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Hydroformylation Reaction of Alkylidenecyclopropane Derivatives: A New Pathway for the Formation of Acyclic Aldehydes Containing Quaternary Stereogenic Carbons

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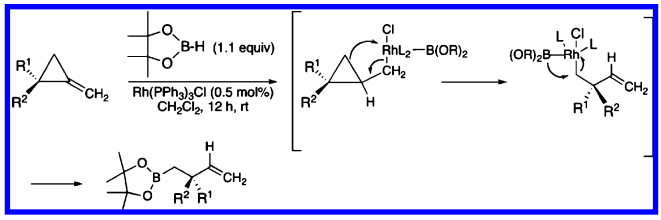
Metal-catalyzed cleavage of carbon−carbon bonds is a field of much current interest since it can lead to the design of new, selective, and efficient processes for the utilization of hydrocarbons.[1] Although the activation of C−C single bonds of high energy molecules such as strained three-membered rings is a relatively old process, the stereoselective carbon−carbon bond activation of alkylidenecyclopropanes (ACPs), through transition metal catalysts,[2] has emerged only lately as an efficient tool in the synthesis of functionalized linear products.[3] In this context, we have recently reported the regioselective rhodium-catalyzed hydroboration, hydrosilylation, and palladium-catalyzed hydrostannation of ACPs as a new access to acyclic building blocks possessing quaternary stereogenic centers. In all these reactions, an anti-Markovnikov addition of an organometallic derivative HML_n, generated from the reaction of H−X (X = BPin, $SiMe_2Ph$, $SnBu_3$) with a transition metal catalyst, occurs on the exomethylenic double bond of the ACP and is followed by a regioselective ring-opening reaction through a selective C−C bond cleavage (see Scheme 1 for the rhodium-catalyzed hydroboration reaction).[4]

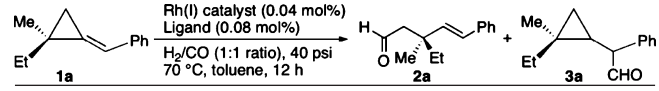
Scheme 1. Rhodium-Catalyzed Hydroboration of ACPs



The transition-metal-catalyzed reaction of carbon monoxide and hydrogen with an alkene, namely the hydroformylation reaction,[5] a one-step transformation of an olefin to an aldehyde having one more carbon, is one of the world's largest homogeneously catalyzed processes in industry and is an extremely important tool for organic synthesis.[6] Surprisingly, the hydroformylation reaction of methylenecyclopropanes was only reported in an in situ infrared spectroscopic study without any synthetic use.[6c] This might arise from the difficulties in controlling the selectivity throughout the course of the hydroformylation of such strained rings.[7] Therefore, we recently questioned whether it might be possible to develop first a clean and reliable hydroformylation reaction of ACPs into acyclic aldehydes and then if the stereochemical integrity of the pre-existing stereogenic center in the ACP would be preserved during the reaction sequence. If so, versatile aldehydes that would be produced could serve as an important building block possessing a quaternary stereogenic carbon for a variety of other products since aldehyde moieties can be easily converted into alcohols, amines, carboxylic acid derivatives, aldol condensation, and many others.[8]

We initially concentrated our efforts to control the selectivity of the hydroformylation reaction with a standard racemic alkylidenecyclopropane **1a** (Table 1). When **1a** was treated with syngas (40 psi) in the presence of a catalytic amount of rhodium acetylacetonate dimer (0.04 mol %) in toluene, using *bis*diphenylphosphinopropane (bppp) as ligand (0.08 mol %) and heated to 70 °C for 12 h, **2a** was obtained as a single product of *E*-configuration but with a low 20% conversion (Table 1, entry 1). However, under the same experimental conditions, the transformation of **1a** is quantitative by using the more classical $Rh(acac)(CO)_2$ catalyst (Table 1, entry 2), but a mixture of two products **2a/3a** was obtained in a 60/40 ratio respectively. In contrast, the combination of $Rh(CO)_2(acac)$ with xantphos as ligand gave mainly the cyclopropylcarboxaldehyde **3a** as two diastereomers (Table 1, entry 3). Only when the electron-rich *bis*diphenylphosphinoferrocene (bppf) was used as ligand, the linear ring-opening product **2a** was obtained with complete conversion as a unique regioisomer (selective ring-opening) and stereoisomer (selective *E*-double bond) without traces of **3a** (Table 1, entry 4).

Table 1. Optimization of Rhodium-Catalyzed Hydroformylation of ACPs



Entry	Catalyst	Ligand	Products	Conversion[a]
1	$Rh_2(acac)_2$	bppp	**2a**	20%
2	$Rh(acac)(CO)_2$	bppp	**2a**:**3a** (60:40)	>99%
3	$Rh(acac)(CO)_2$	xantphos	**2a**:**3a** (10:90)	>99%
4	$Rh(acac)(CO)_2$	bppf	**2a** only	>99%

[a] The conversion and ratio between products **2a** and **3a** was determined by ^1H NMR of the crude reaction mixture. **3a** was obtained as 2 diastereoisomer in a 1/1 ratio.

Having such efficient conditions for the hydroformylation reaction, we investigated the scope of the reaction for several diversely substituted methylene- and alkylidenecyclopropane derivatives as described in Table 2. We were pleased to see that the reaction proceeds smoothly in all cases in good to excellent yields. For alkylidenecyclopropanes possessing one substituent on the double bond (Table 2, entries 1 to 5) as well as two substitutents (Table 2, entries 10 and 11), the fate of the stereochemistry of the double bond in the product was questioned. When the alkylidenecyclopropane possesses one aromatic substituent on the double bond (R^3 = aryl and R^4 = H, Table 2, entries 1 and 2), a single product of *E*-configuration was produced. When the alkylidenecyclopropane has a sterically hindered alkyl group as in entry 3, a high *E*/*Z* ratio was obtained but the stereoselectivity is poor when the double bond is substituted with one aliphatic group (Table 2, entries 4 and 5) or with two different susbstituents (Table 2, entries 10 and 11).

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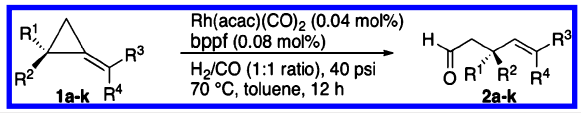
Table 2. Hydroformylation of MCPs and ACPs

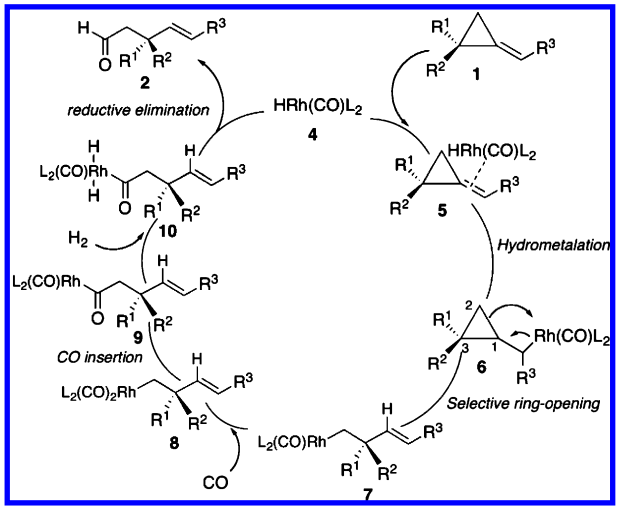


Entry	R^1	R^2	R^3	R^4	Product	*E*/*Z*[a]	Yield[b]
1 (**2a**)	Me	Et	Ph	H	**2a**	100/0	85
2 (**2b**)	Me	Bu	Tol	H	**2b**	100/0	87
3 (**2c**)	Me	Et	$CH(Ph)_2$	H	**2c**	96/4	90
4 (**2d**)	Me	Ph	$(CH_2)_2Ph$	H	**2d**	60/40	85
5 (**2e**)	Ph	Et	Me	H	**2e**	60/40	88
6 (**2f**)	Bu	Hex	H	H	**2f**	–	93
7 (**2g**)	Me	Ph	H	H	**2g**	–	91
8 (**2h**)	Ph	Et	Me	Me	**2h**	–	81
9 (**2i**)	Me	Et	Ph	Ph	**2i**	–	83
10 (**2j**)	Me	Et	Naphtyl	Me	**2j**	50/50	91
11 (**2k**)	Me	Et	Ph	Me	**2k**	50/50	90

[a] *E*/*Z* ratios were determined by ^{1}H NMR [b] Isolated yields after purification by column chromatography.

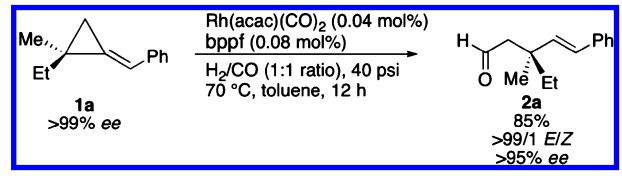
A postulated reaction pathway for the regioselective hydroformylation reaction of an alkylidenecyclopropane is described in Scheme 2.[9] A coordinatively unsaturated $HRh(CO)L_2$ **4** *in situ* generated forms a π-olefin-Rh complex **5** with **1** that then becomes the Rh complex **6** *via* hydrometalation reaction. A selective ring-opening proceeds (selective cleavage of the C_1-C_2 bond without any trace of C_1-C_3 fragmentation). Carbon monoxide coordinates to **7** to form the saturated alkyl rhodium complex **8**, and a migratory insertion takes place to give the unsaturated acyl-Rh **9**. Oxidative addition of molecular hydrogen to **9** gives the acyl-Rh dihydride **10**, and after reductive elimination, the aldehyde **2** is produced and the active catalyst **4** is regenerated. It is worth mentioning that in the presence of bppf, the selective splitting of the C−C bond is faster as compared to CO/H_2 insertion and reductive elimination, since no cyclopropylcarboxaldehydes **3** were detected in the crude reaction mixture.

Scheme 2. Mechanistic Hypothesis for the Hydroformylation of ACP



To further probe the utility of the hydroformylation reaction of alkylidenecyclopropanes in organic synthesis, the transformation of easily obtained enantiomerically pure alkylidenecyclopropane[10] **1a** into a linear aldehyde possessing the challenging enantiomeric enriched quaternary stereogenic carbon center[11] was achieved as described in Scheme 3.

Scheme 3. Formation of Enantioenriched Aldehyde Possessing Quaternary Carbon Center



In conclusion, we have reported the first example of a rhodium-catalyzed hydroformylation reaction of methylene- and alkylidenecyclopropane derivatives under mild conditions and low catalyst loading. One of the most remarkable features of this reaction is the high selectivity of the catalytic process that results in the exclusive formation of the expected linear aldehydes, and the stereointegrity of the quaternary carbon center remains unaffected in the process.

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Supporting Information Available: Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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