

Modular Access to Azepines by Directed Carbonylative C–C Bond Activation of Aminocyclopropanes

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Supporting Information

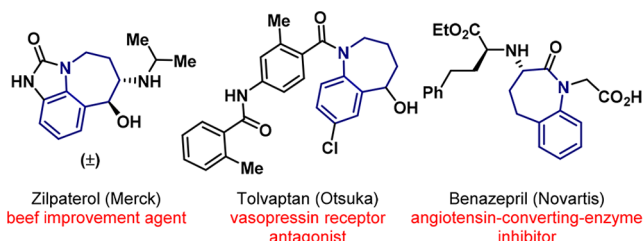
ABSTRACT: A modular Rh-catalyzed entry to azepines is outlined. Under a CO atmosphere, protecting group directed C–C bond activation of aminocyclopropanes provides rhodacyclopentanones. These intermediates are effective for intramolecular C–H metalation of either an N-aryl or N-vinyl unit en route to azepine ring systems. Thus, byproduct-free heterocyclizations are enabled by sequential C–C activation and C–H functionalization steps.

The azepine ring system is present in a wide range of bioactive compounds, with this motif or closely related variants representing the core structure of over 25 pharmaceutical products.¹ For example, the drugs Tolvaptan² and Benazepril,³ and the beef improvement agent Zilpaterol,⁴ all contain the tetrahydrobenzo[*b*]azepine ring system (Scheme 1A). Despite their established pharmaceutical value, azepines and other larger (>6-membered) N-heterocyclic rings are underrepresented in drug discovery libraries,⁵ primarily because of a lack of efficient and modular routes for their preparation. Accordingly, synthetic methods that can address this issue are in high demand.

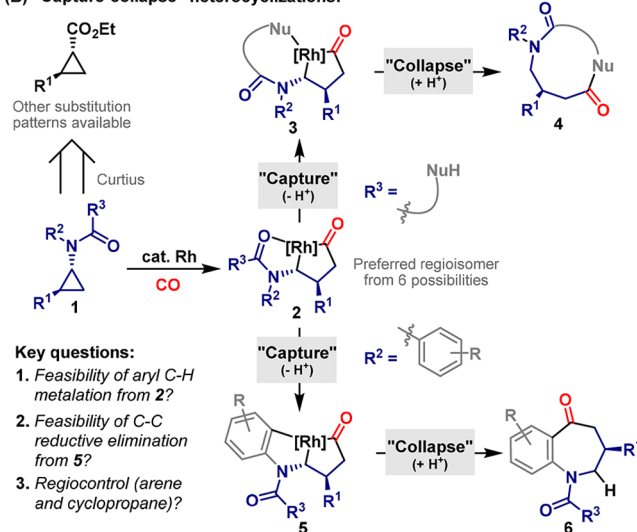
Recently, as part of a broader program,⁶ we outlined an N-heterocyclization strategy where “capture” of transient rhodacyclopentanones **2** by tethered nucleophiles occurs in advance of a C–Nu bond forming “collapse” to the targets (Scheme 1B).^{6e} Conceptually, this approach is appealing because it harnesses the strain embodied within readily available and stereodefined aminocyclopropanes **1** for reaction initiation, and achieves otherwise challenging ring closures via the intermediacy of kinetically accessible bicycles **3**. In our proof-of-concept studies, ureas were used as the nucleophile (**1**, R³ = NHR), such that intermediates **2** were converted to 1,3-diazepanes by C–N reductive elimination from **3**.^{6e} Outside of π -insertion processes, the reactivity of rhodacyclopentanones is relatively unexplored,^{7–9} rendering further extension of our approach uncertain. However, it is well-established that Rh(III)-complexes can promote aryl C–H metalation in other contexts,¹⁰ and we considered whether this type of process might be exploited from **2** to provide benzazepines **6**. Specifically, for cyclopropanes **1** where R² = aryl, we envisaged accessing targets **6** by a sequence of carbonyl directed C–C oxidative addition, metallacyclobutane carbonylation (to **2**), aryl C–H metalation (to **5**), C–C reductive elimination, and protodemetalation. At the outset, the viability of this design was considered tentative because of the absence of reports where

Scheme 1

(A) Biologically important benzazepine-based compounds:



(B) “Capture-collapse” heterocyclizations:



rhodacyclopentanones engage in C(sp²)–H metalation or C(sp²)–C(sp²) reductive elimination processes. Nevertheless, outlined below is the successful realization of this approach, which provides striking examples of how metal-catalyzed carbonylative redistribution of C–C and C–H bonds can be harnessed in reaction design.

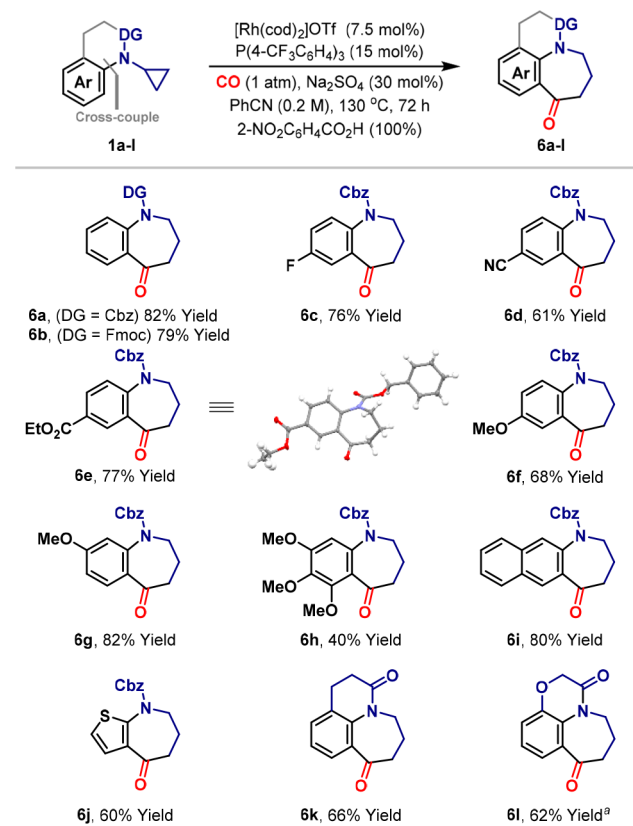
Our investigations commenced by exploring the carbonylative cyclization of **1a**, which was readily prepared in two steps via N-arylation of cyclopropylamine and subsequent Cbz-protection (see the Supporting Information (SI)). Here we found that, using 1 atm CO, the combination of [Rh(cod)₂]-OTf (7.5 mol %), P(4-CF₃C₆H₄)₃ (15 mol %), Na₂SO₄ (30 mol %), and 2-NO₂C₆H₄CO₂H (100 mol %) enabled the generation of **6a** in 82% isolated yield. Notably, neutral Rh-

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precatalysts were completely ineffective and electron-neutral/-rich P-based ligands provided only traces of the product (see the SI). **6a** was formed in less than 30% yield in the absence of 2-NO₂C₆H₄CO₂H, with this additive likely acting as a proton reservoir to facilitate the final protodemetalation step, which otherwise would rely solely on the proton released during the conversion of **2** to **5**.

With optimized conditions in hand, we explored the scope of the process with respect to the aromatic unit (Table 1). A

Table 1. Scope of the Aromatic Component

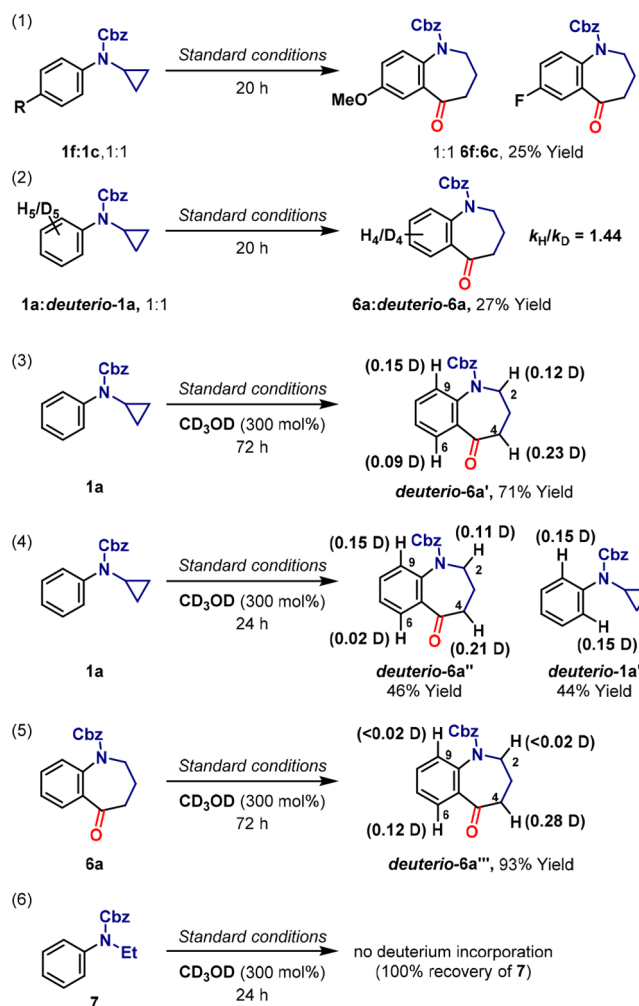


^aReaction carried out at 140 °C.

broad range of arenes are tolerated, with electron-rich (e.g., **1f**), electron-poor (e.g., **1d**), and heteroaromatic systems (e.g., **1j**) all participating with similar levels of efficiency. For systems with *meta*-substituents (**1g** and **1i**), C–C bond formation is highly regioselective, occurring at the more sterically accessible *ortho*-position. In the case of **1h**, where both *meta*-positions are substituted, cyclization to **6h** could be achieved, but the yield of the process was lower than for other examples. At the present stage, the protocol does not tolerate acyclic *ortho*-substituents. The method exhibits useful levels of flexibility with respect to the directing group. For example, other classes of carbamate can be used, as demonstrated by Fmoc-directed cyclization of **1b** which provided **6b** in 79% yield. Cyclic amides can also direct the process, and this allowed access to tricyclic systems **6k** and **6l** in 66% and 62% yield, respectively. However, acyclic amides and N-urea-based directing groups are ineffective (see the SI), highlighting the finely balanced nature of the process, where the DG must be Lewis basic enough to promote C–C bond activation, but also sufficiently labile to allow aryl C–H metalation (**2** to **5**).¹¹

At this stage, a series of experiments was undertaken to probe the mechanism of the process, and this insight proved fundamental in guiding extensions of the approach outlined later (Scheme 2). When a 1:1 mixture of **1f** and **1c** was exposed

Scheme 2. Mechanistic Experiments



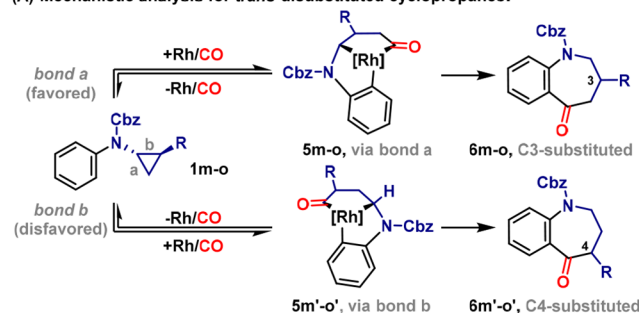
to standard conditions, an approximately equimolar ratio of **6f** and **6c** was obtained at low conversion (eq 1). A similar competition experiment involving a 1:1 mixture of **1a** and deuterio-**1a** revealed a relatively small kinetic isotope effect ($k_H/k_D = 1.44$, eq 2).¹² Taken together, these experiments suggest that aryl C–H metalation is not turnover limiting. Further insight was gained by running the carbonylative cyclization of **1a** in the presence of CD₃OD (300 mol %). At full conversion (eq 3), deuterium incorporation in the product deuterio-**6a'** was observed at C-2 (12%), C-4 (23%), C-6 (9%), and C-9 (15%). Deuteration at C-2 is consistent with protodemetalation at **5**. At partial conversion (eq 4), lower levels of C-6 deuteration were observed (deuterio-**6a''**), which is consistent with exchange at this position occurring via ketone directed C–H activation of the product. In support of this, exposure of product **6a** to standard catalytic conditions in the presence of CD₃OD resulted in 12% deuterium incorporation at C6 (eq 5). In this experiment, significant exchange also occurred at C-4 (28%), suggesting that deuterium incorporation observed at this position in eqs 3 and 4 arises via enolization of the product.

Accordingly, the key issue remains as to how deuterium incorporation at C-9 of *deuterio-6a'*/*6a''* occurs? Equation 5 indicates that this is not via C–H activation of the product **6a**. Analysis of recovered starting material in eq 4 revealed approximately 15% deuterium incorporation at the *ortho*-positions (*deuterio-1a'*); however, a similar exchange experiment involving **7**, which lacks a cyclopropyl unit, resulted in no deuterium incorporation at the *ortho*-positions (eq 6). This seemingly rules out an exchange pathway involving carbonyl directed C–H activation of **1a**. Overall, the collective observations provided in eqs 3–6 indicate that deuterium exchange at C-9 of *deuterio-6a'*/*6a''* and at the *ortho*-C–H bonds of *deuterio-1a'* does not occur directly from **1a** or **6a**, but instead via reversible formation of another catalytically generated intermediate, which is most likely bicycle **5**.¹³ Indeed, our previous studies have shown that rhodacyclopentanone formation (**1** to **2**) is highly reversible using cationic Rh-systems,^{6b,c,e} and the current experiments extend this reversibility to the aryl C–H metalation step. Accordingly, for the current process, we favor C–C reductive elimination as the first irreversible step, and further evidence supporting this assertion is given later.¹⁴

Substituted aminocyclopropanes can be accessed by Curtius rearrangement of cyclopropyl carboxylic acids, and these, in turn, can be synthesized easily in enantioenriched form.¹⁵ Consequently, the reaction design outlined in Scheme 1B potentially allows access to benzazepines bearing stereodefined substituents that might be challenging to install using conventional methods. Key requirements for 1,2-disubstituted cyclopropane-based processes include (a) regioselective generation of the rhodacyclopentanone intermediate (**2**) and (b) transfer of this regiochemistry to the product (*vide infra*). Previous studies have revealed that directed rhodacyclopentanone formation from *trans*-1,2-disubstituted cyclopropanes occurs with high selectivity via the less hindered proximal C–C bond (bond a in **1m-o**, Scheme 3A).^{6c} However, as outlined above, the formation of **2** is likely reversible, such that product regiochemistry can be subject to Curtin–Hammett selectivity.¹⁶ Indeed, initial attempts to access benzazepine **6m** (R = Me) using the conditions from Table 1 afforded approximately equal ratios of C-3 and C-4 adducts **6m** and **6m'**. The former arises from the kinetically favored rhodacyclopentanone **5m**; however, subsequent C–C reductive elimination is likely to be slow because it requires the bulky Rh-center to move into the proximity of the C-3 methyl substituent. As such, reversible metallacycle formation provides kinetically disfavored regioisomer **5m'**, which undergoes more facile C–C reductive elimination to provide C-4 methylated regioisomer **6m'**. Electron-deficient ligand systems are known to accelerate C–C reductive elimination,¹⁷ and so we examined whether replacement of P(4-CF₃C₆H₄)₃ with poorer donors might enforce selective generation of **6m** from **1m** (Scheme 3B). These studies revealed that **6m** could be generated with essentially complete selectivity over **6m'** using either As(4-CNC₆H₄)₃ or P(C₆F₅)₃ as ligand. The latter offered the greatest efficiencies with **6m** isolated in 68% yield and >99:1 e.r. from enantiopure **1m**. These new conditions extended to more sterically demanding systems **1n** and **1o**, which cyclized to provide **6n** and **6o** as single regioisomers in 52% and 67% yield, respectively (Scheme 3C); **6o** was prepared from racemic **1o**, whereas **6n** (99:1 e.r.) was accessed from enantioenriched **1n** (99:1 e.r.). For the processes in Scheme 3C, 3-CNC₆H₄CO₂H offered higher efficiencies than 2-NO₂C₆H₄CO₂H, which was

Scheme 3. Benzazepines via *trans*-1,2-Disubstituted Cyclopropanes

(A) Mechanistic analysis for *trans*-disubstituted cyclopropanes:

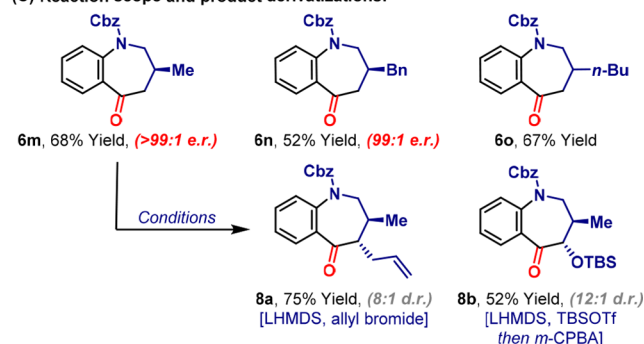


(B) Effect of ligand on product regioselectivity (6m vs 6m', R=Me)

Conditions	Ligand	Yield (6m+6m') ^a	6m:6m' ^a
[Rh(cod) ₂]OTf (7.5 mol%)	P(4-CF ₃ C ₆ H ₄) ₃	32%	1.6:1
Ligand (15 mol%)	P(4-FC ₆ H ₄) ₃	29%	1.9:1
CO (1 atm), Na ₂ SO ₄ (30 mol%)	P(4-CNC ₆ H ₄) ₃	19%	1.4:1
PhCN (0.2 M), 130 °C	P(3,4,5-F ₃ C ₆ H ₂) ₃	33%	2.4:1
3-CNC ₆ H ₄ CO ₂ H (100 mol%)	As(4-CNC ₆ H ₄) ₃	26%	>25:1
	P(C ₆ F ₅) ₃	68% ^b	>25:1 ^b

^a Determined by ¹H NMR analysis of crude material. ^b Isolated yield.

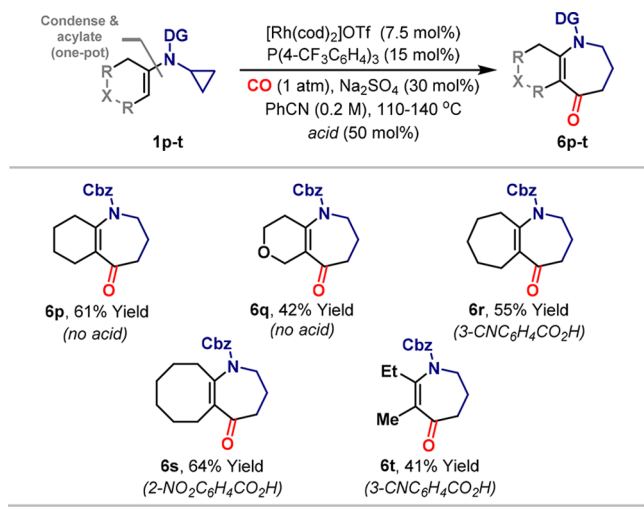
(C) Reaction scope and product derivatizations:



used earlier (see Table 1). So far, we have been unable to obtain high selectivity for the formation of C-4 substituted products (**6m'**–**o'**); however, substitution at this position can be introduced easily using enolate chemistry.¹⁸ For example, highly diastereoselective conversion of **6m** to α -functionalized products **8a** and **8b** was readily achieved, which demonstrates the feasibility of introducing C–C or C–heteroatom bonds at C-4.

The heterocyclizations described so far use an N-aryl unit as the nucleophilic component, and we questioned whether further classes of process might be achieved using other types of π -nucleophile. Specifically, we hoped to access non-benzofused azepines (**6p**–**t**) by harnessing N-vinyl nucleophiles (**1p**–**t**) (Table 2). In the event, by adapting of our previously developed conditions, carbonylative heterocyclization of **1p** to **6p** and **1q** to **6q** occurred in 61% yield and 42% yield, respectively. Here, the carboxylic acid additive was omitted as it promoted competitive polymerization of **1p** and **1q**. However, for subsequent examples (**6r**–**t**), an acid additive was beneficial, with the exact choice made on a case-by-case basis. A key aspect of the method in Table 2 is that the substrates (**1p**–**t**) can be accessed in one pot from the corresponding ketone (see the SI), which, in turn, allows the two-step synthesis of a wide variety of interesting and challenging heterocyclic ring systems. From a mechanistic viewpoint, these processes are significant; in principle, the

Table 2. Processes Using N-Vinyl Carbamates



carboxylic acid additive could facilitate CMD-type metalation of the C(sp²)–H bond (**2** to **5**),¹⁹ but the successful synthesis of **6p** and **6q** in the absence of acid suggests that this is not the case. Accordingly, we suggest that, for both N-aryl and N-vinyl systems, C–H metalation occurs by nucleophilic attack of the electron-rich π -system onto the Rh-center of **2**, and that the primary role of the acid additive is to facilitate the final protodemetalation step.

To conclude, we outline processes where rhodacyclopentanones generated by directed carbonylative C–C bond activation are captured by C-based nucleophiles en route to benzazepines and nonbenzofused variants. Ring systems of this type are difficult to construct in a modular fashion using conventional approaches,²⁰ and the methodology addresses this issue in an atom and step economical manner. Our reaction design is based on the exploitation of rhodacyclopentanones for C(sp²)–H metalation and subsequent C(sp²)–C(sp²) bond forming reductive elimination.^{9,14} One can easily envisage harnessing these fundamental mechanistic steps in further rhodacyclopentanone-based methodologies. Studies toward this broad goal are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b13087.

Experimental details, characterization data (PDF)

Crystallographic data for **6e** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.
- (2) Kondo, K.; Ogawa, H.; Yamashita, H.; Miyamoto, H.; Tanaka, M.; Nakaya, K.; Kitano, K.; Yamamura, Y.; Nakamura, S.; Onogawa, T.; Mori, T.; Tominaga, M. *Bioorg. Med. Chem.* **1999**, *7*, 1743.
- (3) Towson, J. C.; Wong, S.-C. Patent US20150315195, 2013.
- (4) Watthey, J. W. H.; Stanton, J. L.; Desai, M.; Babiarz, J. E.; Finn, B. M. *J. Med. Chem.* **1985**, *28*, 1511.
- (5) Hussain, A.; Yousuf, S. K.; Mukherjee, D. *RSC Adv.* **2014**, *4*, 43241.
- (6) (a) Shaw, M. H.; Melikhova, E. Y.; Kloer, D. P.; Whittingham, W. G.; Bower, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 4992. (b) Shaw, M. H.; McCreanor, N. G.; Whittingham, W. G.; Bower, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 463. (c) Shaw, M. H.; Croft, R. A.; Whittingham, W. G.; Bower, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 8054. (d) Shaw, M. H.; Whittingham, W. G.; Bower, J. F. *Tetrahedron* **2016**, *72*, 2731. (e) McCreanor, N. G.; Stanton, S.; Bower, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 11465. (f) Wang, G.-W.; McCreanor, N. G.; Shaw, M. H.; Whittingham, W. G.; Bower, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 13501.
- (7) For a review on rhodacyclopentanone-based catalysis, see: (a) Shaw, M. H.; Bower, J. F. *Chem. Commun.* **2016**, *52*, 10817. For recent reviews on C–C bond activation-based methodologies, see: (b) Souillart, L.; Cramer, N. *Chem. Rev.* **2015**, *115*, 9410. (c) Fumagalli, G.; Stanton, S.; Bower, J. F. *Chem. Rev.* **2017**, *117*, 9404.
- (8) Selected methodologies that exploit π -insertion into rhodacyclopentanones (or related species) derived from C–C bond activation: (a) Zhou, X.; Dong, G. *J. Am. Chem. Soc.* **2015**, *137*, 13715. (b) Ko, H. M.; Dong, G. *Nat. Chem.* **2014**, *6*, 739. (c) Souillart, L.; Parker, E.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 3001. (d) Souillart, L.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 9640. (e) Matsuda, T.; Tsuboi, T.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12596. (f) Murakami, M.; Itahashi, T.; Ito, Y. *J. Am. Chem. Soc.* **2002**, *124*, 13976.
- (9) To the best of our knowledge, C(sp²)–C(sp²) reductive elimination from C–C activation derived rhodacyclopentanones has not been demonstrated previously. For C–O reductive elimination, see: Murakami, M.; Tsuruta, T.; Ito, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 2484. For C–N reductive elimination, see ref 6e.
- (10) Selected examples: (a) Schröder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298. (b) Romanov-Michailidis, F.; Sedillo, K. F.; Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2015**, *137*, 8892. (c) Xia, Y.; Lu, G.; Liu, P.; Dong, G. *Nature* **2016**, *539*, 546. (d) Xia, Y.; Wang, J.; Dong, G. *Angew. Chem., Int. Ed.* **2017**, *56*, 2376. The latter two references outline processes with closing mechanistic steps that are related to those employed here.
- (11) The specific requirements of the DG were noted for earlier processes developed in our laboratory (see ref 6d).
- (12) For a discussion on the interpretation of KIE measurements, see: Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066. Consistent with our mechanistic interpretation, an internal competition experiment using mono-*ortho*-deuterated **1a** revealed a k_H/k_D of 0.92 (see the SI). The absolute value must be treated with caution because eqs 3 and 4 show that H/D exchange can occur under the reaction conditions.
- (13) The similar levels of deuterium incorporation (approximately 15%) observed at C-9 in eq 3 vs 4 (full vs partial conversion) are consistent with this suggestion.
- (14) Alternative mechanistic pathways cannot be discounted based on available data. For example, protonation of **5** could occur prior to C–C reductive elimination. We deem this pathway less likely because (a) it is less consistent with the data in Scheme 3 and (b) a model neutral rhodacyclopentanone complex does not undergo protonation when exposed to *o*-nitrobenzoic acid (see the SI).

(15) An easy approach is by Wadsworth–Emmons cyclopropanation of the corresponding enantiopure epoxide: (a) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. (b) Delhay, L.; Merschaert, A.; Delbeke, P.; Bri  ne, W. *Org. Process Res. Dev.* **2007**, *11*, 689.

(16) For manifestations of this type of effect see refs [6b](#), [c](#), and [e](#).

(17) For a discussion within the context of C–C reductive elimination from Pd-complexes, see: Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936.

(18) At the present level of development, *cis*-1,2-disubstituted and trisubstituted cyclopropanes are not suitable substrates.

(19) Walsh, A. P.; Jones, W. D. *Organometallics* **2015**, *34*, 3400.

(b) Qi, X.; Li, Y.; Bai, R.; Lan, Y. *Acc. Chem. Res.* **2017**, *50*, 2799.

(20) Recent methodologies for accessing benzazepines and azepines:

(a) Thullen, S. M.; Rubush, D. M.; Rovis, T. *Synlett* **2017**, *28*, 2755.

(b) Mazumdar, W.; Jana, N.; Thurman, B. T.; Wink, D. J.; Driver, T.

G. J. Am. Chem. Soc. **2017**, *139*, 5031. (c) Claraz, A.; Serpier, F.;

Darses, S. *ACS Catal.* **2017**, *7*, 3410. (d) Wang, R.; Jin, R.-X.; Qin, Z.-

Y.; Bian, K.-J.; Wang, X.-S. *Chem. Commun.* **2017**, *53*, 12229. (e) Hu,

Y.; Huang, H. *Org. Lett.* **2017**, *19*, 5070. (f) Guo, C.; Fleige, M.;

Janssen-M  ller, D.; Daniliuc, C. G.; Glorius, F. *J. Am. Chem. Soc.* **2016**,

138, 7840. (g) So, M.; Kotake, T.; Matsuura, K.; Inui, M.; Kamimura,

A. *J. Org. Chem.* **2012**, *77*, 4017. (h) Zhou, M.-B.; Song, R.-J.; Wang,

C.-Y.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 10805. (i) Kotha, S.;

Shah, V. R. *Eur. J. Org. Chem.* **2008**, *2008*, 1054.