C–H Activation

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Combined Rhodium-Catalyzed Carbon–Hydrogen Activation and β-Carbon Elimination to access Eight-Membered Rings**

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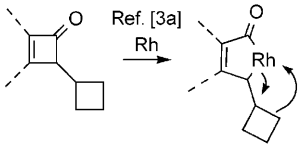
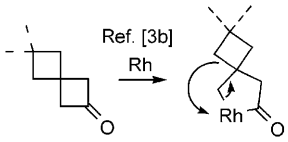
Transition-metal-catalyzed activation of otherwise inert C–H and C–C bonds is widely recognized as a very promising strategy for the development of sustainable synthetic chemistry.[1,2] In this context, β-carbon elimination of putative pentarhodacycles, having an exocyclic C=O double bond, has been used in the design of reactions to promote the ring enlargement of non-functionalized cyclobutanes into larger rings [Eqs. (1) and (2)].[3] Both approaches relied on the insertion of rhodium catalysts into particularly strained cyclobutenones and cyclobutanones, respectively. In contrast, we now disclose the outcome of an alternative strategy which relies on stable aldehydes as precursors in a C–H/C–C activation sequence (Scheme 1).

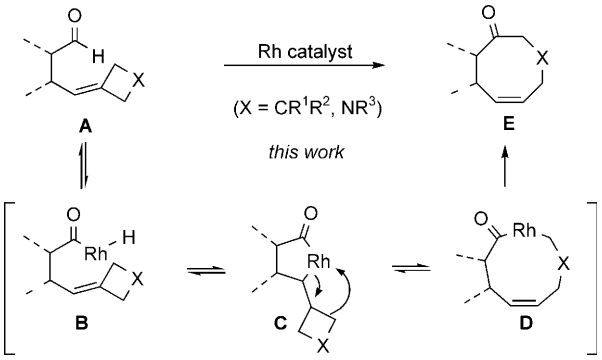


(1)



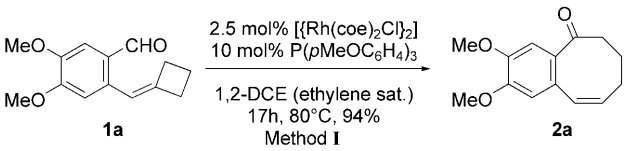
(2)

Encouraged by our recent report of intramolecular hydroacylation of aldehyde-tethered alkylidenecyclopropanes,[4] we anticipated that aldehyde-tethered alkylidenecyclobutanes **A** ($X = CR^1R^2$) would undergo the following sequential steps: C–H activation to give **B**,[5] hydrometalation of the C=C double bond in **B** to give **C**, β-carbon elimination of **C** to give **D**, and finally reductive elimination of **D** to give the eight-membered carbocycle **E**.[6] This approach would complement previous reports of the formation of eight-membered carbocycles which relied on β-carbon elimination of nickel cyclobutanolates[7] or rhodium-catalyzed β-carbon elimination of vinyl cyclobutanones.[8] Moreover, given the similar strain energy of azetidines and cyclobutanes,[9] we hypothesized that this rational design would be applicable to aldehyde-tethered 3-alkylideneazetidines ($X = NR^3$) to afford eight-membered heterocycles.



Scheme 1. Working hypothesis.

We found that exposure of substrate **1a** to [{Rh(coe)$_2$Cl}$_2$] (2.5 mol%; coe = cyclooctene) and P(*p*MeOC$_6$H$_4$)$_3$ (10 mol%) in ethylene-saturated 1,2-dichloroethane (1,2-DCE) at 80 °C (Method I) gave cyclooctenone **2a** in 94% yield (Scheme 2). Encouraged by this result, we explored alternative reaction conditions to avoid the need for saturation of the solution with ethylene.[10] We observed that cationic rhodium complexes were much more active and enable full conversions without requiring the presence of ethylene, giving **2a** more rapidly and in good yield. Hence, treatment of **1a** with [{Rh(coe)$_2$Cl}$_2$] (2.5 mol%), AgBF$_4$ (5 mol%), and P(*p*MeOC$_6$H$_4$)$_3$ (10 mol%) in 1,2-DCE at 80 °C for 30 minutes gave **2a** in 89% yield (Method II),[11] whereas using precatalyst [Rh(nbd)$_2$]BF$_4$ (5 mol%; nbd = norbornadiene) in the presence of binap (5 mol%; binap = 2,2′-bis(disphenylphosphino-1,1′-binaphthyl)[12] in acetone at



Method II: 2.5 mol% [{Rh(coe)$_2$Cl}$_2$], 5 mol% AgBF$_4$, 10 mol% P(*p*MeOC$_6$H$_4$)$_3$, 1,2-DCE, 80 °C, 0.5 h, 89%

Method III: 5 mol% [Rh(nbd)$_2$]BF$_4$, 5 mol% binap, acetone, 56 °C, 3.5 h, 85%

Scheme 2. Rhodium-catalyzed rearrangement of aldehyde-tethered alkylidenecyclobutane **1a** into cyclooctenone **2a**.

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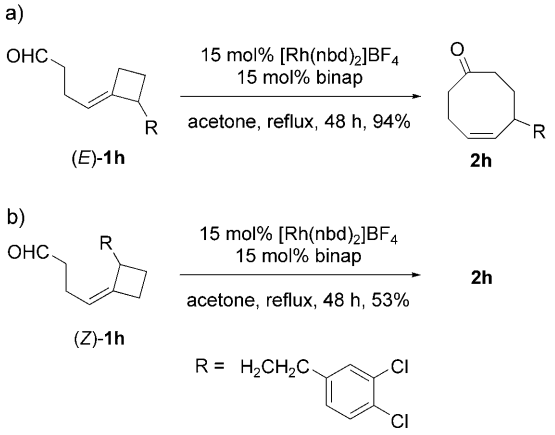
56 °C for 3.5 hours afforded the desired compound in 85 % yield (Method III). This optimization study gave us a set of three reactions conditions (Methods I–III) which could be used on a variety of substrates, thereby demonstrating the general applicability of the reaction design outlined above.

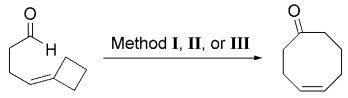
Hence, aromatic cyclooctenone **2b** was isolated in excellent yields from precursor **1b**, using either neutral or cationic rhodium catalysts (Table 1, entries 1 and 2). Additional substitution on the carbon–carbon double bond of the alkylidenecyclobutane moiety shut down the reactivity of all catalytic systems tested, and substrate **1c** was recovered mostly intact after 24 hours (Table 1, entry 3). In contrast, substituents on the ring of the alkylidenecyclobutane moiety of substrates **1d** and **1e** (Table 1, entries 4 and 5) were tolerated, giving compounds **2d** and **2e**, respectively, in good yields, although slightly higher catalyst loadings and prolonged reaction times were necessary. Substitution on the tether (Table 1, entries 6–8) was also compatible with the diverse reaction conditions tested, and treatment of substrates **1f** and **1g** afforded compounds **2f** and **2g**, respectively, in good yields without alteration of the diastereomeric ratios; these ratios were initially equimolar for **1f** and **1g**.

We then examined the regioselectivity of this transformation with both *E* and *Z* isomers of substrate **1h** and observed that both isomers were converted into the same cyclooctenone **2h** when treated with our optimal cationic rhodium catalyst (Scheme 3).[12] The conversion of (*E*)-**1h** was complete within 48 hours and **2h** was obtained in excellent yield (Scheme 3a). In contrast, conversion of (*Z*)-**1h** under the same reaction conditions did not go to completion, and **2h** was isolated in 53 % yield (Scheme 3b). We first hypothesized that this regioconvergence might be a result of the isomerization of the C=C double bond prior to rearrangement. However, (*E*)-**1h** was not present in the recovered starting material (30 %), and treating (*Z*)-**1h** under the same reaction conditions and then stopping the reaction after 4 hours or 18 hours showed incomplete conversion into **2h** (3 % and 20 %, respectively by ^{1}H NMR analysis) without any trace of (*E*)-**1h**. Although we cannot yet completely rule out that a putative isomerization of (*Z*)-**1h** into (*E*)-**1h** occurs at a much slower rate than the rearrangement of (*E*)-**1h** into **2h**, other mechanistic rationales must be investigated before a conclusion can be reached. In this regard, it is noteworthy that this apparent regioconvergence was not observed using Method I. Hence, treating (*E*)-**1h** with a neutral rhodium catalyst at 120 °C gave **2h** in only 30 % yield, whereas (*E*)-**1h** was recovered in 50 % yield. Isomer (*Z*)-**1h** was more reluctant to undergo the rearrangement under the same neutral conditions, and we recovered (*Z*)-**1h** mostly intact (70 % yield), without a trace of (*E*)-**1h** according to ^{1}H NMR analysis. The cationic nature of the rhodium catalyst used in Scheme 3 therefore seems critical to the observed regioconvergence.

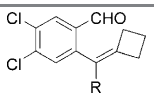
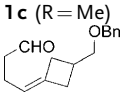
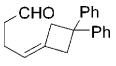
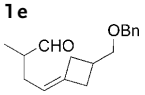
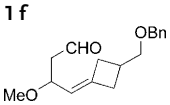


Scheme 3. Apparent regioconvergence of the rearrangement. Reaction of a) (*E*)-**1h** and b) (*Z*)-**1h**.

Table 1: Rhodium-catalyzed C–H activation/β-carbon elimination to access cyclooctenones.[a]



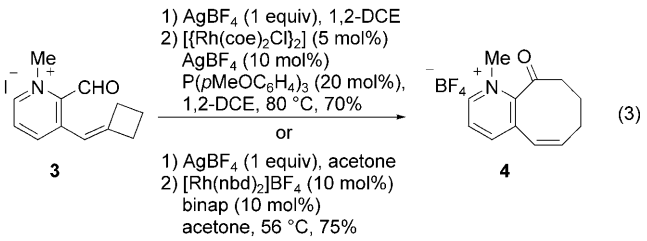
1b-1g **2b-2g**

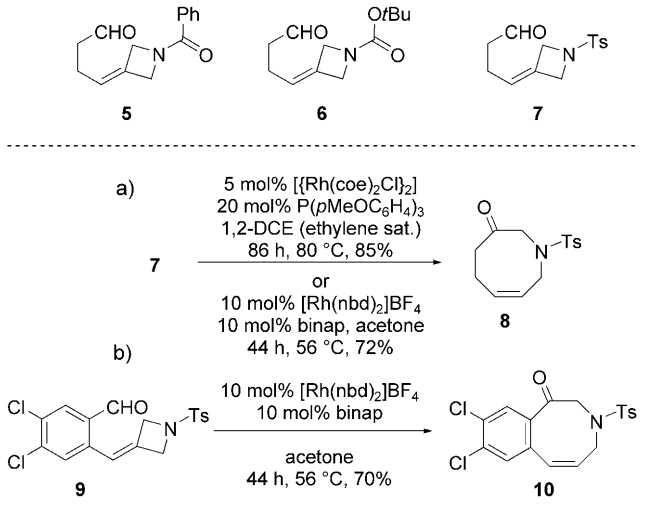
Entry	Substrate	Product	Method	*t* [h]	Yield [%]
					
1	**1b** (R = H)	**2b**	I	17	92
2	**1b** (R = H)	**2b**	II	0.5	89
3	**1c** (R = Me)	**2c**	–[b]	24	0[c]
					
4	**1d**	**2d**	II[d]	16	69[e]
					
5	**1e**	**2e**	II[f]	22	79
					
6	**1f**	**2f**	I[g]	86	75
7	**1f**	**2f**	III[d]	25	71[h]
					
8	**1g**	**2g**	III[d]	24	75

[a] Yields of isolated products. [b] All methods (I–III) employed 10 mol% catalyst. [c] Recovered **1c** in 87–95% yield. [d] Used 5 mol% catalyst. [e] Recovered **1d** in 16% yield. [f] Used 10 mol% catalyst. [g] Used 15 mol% catalyst. [h] Recovered **1f** in 16% yield. Bn = benzyl.

No reaction was observed when a pyridine group was embedded within the substrate. We reasoned that this could be because of the irreversible trapping of the active catalyst by the lone pair of electrons on the nitrogen atom. Accordingly, this limitation was easily circumvented by alkylation of the pyridine and counteranion exchange [Eq. (3)]. Hence, substrate **3** afforded compound **4** in yields ranging from 70 to 75 % in the presence of cationic rhodium catalysts.

The detrimental effect of the lone pair of electrons, on the nitrogen atom, upon reactivity prompted us to install electron-withdrawing groups on the nitrogen atom of aldehyde-tethered 3-alkylideneazetidines when we turned our attention to these substrates (Scheme 4). However, treating





Scheme 4. Preparation of eight-membered heterocycles through rhodium-catalyzed rearrangement of aldehyde-tethered 3-alkylidene-azetidines. a) Compound **7** reacts under either of two sets of reaction conditions. b) Aryl-containing substrates also undergo the C–H/C–C activation sequence. Ts = *para*-toluenesulfonyl.

amide **5** or carbamate **6** with rhodium catalysts according to Methods I–III gave poor results, and some decomposition was observed. In contrast, changing the protective group to a tosyl (4-toluenesulfonyl) group gave much better results. Hence, compound **8** was isolated in good yields after exposure of **7** to either neutral or cationic rhodium catalysts according to Methods I and III (Scheme 4 a). Similarly, aromatic substrate **9** gave **10** in good yield upon isolation (Scheme 4 b).

In conclusion, we have demonstrated that by using simple and stable aldehydes as starting materials, the strain energy of simple cyclobutanes and azetidines can be exploited through rhodium-catalyzed β-carbon elimination. To the best of our knowledge, previous reports of metal-mediated ring opening of azetidines are extremely scarce and describe only β-nitrogen elimination.[13] Hence, the β-carbon elimination of azetidines proposed between putative intermediates **C** and **D** (Scheme 1), and exemplified herein in Equation (3), suggests the possibility of new transition-metal-catalyzed reactions with these substrates. Moreover, this study opens new access to eight-membered rings and expands the scope of rhodium-catalyzed intramolecular hydroacylation.[6,14] Additional mechanistic investigation of the regioconvergent ring opening of alkylidenecyclobutanes is currently ongoing in our laboratories.

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[11] Treatment of **1a** with only $AgBF_4$ (10 mol%) or with $AgBF_4$ (10 mol%) and $P(pMeOC_6H_4)_3$ (10 mol%) in refluxing 1,2-DCE led to complete degradation of the starting material.

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