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Capture–Collapse Heterocyclization: 1,3-Diazepanes by C–N Reductive Elimination from Rhodacyclopentanones

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Supporting Information

Abstract: Rhodacyclopentanones derived from carbonylative C–C activation of cyclopropyl ureas can be "captured" by pendant nucleophiles prior to "collapse" to 1,3-diazepanes. The choice of N-substituent on the cyclopropane unit controls the oxidation level of the product, such that C4–C5 unsaturated or saturated systems can be accessed selectively.

The Biginelli multicomponent reaction provides high versatility for the synthesis of 6-ring cyclic ureas and is used widely in diversity oriented synthesis. However, equally direct and flexible entries to homologated systems have not been reported despite the biological significance of the 1,3-diazepane scaffold (Scheme 1A). This is the core motif in a family of highly potent HIV protease inhibitors, as exemplified by DMP 450. Other important 1,3-diazepanes include the structurally intriguing β-lactamase inhibitor MK-7655 developed by Merck, and the mast cell inhibitory alkaloid (+)-monanchorin. The lack of general methods for accessing 1,3-diazepanes reflects wider difficulties in preparing medium ring systems containing multiple heteroatoms. Consequently, modular catalytic methodologies that address this issue are likely to be of interest to the pharmaceutical sector.

Our laboratory has developed a cycloaddition strategy that relies on N-directing group controlled insertion of Rh and CO into the proximal C–C bond of aminocyclopropanes (Scheme 1B). The resulting rhodacyclopentanones 2 engage pendant alkynes or alkenes to provide (3 + 1 + 2)7a,b,d or (7 + 1)7c cycloaddition products. This approach harnesses the strain embedded within readily prepared (and enantiopure) aminocyclopropanes to provide byproduct-free access to complex N-heterocyclic ring systems. In seeking to expand further the scope of this catalysis platform, we considered whether rhodacyclopentanones 2 might be susceptible to attack by pendant nucleophiles. If successful, this would provide medium rings 4 via the intermediacy of kinetically accessible bicycles 3, with a key issue being the scope of the C–Nu reductive elimination step, a process only known for C–O bond formation. Such catalytic metallacycle "capture–collapse" sequences have the potential to generate a wide range of challenging rings containing multiple heteroatoms. In this report we outline our proof-of-concept studies toward this broad goal by demonstrating that readily prepared urea-based systems 5 can be converted directly to substituted 1,3-diazepanes via previously unknown C–N reductive elimination from rhodacyclopentanones 7 (Scheme 1C). We also show that the oxidation level of the product (8 vs 9) can be controlled by the choice of R1-substituent, thereby providing valuable additional flexibility to the methodology.

Initial studies examined a range of Rh-catalysts for the carbonylative cyclization of 5a (Table 1). Under 1 atm of CO, we found that a cationic Rh(I)-system derived from [Rh(cod)₂]BARF and triphenylphosphine provided oxidative product 8a in 82% yield and 20:1 selectivity over the alternate C4–C5 saturated variant 9a. Notably, neutral Rh(I)-complexes were completely ineffective and higher CO pressures (e.g., 5 atm) offered no benefits. The presence of an acid cocatalyst (PhCO₂H) was found to have a significant effect, providing approximately 20% enhancements to the yields of cyclizations.

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Table 1. Oxidative Carbonylative Heterocyclizations

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Regioselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>5:1 saturated/unsaturated</td>
</tr>
<tr>
<td>H</td>
<td>R</td>
<td>3:1 to 12:1 selectivity over the corresponding C4−C5 unsaturated variants (8:1−r)</td>
</tr>
</tbody>
</table>

Table 2. Redox Neutral Carbonylative Heterocyclizations

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>Regioselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>5:1 saturated/unsaturated</td>
</tr>
<tr>
<td>R</td>
<td>H</td>
<td>3:1 to 12:1 selectivity over the corresponding C4−C5 unsaturated variants (8:1−r)</td>
</tr>
</tbody>
</table>

The ratio of 8a−r:81−r is given in parentheses (determined by 1H NMR analysis of crude material). Dioxane was used as solvent.
the absence of CO2 decomposition products generated from the putative rhodacyclobutane intermediate (not depicted) indicate the kinetically favored site of C−Co oxidative addition.13 Trans-disubstituted cyclopropane trans-5s generated selectively alkene 11b, which is derived from C−C activation of bond a, whereas cis-disubstituted system cis-5s provided predominantly 11a (11:1 11a:11b), via preferential activation of bond b. Thus, in both cases, C−C activation regioselectivity is in line with previous stoichiometric studies7b,c but opposite to that observed in Scheme 3A/B.

We have shown in earlier work that directed rhodacyclopentanone formation is (highly) reversible when cationic Rh−systems are employed.7b,c As such, product regioselectivity can be controlled by the facility of processes other than the initial directed C−C activation step. This type of Curtin−Hammett scenario (i.e., reversible formation of 7 from 5, see Scheme 1C) underpins proposed mechanisms for the processes described here. For trans-disubstituted systems, rhodacyclopentanone formation via cleavage of bond a is preferred leading to metallacycle 1A (Scheme 4B). However, subsequent C−N reductive elimination to 1IA is slow because of the developing steric clash between the Rh-center and the R3-substituent. Accordingly, reprotonation of nitrogen, retro-carbonylation, and C−C reductive elimination regenerate the cyclopropane and enable equilibration to disfavored metallacycle 1B. Here, C−N reductive elimination is likely more facile because the Rh-center of 1IB is further from the R3-substituent (cf. 1IA, 1,2- vs 1,3-relationship); consequently, the C3-substituted product is generated selectively.

The minor component (8x) had C3−C4 unsaturation.

\[\text{Scheme 4} \]

\[\text{The ratio of 8:9 is given in parentheses (major product depicted; ratio determined by }^1\text{H NMR analysis of crude material).} \]

\[\text{[Rh-(cod)2]BF4 (7.5−10 mol %) used as precatalyst.} \]

\[\text{The minor component (8x) had C3−C4 unsaturation.}\]
allows equilibration to IC, where this steric impediment is alleviated en route to the C4-substituted product. Thus, we suggest that for both systems the unexpected product regioselectivities are determined by the facility of C–N reductive elimination rather than C–C activation.\textsuperscript{13}

Why does the presence or absence of an R\textsuperscript{1}-substituent control selectivity for C4–C5 unsaturated or saturated products (8 vs 9) (Scheme 4D)? Preliminary studies indicate that the conversion of II to 8 occurs in both cases, but this is reversible for R\textsuperscript{1} = H allowing eventual protodemetalation to 9. Cyclization of \textit{deutero-cis-5v} provided \textit{deutero-9v}, where deuterium transfer from the urea to both diastereotopic C5 positions supports reversible β-hydride elimination and alkene dissociation (to 8)\textsuperscript{16} in advance of irreversible protodemetalation (to 9); incomplete deuterium transfer may be due to exchange with protic impurities (e.g., H\textsubscript{2}O) prior to C–H formation. For systems lacking a C4-substituent, isomerization along the ring occurs prior to protodemetalation; cyclization of \textit{deutero-S1} generated \textit{deutero-9l}, where deuterium incorporation was observed at C3, C4, and C5. Heterocyclization to 8 is oxidative, and we speculate that the active Rh(I) species is regenerated by protonation triggered reductive elimination of dihydrogen; this process is known for related systems.\textsuperscript{7,17}

Presumably, the PhCO\textsubscript{2}H additive acts as a proton reservoir for both pathways, which otherwise would be reliant solely on the proton released by conversion of dihydrogen; this process is known for related systems.\textsuperscript{8,17}

In summary, we demonstrate an approach to substituted 1,3-diazepanes as proof-of-concept for a general metallacycle capture–collapse strategy. We anticipate that the strategy will allow the generation of a range of medium ring systems containing multiple heteroatoms; studies toward this broad goal are underway.\textsuperscript{18} The findings described here enhance significantly the scope of the catalysis platform outlined in Scheme 1B (1 to 2), opening up numerous avenues for further exploration, while at the same time adding to the wider and emerging area of rhodacyclopentanone-based catalysis.\textsuperscript{7,8,19}

\section{ASSOCIATED CONTENT}

\subsection{Supporting Information}

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07046.

Experimental details, characterization data (PDF)

Crystallographic data (CIF, CIF, CIF)

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N.G.McC. and S.S. contributed equally.

\subsection{Notes}

The authors declare no competing financial interest.

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\section{REFERENCES}


(9) A one-pot synthesis of 9l (57% yield, 6:1 saturated:unsaturated) from cyclopentylamine is given in the Supporting Information (SI).

(10) Cyclization of (SS)-\textit{trans-5s} (>98% ee) provided (S)-8s in >98% ee (see the SI).

(11) Replacement of the n-butyl group with methyl or cyclohexyl substituents gave analogous results (see the SI).

(12) The relative stereochemistry of 1,2-disubstituted cyclopropene substrates was determined using a combination of X-ray crystallographic analysis (trans-5s) and NOE experiments.

(13) Similar results were obtained in the presence of PhCO\textsubscript{2}H (15 mol%). The SI details analogous experiments for carbamate protected systems, confirming that C–C activation selectivity is the same in the absence and presence of CO.

(14) For the conversion of \textit{trans-5v} to 8v, β-hydride elimination presumably occurs via N6-H.

(15) Alternate explanations cannot be discounted on the basis of available data. For example, the steric effects of the R\textsuperscript{1}-group may result in slow formation of ID, rather than slow reductive elimination from this intermediate.

(16) The suggestion that the alkene dissociates assumes stereo-specific protodemetalation.


(18) By the strictest (IUPAC) definition, 7-ring systems are not classed as medium rings. However, the chemistry described here is an important conceptual stepping stone towards this goal because conventional 7-ring cyclizations are, in terms of kinetics, significantly more demanding than 5- or 6-ring variants: Illuminati, G.; Mandolini, L.; Masci, B. \textit{J. Am. Chem. Soc.} 1975, 97, 4960.