; this substrate is unreactive to directed S_EAr. The rigid arylnorbornane scaffold **18** is incompatible with directed S_EAr, but was iodinated selectively at the ortho position under Pd-catalyzed conditions without the formation of regioisomeric side products. The strong *para*-directing effect exerted by aryl fluoride substituents overrides directed S_EAr selectivity [38,39]. Thus, we observed only *para*-iodinated compound **23** when **21** was subjected to the directed S_EAr protocol. In contrast, using our Pd-catalyzed iodination (conditions B), *ortho*-iodinated product **22** was obtained

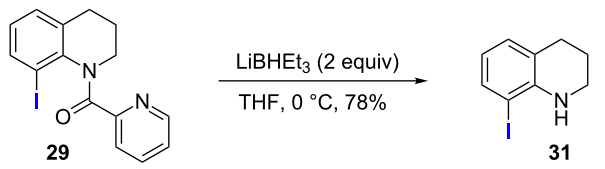
via Pd-catalyzed iodination as the only product in excellent yield. The iodinated intermediates could be readily cyclized under our previously reported Cu-catalyzed conditions to give PA-coupled THQ products with various substitution patterns in good yields (Scheme 2) [8].

As shown in Scheme 2, Pd-catalyzed PA-directed ε-C−H iodination can be used in concert with PA-directed γ-C−H arylation, PA-directed S_EAr iodination, and undirected S_EAr iodination to quickly access THQs **27**–**30** bearing iodo groups at different positions on the arene ring [40-42]. *Ortho*-diiodinated product **4** was obtained from **2** in 69% yield using optimized Pd-catalyzed ε-C–H iodination conditions, and Cu-catalyzed C–N cyclization of **4** gave 5-iodo-THQ **27**. PA-THQ **8** was susceptible to iodination at two positions. Under undirected S_EAr conditions, 6-iodo-THQ **28** was produced in excellent yield and regioselectivity. Alternatively, a Pd-catalyzed C–H iodination reaction of **8** was developed which provides 8-iodo-THQ **29**. Pd-catalyzed C−H arylation of **1** with *para*-diiodobenzene under the standard arylation conditions gave **25** in moderate yield. Iodination of **25** via PA-directed S_EAr gave diiodinated compound **26**, which was cyclized under Cu catalysis to give



Scheme 2: Preparation of iodo-substituted THQs via PA-directed C−H functionalization strategy. a) ArI (2 equiv), $Pd(OAc)_2$ (10 mol %), $(BnO)_2PO_2H$ (20 mol %), Ag_2CO_3 (1.5 equiv), *t*-AmylOH, 110 °C, 24h; b) $Pd(OAc)_2$ (10 mol %), I_2 (4 equiv), $PhI(OAc)_2$ (4 equiv), $KHCO_3$ (1 equiv), 130 °C, DMF, 24 h; c) NIS (1.1 equiv), $HBF_4{\cdot}OEt_2$ (4), TFA/DCM (1:9), 2.5 mM, 0 °C, 4 h; d) CuI (10 mol %), CsOAc (2.5 equiv), DMSO, Ar, 90 °C, 20 h; e) NIS (1.1 equiv), TFA/DCM (1:9), 2.5 mM, rt, 16 h; f) $Pd(OAc)_2$ (15 mol %), NIS (2.5 equiv), α,α,α-trifluorotoluene, Ar, 100 °C, 24 h.

7-iodo-THQ **30** in good yield. The PA group of 8-iodo-THQ **29** was readily removed with $LiBHEt_3$ to give **31** (Scheme 3) [10].



Scheme 3: Removal of PA auxiliary from THQ product.

Conclusion

In summary, we have developed a new palladium-catalyzed picolinamide (PA)-directed iodination reaction of ε-C(sp^2)−H bonds of γ-arylpropylamine substrates. This method works well for arenes with a broad range of substituents and offers a complementary scope to our previously reported PA-directed S_EAr approach. This Pd-catalyzed PA-directed ε-C−H iodination can be used in concert with the PA-directed γ-C−H arylation, PA-directed S_EAr iodination, undirected S_EAr iodination, and Cu-catalyzed C−N cyclization to quickly access tetrahydroquinolines bearing diverse substitution patterns from readily accessible starting materials.

Supporting Information

Supporting Information File 1

Detailed synthetic procedures and characterizations of all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-12-119-S1.pdf]

Acknowledgements

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