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Rh-Catalyzed Carbonyl Hydroacylation: An Enantioselective Approach to Lactones

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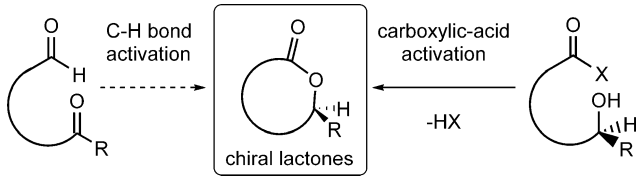
The ester is a prevalent motif found in diverse synthetic and biological architectures, from fatty acid triesters to macrolide antibiotics. Nature uses enzymes (e.g., polyketide synthase) to form ester bonds by coupling alcohols to activated thioesters.[1] The majority of synthetic approaches to constructing esters involve this same *natural* carbon−oxygen bond formation. For example, many stoichiometric reagents, including Corey-Nicolaou's PySSPy and Yamaguchi's acid chloride, have been developed to activate carboxylic acids and achieve macrolactonizations.[2] We envisioned a fundamentally different approach to lactonization based on the ability of Rh(I) complexes to activate the C−H bond of aldehydes (Scheme 1). Herein, we report a novel and atom economical strategy for making chiral lactones starting from keto-aldehydes. In contrast to conventional strategies, this ester synthesis features an unprecedented regio- and enantioselective carbonyl hydroacylation.

Scheme 1. An Atom Economical Strategy for Lactonization

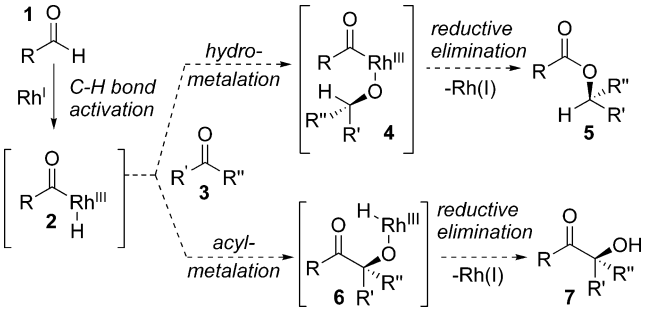


While the Rh-catalyzed hydroacylation of alkenes and alkynes has been reported,[3] the analogous hydroacylation of carbonyl compounds, specifically prochiral ketones, has been virtually unexplored.[4] Since Tsuji's discovery,[5] it has become well-established that Rh(I) complexes can undergo oxidative addition of aldehydes **1** to form acyl-Rh(III) intermediates **2** (Scheme 2).[6] We hypothesized that, in the presence of a ketone, intermediate **2** could react via two regio-divergent pathways: a "Tishchenko-type"[7] or a "benzoin-type" hydroacylation.[8] In the Tishchenko-type hydroacylation, **2** undergoes hydrometalation of ketone **3** to form organorhodium intermediate **4**. Subsequent reductive elimination from **4** would yield the desired chiral ester **5**. Conversely, intermediate **2** could undergo acylmetalation of carbonyl **3** to form a rhodium-alkoxide **6**. Reductive elimination from **6** would generate α-hydroxy ketone **7**, the formal benzoin product.

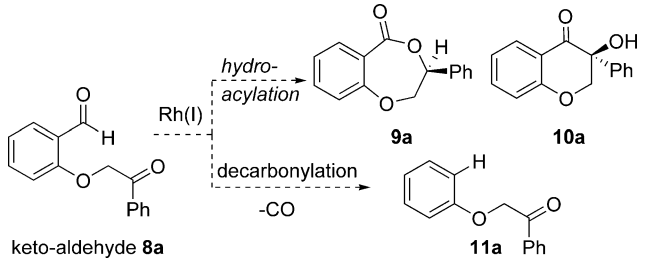
For our initial investigation of the proposed lactonization, we chose readily available keto-aldehyde **8a** as the test substrate (Scheme 3).[9] Intramolecular hydroacylation of **8a** could yield a seven-membered ring lactone **9a** and/or the six-membered ring chromanone **10a**.[10] The Rh-promoted decarbonylation of **8a** to form benzene derivative **11a** would be a competing and nonproductive pathway. Based on previous studies,[11] we considered that the coordinating ability of the ether-oxygen in **8a** could help suppress decarbonylation and facilitate hydroacylation.

A number of catalysts were examined to achieve regio- and enantioselective hydroacylation of **8a**, including the use of cationic Rh(I) salts and various phosphine ligands, in dichloroethane at

Scheme 2. Proposal for Tishchenko versus Benzoin Hydroacylation



Scheme 3. Competing Transformations for Model Substrate



120 °C. An illustrative study of six chiral diphosphine ligands is shown in Table 1. These ligands are listed in order of increasing basicity to highlight a trend between phosphine basicity and catalyst selectivity (*cf* entry 1−6). (*R*)-Ph-MeOBIPHEP (**12**) (the least basic phosphine in this series) was ineffective at promoting hydroacylation. Use of ligand **12** resulted in complete decarbonylation (98% yield **11a**, entry 1). (*R*)-Ar-MeOBIPHEP **13** is structurally related to **12**, except that **13** is more basic and sterically encumbering due to the presence of the substituted-aryl rings on phosphine (Ar = 3,5-*t*-Bu-4-MeOC_6H_2). Remarkably, catalyst [Rh(**13**)]BF_4 transformed **8a** into lactone **9a** in 63% yield and 95% ee. While formal benzoin product **10a** was not observed, decarbonylated product **11a** was formed in 31% yield (entry 2). By using the more electron-rich biphenyl-phosphine ligand (*R*)-DTBM-SEGPHOS **14**, hydroacylation efficiency was improved without compromising enantioselectivity (76% yield **8a**, 96% ee, no **10a**, and 22% yield **11a**, entry 3).

Based on this trend, we studied several alkyl-substituted phosphine ligands which were expected to further improve reaction efficiency due to their increased phosphine basicity. As anticipated, achiral ligand 1,3-bis(diphenylphosphino)propane (dppp) enabled Rh-catalyzed hydroacylation of **8a** to yield **9a** exclusively in 96% yield. However, a chiral analogue of dppp, (*S*,*S*)-BDPP **15**, gave only 4% ee and 67% yield of **9a** (entry 4). (*R*,*R*)-Me-Duphos **16** also afforded lactone **9a** with excellent efficiency (95% yield) albeit in 82% ee (entry 5). (*R*,*R*)-Me-BPE **17**, the most basic ligand in this series, appears to be too electron-rich, affording sluggish

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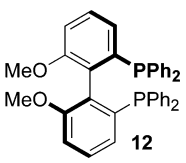
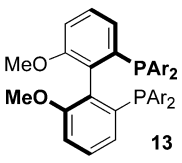
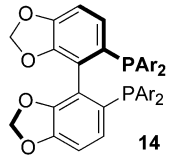
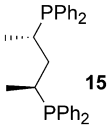
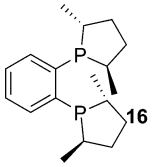
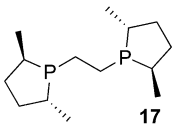
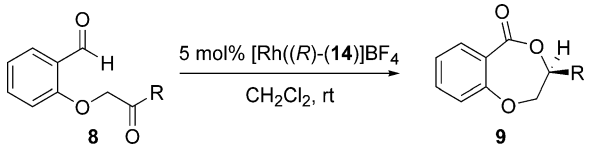
Table 1. Phosphine Effect on Catalytic Selectivity[a]

entry:	1	2	3
ligand:	 **12**	 **13**	 **14**
		Ar = 3,5-*t*-Bu-4-MeOC$_6$H$_2$	
yield **9a**:	<1%	63%	76%
ee **9a**:	n/a	95% ee	96% ee
yield **11a**:	98%	31%	22%

entry	4	5	6
ligand:	 **15**	 **16**	 **17**
yield **9a**:	67%	95%	46%
ee **9a**:	4% ee	82% ee	76% ee
yield **11a**:	33%	<5%	6%

[a] General conditions: **8a**, 5 mol % [Rh(Ligand)]BF$_4$, dichloroethane, 120 °C, 3 d in a sealed tube. Yields based on integration by ^{1}H NMR. Formal benzoin product **10a** was not observed under these conditions. Enantiomeric excess determined by chiral HPLC.

Table 2. Intramolecular Hydroacylation of Various Ketones



8 **9**

entry	R	lactone	time (d)	% yield[a]	% ee[b]	% decarbon.[c]
1	Ph	**9a**	3	92	99	7
2	4-Cl−Ph	**9b**	2	89	99	7
3	2-naphthyl	**9c**	2	85	99	9
4	Me	**9d**	2	91	99	6
5	*n*-Bu	**9e**	2	99	>99	0
6	Bn	**9f**	3.5	93	>99	0
7	*i*-Pr	**9g**	1.5	98	>99	0
8	*t*-Bu	**9h**	1.5	94	>99	0

[a] Isolated yields. [b] Determined by chiral HPLC. [c] Decarbonylated product yields based on ^{1}H NMR integration relative to product peaks.

reactivity (46% yield **9a**, 6% yield **11a**) and moderate enantioselectivity (76% ee) (entry 6).

By varying the solvent and temperature, we found that use of catalyst [Rh((*R*)-(**14**)]BF$_4$ in dichloromethane at room temperature afforded optimal results. Under these conditions, lactone **9a** was formed in 92% yield and 99% enantiomeric excess, while decarbonylated product **11a** was formed in only 7% yield (Table 2, entry 1). Next, we investigated the scope of the reaction by varying the substituents on the prochiral ketone component (Table 2). Other aromatic ketones (e.g., R = 4-Cl−Ph and 2-naphthyl) were hydroacylated to form the corresponding lactones in good yields and excellent enantioselectivities (entries 2 and 3). Aliphatic ketones bearing substituents of varying sizes were also transformed with remarkable efficiency. The methyl substituted ketone underwent hydroacylation to form lactone **9d** in 91% yield and 99% ee (entry 4). Notably, *n*-butyl, benzyl, *i*-Pr, and *tert*-butyl substituted lactones were isolated in high yields (≥93%) as essentially single enantiomers (>99% ee, entries 5−8). Single-crystal X-ray analysis of chloro-substituted lactone **9b** reveals the absolute configuration to be the *S*-configuration as depicted.

In summary, we have designed and executed a new approach to forming chiral lactones. This C−H bond functionalization strategy involves an unprecedented Rh-catalyzed hydroacylation of ketones. The basicity of the phosphine ligand plays a critical role in promoting hydroacylation over competitive decarbonylation. Intramolecular hydroacylation of keto-aldehydes **8** occurs with complete regiocontrol to yield formal Tishchenko lactones in large enantiomeric excess. Further scope and mechanistic studies are underway to determine the origin of regio- and enantioselectivity in this transformation.

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Supporting Information Available: Experimental procedures, X-ray crystallographic data, and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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