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Iodination of Remote *Ortho*-C−H Bonds of Arenes via Directed S_EAr: A Streamlined Synthesis of Tetrahydroquinolines

William A. Nack, Gang He, Shu-Yu Zhang, Chengxi Lu, and Gong Chen*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, United States

guc11@psu.edu

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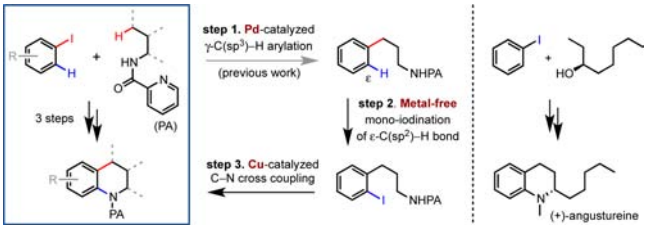
ABSTRACT



A new strategy for the synthesis of tetrahydroquinolines (THQs) via the sequential functionalizations of remote C−H bonds is reported. This method uses a single picolinamide directing/protecting group to effect Pd-catalyzed γ-C(sp^3)−H arylation, metal-free ε-C(sp^2)−H iodination, and Cu-catalyzed intramolecular C−N cross-coupling. The overall sequence is efficient and versatile, and offers a streamlined synthesis of THQs with complex substitution patterns from readily available aryl iodide and aliphatic amine precursors.

Tetrahydroquinoline (THQ) is a privileged *N*-heterocyclic scaffold found in many natural products and pharmaceutical agents.[1] In contrast to most conventional synthesis strategies, which typically begin from prefunctionalized arene or arylamine precursors, we envisioned that THQs could be quickly assembled by connection at the C_2-C_γ and C_1-N positions through directed C−H functionalization reactions from simple aryl halide and alkyl amine precursors (Scheme 1A).[2−4] The picolinamide (PA) group has been shown to effect the palladium-catalyzed arylation of γ-C(sp^3)−H bonds of *N*-alkylpicolinamides (e.g., **1**) with aryl iodides, providing γ-arylpropylamine products (e.g., **2**, Scheme 1B).[5−7] We postulated that the installation of a halogen group at the *ortho* position of **2**, followed by intramolecular C−N cross coupling could afford the desired THQ product in two discrete steps.[8−10] Herein, we report a highly efficient and readily applicable

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(2) For selected recent syntheses of THQs, see: (a) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (b) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *131*, 4598. (c) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182. (d) Rousseaux, S.; Liégault, B.; Fagnou, K. *Chem. Sci.* **2012**, *3*, 244. For an elegant recent study on enantioselective THQ synthesis via Pd-catalyzed C−H functionalization approach, see: (e) Saget, T.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 12842.

(3) For an excellent review on C−H functionalization in the synthesis of *N*-heterocycles, see: Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874.

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(5) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *133*, 7. (c) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237.

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(7) Recently, we found that PA-directed Pd-catalyzed γ-C(sp^3)−H arylation could be notably improved with the application of catalytic amount of $(BnO)_2PO_2H$. Detailed studies will be reported in a separate account.

(8) Direct formation of THQs from γ-arylpropylpicolinamides via Pd-catalyzed intramolecular dehydrogenative ε-C(sp^2)−H amination is under current investigation.

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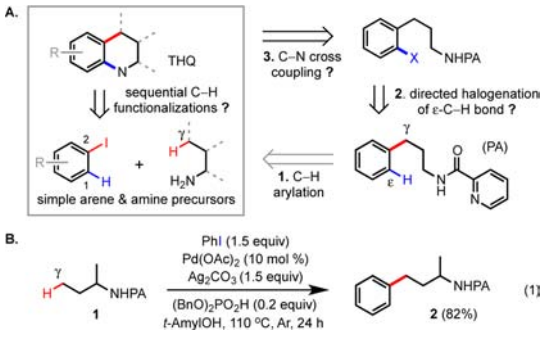
method for the selective iodination of the ε-C(sp^2)−H bonds of these γ-arylpropyl picolinamides under metal-free conditions. The *ortho*-iodinated products can be cyclized under copper catalysis to give tetrahydroquinolines (THQs) in high yields.

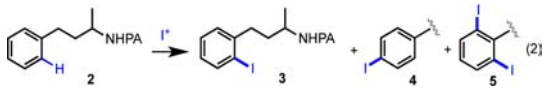
Neighboring group-directed halogenation of the *ortho*-C(sp^2)−H bonds of arenes has been achieved under a variety of metal-catalyzed or directed lithiation conditions.[11,12] However, generally applicable methods for the selective halogenation of *ortho*-C−H bonds at the more remote ε position are very rare.[13,14] In our initial attempts, C−H iodination of substrate **2** under an extensively optimized Pd-catalyzed condition gave a mixture of mono-*ortho*-iodinated product **3** and di-*ortho*-iodinated product **5** (entry 1, Table 1).[15]

Scheme 1. New Synthetic Strategy for THQs



In 2007, the Barluenga laboratory reported that the *ortho*-C(sp^2)−H bonds of γ-phenylpropyl trifluoroacetamide (**57** in Scheme 4) can be selectively monoiodinated with bis(pyridine) iodonium(I) tetrafluoroborate ($IPy_2 \cdot BF_4$) under metal-free conditions.[16] This reaction presents

Table 1. Iodination of ε-*o*-C−H Bonds of **2** via S_EAr



entry	reagents (equiv)	solvents	temp (°C)/h	yield (%)[a] 3	4/5
1	$Pd(OAc)_2$ (10%), $PhI(OAc)_2$ (2), I_2 (2) $KHCO_3$ (1)	DMF	130/24	44	<2/37
2	$IPy_2 \cdot BF_4$ (1.5), $HBF_4 \cdot OEt_2$ (3)	T/D (1:10)[b,c]	rt/2	60	5/24
3	$IPy_2 \cdot BF_4$ (1.1), $HBF_4 \cdot OEt_2$ (2.2)	T/D (1:10)[c]	rt/2	88	6/3
4	NIS (1.1), $HBF_4 \cdot OEt_2$ (4)	T/D (1:9)	0/4	90 (83)[d]	4/3
5	NIS (1.1), TfOH (4)	T/D (1:9)	0/4	41	26/4
6	NIS (1.1), $BF_3 \cdot OEt_2$ (4)	T/D (1:9)	0/4	68	28/<2
7	NIS (1.5), $HBF_4 \cdot OEt_2$ (4)	T/D (1:9)	0/4	48	4/26
8	NIS (1.1)	T/D (1:9)	0/4	30	24/<2

[a] All screening reactions were carried out on a 0.2 mmol scale at 6.7 mM concentration unless noted; yields are based on ^1H NMR analysis of the reaction mixture after workup. [b] T/D: TFA(T)/CH_2Cl_2 (D). [c] Performed at 4.5 mM concentration. [d] Isolated yield.

a very rare example of remote functional group-directed ε-*ortho*-C−H functionalization of arenes via an electrophilic aromatic substitution (S_EAr) pathway.[17] Inspired by Barluenga's seminal discovery, we proceeded to evaluate whether the ε-C(sp^2)−H bond of γ-arylpropylpicolinamide **2** could be iodinated in a similar fashion (Table 1).[18] Following Barluenga's protocol (1.5 equiv of $IPy_2 \cdot BF_4$, 3 equiv of $HBF_4 \cdot OEt_2$ in mixed solvent of TFA/CH_2Cl_2 at room temperature), substrate **2** generated a mixture of mono- and di-*ortho*-iodinated product (**3** and **5**, entry 2). The selectivity was improved when only 1.1 equiv of $IPy_2 \cdot BF_4$ was applied (entry 3). To augment the utility of this reaction, we next surveyed more economical and convenient to handle I^+ precursors.[19] Gratifyingly, we found that 1.1 equiv of *N*-iodosuccinimide (NIS)[20,21] provided excellent iodination results with further improved *o*/*p* selectivity when the reaction was performed at 0 °C (entry 4). No iodination of the PA group was observed. NCS and NBS gave monohalogenated products in a nonselective fashion. Notably, the addition of the Brønsted acid $HBF_4 \cdot OEt_2$ is critical to the *ortho* selectivity of the reaction (entry 8).

(9) For an excellent study on the synthesis of indolines and tetrahydroisoquinolines via Pd-catalyzed C−H activation, see: Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452.

(10) γ-C(sp^3)−H arylation using *o*-arene dihalide precursors usually proceeds in low yield under the standard conditions. Preparation of the *o*-dihalides often requires a multistep sequence.

(11) For selected examples of metal-catalyzed halogenation of neighboring *o*-C−H bonds, see: (a) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483. (b) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (c) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215. (d) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 5524. (e) Schröder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298.

(12) (a) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(13) For selected examples of the metal-catalyzed functionalization of remote C−H bonds, see: (a) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2. (b) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849. (c) Shi, F.; Larock, R. C. *Top. Curr. Chem.* **2010**, *292*, 123. (d) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518.

(14) For pioneering work on remote C−H functionalization by Breslow, see: Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.

(15) Similar conditions were originally applied in Yu's Pd-catalyzed iodination of remote *ortho* C(sp^2)−H bonds; see: (a) Li, J.-J.; Giri, R.; Yu, J.-Q. *Tetrahedron* **2008**, *64*, 6979. (b) ref 9.

(16) (a) Barluenga, J.; Álvarez-Gutiérrez, J. M.; Ballesteros, A.; González, J. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1281. (b) Espuña, G.; Arsequell, G.; Valencia, G.; Barluenga, J.; Álvarez-Gutiérrez, J. M.; Ballesteros, A.; González, J. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 325.

(17) For another example of functional group-directed halogenation of remote C−H bonds via S_EAr, see: (a) O'Connell, J. L.; Simpson, J. S.; Dumanski, P. G.; Simpson, G. W.; Easton, C. J. *Org. Biomol. Chem.* **2006**, *4*, 2716. For an elegant study on peptide-mediated regio and enantioselective bromination of biaryl compounds, see: (b) Gustafson, J. L.; Lim, D.; Miller, S. J. *Science* **2010**, *328*, 1251.

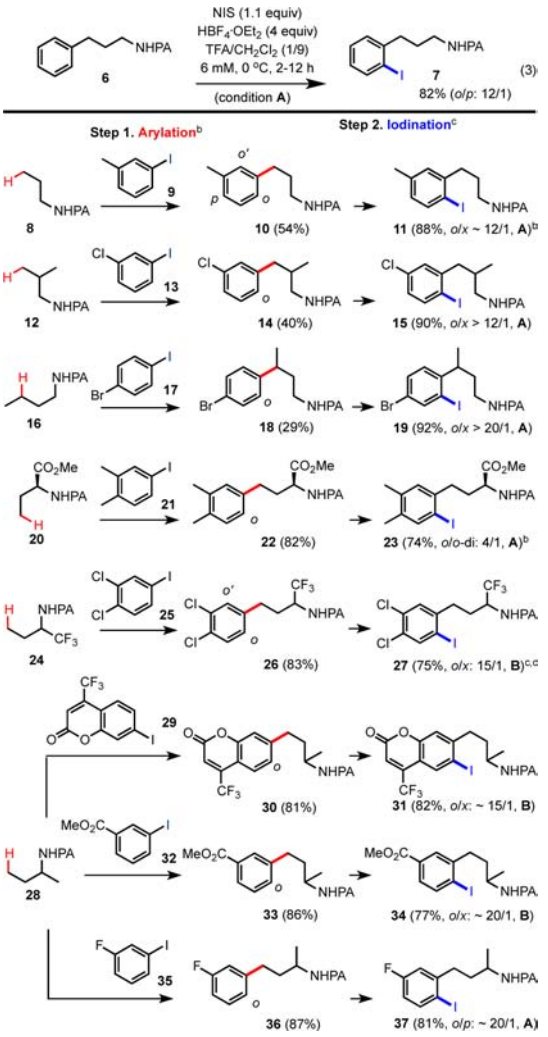
(18) A single example of iodination of the δ-*o*-C−H bond of β-phenylethyl picolinamide was first demonstrated in Barluenga's 2007 paper as a control substrate; see ref 16a.

(19) $IPy_2 \cdot BF_4$ is commercially available (1 g/$76 from Aldrich). Freshly prepared or recrystallized $IPy_2.BF_4$ is often recommended for use in reactions.

(20) NIS (97%, Alfa Aesar) was used without further purification.

(21) Prakash, S.; G., K.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770.

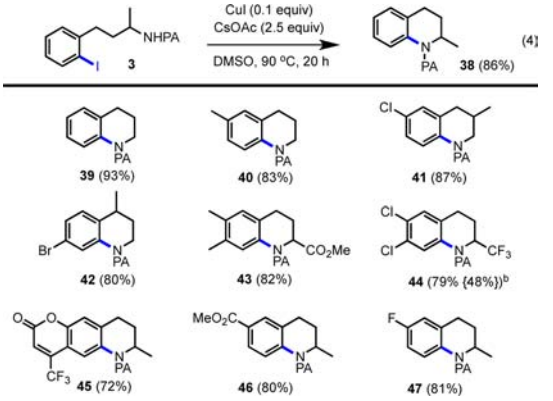
Scheme 2. Substrate Scope of PA-Directed Sequential C(sp^3)−H Arylation and C(sp^2)−H Iodination[a]



[a] All reactions were carried out on a 0.2 mmol scale; yields are based on isolated product. See the Supporting Information for experimental details pertaining to C−H arylations and iodinations. [b] *o*-di: *ortho*-diiodinated isomer. *x*: unidentified iodinated products. [c] Conditions B: NIS (3.3 equiv), $HBF_4.OEt_2$ (12 equiv), 2.5 mM, rt, 16 h. [d] 13% of **26** recovered.

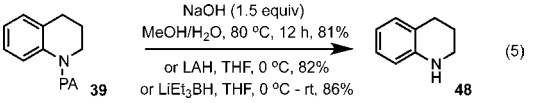
As shown in Scheme 2, γ-arylpropylpicolinamides bearing different substituents at the α, β and γ positions (**10**, **14**, **18**, and **22**) were readily prepared from the corresponding aryl iodides and *N*-alkylpicolinamides via Pd-catalyzed C(sp^3)−H arylation.[7] Good to excellent iodination yields were obtained for these substrates under the standard conditions (**A**). Excellent *ortho*-selectivities were observed for substrates bearing moderately electron-donating or -withdrawing substitutents such as alkyl and halogen groups (see **11**, **15**, and **37**). In general, electron-deficient arene substrates such as **26** and **33** were less reactive; moderate to good yields were obtained under more forcing conditions (**B**) with excess NIS and $HBF_4 \cdot OEt_2$ at room temperature. Sterics also strongly influence the regioselectivity of the reaction; substrates **10**, **14**, **30**, and **36** bearing

Scheme 3. Cu-Catalyzed Formation of THQs[a]



[a] All reactions were carried out on a 0.2 mmol scale; yields are based on isolated product. [b] Yield of PA-deprotected product is shown in parentheses.

meta substituents were iodinated with excellent selectivity at the less hindered *ortho* position.



Treatment of *ortho*-iodinated compound **3** with Cu-catalyzed cyclization conditions (10 mol % of CuI, 2.5 equiv of CsOAc in DMSO at 90 °C) afforded the desired THQ product **38** in excellent yield (eq 4, Scheme 3).[9,22] THQ products **39**−**47** were also obtained in high yields under the same conditions. The PA group of the cyclized THQ products, linked through an aromatic tertiary amide bond, can be readily removed with nucleophilic bases or metal hydride reagents (eq 5).[23] The PA group of THQs bearing electron-withdrawing groups was partially removed during the Cu-mediated cyclization step (see **44** in Scheme 3).

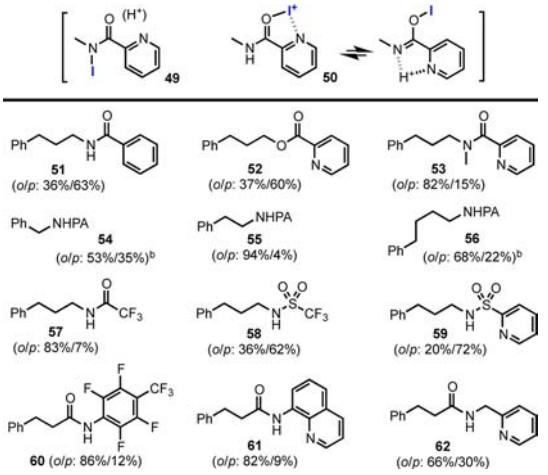
To investigate the mechanism of this PA-directed *ortho*-iodination reaction, control substrates **51**−**58** were evaluated (Scheme 4). Substrates **59**−**62** are equipped with auxiliary groups known to direct metal-catalyzed C(sp^3)−H functionalization.[24] All reactions proceeded with >90% conversion under the standard conditions (**A**), giving predominately monoiodinated products. For benzamide **51** and picolinic ester **52**, we observed 2:3 *ortho*/*para* selectivity, indicating that both *N* atoms of the PA

(22) (a) Kubo, T.; Katoh, C.; Yamada, K.; Okano, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron* **2008**, *64*, 11230. For previous reports on Cu-catalyzed C−N cross-coupling, see: (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (c) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459.

(23) (a) Tanaka, H.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 4417. (b) Reference 5b.

(24) (a) For directing group (DG) in **59**, see: Rodríguez, N.; Romero-Revilla, J. A.; Fernández-Ibáñez, M. Á.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175. (b) For DG in **60**, see: Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. (c) For DG in **61**, see ref 5a. (d) For DG in **62**, see: Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898.

Scheme 4. Mechanistic Study of S_EAr-Mediated Iodination[a]



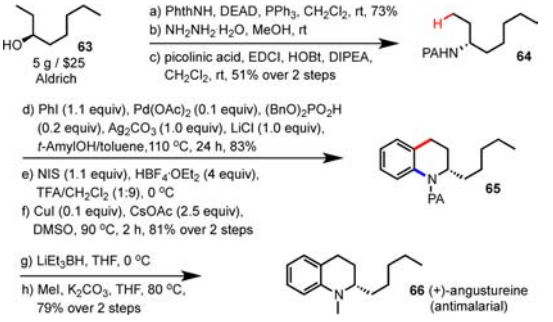
[a] All reactions were performed under the standard conditions (**A**) for 4 h. Yields and selectivities are based on ^{1}H NMR analysis of reaction mixture after workup. [b] ~10% unidentified iodinated product formed. See the Supporting Information for experimental details.

group were involved in the directed *ortho*-iodination process. *N*-methylpicolinamide **53** also underwent *ortho*-iodination, with diminished selectivity relative to non-alkylated picolinamide **6**, suggesting that *O*- iodoimidate **50** is likely the critical intermediate in this intramolecular S_EAr reaction, rather than *N*-iodoamidate **49**.[17a] Interestingly, the quinolyl carboxamide substrate **61**[5a] also underwent *ortho*-selective monoiodination in excellent yield and selectivity.

To demonstrate the utility of this new THQ synthesis strategy, we applied it to the synthesis of the natural product (+)-angustureine (**66**, Scheme 5).[25] Commercially available (*S*)-(+)-3-octanol **63** was converted to picolinamide **64** via Mitsunobo chemistry, followed by deprotection and amide coupling. The standard sequence of PA-directed C−H arylation followed by iodination, and cyclization gave intermediate **65** in 67% yield. Deprotection of the PA group of **65** followed by *N*-methylation, furnished **66** in good yield.

(25) Lin, X.-F.; Li, Y.; Ma, D.-W. *Chin. J. Chem.* **2004**, *22*, 932.

Scheme 5. Total Synthesis of (+)-Angustureine



In summary, we have developed a new strategy to synthesize tetrahydroquinolines via the sequential functionalization of two different types of remote C−H bonds. This method uses only the picolinamide directing/protecting group to effect Pd-catalyzed γ-C(sp^3)−H arylation, metal-free ε-C(sp^2)−H iodination, and Cu-catalyzed intramolecular C−N cross-coupling. The PA group of cyclized products could be easily removed. The overall sequence is efficient and versatile and allows for the streamlined synthesis of THQs with complex substitution patterns at both arene and aliphatic positions from readily available aryl iodide and alkylamine precursors. The monoselective *ortho*-iodination of γ-arylalkyl picolinamides with NIS/HBF_4 presents a generally applicable synthetic method for remote C−H functionalization based on the underexplored reaction pathway of directed S_EAr.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.