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Modular Access to Substituted Azocanes via a Rhodium-Catalyzed Cycloaddition–Fragmentation Strategy

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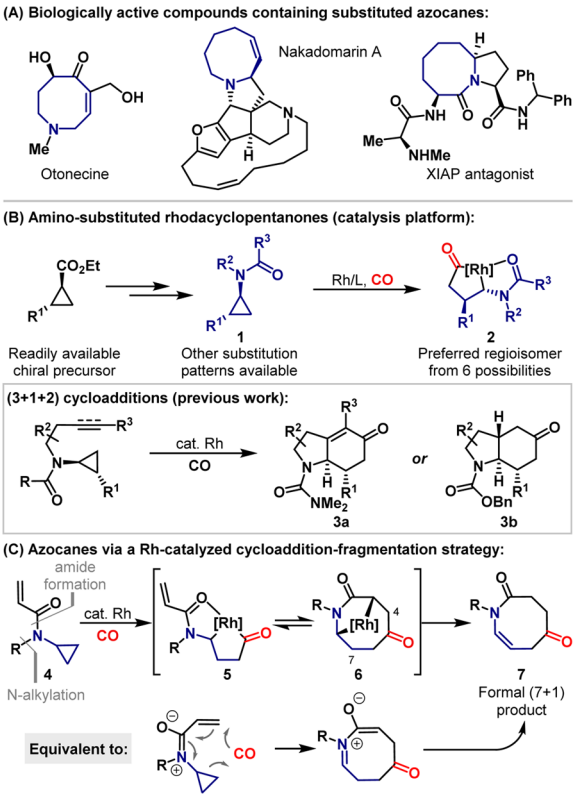
Supporting Information

ABSTRACT: A short entry to substituted azocanes by a Rh-catalyzed cycloaddition–fragmentation process is described. Specifically, exposure of diverse *N*-cyclopropylacrylamides to phosphine-ligated cationic Rh(I) catalyst systems under a CO atmosphere enables the directed generation of rhodacyclopentanone intermediates. Subsequent insertion of the alkene component is followed by fragmentation to give the heterocyclic target. Stereochemical studies show, for the first time, that alkene insertion into rhodacyclopentanones can be reversible.

Direct and modular entries to eight-membered N-heterocyclic ring systems (e.g., azocanes) are rare, and this in turn limits the ability of medicinal chemists to exploit a potentially fertile region of chemical space.[1] Transition-metal-catalyzed cycloadditions provide exceptional versatility for the synthesis of eight-membered-ring carbocycles,[2] but related processes that generate N-heterocyclic systems have been slow to emerge.[3,4] Within this area, important methodologies that provide concise entries to specific classes of bicyclic azocanes include isocyanate-based (4 + 2 + 2) cycloadditions[3a] and azetidinone-based (4 + 2 + 2)[3b] and (4 + 4)[3c] cycloadditions. Nevertheless, the relative paucity of available methodologies is notable, especially given the prevalence of the azocane ring system in a range of biologically significant targets, such as otonecine,[5] nakadomarin A,[6] and a series of recently reported XIAP antagonists (Scheme 1A).[7]

We have outlined a directing-group-controlled strategy that enables the regioselective generation of rhodacyclopentanones, such as **2**, from readily available aminocyclopropane derivatives (Scheme 1B).[8,9] Specifically, aminocyclopropanes **1**, modified with carbonyl-based N-protecting groups, direct Rh and CO insertion into the less hindered proximal C–C bond to afford adduct **2** selectively at the expense of five other potential regioisomers. Trapping of **2** with N-tethered alkynes or alkenes generates (3 + 1 + 2) cycloaddition products **3a** or **3b**, respectively.[8a,b] In this report, we disclose that acrylamides **4** undergo an alternate reaction pathway involving formal fragmentation[10] after alkene insertion (rather than C–C reductive elimination) to provide a direct and modular entry to azocanes **7** (Scheme 1C). The overall process is equivalent to a (7 + 1) cycloaddition–tautomerization sequence and can be considered a catalytic mimic of classical stepwise bicycle assembly–fragmentation approaches to medium ring systems.[11] We also provide, for the first time, compelling evidence that migratory insertion of alkenes into rhodacyclopentanones can be a reversible process, thereby offering key insight into a fundamental mechanistic step that underpins a range of recently reported C–C bond activation methodologies.[8b,12−14]

Scheme 1



In preliminary experiments we established that cationic Rh(I) systems are effective for the transformation outlined in Scheme 1C. The most pertinent studies were conducted on cyclopropane **4e**, which was easily prepared in 60% yield over two steps (see the Supporting Information (SI)). At 150 °C under 1 atm CO, a series of cationic Rh(I) systems, modified with the electron-deficient phosphine P(4-(CF_3)C_6H_4)$_3$, were effective in delivering the azocane target **7e** in 34–53% yield (Table 1, entries 1 and 3–5). The use of PhCN as the solvent was crucial for reaction efficiency, perhaps because it is able to stabilize active catalytic species and prevent saturation of the Rh center by CO.

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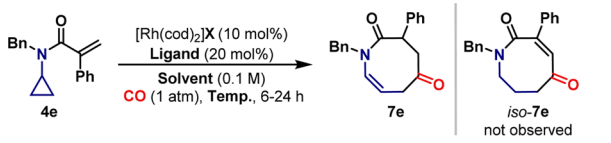
Table 1. Optimization of the Synthesis of Azocane 7e



entry	X	ligand	solvent	T (°C)	yield (%)[a]
1	BARF	P(4-(CF_3)C_6H_4)$_3$	PhCN	150	38
2	BARF	P(4-(CF_3)C_6H_4)$_3$	1,2-DCB	150	<5
3	BF_4	P(4-(CF_3)C_6H_4)$_3$	PhCN	150	48
4	SbF_6	P(4-(CF_3)C_6H_4)$_3$	PhCN	150	34
5	OTf	P(4-(CF_3)C_6H_4)$_3$	PhCN	150	53
6	OTf	P(4-(CN)C_6H_4)$_3$	PhCN	150	52
7	OTf	P(C_6F_5)$_3$	PhCN	150	16
8	**OTf**	**P(3,5-(CF_3)$_2C_6H_3$)$_3$**	**PhCN**	**150**	**63**
9	OTf	P(3,5-(CF_3)$_2C_6H_3$)$_3$	PhCN	140	16
10	OTf	P(3,5-(CF_3)$_2C_6H_3$)$_3$	PhCN	160	54

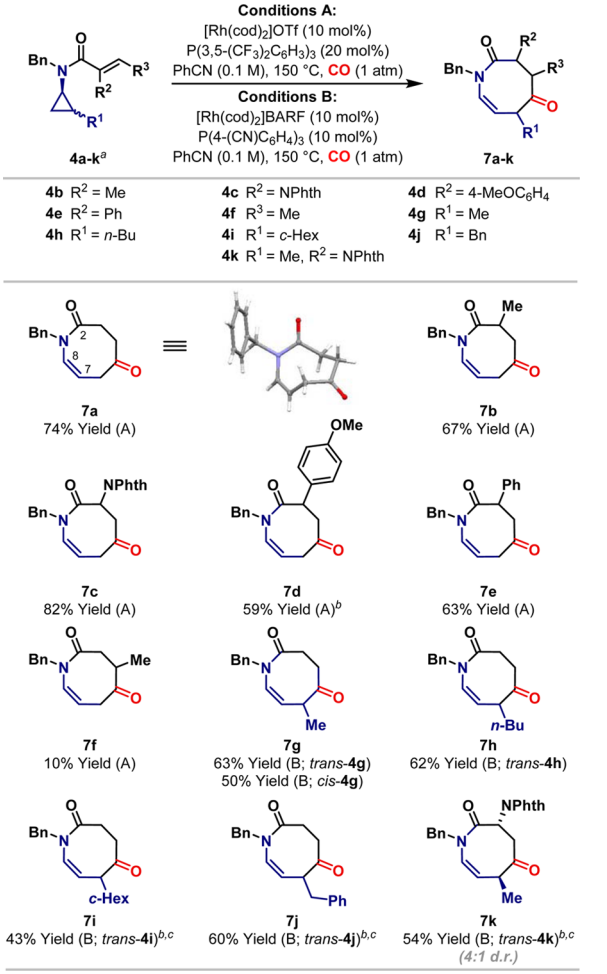
[a]Isolated yields. Reactions were run until full consumption of starting material was observed by TLC.

Notably, non-coordinating solvents, such as 1,2-dichlorobenzene (1,2-DCB), were completely ineffective (entry 2). With [Rh(cod)$_2$]OTf as the precatalyst, a series of electron-deficient phosphine ligands were evaluated, and this led to the conditions outlined in entry 8 ("conditions A"), which delivered **7e** in 63% yield. Lower or higher reaction temperatures resulted in diminished yields of **7e** (entries 9 and 10). Throughout these studies, *iso*-**7e**, which could arise from rhodabicycle **6** via β-hydride elimination of C4−H, was not observed, and products of this type were not encountered elsewhere.[15]

The scope and limitations of the new process are shown in Table 2. Cyclization of unsubstituted system **4a** (R^{1-3} = H) delivered azocane **7a** in 74% yield. The structure of **7a** was confirmed by single-crystal X-ray diffraction (scXRD), which revealed an unusual twisted enamide (C7−C8−N−C2 torsion angle = 50.9°), highlighting the ring strain associated with these products. A range of substrates **4b−e** possessing alkyl, aryl, or amino substituents at R^2 cyclized smoothly to provide the target azocanes **7b−e** in good to excellent yield. The protocol is relatively insensitive to the steric and electronic demands of the R^2 group, and in all cases efficient cyclization was observed. However, 1,2-disubstituted alkenes are not well tolerated, and cyclization of **4f** (R^3 = Me) generated **7f** in only 10% yield. The structural assignments of **7b−f** were made by analogy to **7a** and were also supported by detailed NMR analysis (see the SI).

The development of processes involving substituted aminocyclopropanes proved to be challenging and required separate optimization. This led to "conditions B", which employ a catalyst system derived from [Rh(cod)$_2$]BARF and P(4-(CN)C_6H_4)$_3$. With this protocol, cyclization of *trans*-**4g** to **7g** proceeded in 63% yield. In this case, the product arises from insertion of Rh and CO into the more hindered proximal cyclopropane C−C bond of **4g**. This is inconsistent with our earlier work and the mechanistic implications of this observation are discussed later.[8] Notably, **7g** is also accessible from the corresponding *cis*-1,2-disubstituted cyclopropane (*cis*-**4g**), which cyclized in 50% yield under the same conditions as used for *trans*-**4g**. Extension to a range of *trans*-1,2-disubstituted systems **4h−j**, possessing linear or branched alkyl substituents at R^1, provides modular access to the corresponding azocanes **7h−j**. In all cases, the products were formed as single regioisomers, and products derived from Rh/CO insertion into the less hindered proximal aminocyclopropane

Table 2. Scope of the Cycloaddition−Fragmentation Process



[a]R^{1-3} = H unless otherwise noted. [b]160 °C. [c]Using [Rh(cod)$_2$]OTf.

C−C bond were not observed. In favorable cases, substitution on both the alkene and cyclopropane components is tolerated. For example, cyclization of *trans*-disubstituted system **4k** provided **7k** in 54% yield as a 4:1 mixture of diastereomers.[16] The relative stereochemistry of the major diastereomer of **7k** was assigned by nuclear Overhauser effect studies (see the SI).

The functionality present in the products described here provides many opportunities for derivatization. Of particular interest was the reactivity of the enamide moiety, which, as revealed by the X-ray structure of **7a**, is twisted from planarity. Thus, on first inspection, its ability to engage in "conventional" enamide chemistry was unclear.[17] To probe this, we evaluated a cyclization/Pictet−Spengler (PS) sequence leading to challenging tricyclic derivatives (Scheme 2).[18] Carbonylative cyclizations of **8a** and **8b** proceeded smoothly under conditions A, giving **9a** in 65% yield and **9b** in 68% yield. Brønsted acid-catalyzed PS cyclization of **9a** provided adduct **10a** in 59% yield. For **9b**, competing hydrolysis of the enamide was problematic under protic conditions, but a Au-catalyzed protocol[19] was effective, generating **10b** in 54% yield. The structures of **10a** and **10b** were confirmed by scXRD (see the SI for the structure of **10b**). This strategy provides access to challenging polycyclic systems and shows that the strained enamide moiety can engage in reactions typical of non-strained variants.

Key observations made in our earlier studies underpin a mechanistic rationale for the processes described here. We have

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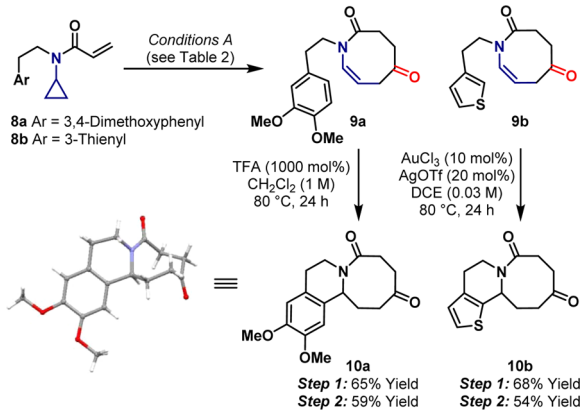
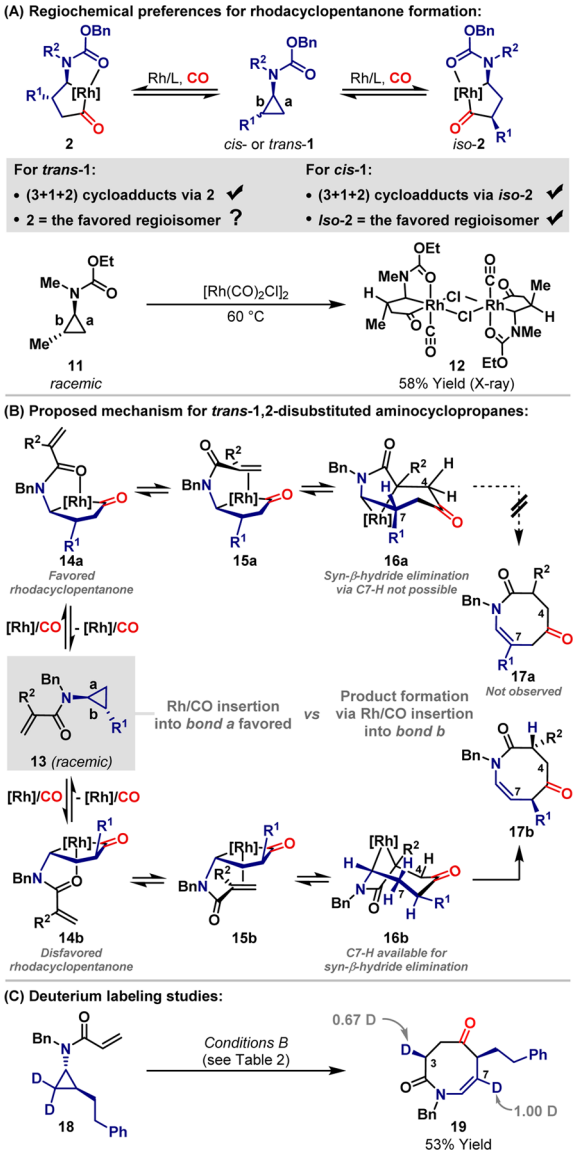
Scheme 2. Tricyclic Systems via Pictet–Spengler Cyclizations



Scheme 3



demonstrated that carbonylative rhodacyclopentanone formation is highly reversible when cationic Rh(I) systems are employed.[8b] We have also shown that *cis*-1,2-disubstituted aminocyclopropanes undergo carbonylative (3 + 1 + 2) cycloadditions via cleavage of the more hindered bond **b** (i.e., via *iso*-**2**) (Scheme 3A).[8b] This regioselectivity is consistent with that observed here (e.g., for *cis*-**4g** to **7g**), and stoichiometric studies have shown that this also reflects the inherent preference of rhodacyclopentanone formation.[8b] Conversely, *trans*-1,2-disubstituted aminocyclopropanes provide (3 + 1 + 2) cycloaddition products via cleavage of the less hindered proximal C–C bond **a** (i.e., via **2**).[8a,b] *This selectivity is the inverse of that observed here*. In previous studies, there was the possibility that product regioselectivity was subject to Curtin–Hammett effects, and consequently, we sought confirmation of the regiochemical preference of rhodacyclopentanone formation from *trans*-1,2-disubstituted systems. Accordingly, carbamate **11** was exposed to stoichiometric quantities of $[Rh(CO)_2Cl]_2$, and this generated complex **12** in 58% yield. The structure of **12** was confirmed by XRD, which revealed a heterochiral dimer formed by exclusive insertion of Rh and CO into the less hindered proximal C–C bond **a**.[20] Consequently, the product regioselectivities observed in this study for *trans*-1,2-disubstituted aminocyclopropanes (e.g., *trans*-**4g** to **7g**) *do not* reflect the preferred regioselectivity for rhodacyclopentanone formation.

On the basis of the considerations outlined above, a plausible mechanism for cyclizations involving *trans*-1,2-disubstituted aminocyclopropanes is proposed in Scheme 3B. Directed insertion of Rh and CO into bond **a** or bond **b** of **13** generates rhodacyclopentanone **14a** or **14b**, respectively. Insertion to provide **14a** is favored on steric grounds, but ultimately this pathway is non-productive because, following directing-group dissociation and migratory insertion of the alkene into the acyl–Rh bond, *syn*-*β*-hydride elimination via C7–H of **16a** is not possible. However, reversible alkene, CO, and Rh insertion regenerates cyclopropane **13**, and this in turn enables equilibration to regioisomeric rhodacyclopentanone **14b**. Migratory insertion of the alkene into the Rh–acyl bond of **15b** generates regioisomer **16b**, which is set up for *syn*-*β*-hydride elimination via C7–H to deliver the observed regioisomer of the product. To support the proposed mechanism, we prepared deuterium-labeled substrate **18** (Scheme 3C). Cyclization under standard conditions provided adduct **19**, where deuterium transfer to C3 is observed solely on the same face as the C6 substituent (cf. **16b** to **17b**).[21] Incomplete levels of deuterium transfer may be due to the presence of protic impurities (e.g., water) in the reaction mixture, which would facilitate exchange at the stage of the intermediate Rh hydride (not depicted). The mechanism in Scheme 3B is consistent with the contrasteric regioselectivities observed in this study for *trans*-1,2-disubstituted aminocyclopropanes and invokes, for the first time, reversibility for alkene insertion into rhodacyclopentanones. Notably, this is a key step in a number of recently reported methods,[8b,12−14] and the present study highlights a key aspect that may be important for further development of the area.

Two other points regarding product selectivity require clarification. First, products of C–C bond-forming reductive elimination from **6** (see Scheme 1C) have not been observed, and this presumably reflects the strain associated with the *β*-lactam (not depicted) that would result. Second, and in contrast to related systems,[13b] *β*-hydride elimination from **6** is highly regioselective for C7–H, and products of elimination via C4–H (e.g., *iso*-**7e**; Table 1) are not formed. This may be due to (a) a reduction in the hydridic character of the C4 protons (relative to those at C7) as a result of the adjacent ketone and/or (b) the high strain associated with accommodating five adjacent sp^2 centers within the eight-membered ring of, for example, *iso*-**7e**.

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To conclude, we report a direct approach to functionalized azocanes by a Rh-catalyzed cycloaddition−fragmentation sequence. Significantly, these studies expand the scope of the catalysis platform outlined in Scheme 1B to include processes that do not afford products of C−C bond-forming reductive elimination. This in turn suggests that a distinct range of methodologies may be accessible by harnessing bicyclic intermediates such as **6**. Mechanistic and stereochemical studies have provided, for the first time, strong support that alkene insertion into rhodacyclopentanones can be reversible. This observation is likely to have wider implications given the emerging family of processes that are dependent upon this key mechanistic step.[8b,13,14] Current studies are focused upon the development of other medium-ring methodologies inspired by the mechanistic insights gained here.

■ ASSOCIATED CONTENT

Supporting Information

Methods, characterization data, and crystallographic data (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05215.

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Notes

The authors declare no competing financial interest.

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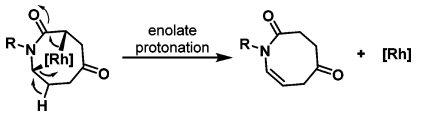
(10) Heterolytic fragmentations have been defined as processes where three components are generated and C is an electrofuge. See: Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. A *formal* representation of the current scenario, which generates an alkene, Rh(I), and an enolate:



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(15) Reactions run in the absence of CO result in a complex mixture of products derived from decomposition of the rhodacyclobutane intermediate to alkene byproducts (see ref 8a).

(16) Factors governing the diastereoselectivity of this process will be a focus of an in-depth study (also see ref 21).

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(20) Attempted isolation of an analogous rhodacyclopentanone complex containing an acrylamide directing group was unsuccessful.

(21) The high diastereoselectivity of this process indicates that the C3 and C6 stereocenters of **19** are not labile under the reaction conditions.

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