Cyclopropane-Fused N-Heterocycles via Aza-Heck-Triggered C(sp<sup>3</sup>)–H Functionalization Cascades

Changcheng Jing, Benjamin T. Jones, Ross J. Adams, and John F. Bower*

Cite This: J. Am. Chem. Soc. 2022, 144, 16749−16754

ABSTRACT: Unique examples of aza-Heck-based C(sp<sup>3</sup>)–H functionalization cascades are described. Under Pd(0)-catalyzed conditions, the aza-Heck-type cyclization of N-(pentafluorobenzoyloxy)carbamates generates alkyl–Pd(II) intermediates that effect C(sp<sup>3</sup>)–H palladation en route to cyclopropanes. Key factors that control the site selectivity of the cyclopropanation process have been elucidated such that selective access to a wide range of ring- or spiro-fused systems can be achieved.

Cyclopropanes are routinely employed in pharmaceutical design to moderate compound lipophilicity or N-centered basicity. Reflecting their relative ease of synthesis, peripheral cyclopropane units are featured in many marketed drugs, whereas core cyclopropane units are encountered less often (Scheme 1A). An example of the latter is the DPP-4 inhibitor saxagliptin, which possesses a cyclopropane-fused pyrrolidine. This subunit is derived from pyroglutamic acid via a lengthy Simmons–Smith-based route, making access to more complex derivatives challenging. Accordingly, direct and flexible methods that can address these issues are likely to be of interest. A powerful but underdeveloped option involves the intramolecular aza-palladation of an alkene (step a) in advance of C–H palladation-initiated cyclopropanation (step b) (Scheme 1B). Yang and co-workers have demonstrated such processes under oxidative conditions (Scheme 1C).

Although conceptually important, specific constraints hamper both steps; for example, step a requires a conformationally biasing and acidifying anilide unit and is not well suited to six-membered alkene aza-palladation-based processes can be enhanced substantially by replacing an external oxidant (e.g., O<sub>2</sub> in Scheme 1C) with a N–O bond. In this approach, N–O oxidative addition unites the key processes of substrate binding and catalyst oxidation, so the catalysis is often more robust. The non-oxidative conditions also mean that highly tunable P-based ligands can be used to moderate the properties of the Pd center. Indeed, aza-Heck-based approaches of this type now allow an expanding range of nonconformationally biased cyclizations and cascades involving sterically and electronically diverse alkenes. This includes asymmetric aza-Heck cyclizations and cascade reactions involving aryl C(sp<sup>3</sup>)–H palladation. In the present study, we outline aza-Heck-triggered cyclopropanation processes that involve a more challenging C(sp<sup>3</sup>)–H palladation step (Scheme 1D). To the best of our knowledge, these are the first examples of C(sp<sup>3</sup>)–H functionalization cascades that use newer classes of N–O units (i.e., nonoxime ester-based). Compared to Scheme 1C, notable features of these new processes include (a) the

Scheme 1. Introduction

(A) Pharmaceuticals possessing cyclopropanes

![Lenvatinib and Saxagliptin](image)

(B) Cyclopropane-fused heterocycles via alkene aza-palladation:

![Scheme 1B](image)

(C) Yang’s oxidative processes:

![Scheme 1C](image)

(D) Proposed aza-Heck C(sp<sup>3</sup>)–H functionalization cascades:

![Scheme 1D](image)
efficient participation of sterically encumbered alkenes, (b) efficient 5-exo cyclizations in the absence of a conformational biasing and acidifying anilide unit, (c) efficient 6-exo cyclizations, and (d) no requirement for the benzylic activation of the target C(sp^3)–H bond. We also demonstrate that either steric or electronic control can be used to enforce the regioselectivity of the cyclopropanation event, thereby providing selective access to ring- or spiro-fused systems. In broader terms, these studies offer rare examples of C(sp^3)–H cyclopropanation processes that are triggered by alkene heteropalladation, a sequence that is likely challenging because of the reversibility of the migratory insertion step (vide infra).^{3,7,8}

A mechanistic analysis of the processes developed here is outlined in Scheme 2A. The N–O oxidative addition of 1 is expected to provide the aza-Pd(II) intermediate Int-I. Prior work has indicated that efficient alkene aza-palladation requires the dissociation of pentafluorobenzoate from Int-I to give Int-I′.^{5,8} Int-I′ undergoes cyclization and carboxylate association to give the alkyl–Pd(II) intermediate Int-II, which can provide palladacyclobutane Int-III via concerted metalation deprotonation-type metalation. Reductive elimination from Int-III then releases the cyclopropane product 2. Depending on the nature of R (vide infra), alternative palladacyclobutanes may be accessible. The carboxylic acid released during the cyclopropanation sequence is expected to undergo deprotonation by triethylamine, and the resulting triethylammonium salt will trigger the facile protodecarboxylation of pentafluorobenzoate to release CgPzH.^{9} Previous studies indicated that alkene aza-palladation is reversible under cationic conditions (vide infra),^{9,10} so the success of the process is likely to depend on the efficiency of the carboxylate-mediated C(sp^3)–H metalation step (Int-II to Int-III). Here, external carboxylate additives (RCO2M) are likely required because the pentafluorobenzoate released during N–O oxidative addition is highly dissociative and a relatively weak base. Note that the optimal mechanistic scenario requires a cationic species for aza-palladation (Int-I′) and a neutral intermediate for C(sp^3)–H metalation (Int-II). As such, optimal conditions require an appropriate trade-off because the complete partitioning of pathways at each stage is likely unattainable.

Proof-of-concept studies focused initially on the cyclization of the O-pentafluorobenzoyle system 1a to target 2a (Scheme 2B). Under the indicated conditions and in the absence of a carboxylate additive, target 2a was generated in only a 13% yield (entry 1). The addition of 100 mol% CsOPiv markedly increased the efficiency such that 2a was formed in a 56% yield (entry 2). During these initial studies, other optimal parameters were established. Most significantly, from a screen of P ligands commonly employed in aza-Heck processes, it was found that L1 (CgPPh) was by far the most efficient.^{5,6} Note that P ligands were specifically noted as being incompatible with the method in Scheme 1C.^{4} To optimize the process further, a library of approximately 15 derivatives was prepared from CgPH (Scheme 2C and the SI).^{11} Selected evaluation results are shown in entries 3–6, with the key finding being that the benzofuryl system L3 could provide 2a in an 80% yield over 6 h. At this stage we evaluated the choice of the O-based leaving group (entries 7 and 8), which confirmed that the O–Bz system (1a) was superior to both –OTs and –OPiv variants 1a′ and 1a″, respectively. The latter result is consistent with the idea that a cationic aza-palladium intermediate offers an optimal aza-palladation efficiency (Int-I′ to Int-II).

The optimized conditions were proven to be applicable to the synthesis of a wide range of cyclopropane-fused pyrrolidines (Table 1A). For example, a variety of alkyl substituents were tolerated at R1, as evidenced by the efficient formation of 2b–f. Note that the bulky secondary alkyl substituents of 2b and 2f did not significantly diminish the reaction efficiency relative to, for example, that of 2c. The electronically distinct styrenyl system 1g also participated to provide adduct 2g, albeit with a more modest efficiency. Substituents can be introduced at C4 and C5 of the targets, as demonstrated by the formation of 2h and 2i, respectively. For the former, minimal diastereoselectivity was observed, whereas the latter was generated as a single diastereomer. The hydrogenolytic N–Cbz deprotection of 2i allowed access to the N–DNs derivative 2j. 2f′ was characterized by single-crystal X-ray diffraction, which revealed a syn-relationship between the methyl and ethyl substituents.^{12} This outcome is consistent with the alkene aza-palladation step being reversible because the productive palladacyclobutane Int-2i is formed via

| Entry | LG | A | L (B) | Additive (C) | Time (h) | NMR Yield |
|-------|----|---|------|-------------|----------|-----------|
| 1     | O'Bz | 5  | L1 (20) | None        | 24       | 13%       |
| 2     | O'Bz | 5  | L1 (20) | CsOPiv (100) | 24       | 56%       |
| 3     | O'Bz | 5  | L2 (20) | CsOPiv (100) | 8        | 68%       |
| 4     | O'Bz | 5  | L3 (20) | CsOPiv (100) | 6        | 72%       |
| 5     | O'Bz | 5  | L3 (25) | CsOPiv (100) | 6        | 80%*      |
| 6     | O'Bz | 5  | L4 (25) | CsOPiv (100) | 6        | 58%       |
| 7     | OTs | 5  | L3 (25) | CsOPiv (100) | 6        | 43%       |
| 8     | OPiv | 5  | L3 (25) | CsOPiv (100) | 24       | 39%       |

(C) Ligand synthesis:

- Isolated yield. Further optimization results, including the evaluation of other ligands, are given in the SI.
the disfavored cyclization mode (TS-2i) (Table 1B). For system 1j, where R1 = Me, the expected product 2j was formed in a 55% yield alongside smaller quantities of spiro-fused cyclopropane iso-2j (14% yield) (Table 1C). The formation of the latter is presumably facilitated by the C(sp3)–H metatation of the more sterically accessible (versus Table 1A) methyl group of Int-II.14 To enforce this selectivity, systems possessing a substitution at the internal allylic position (C3) were investigated (Table 1D). In the reaction, the cyclization of the ethyl-substituted system 1k provided iso-2k in a 73% yield, and the corresponding ring-fused cyclopropane was not observed. This process required an increased reaction temperature (160 °C) and an alternate carboxylate additive (KOAc). These modified conditions were also effective for the selective formation of iso-2l and the intriguing vicinally dispirofused adduct iso-2m.15

Applying the reaction conditions to, for example, the homologue of 1a did not provide the corresponding cyclopropane-fused piperidine (see the SI), presumably because 6-exo aza-palladation is relatively demanding. This limitation can be circumvented by instead using systems that possess a degree of conformational bias (Table 2). Indeed, the cascade cyclization of 1n, which possesses an aromatic linker, was efficient, delivering the cyclopropane-fused tetrahydroisoquinoline 2n in a 76% yield. As mentioned earlier, the process is relatively insensitive to the steric demands of the alkene substituent (R1), so the bulky isopropyl group of 2p was well-tolerated. The protocol offers a useful scope with respect to the aromatic component, with both electron-rich (2q, 2r, and 2t) and electron-poor (2s) units participating. Diastereoselective processes are achievable for systems where R2 ≠ H; this was demonstrated by the highly stereocontrolled cyclization of 1u to 2u, which favored the syn-diastereomer (>15:1 dr). For these processes, spiro-fused cyclopropanes (cf. iso-2j) were not observed, which likely reflects the inherent preference for C(sp3)–H palladation at the benzylic position. For many of the examples in Table 2, the use of Pd2(dba)3 as the precatalyst was used.
the product during chromatography. This issue was alleviated by instead using Pd$_3$-(p-MeO-dba)$_2$.$^{16,17}$

We have established that the cascade cyclopropanation procedure can be used to generate reactive donor–acceptor cyclopropanes. A preliminary example process involves the conversion 3a to piperidine 4a via initial (nonconformationally biased) 5-exo aza-palladation (Table 3A). This generates Int-

Table 3. Rearrangement Processes via the Generation of Donor–Acceptor Cyclopropanes

(A) Preliminary studies and mechanistic considerations:

| Reaction | Conditions | Product | Yield | Ref. |
|----------|------------|---------|-------|------|
| Int-II$^*$ | L1 (30 mol%), Et$_2$N (100 mol%) | C$_2$-C$_3$ | 60% | 19,20 |
| Int-IV | L3 (15 mol%), Et$_2$N (100 mol%) | C$_3$-C$_4$ | 79% | 18 |

(B) Optimized conditions and reaction scope:

| Reaction | Conditions | Product | Yield | Ref. |
|----------|------------|---------|-------|------|
| Int-II$^*$ | L1 (30 mol%), Et$_2$N (100 mol%) | C$_2$-C$_3$ | 60% | 19,20 |
| Int-IV | L3 (15 mol%), Et$_2$N (100 mol%) | C$_3$-C$_4$ | 79% | 18 |

“The major regioisomer is depicted. $^4$L3 (25 mol %) was used. $^6$The reaction time was 42 h, and the regioisomers were isolated in 81:1 and >15:1 d.r., respectively (see the SI). $^7$The substrate was prepared from (S)-propylene oxide.

II” in which there is a choice of three different C(sp$^3$)–H bonds for metalation, leading to either four- or six-membered palladacycles (not depicted).$^{18}$ The productive pathway involves metalation at the C3 position en route to donor–acceptor cyclopropane Int-IV. This is primed for thermally promoted ring opening to provide piperidine 4a.$^{19,20}$ Accordingly, the rearrangement process transfers the methylidene CH$_2$ unit of the starting material (3a) to C3 of the target. The metalation selectivity at the stage of Int-II” contrasts with the processes in Table 1D; this is presumably due to the electronic activation provided by the ketone substituent, which also allows the process to operate at a lower temperature (110 °C versus 140–160 °C). To improve the efficiency, optimization studies were undertaken, resulting in the conditions shown in Table 3B. The protocol was applicable to a range of systems 3a–g with different substituents at R$^1$, R$^2$, or R$^3$. In general, the processes were efficient, and a mixture of alkene regioisomers was obtained in each case. Based on the mechanistic analysis in Table 3A, the C3–C4 regioisomers of 4a–g result from the isomerization of the initially generated C2–C3 regioisomer under the reaction conditions. Attempts to intercept the donor–acceptor cyclopropane intermediates (Int-IV) in cycloaddition processes using either internal (4d) or external π-unsaturates (e.g., activated ketones) have so far been unsuccessful.$^{20}$

In summary, we demonstrate the first examples of aza-Heck-triggered C(sp$^3$)–H functionalization cascades that lead to ring- or spiro-fused cyclopropanes. To enable these processes, a library of largely novel P ligands was designed and evaluated, from which L3 emerged as the optimal ligand. The resulting methodology provides an attractive approach to the synthesis of diverse heterocycles containing core cyclopropanes. These are medicinally valuable scaffolds that are challenging to access by other means. From a reactivity viewpoint, our observations have elucidated how steric or electronic control can be used to govern the C(sp$^3$)–H metalation selectivity. In broader terms, the processes described here are unusual because they exploit alkene heteropalladation to trigger C(sp$^3$)–H cyclopropanation.

**ASSOCIATED CONTENT**

*Supporting Information*

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c08304.

Experimental details, characterization data, and crystallographic data (PDF)

**Accession Codes**

CCDC 2189444 contains 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.

**AUTHOR INFORMATION**

**Corresponding Author**

John F. Bower – Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, United Kingdom; orcid.org/0000-0002-7551-8221; Email: john.bower@liverpool.ac.uk

**Authors**

Changcheng Jing – Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, United Kingdom
Benjamin T. Jones – School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom
Ross J. Adams – Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, United Kingdom; orcid.org/0000-0002-7402-2232

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.2c08304

**Notes**

The authors declare no competing financial interest.
We thank the European Research Council for financial support via the EU’s Horizon 2020 Programme (ERC Grant 639594 CatHet), the Leverhulme Trust (Philip Leverhulme Prize to J.F.B.), the EPSRC (EP/N509619/1) (studentship to B.T.J.), and the University of Liverpool (Regius Chair to J.F.B.). We thank the University of Liverpool’s Department of Chemistry X-ray crystallography service for analysis.

REFERENCES

(1) (a) Talete, T. T. The “Cyclopolyr Compound” is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules. J. Med. Chem. 2016, 59, 8712. (b) Časar, Z. Synthetic Approaches to Contemporary Drugs that Contain the Cyclopolyr Moiety. Synthesis 2020, S2, 131S.

(2) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. J. Chem. Educ. 2010, 87, 1348.

(3) (a) Tahrooei, A. A.; Pyla, M. K.; Barnett, A. H. Saxagliptin: a New DPP-4 Inhibitor for the Treatment of Type 2 Diabetes Mellitus. Adv. Ther. 2009, 26, 249. (b) Dong, J.; Gong, Y.; Liu, J.; Chen, X.; Wen, X.; Sun, H. Synthesis and Biological Evaluation of All Eight Stereoisomers of DPP-IV Inhibitor Saxagliptin. Bioorg. Med. Chem. 2014, 22, 1383.

(4) Du, W.; Gu, Q.; Li, Z.; Yang, D. Palladium(II)-Catalyzed Intramolecular Tandem Aminolkylation via Divergent C(sp^2)H Functionalization. J. Am. Chem. Soc. 2015, 137, 1130.

(5) For recent processes, see: (a) Bao, X.; Wang, Q.; Zhu, J. Palladium-Catalyzed Enantioselective Narasaka-Heck Reaction/Direct C-H Alklylation of Arenes: Iminoaorylation of Alkenes. Angew. Chem., Int. Ed. 2017, 56, 9577. (b) Hazelden, I. R.; Carmona, R. C.; Langer, T.; Pringle, P. G.; Bowen, J. F. Pyrrolidines and Piperidines by Pd:Oligar C-H Bond Activation/Remote C(sp^2)=O cleavage under Pd catalysis, see: (b) Wei, W.-X.; Kong, X.; Jiao, R.-Q.; Li, X.-S.; Wang, C.-T.; Liu, H.-C.; Xia, Y.; Zhang, B.-S.; Jiao, R.-Q.; Liang, Y.-M. Experimental and Computational Studies of Palladium-Catalyzed Spirocyclization via a Narasaka–Heck/C(sp^3)=O–H Activation Cascade Reaction. J. Am. Chem. Soc. 2021, 143, 7868. For other recent C–H functionalization processes that involve N–O cleavage under Pd catalysis, see: (b) Wei, W.-X.; Kong, X.; Jiao, R.-Q.; Li, X.-S.; Wang, C.-T.; Li, Y.; Liang, Y.-M. Regioselective Synthesis of Spirocyclic Pyrrolines via A Palladium-catalyzed Narasaka-Heck/C–H Activation/[4+2] Annulation Cascade Reaction. Chem. Sci. 2022, 13, 6348. (c) Zhang, B.-S.; Jia, W.-Y.; Gou, X.-Y.; Yang, Y.-H.; Wang, F.; Wang, Y.-M.; Wang, X.-C.; Quan, Z.-J. Synthesis of C8-Aminated Pyrrollo-Phenanthridines or -Indoles via Series C(sp^3)–H Activation and Fluorescence Study. Org. Lett. 2022, 24, 2104.

(7) Selected examples involving alkenes carbopalladation, see: (a) Liron, F.; Knochel, P. Reactivity of Stable Neopentyl-Pd Intermediates in the Absence of Nucleophile. Tetrahedron Lett. 2007, 48, 4943. (b) Kim, H. S.; Gowrisankar, S.; Kim, S. H.; Kim, J. N. Synthesis of 6-Oxacycloprop[a][1]indene Derivatives Starting from Baylis–Hillman Adducts via Pd-Mediated C(sp^3)=O–H Activation. Tetrahedron Lett. 2008, 49, 3858. (c) Huang, Q.; Larock, R. C. Synthesis of Cyclopropanes by Pd-Catalyzed Activation of Alkyl C–H Bonds. Tetrahedron Lett. 2009, 50, 7235. (d) Chung, D. S.; Lee, J. S.; Ryu, H.; Park, J.; Kim, H.; Lee, J. H.; Kim, U. B.; Lee, W. K.; BaiK, M.-H.; Lee, S-g. Palladium-Catalyzed Divergent Cyclopropanation by Regioselective Solvent-Driven C(sp^3)=O–H Bond Activation. Angew. Chem., Int. Ed. 2018, 57, 15460.

(8) To the best of our knowledge, reference 4 details the only prior examples involving alkenesaza-palladation. We are unaware of examples involving alkenesaza-palladation.

(9) Gierczyk, B.; Wojciechowski, G.; Brzezinski, B.; Grech, E.; Schroeder, G. Study of the Decarboxylation Mechanism of Fluorobenzoic Acids by Strong N-Bases. J. Phys. Org. Chem. 2001, 14, 691.

(10) White, P. B.; Stahl, S. S. Reversible Alkene Insertion into the Pd–N Bond of Pd(II)-Sulfoximides and Implications for Catalytic Amidation Reactions. J. Am. Chem. Soc. 2011, 133, 18594.

(13) The favored azapalladation mode is supported by previous observations in processes terminated by (fast) β-hydride elimination (see references 5b and 5c). We favor a mechanism where C(sp3)=H palladation (rather than C=C reductive elimination) is the product determining step on the basis of DFT calculations reported in reference 7d and KIE studies reported in reference 4.

(14) The preference for 2j over iso-2j may be due to the minimization of steric interactions with the Cbz unit at the stage of the palladacycle. When the cyclization of 1k to iso-2k was performed in the presence of D2O (300 mol%), no deuterium incorporation was observed in the product (see the SI): this is consistent with the suggestion that C–H metathesis is irreversible.

(15) For other approaches to spirofused pyrrolidines related to those in Table 1D, see: (a) Melnykov, K. P.; Artemenko, A. N.; Ivanenko, B. O.; Sokolenko, Y. M.; Nosik, P. S.; Ostapchuk, E. N.; Grygorenko, O. V.; Volochynskyy, D. M.; Ryabukhin, S. V. Scalable Synthesis of Biologically Relevant Spirocyclic Pyrrolines. ACS Omega 2019, 4, 7498. (b) Lin, K.-W.; Yan, S.; Hsieh, L.-L.; Yan, T.-H. Unusual Ambiphilic Carbene Equivalent in Amide Cyclopropanation. Org. Lett. 2006, 8, 2265.
(16) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F. η²-dba Complexes of Pd(0): The Substituent Effect in Suzuki–Miyaura Coupling. Org. Lett. 2004, 6, 4435.

(17) Compounds related to those in Table 2 have been accessed by the intramolecular C(sp³)−H arylation of cyclopropanes, see: Pedroni, J.; Saget, T.; Donets, P. A.; Cramer, N. Enantioselective Palladium(0)-Catalyzed Intramolecular Cyclopropane Functionalization: Access to Dihydroquinolones, Dihydroisoquinolones and the BMS-791325 Ring System. Chem. Sci. 2015, 6, 5164.

(18) Other metalation modes can also be envisaged.

(19) Isomerization of the alkene of 3a was not observed after 1 h under the conditions shown in Table 3B. At the stage of Int-II″, the metalation selectivity may be controlled by the closer proximity of the C3−H bond compared to the C7 methyl group. The full 2D NMR analysis of 4a is presented in the SI.

(20) For a review encompassing this aspect, see: Sokolova, O. O.; Bower, J. F. Selective Carbon-Carbon Bond Cleavage of Cyclopropylamine Derivatives. Chem. Rev. 2021, 121, 80.