Rhodacyclopentanones as Linchpins for the Atom Economical Assembly of Diverse Polyheterocycles

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Supporting Information Placeholder

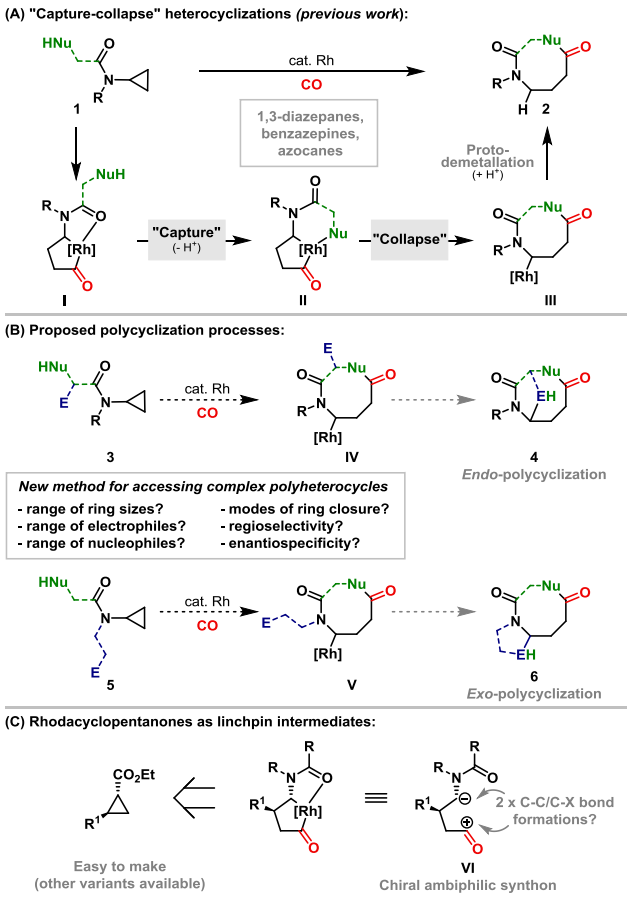
ABSTRACT: We outline a conceptual blueprint that provides direct and atom economical access to a wide range of complex polyheterocycles. Our method capitalizes on the ambiphilic reactivity of rhodacyclopentanones that arise upon exposure of cyclopropanes to Rh(I)-catalysts and CO. Using this approach, a wide array of polycyclizations are achieved, including variants that involve powerful dearomatizations and medium ring formations.

Expeditious strategies for the assembly of complex heterocycles are of significant value to synthetic chemists. In particular, there is high demand for protocols that generate challenging scaffolds, such as medium rings, sp^3-rich systems and complex polycycles.[1] Within this context, we have developed a suite of by-product free processes where cyclopropane-derived metallacycles engage tethered π-unsaturates or nucleophiles in cycloadditions[2] or "capture-collapse" heterocyclizations,[3] respectively.[4] The latter exploits the electrophilicity of rhodacyclopentanones **I** that arise upon directing group controlled carbonylative C-C bond activation of aminocyclopropanes **1** (Scheme 1A).[5] These can be accessed with a variety of substitution patterns and, where appropriate, in enantiopure form. Our heterocyclizations harness these features to provide high levels of regioselectivity and stereospecificity in the formation of challenging 7- and 8-membered N-heterocycles **2**.[3] These are generated from key metallacyclic intermediate **II** by a sequence of C-Nu reductive elimination (to **III**) and protodemetallation.

The C-C bond activation triggered heterocyclizations we have developed so far generate one new ring, where C-H bond formation is the terminating step (**III** to **2**). If protodemetallation could be averted then the tantalizing opportunity of using $C(sp^3)$-Rh(I)-intermediates related to **III** in subsequent C-C bond formations would emerge (Scheme 1B). This design offers tremendous flexibility because a wide range of *endo*- or *exo*-polycyclizations can be envisaged by varying the nature and position of the electrophile. Significantly, this approach uses the rhodacyclopentanone as a linchpin for the assembly of two rings rather than one – its electrophilicity enables the first annulation, whereas its latent nucleophilicity facilitates the second (via **IV**/**V**). Accordingly, the rhodacyclopentanone functions as a synthetic equivalent to ambiphilic synthon **VI** (Scheme 1C), with this reactivity mode unveiled simply by carbonylative C-C bond activation of the easily installed aminocyclopropane moiety. In this report, we outline extensive studies concerning this broad concept. These results show how C-C bond activation of simple functionality can enable by-product free access to powerful and unusual reactivity patterns.[6]

The development of the polycyclizations in Scheme 1B was driven by the observation that cyclopropane **3a** is converted to

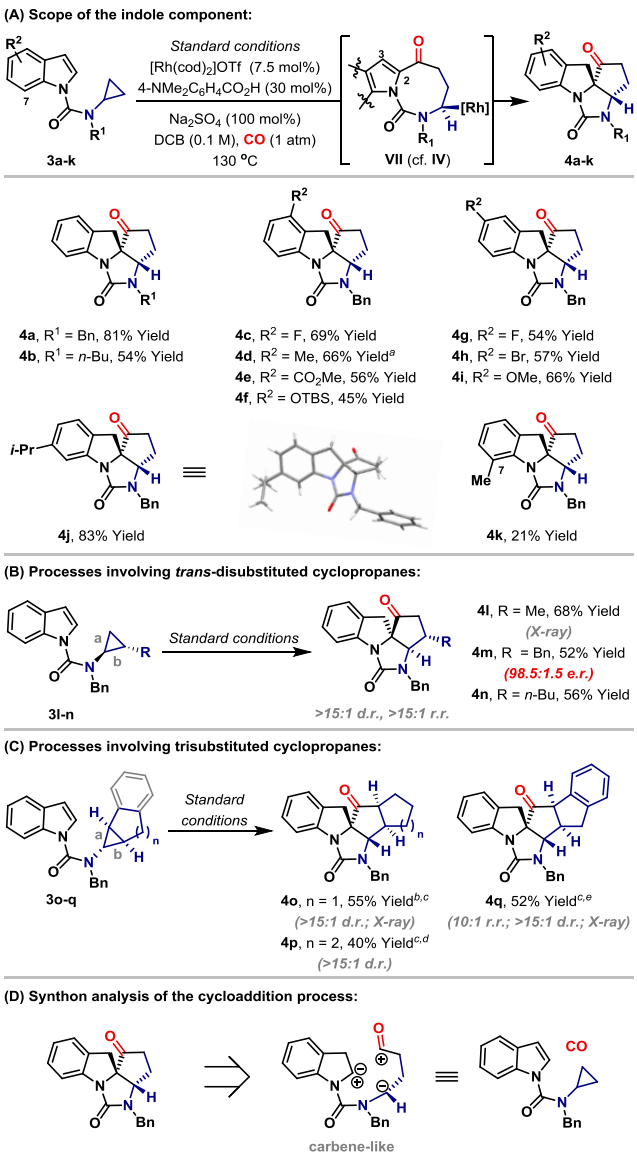
Scheme 1. Polyheterocycles via rhodacyclopentanones.



complex polycycle **4a** in 10% yield when exposed to $[Rh(cod)_2]OTf$ (7.5 mol%), $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ (15 mol%), $PhOCH_2CO_2H$ (30 mol%) and CO (1 atm) at 140 °C (Table 1A). This process can be rationalized by invoking *endo*-polycyclization of key alkyl-Rh(I) intermediate **VII** (cf. **IV**) onto the C2-C3 π-system of the indole (vide infra). Extensive studies were undertaken to improve efficiency; ultimately, we found that the combination of $[Rh(cod)_2]OTf$ (7.5 mol%) and $4\text{-}NMe_2C_6H_4CO_2H$ (30 mol%) delivers **4a** in 81% yield. The inclusion of phosphine ligands resulted in reduced yields, and neutral Rh-sources were ineffective. The acid additive had the most profound effect, with $4\text{-}Me_2NC_6H_4CO_2H$ (30 mol%) emerging as optimal from a broad

screen (see the SI). Higher or lower CO pressures offered no benefits and lower reaction temperatures were ineffective. The inclusion of Na_2SO_4 as a desiccant provided a small but reproducible benefit.[7]

Table 1. Dearomatizing *endo*-polycyclizations of indole systems.



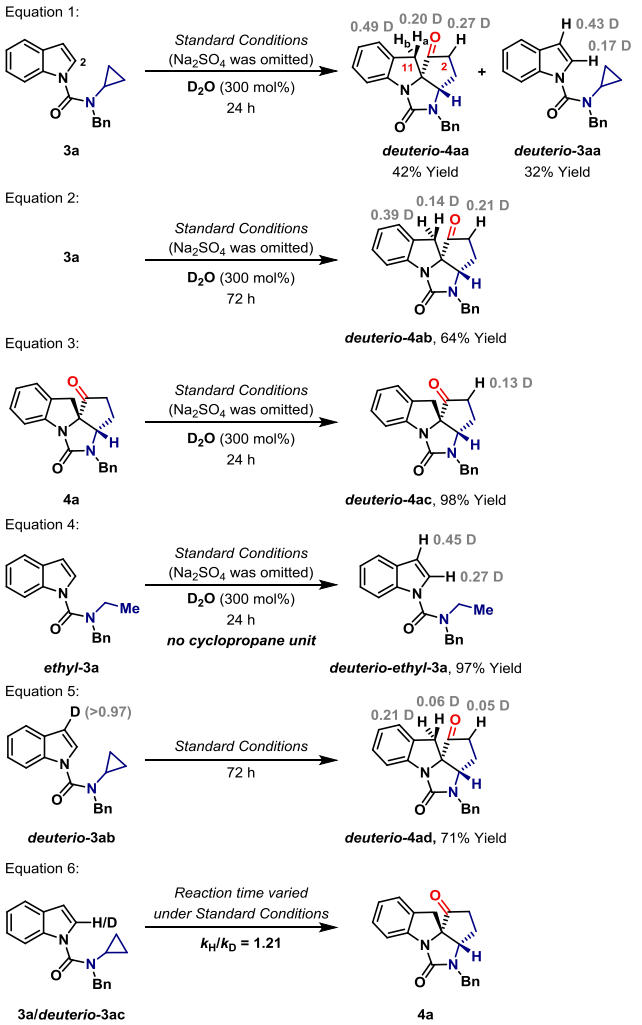
[a] Run at 140 ˚C; [b] Run in DCB (0.2 M); [c] $[Rh(cod)_2]OTf$ (10 mol%) was used; [d] Run at 150 ˚C; [e] Run at 125 ˚C.

The process has broad scope with respect to the indole unit (Table 1A). Systems **3c-j** possessing electronically diverse substituents generated polycycles **4c-j** in good to excellent yield. Substitution at C7 results in diminished efficiencies such that **4k** was formed in only 21% yield. The process can be transferred to substituted aminocyclopropanes (Table 1B); for example, polycyclization of *trans*-1,2-disubstituted systems **3l-n** generated **4l-n** with excellent levels of diastereo- and regiocontrol. These features arise from selective cleavage of the less hindered proximal C-C *bond a* of **3l-n**, followed by transfer of cyclopropane stereochemistry to the product.[8] The starting materials are easily accessed in enantioenriched form, and this allowed enantiospecific conversion of **3m** to **4m** (98.5:1.5 e.r.). Polycyclizations of trisubstituted cyclopropanes **3o** and **3p** resulted in efficient desymmetrization to provide **4o** and **4p** with exquisite levels of diastereocontrol (Table 1C). For non-symmetrical system **3q**, C-C bond activation was selective for benzylic C-C *bond a* leading to regioselective generation of **4q**, again with complete diastereocontrol.

The processes in Table 1 validate the conceptual blueprint in Scheme 1B, and also provide a notable contribution to indole dearomatization chemistry.[9] Uniquely, the method enables the concurrent formation of two C-C bonds at C-2 (i.e. "dual C-H functionalization")[10] such that this position formally functions as a carbene equivalent (Table 1D). Prior methods for accessing similar structures require preinstallation of a substituent at C-2.[11] Other catalytic dual functionalizing indole dearomatizations usually generate new C-C/C-X bonds at both C-2 and C-3.[12]

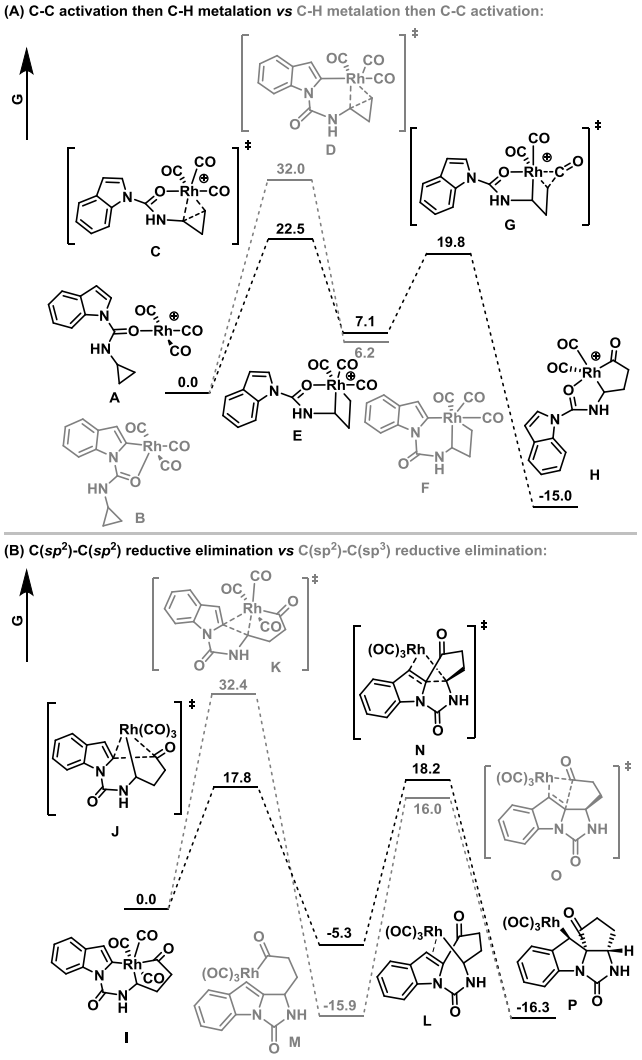
Polycyclization of **3a** in the presence of D_2O (300 mol%) delivered ***deuterio*-3aa** and ***deuterio*-4aa** in 32% and 42% yield, respectively (Equation 1). For ***deuterio*-3aa**, deuterium incorporation was observed at C2-H (17%) and C3-H (43%). Exchange at these positions is dependent on the presence of the Rh-catalyst but not the cyclopropane (Equation 4) or the acid additive (see the SI); these data support exchange by reversible C-H activation of **3a**. For ***deuterio*-4aa**, deuterium incorporation was observed at C2-H (27%), C11-H_a (20%) and C11-H_b (49%). When the same reaction was run for 72 hours, a similar pattern of deuterium incorporation was observed (Equation 2). Deuterium incorporation at C11-H_b of ***deuterio*-4aa/4ab** likely occurs at the stage of **3a** because similar levels

Scheme 2. Mechanistic Experiments.



of exchange are observed at C3-H of this system. When **4a** was re-subjected to the reaction conditions, but in the presence of D_2O, deuterium incorporation was observed at C2-H, likely due to enolization (Equation 3). Deuterium incorporation at C11-H_a of ***deuterio*-4aa/4ab** is consistent with *syn*-carbometallation of the C2-C3 π-system (from **VII**) prior to protodemetallation. The necessary proton originates from either the acid additive or C2-H of **3a**. When ***deuterio*-3ab** was exposed to standard conditions, the deuterium label was transferred predominantly to C11-H_b (Equation 5). Finally, exposure of equimolar quantities of **3a** and ***deuterio*-3ac** to standard conditions revealed a small KIE (k_H/k_D = 1.21), suggesting that C-H cleavage is not turnover limiting (Equation 6).[13]

Scheme 3. DFT analysis of C-C bond activation and C-C bond forming pathways.[a]



[a] Calculations performed at the B3PW91-D3BJ/6-311+G(2d,p),Rh(LANTZ(f))/SMD(DCB)//B3PW91-D3BJ/6¬31G(d),Rh(MWB28) level of theory, with thermochemical corrections calculated at T = 403 K and a 1 M standard state.

The experiments above are consistent with a pathway involving stereoretentive protodemetallation of a C11-alkyl-Rh(I) species. To provide insight into (a) the mode of C-C bond activation and (b) the C-C bond forming sequence from the rhodabicycle (cf. **II**), we undertook DFT studies (Scheme 3). The detail of the ligand environment around rhodium cannot be confirmed, and so the calculations are informative purely from a comparative viewpoint. It is also challenging to compare the relative stabilities of intermediates with different overall charge (neutral vs cationic);[14] accordingly, we rely on the observation that C-H metallation is reversible, such that **A** and **B** are not separated by more than a few kcal mol^{-1} and zero points in energy can be set for these species (Scheme 3A). Directed C-C bond activation of **A** to form **E** is endergonic (ΔG = 7.1 kcal mol^{-1}) with a barrier of 22.5 kcal mol^{-1}. Migratory insertion of CO proceeds with a lower barrier (12.7 kcal mol^{-1} vs 15.4 kcal mol^{-1} for **E** to **A**) to provide rhodacyclopentanone **H** (ΔG = -22.1 kcal mol^{-1}).[15] Equation 4 suggests that a C2-H metallation complex akin to **B** is accessible; however, C-C bond activation from this (via **D**) is discounted due to the higher energy barrier (ΔG = 32 kcal mol^{-1}). Accordingly, we favor a carbonyl directed C-C bond activation pathway for the generation of **H**, from which C2-H metallation (cf. Equation 6) provides **I** (Scheme 3B). Two different sequences could lead to alkyl-Rh(I) species **P**. In one scenario, 5-ring C(sp^2)-C(sp^3) reductive elimination to **M** is followed by carbometallation of the indole C2-C3 π-system via **O**. Both steps have high barriers (32.4 and 31.9 kcal mol^{-1}). The second option is in accord with Table 1A, and is supported by Scheme 2, Equation 5. Here, 8-ring C(sp^2)-C(sp^2) reductive elimination to **L** is followed by carbometallation of the indole π-system via **N**. Both steps are accessible with barriers of 17.8 and 23.5 kcal mol^{-1}, respectively. Thus, the analysis supports a sequence involving C(sp^2)-C(sp^2) reductive elimination from **I**. Additional evidence discounting the alternate C(sp^2)-C(sp^3) reductive elimination pathway lies in the observation that products arising from decarbonylation of intermediates of type **M** have not been observed.[16] The relative facility of C(sp^2)-C(sp^2) vs C(sp^2)-C(sp^3) reductive elimination from Rh(III) has been demonstrated in other studies.[17] It is striking that this reactivity facet overrides the energetic penalty associated with formation of a strained 8-membered ring (**L**).[18] The role of the acid additive (4-$NMe_2C_6H_4CO_2H$) is likely to facilitate protodemetallation of **P**; alternate or additional roles are possible (e.g. as a carboxylate ligand facilitating CMD-type conversion of **H** to **I**).[19]

The mechanistic pathway proposed above suggested that further polycyclizations should be achievable by carbometallation of other π-unsaturated units at the stage of **VII** (see Table 1A). In particular, we envisaged accessing distinct ring systems via *exo*-selective trapping of this intermediate (cf. Scheme 1B, **5** to **6**). To this end alkenyl and alkynyl systems **3r** and **5a** were exposed to carbonylative polycyclization conditions, but in the presence of P(4-FC_6H_4)$_3$ (15 mol%), an additive that suppresses the dearomatization processes in Table 1 (Table 2A). **3r** afforded solely dearomatization product **4r**, and the product of alkene carbometallation was not observed. Conversely, cyclization of **5a**, which contains a strongly coordinating alkyne, led to **6a** in 26% yield and the corresponding dearomatization product was not observed. **6a** formed as a single geometric isomer, which is consistent with *syn*-stereospecific alkyne carbometallation from **VII**.[20] When these processes were conducted without P(4-FC_6H_4)$_3$ (cf. Table 1) **4r** formed in 42% yield whereas **6a** was not observed. Optimization of **5a** to **6a** was achieved primarily by switching the P-ligand to P(3,5-$(CH_3)_2C_6H_3$)$_3$; using this modification **6a** was generated in 55% yield (Table 2B). This protocol extended to a variety of related polycyclizations, which provided indole and pyrrole systems **6b-e** in 39-82% yield. When **5d** to **6d** was run in the presence of D_2O, deuterium incorporation (10%) was observed only at the alkenyl C-H (see the SI).[21] This is consistent with the second ring forming via a *syn*-carbometallation-protodemetallation sequence from an intermediate akin to **VII**.

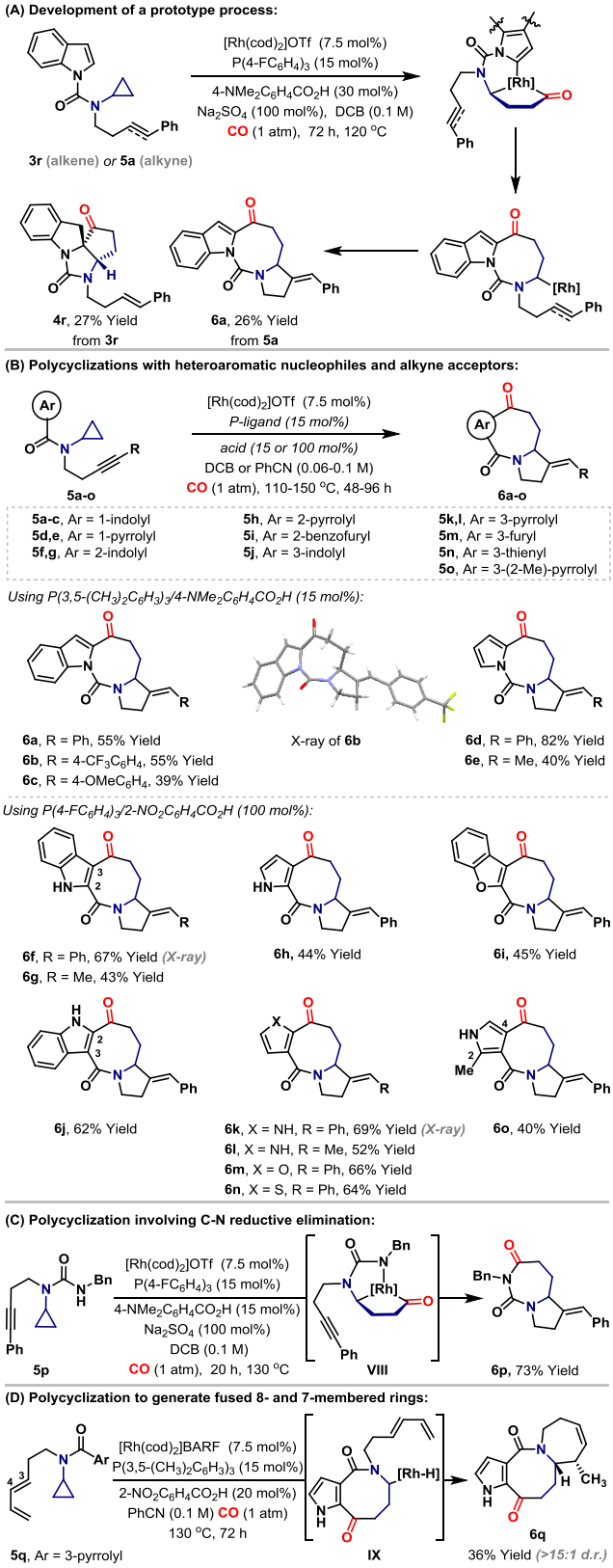
The processes above provided the impetus for exploring the scope of the nucleophilic component (Table 2B). 2-Carbamoyl indole, pyrrole and benzofurans are also effective and **6f-i** were generated in 43-67% yield. *Exo*-selective polycyclizations via the C-2

position of heteroarenes with C3 directing groups led to **6j-n**; here, competing cyclization via C4 was not observed. By blocking C-2, pyrrole **5o** could be induced to cyclize via C-4 to provide **6o** in 40% yield. Use of less nucleophilic arenes (e.g. N-benzoyl) for the first ring formation was unsuccessful. Rh-catalyzed 8-membered ring formations have been reported previously, but they are not transferable to the polycyclizations described here.[22]

Other types of bond formation can be incorporated into these cascades. Directed rhodacyclopentanone formation from **5p** was followed by N-H metallation to generate **VIII** (Table 2C). At this stage, 7-ring C-N reductive elimination occurs prior to alkyne hydrometallation and protodemetallation, which afforded **6p** in 73% yield. This example is unique because reductive elimination (a) generates a C-N rather than a C-C bond, and (b) provides a 7- rather than 8-membered ring. To examine scope further, we subjected 1,3-diene **5q** to polycyclization conditions (Table 2D). Remarkably, this led to 8,7-fused ring system **6q** as a single diastereomer. Here, formation of the first ring likely follows a pathway akin to that outlined earlier. However, the second ring formation is most easily rationalized via a mechanistically distinct hydrometallation pathway, wherein protonation of the alkyl-Rh(I) intermediate provides Rh(III)-hydride **IX**.[23] Hydrometallation of the 1,3-diene generates a Rh-π-allyl which undergoes C-C reductive elimination to **6q**. The intermediacy of Rh-π-allyl species is favored because π→σ→π isomerization can account for the switch from the *trans*-C3-C4 linkage in **5q** to the *cis*-geometry in **6q**.[24]

In summary, the latent ambiphilic reactivity of rhodacyclopentanones can be harnessed for the design of polycyclization cascades. The key intermediates are unveiled by carbonylative C-C bond activation of cyclopropanes, an initiating motif that is otherwise stable and can be accessed easily (if required) in a stereocontrolled manner. The method offers high flexibility for the construction of diverse polyheterocycles that are challenging or inaccessible using other methods. We anticipate that reactivity platforms of the type outlined here will be of increasing importance for accessing molecular scaffolds that lie in underexplored regions of chemical space.

Table 2. *Exo*-polycyclizations.



ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data and crystallographic data. This material is available free of charge via the Internet at *http://pubs.acs.org.*

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Notes

The authors declare no competing financial interest

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(21) Low deuterium incorporation can be explained by 4-$NMe_2C_6H_4CO_2H$, C2-H of **5d** and adventitious water serving as competing proton sources.

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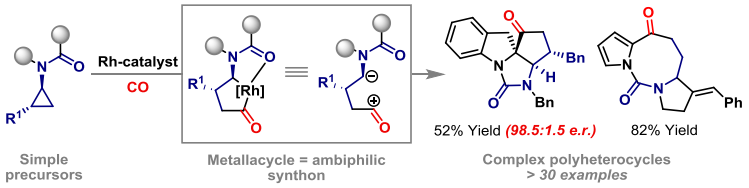
Rh-catalyst
CO
[Rh]
Bn
H
Bn
52% Yield (98.5:1.5 e.r.)
82% Yield
Ph
Simple precursors
Metallacycle = ambiphilic synthon
Complex polyheterocycles
> 30 examples