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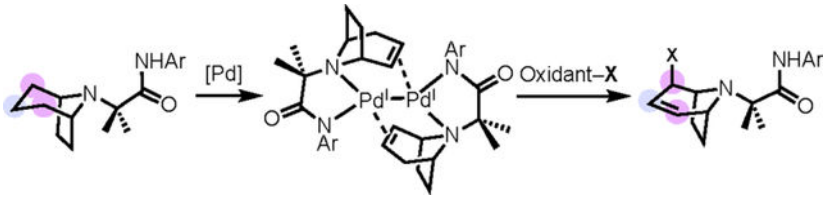
Transannular Functionalization of Multiple C(sp³)–H Bonds of Tropane via an Alkene-Bridged Palladium(I) Dimer

Ellen Y. Aguilera,
En-Chih Liu,
Scott M. Thullen,
Melanie S. Sanford*
Department of Chemistry, University of Michigan, 930 N. University Avenue, Ann Arbor, Michigan 48109, United States

Abstract

This communication describes the Pd-catalyzed C(sp^3)–H functionalization of a tropane derivative to generate products with functionalization at two (β/γ) or three (β/γ/β) different sites on the alicyclic amine core. These reactions proceed via an initial dehydrogenation to generate an alkene product that can react further to form a Pd(I) alkene-bridged dimer. Functionalization of this dimer affords β/γ/β-functionalized allylic arylation and allylic acetoxylation products.

Grahical Abstract



Six-membered alicyclic amines are the single most common heterocycle in pharmaceutically relevant architectures.[1–2] As such, there is significant interest in approaches for the selective C(sp^3)–H functionalization of these scaffolds. To date, synthetic methods have been identified to target each of the individual C(sp^3)–H sites on the core (Scheme 1a–c).[3–5] Most relevant to this report, our group has developed a Pd-catalyzed g-selective C(sp^3)–H functionalization of alicyclic amines (Scheme 1c) in which the amine nitrogen and an appended directing group bind the catalyst and enable selective transannular C_γ–H activation.[6] A complementary approach (Scheme 1d) would be to functionalize multiple sites on an alicyclic amine in a single transformation.[7] This would enable the rapid generation of derivatives for biological evaluation.

In this communication, we demonstrate the realization of this goal in the context of the Pd-catalyzed triple C–H functionalization of tropane substrate **1**.[8] We show that selective

*Corresponding Author: mssanfor@umich.edu.
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β/γ/β functionalization can be achieved by the transannular dehydrogenation of **1** followed by further functionalization of the resulting alkene. An alkene-bridged Pd(I) dimer was isolated from the stoichiometric reaction of **1** with $Pd(OAc)_2$, and this complex reacts with oxidants to form β/γ/β functionalized products in high yield and selectivity.

This work commenced with studies of the $Pd(OAc)_2$-catalyzed reaction between tropane substrate **1** and PhI using conditions previously reported by our group for C_γ–H arylation (Scheme 2).[6b] The expected γ-arylation product **2** was obtained in 63% yield after 18 h at 140 °C. However, careful inspection of the crude reaction mixture revealed the minor side product **3**, derived from functionalization at three different sites β/γ/β on the tropane core (9% yield). The structure and stereochemistry of **3** were confirmed by NMR spectroscopy and x-ray crystallography (see SI for details). Variation of the solvent, base, and picolinic acid derivative led to conditions where **3** is the major product (Scheme 2b). However, even under these optimized conditions, significant quantities of **2** were formed (~9%). Furthermore, the yield of **3** was variable, ranging from 27–64% from run-to-run.[9]

In an effort to address these issues, we interrogated the pathway to the β/γ/β functionalization product, **3**. We hypothesized that **3** is formed via sequential Pd-catalyzed dehydrogenation followed by allylic arylation (Scheme 3a). Notably, Yu and coworkers have reported related $Pd(OAc)_2$-catalyzed oxazoline-[10] and carboxylic acid-directed[11] dehydrogenations of alkanes to afford alkenes.[12] Furthermore, Pd-catalyzed Heck-type reactions between cyclic alkenes and aryl iodides to form allylic arylation products are well precedented.[13]

To test the feasibility of an initial dehydrogenation, we conducted the reaction from Scheme 2a in the absence of PhI, substituting trifluorotoluene as an inert aromatic solvent. This afforded alkene **4** as the major product in 48% yield (Scheme 3b). The conditions were optimized (by varying the solvent, base, temperature, and picolinic acid derivative) to afford alkene **4** in 63% isolated yield (see SI for details). An isolated sample of **4** was then re-subjected to the original Pd-catalyzed C–H arylation conditions. After 18 h at 140 °C, the reaction afforded **3** in 30% yield, consistent with **4** as an intermediate en route to **3**.[14]

Our previous work has shown that transannular C_γ–H functionalization of related alicyclic amine substrates can be achieved in enhanced yield and selectivity via stoichiometric reactions of palladium-amine coordination complexes.[15] For example, as shown in Scheme 4a, we demonstrated that Pd^{II} complex **A** forms under mild conditions from the reaction between $Pd(OAc)_2$/pyridine and alicyclic amines bearing fluoroarylamide directing groups. **A** then reacts with oxidants (FG in Scheme 4a) to afford γ-functionalized products.[16] In some instances, the analogous organic products were formed in poor yield under catalytic conditions. Thus, we hypothesized that an analogous stoichiometric sequence might provide cleaner access to the target β/γ/β-functionalized product **3** and analogues thereof.

In the event, the reaction of tropane substrate **1** with $Pd(OAc)_2$ and pyridine (identical conditions to those in Scheme 4a) did not afford the expected coordination complex **B**. Instead, it resulted in dehydrogenation of **1** and formation of the Pd^{I} alkene-bridged dimer **C** as the major distinguishable organometallic product.[17] This dimer, which shows four

diagnostic ^{1}H NMR resonances between 5.28 and 3.79 ppm, was formed in 17% yield as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Modifying the reaction conditions (by changing the solvent from *t*-amyl alcohol to MeCN and removing the pyridine) resulted in a 36% crude yield of **C**. Purification by column chromatography on silica gel afforded an analytically pure sample of **C** in 35% isolated yield. X-ray quality crystals were obtained from a dichloromethane/hexanes solution at room temperature. The x-ray crystal structure is provided in Figure 1 and shows that this is a dimeric complex with the alkene ligands bridging two palladium(I) centers. The Pd–Pd distance is 2.445 Å, which is comparable to that in structurally similar Pd^{I} dimers.[18]

With **C** in hand, we investigated stoichiometric reactions of this complex with oxidants to generate β/γ/β-functionalized products. As shown in Scheme 5, the treatment of **C** with phenyl iodide at 100 °C afforded **3** in 72% yield.[19a–b] In contrast to the catalytic reactions in Schemes 1 and 2, this transformation was reproducible and high yielding. Analogous reactivity was observed using 3,5-dimethylphenyl iodide, providing **5** in 77% yield.[19a]

Based on literature reports from White[20] and others,[21] we hypothesized that allylic oxygenation might also be feasible from **C** using carboxylic acids in conjunction with benzoquinone (BQ). Indeed, the treatment of **C** with benzoic acid and 2 equiv of BQ formed the allylic benzoylation product **6** in 71% yield.[19a] This reaction proceeded similarly with propionic acid to afford **7** in 67% yield.[19a] The structure and stereochemistry of the latter product was confirmed via x-ray crystallography (see SI for details). Overall, the stoichiometric formation and subsequent functionalization of **C** offers a clean, selective, reproducible, and high yielding route to the tri-functionalized products **3** and **5–7**.

In summary, this report describes a route to β/γ/β-functionalized tropane derivatives via dehydrogenation/functionalization. The $Pd(OAc)_2$-catalyzed reaction requires high temperatures (≥140 °C) and exhibits poor reproducibility, yield, and product selectivity. To address these challenges, we developed a stoichiometric sequence involving initial dehydrogenation to form a dimeric Pd(I) intermediate followed by subsequent functionalization of this complex. This sequence proceeds under relatively mild conditions (60–100 °C) with high reproducibility. Furthermore, it provides a route to diverse C–C and C–O coupled products in good yield/selectivity. These studies highlight the value of interrogating stoichiometric reactions between metal and substrate as a pathway to achieving selective C–H functionalization reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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REFERENCES

1. (a)Taylor RD; MacCoss M; Lawson ADG Rings in Drugs. J. Med. Chem. 2014, 57, 5845–5859. [PubMed: 24471928] (b)Top 200 Pharmaceutical Products by Prescription in 2016; University of Arizona, 2016. http://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/2016Top200PharmaceuticalPrescriptionSalesPosterLowResV2.pdf (accessed January 2023).
2. (a)Vitaku E; Smith DT; Njardarson JT Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. J. Med. Chem. 2014, 57, 10257–10274. [PubMed: 25255204] (b)Källström S; Leino R Synthesis of Pharmaceutically Active Compounds Containing a Disubstituted Piperidine Framework. Bioorg. Med. Chem. 2008, 16, 601–635. [PubMed: 17980609]
3. (a)Wencel-Delord J; Glorius F C–H Bond Activation Enables the Rapid Construction and Late-Stage Diversification of Functional Molecules. Nature Chem 2013, 5, 369–375. [PubMed: 23609086] (b)Cernak T; Dykstra KD; Tyagarajan S; Vachal P; Krska SW The Medicinal Chemist's Toolbox for Late-Stage Functionalization of Drug-like Molecules. Chem. Soc. Rev. 2016, 45, 546–576. [PubMed: 26507237]
4. For examples of α–functionalization of alicyclic amines, see:(a)Pastine SJ; Gribkov DV; Sames D sp^3 C–H Bond Arylation Directed by Amidine Protecting Groups: α-Arylation of Pyrrolidines and Piperidines. J. Am. Chem. Soc. 2006, 128, 14220–14221. [PubMed: 17076471] (b)Campos KR Direct sp^3 C–H Bond Activation Adjacent to Nitrogen in Heterocycles. Chem. Soc. Rev. 2007, 36, 1069–1084. [PubMed: 17576475] (c)Mitchell EA; Peschiulli A; Lefevre N; Meerpoel L; Maes BUW Direct α-Functionalization of Saturated Cyclic Amines. Chem. Eur. J. 2012, 18, 10092–10142. [PubMed: 22829434] (d)Shi L; Xia W Photoredox Functionalization of C–H Bonds Adjacent to a Nitrogen Atom. Chem. Soc. Rev. 2012, 41, 7687–7697. [PubMed: 22869017] (e)He J; Hamann LG; Davies HML; Beckwith REJ Late-Stage C–H Functionalization of Complex Alkaloids and Drugs Molecules via Intermolecular Rhodium-Carbenoid Insertion. Nat. Commun. 2015, 6, 5943. [PubMed: 25581471] (f)Spangler JE; Kobayashi Y; Verma P; Wang D-H; Yu J-Q α-Arylation of Saturated Azacycles and N-methylamines via Palladium(II)-Catalyzed C(sp3)–H Coupling. J. Am. Chem. Soc. 2015, 137, 11876–11879. [PubMed: 26322957] (g)Chen W; Ma L; Paul A; Seidel D Direct α-C–H Bond Functionalization of Unprotected Cyclic Amines. Nat. Chem. 2017, 10, 165–169. [PubMed: 29359746] (h)Nagaraaj P; Vijayakumar V Oxidation of Amine α-Carbon to Amide: A Review on Direct Methods to Access the Amide Functionality. Org. Chem. Front. 2019, 6, 2570–2599.(i)Paul A; Seidel D α-Functionalization of Cyclic Secondary Amines: Lewis Acid Promoted Addition of Organometallics to Transient Imines. J. Am. Chem. Soc. 2019, 141, 8778–8782. [PubMed: 31117670] (j)Copper-Catalyzed Late-Stage C(sp3)–H Functionalization of Nitrogen Heterocycles. Nature Commun. 2021, 12, article number 4342. [PubMed: 34267229] (k)Yu F; Valles DA; Chen W; Daniel SD; Ghiviriga I; Seidel D Regioselective α-Cyanation of Unprotected Alicyclic Amines. Org. Lett. 2022, 24, 6364–6368. [PubMed: 36036764]
5. For examples of β–functionalization of alicyclic amines, see: Ye S; Yang W; Coon T; Fanning D; Neubert T; Stamos D; Yu J-Q N-Heterocyclic Carbene Ligand-Enabled C(sp3)–H Arylation of Piperidine and Tetrahydropyran Derivatives. Chem. Eur. J. 2016, 22, 4748–4752. [PubMed: 26841330] (b)Affron DP; Bull JA Palladium-Catalyzed Directed C(sp3)-H Arylation of Saturated Heterocycles at C-3 Using a Concise Optimization Approach: Pd-Catalyzed Directed C(sp3)-H Arylation. Eur. J. Org. Chem. 2016, 139–149.(c)Van Steijvoort BF; Kaval N; Kulago AA; Maes BUW Remote Functionalization: Palladium-Catalyzed C5(sp3)-H Arylation of 1-Boc-3-Aminopiperidine through the Use of a Bidentate Directing Group. ACS Catal. 2016, 6, 4486–4490. (d)Zhou M-J; Zhu S-F; Zhou Q-L Copper-Catalyzed Mannich-Type Oxidative β-Functionalization of Tertiary Amines. Chem. Commun. 2017, 53, 8770–8773.(e)Griffiths RJ; Kong WC; Richards SA; Burley GA; Willis MC; Talbot EPA Oxidative β-C–H Sulfonylation of Cyclic Amines. Chem. Sci. 2018, 9, 2295–2300. [PubMed: 29719703] (f)Chen W; Paul A; Abboud KA; Seidel D Rapid Functionalization of Multiple C–H Bonds in Unprotected Alicyclic Amines. Nature Chem. 2020, 12, 545–550. [PubMed: 32231260] (g)Chang Y; Cao M; Chan JZ; Zhao C; Wang Y; Yang R; Wasa M Enantioselective Synthesis of N-Alkylamines through β-Amino C–H Functionalization Promoted by Cooperative Actions of B(C6F5)3 and a Chiral Lewis Acid Co-Catalyst. J. Am. Chem. Soc. 2021, 143, 2441–2455. [PubMed: 33512998] (h)Holmberg-Douglas N; Choi Y; Aquila B; Huynh H; Nicewicz DA β-Functionalization of Saturated Aza-Heterocycles Enabled by Organic

Photoredox Catalysis. ACS Catal. 2021, 11, 3153–3158. [PubMed: 36093286] (i) Piticari A-S; Antermite D; Higham JI; Moore HJ; Webster MP; Bull JA Stereoselective Palladium-Catalysed C(sp3)–H Mono-Arylation of Piperidines and Tetrahydropyrans with a C(4) Directing Group. Adv. Syn. Catal. 2022, 364, 1488–1497.

6. (a)Topczewski JJ; Cabrera PJ; Saper NI; Sanford MS Palladium-Catalysed Transannular C–H Functionalization of Alicyclic Amines. Nature 2016, 531, 220–224. [PubMed: 26886789] (b)Cabrera PJ; Lee M; Sanford MS Second Generation Palladium Catalyst System for Transannular C–H Functionalization of Azabicycloalkanes. J. Am. Chem. Soc. 2018, 140, 5599–5606. [PubMed: 29652497] (c)Lee M; Adams A; Cox PB; Sanford MS Access to 3D Alicyclic Amine-Containing Fragments through Transannular C–H Arylation. Synlett 2019, 30, 417–422. [PubMed: 35821894] (d)Li Z; Dechantsreiter M; Dandapani S Systematic Investigation of the Scope of Transannular C–H Heteroarylation of Cyclic Secondary Amines for Synthetic Application in Medicinal Chemistry. J. Org. Chem. 2020, 85, 6747–6760. [PubMed: 32295349] (e)Daugulis O; Roane J; Tran LD Bidentate, Monoanionic Auxiliary-Directed Functionalization of Carbon-Hydrogen Bonds. Acc. Chem. Res. 2015, 48, 1053–1064. [PubMed: 25756616]
7. For examples of difunctionalization of piperidine derivatives, see:(a)Xu G-Q; Xu J-T; Feng Z-T; Liang H; Wang Z-Y; Qin Y; Xu P-F Dual C(sp^3)–H Bond Functionalization of N-Heterocycles through Sequential Visible-Light Photocatalyzed Dehydrogenation/[2 + 2] Cycloaddition Reactions. Angew. Chem., Int. Ed. 2018, 57, 5110–5114.(c)Visible-Light-Induced α,γ-C(sp3)–H Difunctionalization of Piperidines. Org. Lett. 2022, 24, 2894–2898. [PubMed: 35416677] (c)Colson E; Andrez J; Dabbous A; Denes F; Maurel V; Mouesca J-M; Renaud P Tropane and Related Alkaloid Skeletons via a Radical [3+3]-Annulation Process. Commun. Chem. 2022, 5, 57. [PubMed: 36697883]
8. Recent report of C–H functionalization approach to β/γ/β functionalized tropanes: Zayene M; Le Bideau F; Retailleau P; Jannet HB; Alami M; Romdhane A; Messaoudi S Site-Selective Palladium(II)-Catalyzed Methylene C(sp3)–H Diarylation of a Tropane Scaffold. J. Org. Chem. 2022, 87, 16399–16409. [PubMed: 36473230]
9. Product 3 is always observed in these reactions, but its yield is variable. Reactions with lower yields typically show low (<50%) conversion of starting material 1. Despite extensive studies, we have been unable to pinpoint the origin of this poor reproducibility.
10. Giri R, Maugel N, Foxman BM, Yu J-Q, Dehydrogenation of Inert Alkyl Groups via Remote C–H Activation: Converting a Propyl Group into a π-Allylic Complex. Organometallics 2008, 27, 1667–1670.
11. Wang Z; Hu L; Chekshin N; Zhuang Z; Qian JX; Yu J-Q Ligand-Controlled Divergent Dehydrogenative Reactions of Carboxylic Acids via C–H Activation. Science 2021, 374, 1281–1285. [PubMed: 34762490]
12. For a different mechanism for the Pd-catalyzed desaturation of amines, see: Chuentragool P; Parasram M; Shi Y; Gevorgyan V General, Mild, and Selective Method for the Desaturation of Aliphatic Amines. J. Am. Chem. Soc. 2018, 140, 2465–2468. [PubMed: 29400959]
13. (a)Cabri W; Candiani I Recent Developments and New Perspectives in the Heck Reaction. Acc. Chem. Res. 1995, 28, 2–7.(b)Beletskaya IP; Cheprakov AV Heck Reaction as a Sharpening Stone of Palladium Catalysis. Chem. Rev. 2000, 100, 3009–3066. [PubMed: 11749313] (c)Berthiol F; Doucet H; Santelli M Heck Reaction of Aryl Halides with Linear or Cyclic Alkenes Catalysed by a Tetraphosphine/Palladium Catalyst Tetrahedron Lett. 2003, 44, 1221–1225.(d)Zafar MN; Mohsin MA; Danish M Palladium Catalyzed Heck-Mizoroki and Suzuki-Miyaura coupling reactions (Review). Russ. J. Coord. Chem. 2014, 40, 781–800.(e)Biffis A; Centomo P; del Zotto A; Zecca M Pd Metal Catalysts for Cross-Couplings and Related Reactions in the 21st Century: A Critical Review. Chem. Rev. 2018, 4, 2249–2295.(f)Li C; Qiang XY; Qi ZC; Cao B; Li JY; Yang SD Pd-Catalyzed Heck-Type Reaction: Synthesizing Highly Diastereoselective and Multiple Aryl-Substituted P-Ligands. Org. Lett. 2019, 21, 7138–7142. [PubMed: 31453704] (g)Xie JQ; Liang RX; Jia YX Recent Advances of Catalytic Enantioselective Heck Reactions and Reductive-Heck Reactions. Chin. J. Chem. 2021, 710–728.(h)Reznikov AN; Ashatkina MA; Klimochkin YN Recent Developments in Asymmetric Heck Type Cyclization Reactions for Constructions of Complex Molecules. Org. Bio. Chem. 2021, 5673–5701.
14. As expected, no allylic arylation of 4 was detected in the absence of Pd(OAc)2.

15. Aguilera EY; Sanford MS Model Complexes for the Palladium-Catalyzed Transannular C–H Functionalization of Alicyclic Amines. Organometallics 2019, 38, 138–142. [PubMed: 31118540]

16. Aguilera EY; Sanford MS Palladium-Mediated C_{γ}–H Functionalization of Alicyclic Amines. Angew. Chem. Int. Ed. 2021, 60, 11227–11230.

17. A proposed pathway for the formation of **C** is outlined in Figure S9.

18. (a)Nuricumbo-Escobar JJ; Campos-Alvarado C; Ríos-Moreno G; Morales-Morales D; Walsh PJ; Parra-Hake M Binuclear Palladium(I) and Palladium(II) Complexes of Ortho-Functionalized 1,3-Bis(Aryl)Triazenido Ligands. Inorg. Chem. 2007, 46, 6182–6189. [PubMed: 17580936] (b)Yamaguchi Y; Yamanishi K; Kondo M; Tsukada N Synthesis of Dinuclear (μ−η3-Allyl)palladium(I) and -platinum(I) Complexes Supported by Chelate-Bridging Ligands. Organometallics 2013, 32, 4837–4842.(c)Chu J; Xie XH; Yang SR; Zhan SZ Synthesis and Electro-Catalytic Properties of a Dinuclear Palladium(I) 1,3-Bis[(2-Chloro)Benzene]Triazenide Complex. Inorganica Chim. Acta 2014, 410, 191–194.(d)Correa-Ayala E; Campos-Alvarado C; Chávez D; Hernández-Ortega S; Morales-Morales D; Miranda-Soto V; Parra-Hake M Dipalladium(I) Complexes of Ortho- and Para-Functionalized 1,3-Bis(Aryl)Triazenide Ligands: Synthesis, Structure and Catalytic Activity. Inorganica Chim. Acta 2019, 490, 130–138.(e)Zhan JZ; Xie ZL; Liu QH; Zhan SZ Design, Synthesis, Characterization and Electrocatalytic Behaviour of a Dinuclear Palladium(I) Complex Supported by 1-[(2-Chloro)Benzene]-3-[(2-Carboxmethyl)Benzene]Triazenide Ions. Polyhedron 2019, 163, 108–113.

19. (a)This yield reflects conversion of both of the alkenes in **C** into the organic product.(b)C reacts with 4-CF3-picolinic acid at 100 °C in the absence of ArI to release 4 in 62% yield after 18 h (Figure S10). As such, it is unclear whether the formation of 3/5 under these conditions proceeds directly from C or via the intermediacy of 4.

20. (a)Chen MS; White MC A Sulfoxide-Promoted, Catalytic Method for the Regioselective Synthesis of Allylic Acetates from Monosubstituted Olefins via C–H Oxidation. J. Am. Chem. Soc. 2004, 126, 1346–1347. [PubMed: 14759185] (b)Chen MS; Prabagaran N; Labenz NA; White MC Serial Ligand Catalysis: A Highly Selective Allylic C–H Oxidation. J. Am. Chem. Soc. 2005, 127, 6970–6971. [PubMed: 15884938]

21. (a)Åkermark B; Hansson S; Rein T; Vågberg J; Heumann A; Bäckvall J-E Palladium-Catalyzed Allylic Acetoxylation: An Exploratory Study of the Influence of Added Acids. J. Organometallic Chem. 1989, 369, 433–444.(b)Pilarski LT; Selander N; Böse D; Szabó KJ Catalytic Allylic C–H Acetoxylation and Benzoyloxylation via Suggested (η3-Allyl)Palladium(IV) Intermediates. Org. Lett. 2009, 11, 5518–5521. [PubMed: 19899750] (c)Lin BL; Labinger JA; Bercaw JE Mechanistic Investigations of Bipyrimidine-Promoted Palladium-Catalyzed Allylic Acetoxylation of Olefins. Can. J. Chem. 2009, 87, 264–271.(d)Henderson WH; Check CT; Proust N; Stambuli JP Allylic Oxidations of Terminal Olefins Using a Palladium Thioether Catalyst. Org. Lett. 2010, 12, 824–827. [PubMed: 20099865] (e)Thiery E; Aouf C; Belloy J; Harakat D; Bras J le; Muzart, J. Palladium-Catalyzed Allylic Acyloxylation of Terminal Alkenes in the Presence of a Base. J. Org. Chem. 2010, 75, 1771–1774. [PubMed: 20141222] (f)Campbell AN; White PB; Guzei IA; Stahl SS Allylic C–H Acetoxylation with a 4,5-Diazafluorenone-Ligated Palladium Catalyst: A Ligand-Based Strategy to Achieve Aerobic Catalytic Turnover. J. Am. Chem. Soc. 2010, 132, 15116–15119. [PubMed: 20929224] (g)Mann SE; Aliev AE; Tizzard GJ; Sheppard TD Sulfur-Directed Olefin Oxidations: Observation of Divergent Reaction Mechanisms in the Palladium-Mediated Acetoxylation of Unsaturated Thioacetals. Organometallics 2011, 30, 1772–1775.(h)Kondo H; Yu F; Yamaguchi J; Liu G; Itami K Branch-Selective Allylic C–H Carboxylation of Terminal Alkenes by Pd/Sox Catalyst. Org. Lett. 2014, 16, 4212–4215. [PubMed: 25068764] (i)Liron F; Oble J; Lorion MM; Poli G Direct Allylic Functionalization through Pd-Catalyzed C–H Activation. Eur. J. Org. Chem. 2014, 5863–5883.(j)Malik HA; Taylor BLH; Kerrigan JR; Grob JE; Houk KN; du Bois J; Hamann LG; Patterson AW Non-Directed Allylic C–H Acetoxylation in the Presence of Lewis Basic Heterocycles. Chem. Sci. 2014, 5, 2352–2361. [PubMed: 25685311] (k)Xing X; O'Connor NR; Stoltz BM Palladium(II)-Catalyzed Allylic C–H Oxidation of Hindered Substrates Featuring Tunable Selectivity Over Extent of Oxidation. Angew. Chem. Int. Ed. 2015, 54, 11186–11190.(l)Li X; Sun B; Zhou J; Jin C; Yu C Regioselective Acetoxylation of Terminal Olefins Using a Palladium(II)–Thiadiazole Catalyst. Eur. J. Org. Chem. 2019, 15, 2635–2638.

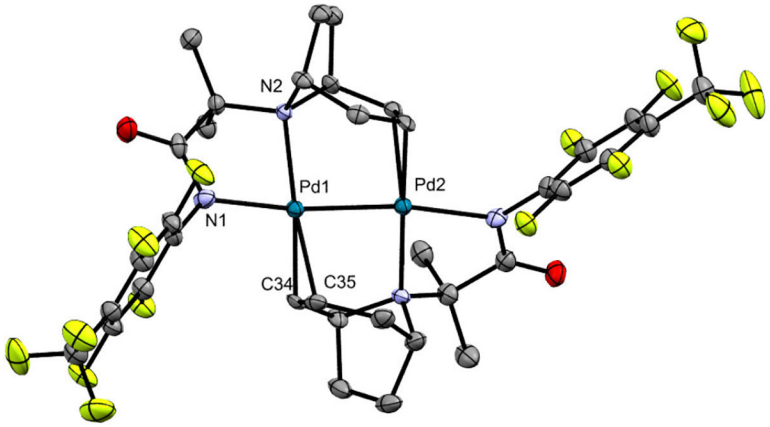
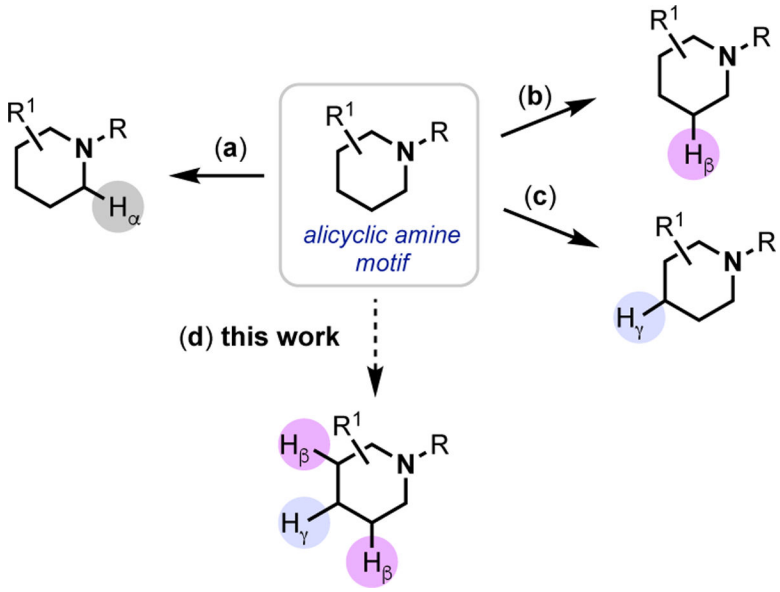


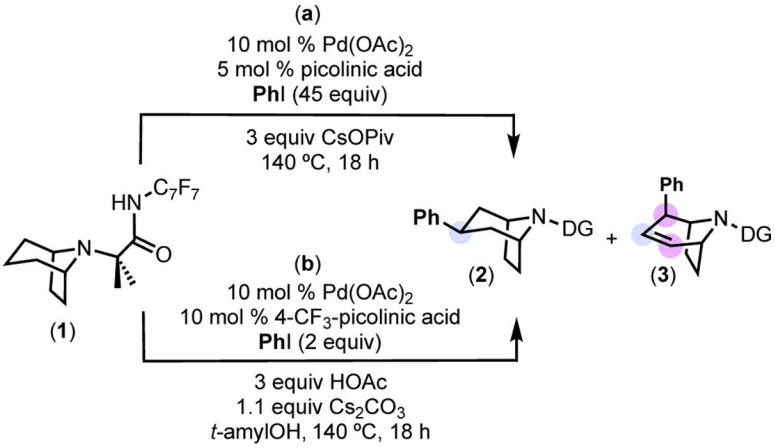
Figure 1.

X-ray crystal structure of **C**. Selected bond distances (Å): N1−Pd1 2.113, N2−Pd1 2.139, C34−Pd1 2.131, C35−Pd1 2.184, Pd1–Pd2 2.445. Hydrogen atoms are omitted for clarity.



Scheme 1.

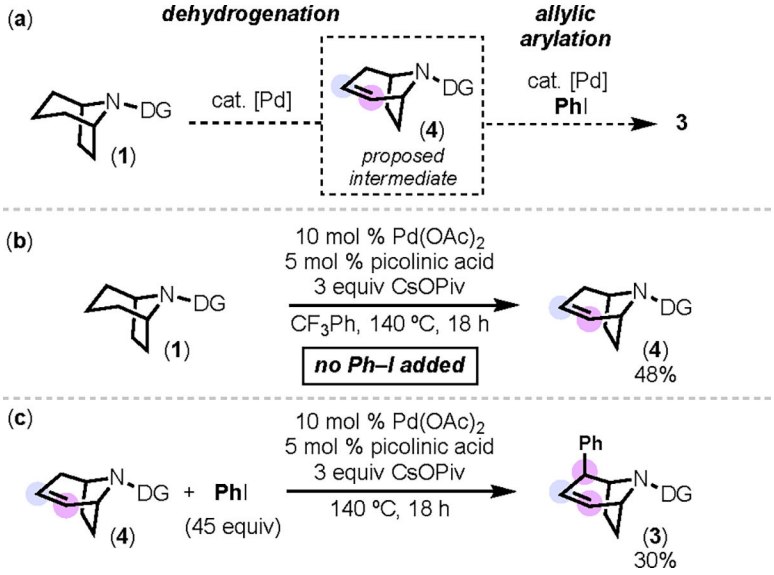
(**a-c**) C(sp^3)–H functionalization reactions that selectively target the α-, β-, and γ-C(sp^3)–H bonds of 6-membered alicyclic amines. [R, R^1 = hydrogen, alkyl, aryl, or directing group (DG), depending on the transformation.] (**d**) This work: C(sp^3)–H functionalization of the β/γ/β sites in a single transformation. [R = directing group, DG]



entry	conditions	**2** (%)	**3** (%)
1	(**a**)	**63**	9
2	(**b**)	9	**27-64**

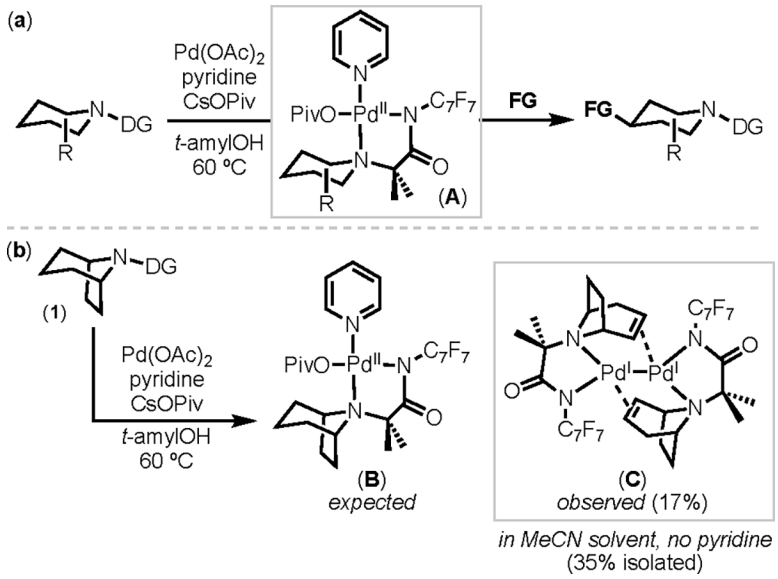
Scheme 2.

(**a**) Pd-catalyzed reaction of **1** with PhI affords products functionalized at the γ (**2**) and β/γ/β positions (**3**). (**b**) Optimized conditions afford **3** as the major product, but selectivity is modest, and yield is variable.



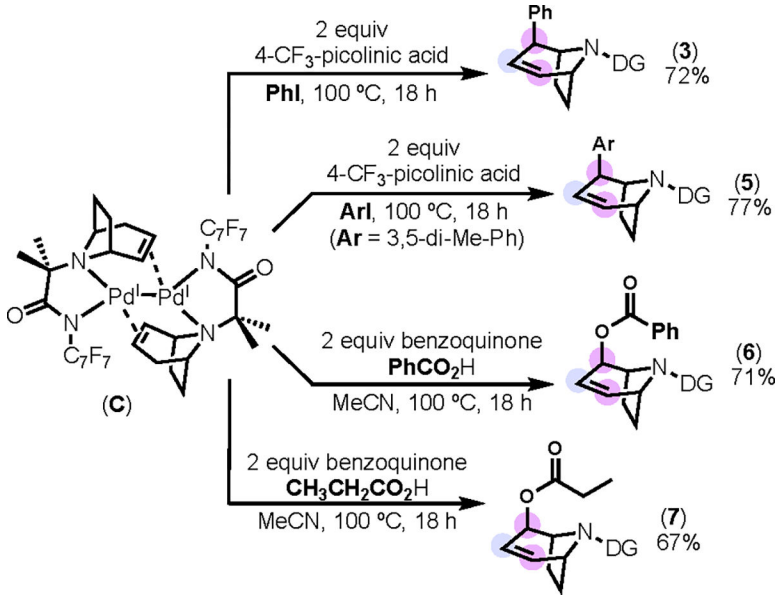
Scheme 3.

(**a**) Proposed pathway to **3**. (**b**) Alkene **4** is formed in the absence of PhI. (**c**) Resubjecting **4** to the reaction conditions affords **3**.



Scheme 4.

(**a**) Previous work on isolation and selective C–H functionalization of **A**. (**b**) Stoichiometric reaction of **1** with $Pd(OAc)_2$ forms alkene-bridged dimer **C**



Scheme 5.

High yielding functionalization of dimer **C** to form **3** and **5–7**.