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Palladium-Catalyzed Regioselective *Syn*-Chloropalladation−Olefin Insertion−Oxidative Chlorination Cascade: Synthesis of Dichlorinated Tetrahydroquinolines

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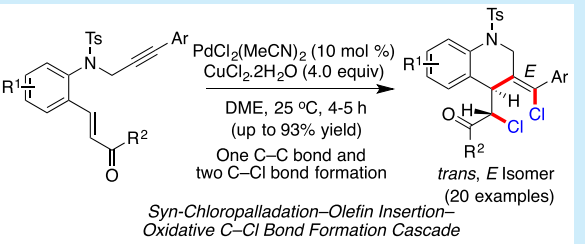
Supporting Information

ABSTRACT: A palladium catalyzed cascade process involving *syn*-chloropalladation, intramolecular olefin insertion, and oxidative C−Cl bond formation reactions was demonstrated for the synthesis of dichlorinated tetrahydroquinolines in high yields (up to 93%). The *N*-propargyl arylamines having a tethered α,β-unsaturated carbonyl moiety underwent a regioselective *syn*-chloropalladation followed by a Heck-type reaction to deliver the tetrahydroquinoline scaffold. The rare insertion of the second chlorine atom was rationalized comprising a $Pd^{II/IV}$ catalytic cycle and oxidative cleavage of the $C-Pd^{II}$ bond.



Syn-Chloropalladation–Olefin Insertion–Oxidative C–Cl Bond Formation Cascade

1,2,3,4-Tetrahydroquinolines, one of the most significant nitrogen heterocycles, represent the privileged structural motifs present in pharmaceuticals and natural products.[1] Numerous natural and synthetic analogs of tetrahydroquinolines display a wide range of biological activities, which were summarized in our comprehensive review.[1a,b] For instance, the 3-chlorotetrahydroquinoline alkaloids virantmycin and benzastatin C showed antiviral,[2] glutamate toxicity, and lipid peroxidation inhibitory activities[3] respectively. In addition, a large number of synthetic analogs of tetrahydroquinolines are known to act at chemotherapeutic targets including antiviral,[4] antiparasitic,[5] antimicrobial,[6] antitumor[7] etc., besides acting as ligands of G-coupled protein receptors (GCPR)[8] and nuclear receptors such as androgen receptor modulators,[9] glucocorticoid receptor,[10] and retinoid receptor.[11] Owing to the increasing demand of these compounds in drug discovery, several synthetic methods have been established which include the formation of the dihydropyridine ring comprising intramolecular strategies starting from suitably tethered arylamines.[12] Despite these advances, direct methods to access highly functionalized tetrahydroquinolines in a single synthetic operation are rather limited.

The nucleopalladation of alkynes, including inter- and intramolecular versions, generates σ-vinylpalladium intermediates, which undergo various cascade transformations including olefin insertion via Heck-type coupling; 1,2-addition to a carbonyl; nucleophilic addition to a nitrile group; arylation; alkyne, carbene, isocyanide, isocyanate insertion etc. for the generation of diverse products in a single operation. The most common nucleopalladation reactions including amino-,[13] oxy-,[14] carboxy-,[15] halo-,[16] carbo-,[17] and hydropalladation[18] reactions and the subsequent cascade reactions allowed access to a wide range of complex molecules by generating multiple bonds in one pot.[19] In continuation of our efforts in developing nucleopalladation-initiated cascade reactions[14a,15a] to access compounds of biological interest, herein, we demonstrate the synthesis of dichlorinated tetrahydroquinolines bearing an exocyclic double bond at the C-3 carbon involving a *syn*-chloropalladation-initiated cascade process.

Halopalladation of alkynes and the successive cascade reactions were recognized as direct approaches for the concurrent construction of C−X and C−C bonds in a single operation. These reactions generate σ-vinylpalladium intermediates *via anti-* or *syn*-halopalladation processes, which could be captured with suitable reactive functionalities to

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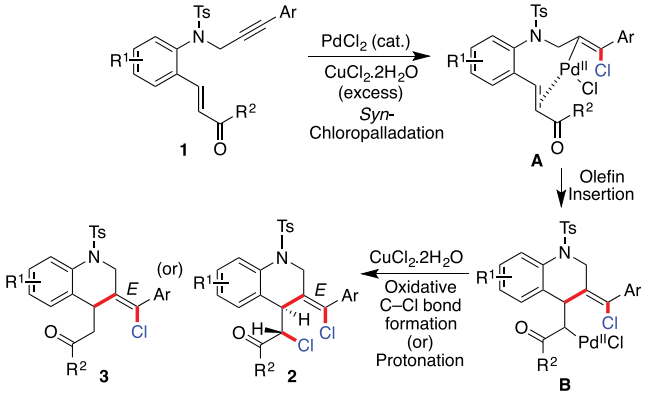
obtain complex molecules.[16] Two distinctive mechanisms involving $Pd^{0/II}$ and $Pd^{II/IV}$ intermediates were proposed for the halopalladation-initiated cascade reactions depending on the nature of the substrates and oxidants employed.[20,21] In this context, we envisaged a chloropalladation-initiated cascade process for the synthesis of tetrahydroquinoline derivative **2** or **3** starting from *N*-propargyl arylamines tethered with *α,β*-unsaturated carbonyl moiety **1** (Scheme 1). The proposed

Scheme 1. Envisioned Regioselective *Syn*-Chloropalladation−Olefin Insertion−Oxidative Chlorination Cascade

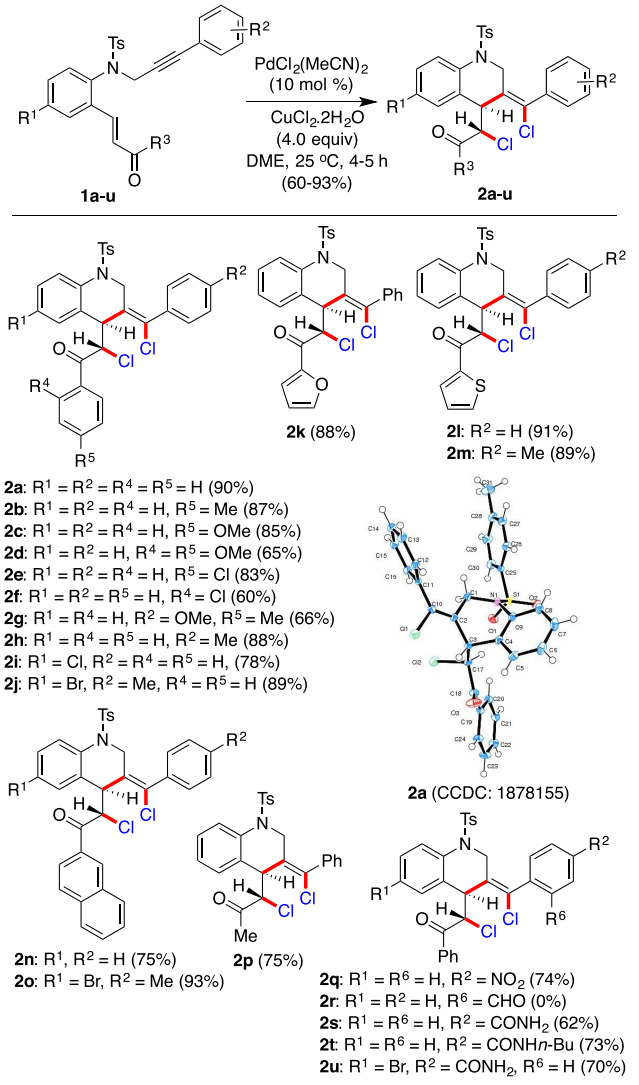


cascade involves a one-pot, three-step cascade consisting of *syn*-chloropalladation, intramolecular olefin insertion, and oxidative C−Cl bond formation or protonation steps. The rare insertion of the second chlorine atom in **2** is rationalized comprising a $Pd^{II/IV}$ catalytic cycle or oxidative cleavage of C−Pd^{II} bond.

The feasibility of the envisioned cascade was examined using *N*-propargyl arylamine **1a** (R^1 = H, R^2, Ar = Ph) as the model substrate in the presence of palladium(II) catalysts and $CuCl_2\cdot 2H_2O$ under various reaction conditions. After an extensive optimization study, use of 10 mol % $PdCl_2(MeCN)_2$, 4 equiv of $CuCl_2\cdot 2H_2O$ in DME at 25 °C was identified as the best conditions to afford the product **2a** in a maximum yield of 90% (see Supporting Information for details).

With the optimized conditions for the chloropalladation-initiated cascade reaction in hand, we next investigated the scope and limitations of the reaction. The alkynes **1a−u** were treated with 10 mol % $PdCl_2(MeCN)_2$ and 4 equiv of $CuCl_2\cdot 2H_2O$ in DME at 25 °C to obtain the corresponding tetrahydroquinolines **2** (Scheme 2). The reaction tolerated both electron-donating and -withdrawing groups in R^1 and R^2 positions (Cl: **2i**; Br: **2j**, **o**, and **u**; Me: **2h**, **j**, **m**, and **o**; OMe: **2g**) affording high yields of the products. Alkyne **1g** having a methoxy group in the R^2 position furnished a moderate yield of 66% of the desired product. In addition, a wide variety of substituents were introduced in the R^3 aryl position including *p*-methyl (**2b** and **g**), *p*-methoxy (**2c**), 2,4-dimethoxy (**2d**), *p*-chloro (**2e**), and *o*-chloro (**2f**) groups. In most of the cases an average yield of 80−90% was attained, and in the case of 2,4-dimethoxy and *o*-chloro substituents, moderate yields were observed (**2d** and **f**, 60−65%). Furthermore, 2-furyl (**2k**), 2-thienyl substituted tetrahydroquinolines (**2l** and **m**) and a couple of 2-naphthyl derivatives (**2n** and **o**) were also synthesized in excellent yields under the optimized reaction conditions. The methyl ketone **1p** derived via Wittig reaction was also transformed into the corresponding tetrahydroquinoline **2p** in 75% yield. The substrate containing strong electron-withdrawing nitro group delivered the product **2q** in 74% yield with no significant change in its reactivity; however, alkyne **1r** bearing highly reactive aldehyde functionality failed to deliver the corresponding tetrahydroquinoline **2r**.

Scheme 2. Scope and Limitations of the Chloropalladation-Initiated Cascade[a]



[a]Reaction conditions: **1** (1 equiv), $PdCl_2(MeCN)_2$ (10 mol %), $CuCl_2\cdot 2H_2O$ (4 equiv), DME, 25 °C, 4−5 h.

Finally, we tested the reactivity of alkynes **1s−u** bearing polar amide functionalities (both primary and secondary) under the optimized reaction conditions. Interestingly, these substrates underwent the chloropalladation-initiated cascade to furnish the dichlorinated tetrahydroquinolines **2s−u** in 62−73% yields. Although this cascade approach has shown good functional group tolerance as demonstrated in Scheme 2, obtaining access to hydroxyl-substituted tetrahydroquinolines was unsuccessful due to the difficulty in synthesizing the required starting materials.

Analysis of the ^1H NMR spectra of the synthesized tetrahydroquinolines **2** showed that the hydrogens present in the chiral carbons were *trans* to each other. The coupling constants of these two doublets were 15.3 Hz thus confirming the *trans* arrangement. Single crystal X-ray analysis of

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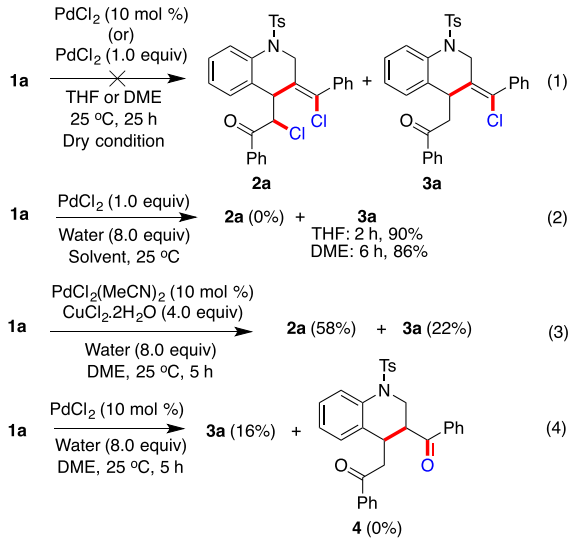
compound **2a** confirmed the proposed *trans* stereochemistry with a dihedral angle of 162.43° (Scheme 2). The geometry of the exocyclic double bond was also established as the *E* configuration from the crystal structure of compound **2a**, which could be explained *via* a *syn*-chloropalladation-initiated mechanism (*vide infra*).

To understand the mechanism of the chloropalladation-initiated cascade, we carried out a set of control experiments shown in Scheme 3. Since both $PdCl_2$ and $PdCl_2(MeCN)_2$

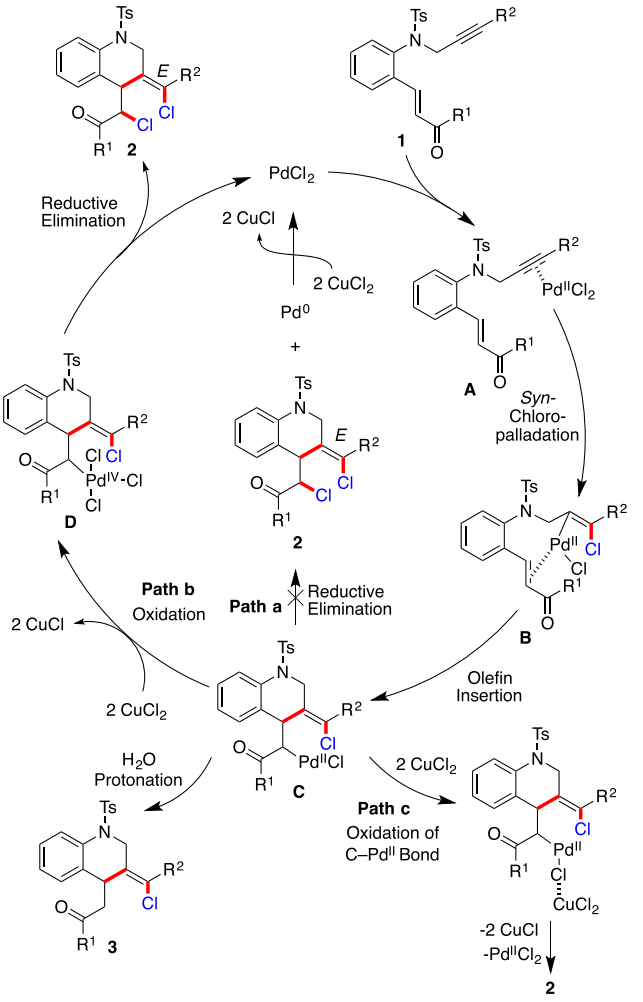
Scheme 3. Control Experiments for the Support of Mechanism



catalysts furnished the products in high yields under the optimized conditions, we selected these catalysts for the control experiments. The reaction proceeds to afford neither monochloro (**2a**) nor dichloro (**3a**) products in the presence of 10 mol % or 1 equiv of $PdCl_2$ and in the absence of $CuCl_2 \cdot 2H_2O$ in dry conditions confirming the crucial role of $CuCl_2 \cdot 2H_2O$ for product formation (eq 1). Interestingly, the same reaction, using 1 equiv of $PdCl_2$ and 8 equiv of water, delivered only the monochloro product **3a** in 90% and 86% yields in THF and DME, respectively (eq 2). The formation of monochloro product **3a** could be explained via chloropalladation−olefin insertion−protonation cascade. A mixture of dichloro (**2a**, 58%) and monochloro (**3a**, 22%) products was obtained when the reaction was carried out under optimized conditions with 8 equiv of water (eq 3). Finally, the hydration−olefin insertion product **4** was not obtained in the presence 10 mol % of $PdCl_2$ and 8 equiv of water (conditions reported for hydration-olefin insertion cascade)[14a] and only the monochloro product **3a** was obtained in 16% yield (eq 4).

On the basis of these control experiments, we proposed a plausible mechanism for the formation of tetrahydroquinolines **2** and **3** as depicted in Scheme 4. Initial coordination of alkyne **1** with $PdCl_2$ followed by *syn*-chloropalladation would generate *σ*-vinylpalladium intermediate **B** via palladium-coordinated species **A**, which would successively undergo olefin insertion with the pendant *α,β*-unsaturated carbonyl moiety to deliver the Pd^{II} tetrahydroquinoline intermediate **C** (*E* isomer). In the presence of water, as demonstrated in Scheme 3, eqs 2−4, the monochloro derivative **3** has formed via protonation after regenerating the Pd^{II} intermediate.[22] However, in our optimized experimental conditions, in the absence of water,

Scheme 4. Plausible Mechanism for the Chloropalladation-Initiated Cascade



no protonation takes place to yield the monochloro compound **3**.

The formation of the observed dichloro product **2** from intermediate **C** could be visualized in three possible pathways: (a) reductive elimination of intermediate **C** to deliver the product **2** followed by oxidation of Pd^0 by $CuCl_2$ to regenerate the Pd^{II} catalyst; (b) oxidation of Pd^{II} to Pd^{IV} by $CuCl_2$ and subsequent reductive elimination of Pd^{IV} intermediate **D** to form the product **2** and the Pd^{II} catalyst; and (c) $CuCl_2$ assisted oxidation of the C−Pd^{II} bond without changing the overall oxidation state of Pd to furnish the product **2** and release the Pd^{II} species. The reductive elimination (*Path a*) can be excluded based on the control experiment (Scheme 4, eq 1), where we used 1 equiv of $PdCl_2$ without the oxidant $CuCl_2$ and no formation of product **2** was observed confirming the role of $CuCl_2$ and an oxidative mechanism. Since the requirement of $CuCl_2$ was established based on the control experiments, the second pathway involving the $Pd^{II/IV}$ catalytic cycle could be involved in the reaction. The formation of Pd^{IV} intermediates in the related transformations was achieved in the presence of urea−H_2O_2,[21a] $CuBr_2$,[21b] H_2O_2,[21c] and CuX_2,[21d] which supports the proposed pathway b. Alternative pathway c could also be in operation as proposed by Henry and others.[21d,23] At this point, it would be difficult to completely exclude any one of these two mechanisms. All

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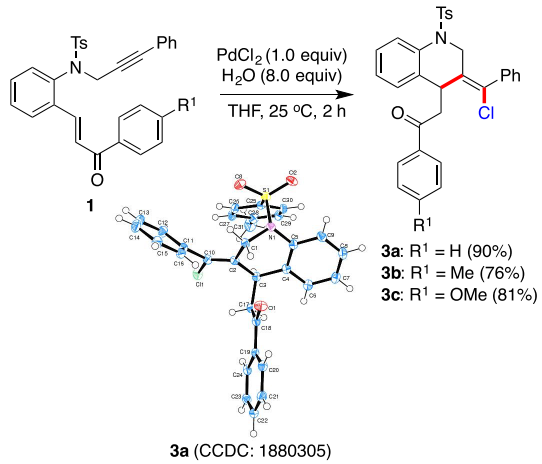
the tested reactions afforded the *E* isomers **2** *via* *syn*-chloropalladation presumably due to the steric nature of the *Z* isomer in the transition state.

As established in Scheme 3, eq 2, we synthesized two more derivatives of the monochloro tetrahydroquinoline **3** employing 1 equiv of $PdCl_2$ in the presence of 8 equiv of water in THF (Scheme 5). The structures of the synthesized compounds were confirmed by NMR analysis and single crystal X-ray analysis of a representative compound **3a**.

Scheme 5. Synthesis of Monochloro Tetrahydroquinoline Derivatives 3



In conclusion, we have established a novel *syn*-chloropalladation-initiated cascade reaction of *N*-propargyl arylamines having a pendant *α,β*-unsaturated carbonyl moiety for the synthesis of tetrahydroquinolines bearing two chlorine atoms in high yields. The reaction takes place in the presence of a catalytic amount of palladium salt and 4 equiv of $CuCl_2 \cdot 2H_2O$ under mild conditions. In this palladium-catalyzed cascade reaction, formation of three new bonds including two C−Cl and one C−C bonds was achieved in a single operation. On the basis of several control experiments a plausible mechanism for the cascade process was proposed involving *syn*-chloropalladation, intramolecular olefin insertion, and oxidative C−Cl bond formation steps. A $CuCl_2$ mediated oxidative mechanism comprising a $Pd^{II/IV}$ catalytic cycle and oxidative cleavage of the C−Pd^{II} bond without change of the overall oxidation state of palladium was visualized for the formation of the final C−Cl bond.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01295.

Experimental details, optimization study, characterization data of products, NMR, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 1878155 and 1880305 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews of tetrahydroquinolines, see: (a) Muthukrishnan, I.; Sridharan, V.; Menéndez, J. C. *Chem. Rev.* **2019**, DOI: 10.1021/acs.chemrev.8b00567. (b) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157−7259. (c) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031−15070.

(2) (a) Nakagawa, A.; Iwai, Y.; Hashimoto, H.; Miyazaki, N.; Oiwa, R.; Takahashi, Y.; Hirano, A.; Shibukawa, N.; Kojima, Y.; Omura, S. *J. Antibiot.* **1981**, *34*, 1408−1415. (b) Omura, S.; Nakagawa, A.; Hashimoto, H.; Oiwa, R.; Iwai, Y.; Hirano, A.; Shibukawa, N.; Kojima, Y. *J. Antibiot.* **1980**, *33*, 1395−1396.

(3) (a) Kim, W.-G.; Kim, J.-P.; Kim, C.-J.; Lee, K.-H.; Yoo, I.-D. *J. Antibiot.* **1996**, *49*, 20−25. (b) Kim, W.-G.; Kim, J.-P.; Yoo, I.-D. *J. Antibiot.* **1996**, *49*, 26−30.

(4) (a) Zhang, J.; Zhan, P.; Wu, J.; Li, Z.; Jiang, Y.; Ge, W.; Pannecouque, C.; De Clercq, E.; Liu, X. *Bioorg. Med. Chem.* **2011**, *19*, 4366−4376. (b) Bedoya, L. M.; Abad, M. J.; Calonge, E.; Astudillo-Saavedra, L.; Gutiérrez, C. M.; Kouznetsov, V. V.; Alcami, J.; Bermejo, P. *Antiviral Res.* **2010**, *87*, 338−344. (c) Su, D.-S.; Lim, J. J.; Tinney, E.; Wan, B.-L.; Young, M. B.; Anderson, K. D.; Rudd, D.; Munshi, V.; Bahnck, C.; Felock, P. J.; Lu, M.; Lai, M.-T.; Touch, S.; Moyer, G.; DiStefano, D. J.; Flynn, J. A.; Liang, Y.; Sánchez, R.; Prasad, S.; Yan, Y.; Perlow-Poehnelt, R.; Torrent, M.; Miller, M.; Vacca, J. P.; Williams, T. M.; Anthony, N. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5119−5123.

(5) (a) Fonseca-Berzal, C.; Merchán-Arenas, D. R.; Romero-Bohórquez, A. R.; Escario, J. A.; Kouznetsov, V. V.; Gómez-Barrio, A. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4851−4856. (b) Romero-Bohórquez, A. R.; Escobar-Rivero, P.; Leal, S. M.; Kouznetsov, V. V. *Lett. Drug Des. Discovery* **2012**, *9*, 802−808.

(6) (a) Gutiérrez, M.; Carmona, U.; Vallejos, G.; Astudillo, L. Z. *Z. Naturforsch., C: J. Biosci.* **2012**, *67*, 551−556. (b) Kumar, A.; Srivastava, S.; Gupta, G.; Chaturvedi, V.; Sinha, S.; Srivastava, R. *ACS Comb. Sci.* **2011**, *13*, 65−71. (c) Kantevari, S.; Yempala, T.; Surineni, G.; Sridhar, B.; Yogeeswari, P.; Sriram, D. *Eur. J. Med. Chem.* **2011**, *46*, 4827−4833.

(7) (a) Jo, H.; Choi, M.; Kumar, A. S.; Jung, Y.; Kim, S.; Yun, J.; Kang, J.-S.; Kim, Y.; Han, S.-B.; Jung, J.-K.; Cho, J.; Lee, K.; Kwak, J. H.; Lee, H. *ACS Med. Chem. Lett.* **2016**, *7*, 385−390. (b) Liu, Y.-M.; Lee, H.-Y.; Chen, C.-H.; Lee, C.-H.; Wang, L. T.; Pan, S. L.; Lai, M.-J.; Yeh, T.-K.; Liou, J.-P. *Eur. J. Med. Chem.* **2015**, *89*, 320−330. (c) Faidallah, H. M.; Rostom, S. A. F. *Eur. J. Med. Chem.* **2013**, *63*, 133−143.

(8) (a) Rivara, S.; Scalvini, L.; Lodola, A.; Mor, M.; Caignard, D.-H.; Delagrange, P.; Collina, S.; Lucini, V.; Scaglione, F.; Furiassi, L.; Mari, M.; Lucarini, S.; Bedini, A.; Spadoni, G. *J. Med. Chem.* **2018**, *61*,

DOI: 10.1021/acs.orglett.9b01295
Org. Lett. XXXX, XXX, XXX−XXX

3726−3737. (b) Spadoni, G.; Bedini, A.; Lucarini, S.; Mari, M.; Caignard, D.-H.; Boutin, J. A.; Delagrange, P.; Lucini, V.; Scaglione, F.; Lodola, A.; Zanardi, F.; Pala, D.; Mor, M.; Rivara, S. *J. Med. Chem.* **2015**, *58*, 7512−7525. (c) Bender, A. M.; Griggs, N. W.; Anand, J. P.; Traynor, J. R.; Jutkiewicz, E. M.; Mosberg, H. I. *ACS Chem. Neurosci.* **2015**, *6*, 1428−1435.

(9) (a) Nagata, N.; Furuya, K.; Oguro, N.; Nishiyama, D.; Kawai, K.; Yamamoto, N.; Ohyabu, Y.; Satsukawa, M.; Miyakawa, M. *ChemMedChem* **2014**, *9*, 197−206. (b) Nagata, N.; Miyakawa, M.; Amano, S.; Furuya, K.; Yamamoto, N.; Inoguchi, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1744−1747.

(10) (a) Hudson, A. R.; Higuchi, R. I.; Roach, S. L.; Adams, M. E.; Vassar, A.; Syka, P. M.; Mais, D. E.; Miner, J. N.; Marschke, K. B.; Zhi, L. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1697−1700. (b) Roach, S. L.; Higuchi, R. I.; Adams, M. E.; Liu, Y.; Karanewsky, D. S.; Marschke, K. B.; Mais, D. E.; Miner, J. N.; Zhi, L. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3504−3508.

(11) (a) Enyedy, I. J.; Powell, N. A.; Caravella, J.; van Vloten, K.; Chao, J.; Banerjee, D.; Marcotte, D.; Silvian, L.; McKenzie, A.; Hong, V. S.; Fontenot, J. D. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2459−2463. (b) Fauber, B. P.; Gobbi, A.; Savy, P.; Burton, B.; Deng, Y.; Everett, C.; La, H.; Johnson, A. R.; Lockey, P.; Norman, M.; Wong, H. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4109−4113.

(12) For recent intramolecular approaches for the synthesis of tetrahydroquinolines, see: (a) Porter, M. R.; Shaker, R. M.; Calcanas, C.; Topczewski, J. J. *J. Am. Chem. Soc.* **2018**, *140*, 1211−1214. (b) Plietker, B.; Alt, I.; Guttroff, C. *Angew. Chem., Int. Ed.* **2017**, *56*, 10582−10586. (c) Li, G.; Nakamura, H. *Angew. Chem., Int. Ed.* **2016**, *55*, 6758−6761. (d) Zhao, Y.; Hu, Y.; Wang, H.; Li, X.; Wan, B. *J. Org. Chem.* **2016**, *81*, 4412−4420. (e) Briones, J. F.; Basarab, G. S. *Chem. Commun.* **2016**, *52*, 8541−8544. (f) Zhang, G.; Wang, S.; Ma, Y.; Kong, W.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 874−879. (g) Han, Y.-Y.; Han, W.-Y.; Hou, X.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 4054−4057. (h) Chowdhury, C.; Das, B.; Mukherjee, S.; Achari, B. *J. Org. Chem.* **2012**, *77*, 5108−5119.

(13) For selected recent aminopalladation-initiated cascade reactions, see: (a) Hu, Y.; Xie, Y.; Shen, Z.; Huang, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 2473−2477. (b) Kundu, P.; Mondal, A.; Das, B.; Chowdhury, C. *Adv. Synth. Catal.* **2015**, *357*, 3737−3752. (c) Xia, G.; Han, X.; Lu, X. *Org. Lett.* **2014**, *16*, 2058−2061. (d) Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12992−12996. (e) Qiu, G.; Chen, C.; Yao, L.; Wu, J. *Adv. Synth. Catal.* **2013**, *355*, 1579−1584. (f) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Iazzetti, A.; Marinelli, F. *Org. Biomol. Chem.* **2013**, *11*, 545−548.

(14) For selected recent oxypalladation-initiated cascade reactions, see: (a) Vinoth, P.; Nagarajan, S.; Maheswari, C. U.; Sudalai, A.; Pace, V.; Sridharan, V. *Org. Lett.* **2016**, *18*, 3442−3445. (b) Zheng, J.; Li, Z.; Wu, W.; Jiang, H. *Org. Lett.* **2016**, *18*, 6232−6235. (c) Li, J.; Zhu, Z.; Yang, S.; Zhang, Z.; Wu, W.; Jiang, H. *J. Org. Chem.* **2015**, *80*, 3870−3879. (d) Tian, P.-P.; Cai, S.-H.; Liang, Q.-J.; Zhou, X.-Y.; Xu, Y.-H.; Loh, T.-P. *Org. Lett.* **2015**, *17*, 1636−1639.

(15) (a) Vinoth, P.; Vivekanand, T.; Suryavanshi, P. A.; Menéndez, J. C.; Sasai, H.; Sridharan, V. *Org. Biomol. Chem.* **2015**, *13*, 5175−5181. (b) Zhou, F.; Han, X.; Lu, X. *J. Org. Chem.* **2011**, *76*, 1491−1494. (c) Wang, Z.; Lu, X. *J. Org. Chem.* **1996**, *61*, 2254−2255.

(16) For general reports of halopalladation-initiated cascade reactions, see: (a) Derosa, J.; Cantu, A. L.; Boulous, M. N.; O'Duill, M. L.; Turnbull, J. L.; Liu, Z.; De La Torre, D. M.; Engle, K. M. *J. Am. Chem. Soc.* **2017**, *139*, 5183−5193. (b) Huang, X.-C.; Wang, F.; Liang, Y.; Li, J.-H. *Org. Lett.* **2009**, *11*, 1139−1142. (c) Dupont, J.; Basso, N. R.; Meneghetti, M. R.; Konrath, R. A. *Organometallics* **1997**, *16*, 2386−2391.

(17) Feng, C.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 17710−17712.

(18) Shen, K.; Han, X.; Xia, G.; Lu, X. *Org. Chem. Front.* **2015**, *2*, 145−149.

(19) For representative reviews on nucleopalladation-triggered cascade reactions, see: (a) Li, J.; Yang, S.; Wu, W.; Jiang, H. *Eur. J. Org. Chem.* **2018**, *2018*, 1284−1306. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981−3019.

(20) For halopalladation-initiated cascade reactions involving a $Pd^{0/II}$ mechanism, see: (a) Zhang, Z.; Wu, W.; Liao, J.; Li, J.; Jiang, H. *Chem. - Eur. J.* **2015**, *21*, 6708−6712. (b) Huang, L.; Wang, Q.; Wu, W.; Jiang, H. *Adv. Synth. Catal.* **2014**, *356*, 1949−1954. (c) Zhang, Z.; Ouyang, L.; Wu, W.; Li, J.; Zhang, Z.; Jiang, H. *J. Org. Chem.* **2014**, *79*, 10734−10742. (d) Ye, S.; Gao, K.; Zhou, H.; Yang, X.; Wu, J. *Chem. Commun.* **2009**, 5406−5408. (e) Liang, Y.; Tang, S.; Zhang, X.-D.; Mao, L.-Q.; Xie; Li, J.-H. *Org. Lett.* **2006**, *8*, 3017−3020. (f) Ma, S.; Wu, B.; Jiang, X.; Zhao, S. *J. Org. Chem.* **2005**, *70*, 2568−2575. (g) Ma, S.; Wu, B.; Zhao, S. *Org. Lett.* **2003**, *5*, 4429−4432. (h) Lu, X.; Zhu, G.; Wang, Z. *Synlett* **1998**, *1998*, 115−121. (i) Ji, J.; Lu, X. *Tetrahedron* **1994**, *50*, 9067−9078. (j) Ma, S.; Lu, X. *J. Org. Chem.* **1993**, *58*, 1245−1250.

(21) For halopalladation-initiated cascade reactions involving a $Pd^{II/IV}$ mechanism, see: (a) Takenaka, K.; Hashimoto, S.; Takizawa, S.; Sasai, H. *Adv. Synth. Catal.* **2011**, *353*, 1067−1070. (b) Savitha, G.; Felix, K.; Perumal, P. T. *Synlett* **2009**, *2009*, 2079−2082. (c) Yin, G.; Liu, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5442−5445. (d) Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618−5621.

(22) When the manuscript was in preparation a related approach was published for the generation of monochlorochromane derivatives: Shukla, R. K.; Pal, K.; Volla, C. M. R. *Chem. - Asian J.* **2018**, *13*, 2435−2439.

(23) (a) Denmark, S. E.; Carson, N. *Org. Lett.* **2015**, *17*, 5728−5731. (b) McCall, A. S.; Wang, H.; Desper, J. M.; Kraft, S. *J. Am. Chem. Soc.* **2011**, *133*, 1832−1848. (c) Hamed, O.; Henry, P. M. *Organometallics* **1998**, *17*, 5184−5189. (d) Henry, P. M. *J. Org. Chem.* **1974**, *39*, 3871−3874.

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