

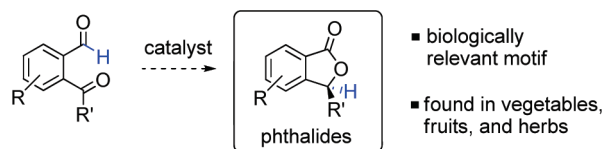
## Phthalides by Rhodium-Catalyzed Ketone Hydroacylation

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Phthalide natural products show a range of bioactivity, from enhancing flavors to slowing memory loss.<sup>1</sup> Although diverse in function, these phytochemicals share a common structure: a benzene ring fused to a  $\gamma$ -lactone. Significant effort has been focused on synthesizing phthalides,<sup>2</sup> but most asymmetric methods require chiral auxiliaries<sup>2a,b</sup> or chiral organometallics,<sup>2c,d</sup> few are catalytic,<sup>2e-i</sup> and none is atom-economical.<sup>3</sup> Toward addressing this challenge, herein we report an efficient and complementary route to phthalides by enantioselective ketone hydroacylation. While hydroacylation of olefins to form cyclopentanones is well-studied,<sup>4</sup> hydroacylation of ketones to form five-membered lactones remains to be explored.<sup>5</sup>

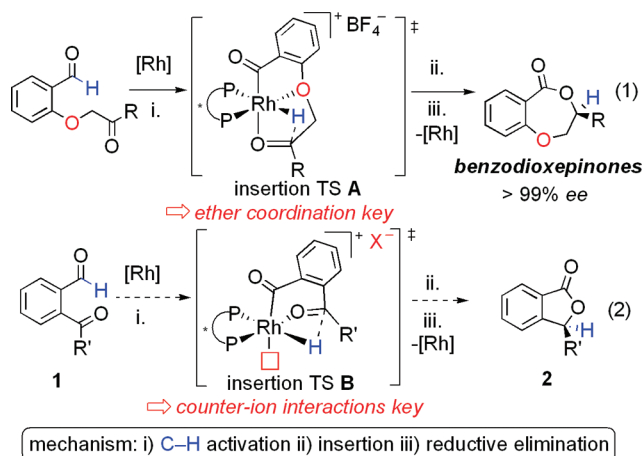


We recently reported that intramolecular hydroacylation is a promising approach to chiral lactones.<sup>6</sup> However, our catalyst, [Rh(DTBM-Segphos)]BF<sub>4</sub>, was tailored for making seven-membered lactones, specifically benzodioxepinones (eq 1 in Scheme 1). Mechanistic studies revealed the turnover-limiting step to be insertion of the ketone C=O bond to the rhodium hydride via transition state **A**.<sup>6b</sup> In **A**, the ether oxygen is coordinated to Rh, and this coordination is critical for promoting insertion over competitive decarbonylation. Indeed, our previous protocol was limited in scope to ketoaldehydes bearing an ether linkage. On the basis of these studies, we imagined 2-ketobenzaldehydes **1** undergoing hydroacylation to form phthalides by an analogous pathway via a distinct transition state **B** (eq 2 in Scheme 1). In **B**, one coordination site would be available for solvent, ligand, or counterion binding. Thus, finding a new catalyst would be critical for promoting the desired reactivity over decarbonylation.

With this mechanism in mind, we set out to develop a Rh catalyst for the preparation of phthalides by varying both the bisphosphine ligand and counterion. Our initial study focused on cyclizing model substrate **1a** into lactone **2a** preferentially over the decarbonylation product **3a** (eq 3 in Table 1). In the absence of catalyst, **1a** was recovered (Table 1, entry 1). After evaluating many chiral phosphines, we identified Duanphos as a promising ligand.<sup>7</sup> With this bulky, electron-rich phosphine, we studied counterions with various coordinating strengths (SbF<sub>6</sub><sup>−</sup> < BF<sub>4</sub><sup>−</sup> < OTf<sup>−</sup> < OMs<sup>−</sup> < NO<sub>3</sub><sup>−</sup> < Cl<sup>−</sup>)<sup>8</sup> (entries 2–8).

This study revealed marked counterion effects on reactivity. Catalysts with more strongly coordinating counterions gave better selectivity for hydroacylation over decarbonylation, with yields increasing from 30 to 97%. These counterions also impacted asymmetric induction, with *ee*'s ranging from 29 to 97%. The cationic complexes appeared to be more reactive than the neutral Rh chloride catalyst. For example, with triflate, hydroacylation was complete in less than 30 min with 10 mol % catalyst (>95% yield, 81% *ee*; entry 4). In contrast, with chloride, the same transformation

Scheme 1. Mechanistic Rationale for Ketone Hydroacylation

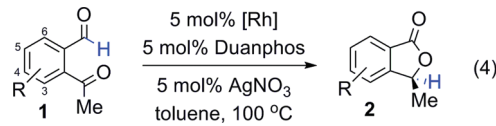
Table 1. Developing a Rh Catalyst for Phthalide Synthesis: Counterion Effects on Reactivity<sup>a</sup>

entry	mol % Rh	counter-ion X	2a (%) <sup>b</sup>	ee (%) <sup>f</sup>	3a (%) <sup>b</sup>	time
1	none	none	0	--	0	1 d
2	10	SbF <sub>6</sub>	30	40	52	1 d
3	10	BF <sub>4</sub>	76	29	24	1 d
4	10	OTf	>95	81	<5	0.5 h
5	10	OMs	>95	91	trace	10 h
6	10	NO <sub>3</sub>	>95	97	trace	7 h
7 <sup>c</sup>	5	NO <sub>3</sub>	97 <sup>e</sup>	97	trace	1 d
8 <sup>d</sup>	10	Cl	92 <sup>e</sup>	97	trace	3 d

<sup>a</sup> Reaction scale: 0.1 mmol of **1a**. <sup>b</sup> Based on <sup>1</sup>H NMR integration.<sup>c</sup> Using 0.2 mmol of **1a** at 100 °C. <sup>d</sup> No silver salt was added. <sup>e</sup> Isolated yields. <sup>f</sup> Determined by chiral HPLC.

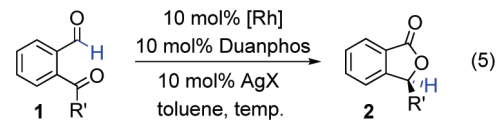
required 3 days with 10 mol % catalyst (97% yield, 97% *ee*; entry 8). We chose AgNO<sub>3</sub> as the optimal additive; nitrate is less strongly coordinating than chloride (giving shorter reaction times) but coordinating enough to suppress decarbonylation and assist in enantioinduction.<sup>8b–d</sup> Use of 5 mol % AgNO<sub>3</sub> and 5 mol % Rh afforded phthalide **2a** in 97% yield and 97% *ee* (entry 7).

To examine catalyst scope, we prepared a series of 2-ketobenzaldehydes **1** with varying substitution on the aromatic backbone. Substituents were tolerated at the 4-, 5-, and 6-positions of the ring (Table 2, entries 2–10). Substrates bearing electron-donating (e.g., *t*-Bu, MeO) and electron-withdrawing (e.g., Cl, NO<sub>2</sub>, CO<sub>2</sub>Me) substituents underwent hydroacylation in 67–97% yields and 92–98% *ee*'s. However, steric bulk at the 3-position of the

**Table 2.** Hydroacylation of Substituted Ketoaldehydes<sup>a</sup>


entry	R	iso. yield of <b>2</b> (%)	ee (%) <sup>d</sup>	time (day)
1	H ( <b>1a</b> )	97 ( <b>2a</b> )	97	1
2	4-Me ( <b>1b</b> )	88 ( <b>2b</b> )	96	2
3 <sup>b</sup>	4-OMe ( <b>1c</b> )	84 ( <b>2c</b> )	96	3
4	5-Me ( <b>1d</b> )	91 ( <b>2d</b> )	92	2
5	5- <i>t</i> -Bu ( <b>1e</b> )	84 ( <b>2e</b> )	98	2
6	5-Cl ( <b>1f</b> )	67 ( <b>2f</b> )	95	1
7	5-NO <sub>2</sub> ( <b>1g</b> )	94 ( <b>2g</b> )	93	1
8	5-CO <sub>2</sub> Me ( <b>1h</b> )	94 ( <b>2h</b> )	95	1
9	6-OMe ( <b>1i</b> )	5 ( <b>2i</b> )	—	1
10 <sup>c</sup>	6-OMe ( <b>1i</b> )	78 ( <b>2i</b> )	97	3
11	3-Me ( <b>1j</b> )	<5 ( <b>2j</b> )	—	1

<sup>a</sup> Conditions: 0.2 mmol of substrate. <sup>b</sup> Using 0.1 mmol of substrate and 10 mol % catalyst; the <sup>1</sup>H NMR yield is given. <sup>c</sup> Using 10 mol % catalyst and no AgNO<sub>3</sub>. <sup>d</sup> Determined by chiral HPLC.

**Table 3.** Intramolecular Hydroacylation of Various Ketones<sup>a</sup>


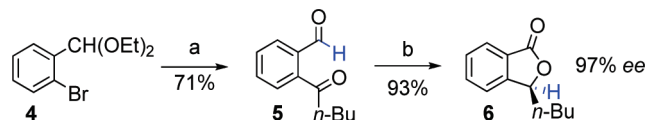
entry	R'	X	iso. yield (%)	ee (%) <sup>d</sup>	T (°C)	time (day)
1 <sup>b</sup>	Et ( <b>1k</b> )	NO <sub>3</sub>	94 ( <b>2k</b> )	96	100	2.5
2 <sup>c</sup>	<i>i</i> -Pr ( <b>1l</b> )	NO <sub>3</sub>	83 ( <b>2l</b> )	97	75	3.5
3	C <sub>6</sub> H <sub>5</sub> ( <b>1m</b> )	OMs	81 ( <b>2m</b> )	93	90	3
4	4-OMeC <sub>6</sub> H <sub>4</sub> ( <b>1n</b> )	OMs	93 ( <b>2n</b> )	96	90	3
5	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>1o</b> )	OMs	88 ( <b>2o</b> )	92	90	3
6	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>1o</b> )	NO <sub>3</sub>	22 ( <b>2o</b> )	89	90	3
7	4-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>1o</b> )	OTf	48 ( <b>2o</b> )	13	90	3
8	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ( <b>1p</b> )	OTf	92 ( <b>2p</b> )	96	75	3
9	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> ( <b>1p</b> )	OMs	25 ( <b>2p</b> )	—	90	3

<sup>a</sup> Conditions: 0.1 mmol of substrate. <sup>b</sup> Using 0.2 mmol of substrate and 7 mol % catalyst. <sup>c</sup> Using 0.2 mmol of substrate and 15 mol % catalyst. <sup>d</sup> Determined by chiral HPLC.

2-ketobenzaldehyde prohibited reactivity (<5% yield; entry 11). In the case of aldehyde **1i**, using the Rh nitrate catalyst resulted in poor reactivity (5% yield; entry 9), while the Rh chloride catalyst was effective (78% yield, 97% ee; entry 10). With Rh nitrate, we imagine that the *o*-methoxy group competes with the ketone carbonyl by coordinating to Rh and preventing the proper geometry for insertion. With Rh chloride, this methoxy coordination must be more dynamic, thus allowing for ketone insertion.

Next, we varied the substituent (R') on the prochiral ketone (eq 5 in Table 3). Ketones with substituents larger than methyl underwent hydroacylation with high enantioselectivity but required increased catalyst loading (Table 3). Ethyl ketone **1k** cyclized to phthalide **2k** (94% yield, 96% ee; entry 1) and isopropyl ketone **1l** to **2l** (83% yield, 97% ee; entry 2). In studying biaryl ketones, we observed counterion effects that were remarkably substrate-specific. For the biaryl ketones **1m** (R' = Ph) and **1n** and **1o** (R' = phenyl with electron-donating groups), mesylate was the best counterion (81–93% yield, 92–96% ee; entries 3–5), while nitrate and triflate resulted in poor results (entries 6 and 7). In contrast, ketone **1p** (R' = phenyl with an electron-withdrawing group) forms lactone **2p** more efficiently with AgOTf (92% yield, 96% ee; entry 8) than AgOMs (25% yield; entry 9).<sup>10</sup>

Lastly, we present an asymmetric synthesis of the natural product (S)-(-)-3-*n*-butylphthalide (**6**).<sup>2a</sup> This phthalide is responsible for the flavor of celery, and its racemate was in phase-III clinical trials

**Scheme 2.** Total Synthesis of Celery Extract (S)-(-)-3-*n*-Butylphthalide (**6**)<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) MeN(OMe)(C=O)*n*-Bu, 1.6 M *n*-BuLi, THF, -78 °C to rt, overnight, then 2 M HCl(aq), rt, 3 h; (b) 5 mol % [Rh(cod)Cl]<sub>2</sub>, 10 mol % (S,S,R,R)-Duanphos, 10 mol % AgNO<sub>3</sub>, toluene, 75 °C, 3 days.

for treating strokes.<sup>9</sup> As shown in Scheme 2, we converted commercial acetal **4** to ketoaldehyde **5** in 71% yield in one pot. In the presence of [Rh((S,S,R,R)-Duanphos)]NO<sub>3</sub>, **5** cyclized to phthalide **6** in 93% yield and 97% ee.

In conclusion, we have reported an atom-economical approach to phthalides by enantioselective C–H bond functionalization. A hydroacylation catalyst for making five-membered lactones has been discovered. The appropriate choice of counterion was crucial in suppressing decarbonylation and controlling enantioselectivity. Mechanistic studies to better understand the counterion effects and develop future carbonyl hydroacylations are underway.

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**Note Added after ASAP Publication.** The yield of **2a** was corrected in Table 2 on October 14, 2009.

**Supporting Information Available:** Experimental procedures, characterization data for new compounds, and chiral chromatographic analyses. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (10) Phthalide **2p** was observed to epimerize in polar solvent over time (see the Supporting Information for details).

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