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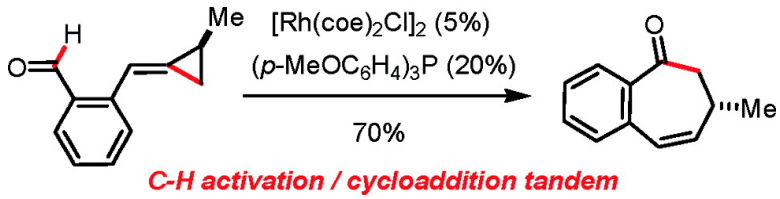

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A Rhodium-Catalyzed C−H Activation/Cycloisomerization Tandem

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Transition-metal-catalyzed C−H activation has recently gained considerable momentum and is now widely recognized for its potential to form a host of C−C and C−heteroatom bonds in an inherently benign fashion.[1] We now present a further expansion of the scope of this methodology by merging catalytic C−H activation with higher order cycloaddition into an efficient manifold for the formation of seven-membered rings.

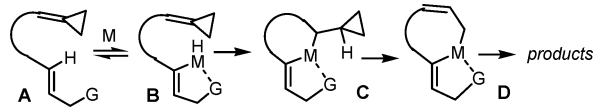
Our first approach employed substrates of type **A** bearing an anchor group G to direct a suitable catalyst M toward a proximal olefinic Csp^2−H bond (Scheme 1).[2] Following initial C−H activation, the resulting vinylmetal hydride species **B** might undergo hydrometalation of an alkylidenecyclopropane in vicinity to give metallacycle **C** poised for cleavage of the C−C bond of the adjacent cyclopropane[3] to give the ring enlarged complex **D**. Reductive elimination then delivers a functionalized cycloalkene and regenerates the catalytically competent species.[4]

Relying on the proven efficiency of pyridines as directing groups in catalytic C−H activation,[2b,5] substrate **1** was chosen as a suitable model.[6,7] As shown in Scheme 2, exposure of **1** to $(PPh_3)_3RhCl$ (5 mol %) and $AgSbF_6$ (7.5 mol %) in THF or 1,2-dichloroethane (DCE) at 120 °C furnished cycloheptene **2** in 77% yield. It should be noted that the addition of $AgSbF_6$ was necessary to achieve clean conversions. The phosphine-free complexes $[Rh(CO)_2Cl]_2$ and $[Rh(coe)_2Cl]_2$ (coe = cyclooctene) were also suitable, yet somewhat less efficient. As can be seen from Table 1, substrates with aromatic as well as aliphatic backbones reacted well with $(PPh_3)_3RhCl/AgSbF_6$, independent of whether they are conformationally biased for ring closure or not; pre-existing chiral centers next to the reacting sites remained uncompromised. The geometry of the newly formed trisubstituted exocyclic double bond is evident from pertinent NOE data and from the X-ray crystal structure of compound **2** (Scheme 2).

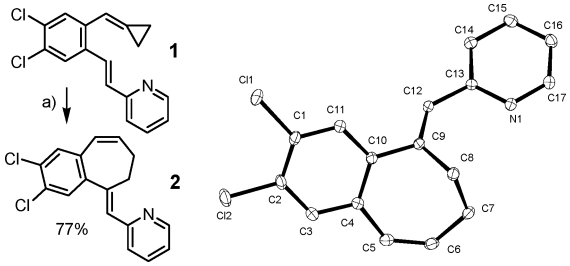
The formation of an *E*-configured exocyclic olefin is consistent with a mechanistic scenario comprising a C−H activation/hydrometalation/cycloaddition sequence directed by the basic nitrogen atom of the pyridine ring. This interpretation is also strongly supported by the labeling experiment depicted in Scheme 3, which features the expected and, within the limits of detection, quantitative transfer of the deuterium atom from the site of initial C−H(D) activation to the newly formed double bond.

Next, we aimed at replacing the 2-vinylpyridine trigger by other moieties amenable to catalytic C−H activation.[7] To this end, alkylidenecyclopropanes with a pendant aldehyde group were subjected to rhodium-catalyzed cycloisomerization.[6,8−10] After some experimentation, it was found that these substrates convert into cycloheptenones on exposure to catalytic amounts of $[Rh(coe)_2Cl]_2$ and $(p\text{-}MeOC_6H_4)_3P$ in DCE at 80−120 °C. Thereby it was necessary to perform the reaction under ethylene atmosphere to ensure high yields.[11] Under these conditions, the outcome was largely insensitive to changes in the electronic nature of the substrate (Table 2, entries 1−3). Like in the pyridine series, compounds with aliphatic and aromatic backbones worked equally well and chiral centers remained unaffected.

Scheme 1. Envisaged C−H Activation/Cycloaddition Crossover

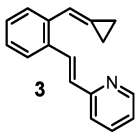
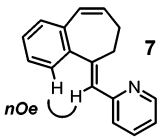
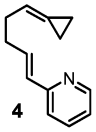
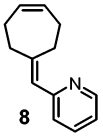
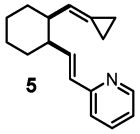
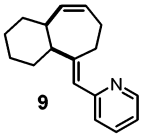
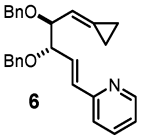
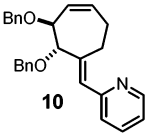


Scheme 2 [a]



[a] Conditions: (a) $(PPh_3)_3RhCl$ (5 mol %), $AgSbF_6$ (7.5 mol %), THF, 120 °C (sealed tube); structure of product **2** in the solid state.

Table 1. Preparation of Cycloheptene Derivatives by a Pyridine-Directed, Rhodium-Catalyzed C−H Activation/Cycloisomerization[a]

Entry	Substrate	Product	Yield
1	 **3**	 **7** *nOe*	68%
2	 **4**	 **8**	62%
3	 **5**	 **9**	67%
4	 **6**	 **10**	53%

[a] Isolated yields. All reactions were preformed with $(PPh_3)_3RhCl$ (5 mol %) and $AgSbF_6$ (7.5 mol %) in THF at 120 °C (sealed tube).

The regio- and stereoselectivity of this novel transformation was further examined with the enantiopure substrates **19** and **20** bearing a methyl substituent on the reacting cyclopropyl ring (Scheme 4).[6] Insertion of the catalyst into the C−H bond of the aldehyde group of **19** followed by *syn*-addition of the resulting Rh−H species to the adjacent alkene provides metallacycle **E** as the primary product.

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Scheme 3. Deuterium Labeling Experiment

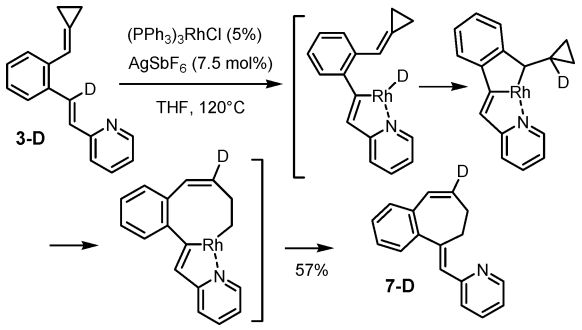
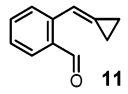
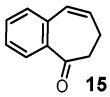
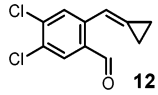
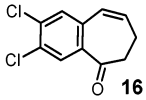
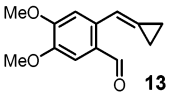
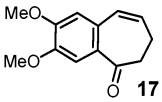
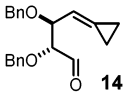
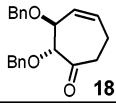
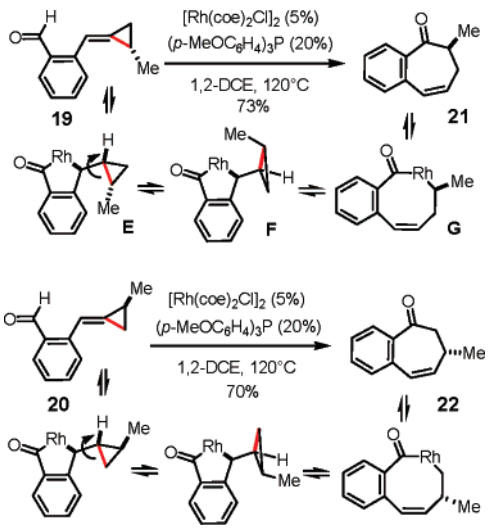


Table 2. Cycloheptenones by Rhodium-Catalyzed C−H Activation/ Cycloisomerization of Aldehyde Derivatives[a,b]

Entry	Substrate	Product	Yield
1	 **11**	 **15**	76%
2	 **12**	 **16**	87%[c]
3	 **13**	 **17**	72%
4	 **14**	 **18**	72%

[a] Isolated yields. [b] $[Rh(coe)_2Cl]_2$ (5 mol %), (p-$MeOC_6H_4)_3P$ (20 mol %), DCE, ethene, 120 °C (sealed tube). [c] $[Rh(coe)_2Cl]_2$ (2.5 mol %), (p-$MeOC_6H_4)_3P$ (10 mol %), DCE, ethene, 80 °C (sealed tube).

Scheme 4. Regio- and Stereoselectivity



Rotation as indicated in Scheme 4 is necessary to eclipse the C−Rh bond with the C−C bond of the cyclopropane; a subsequent strain-driven ring expansion followed by reductive elimination of the ensuing metallacycle **G** then leads to ketone **21** as the only observed product. The analogous pathway explains the formation of product **22** from aldehyde **20**. In both cases, it is the C−C bond of the cyclopropane that is *cis* relative to the C−Ar unit (color coded in red) which is broken during the cycloisomerization, *independent* of the degree of substitution. The absolute configuration of the newly formed stereogenic center in **21**, which was established by a combination of NMR-based conformational analysis and chiroptical methods (cf. Supporting Information), indicates that C−C bond cleavage as well as reductive elimination took place with retention of configuration. This finding is in excellent agreement with conclusions previously reached for related metal-catalyzed higher order cycloadditions.[12]

In summary, we have outlined a productive crossover between catalytic C−H activation and cycloisomerization chemistry. Further studies on this and related catalysis tandems are subject to ongoing studies in our laboratories.

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Supporting Information Available: Experimental part, NMR spectra of new compounds, and CD spectra of compound **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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