Literature Report (10)

Enantioselective Hydroacylation of Ketones

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Date: 2016/09/26

Dong, V. M. *et al*.
J. Am. Chem. Soc. **2016**, *138,* 12013.

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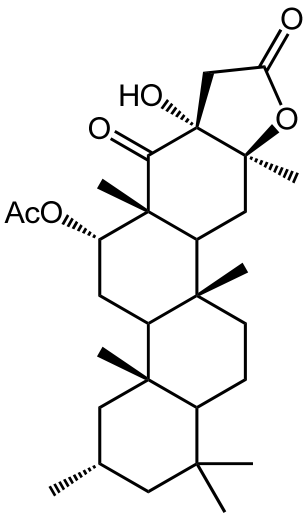
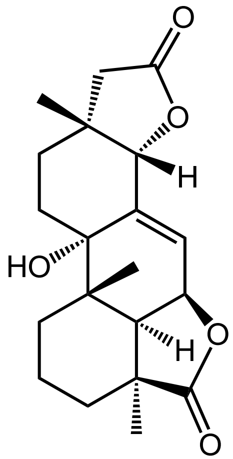
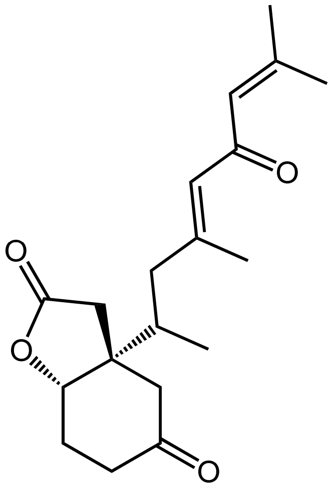
Introduction



(+)-Hyatelone A



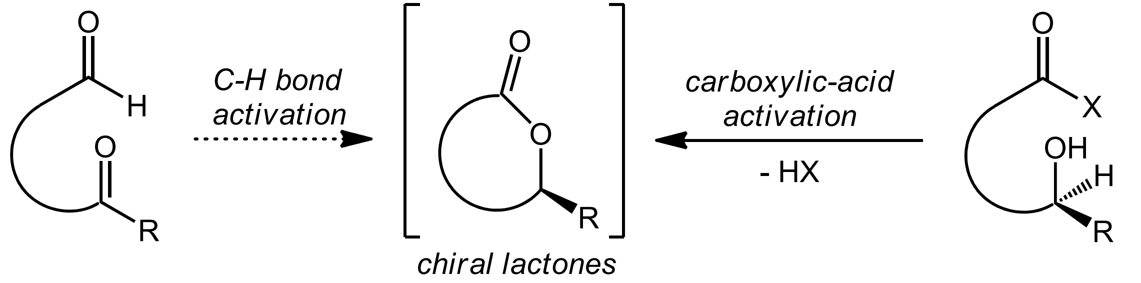
(-)-Xylallantin B



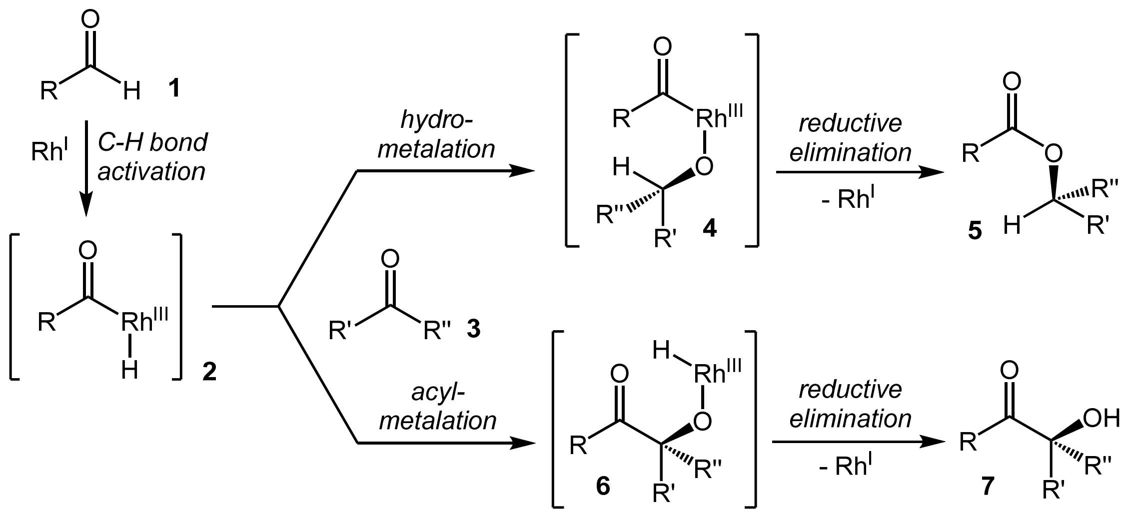
(-)-Panamomon B

Rh-Catalyzed Enantioselective Hydroacylation of Ketones

An atom economical strategy for lactonization

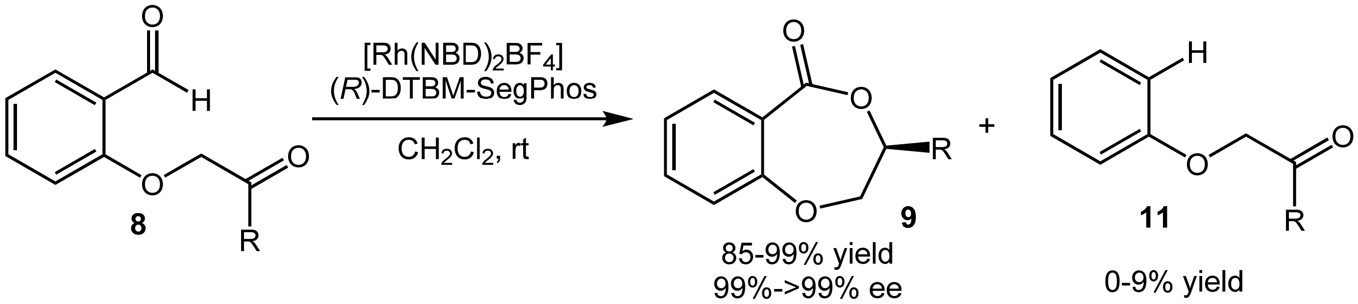


Proposal for Tishchenko versus benzoin hydroacylation

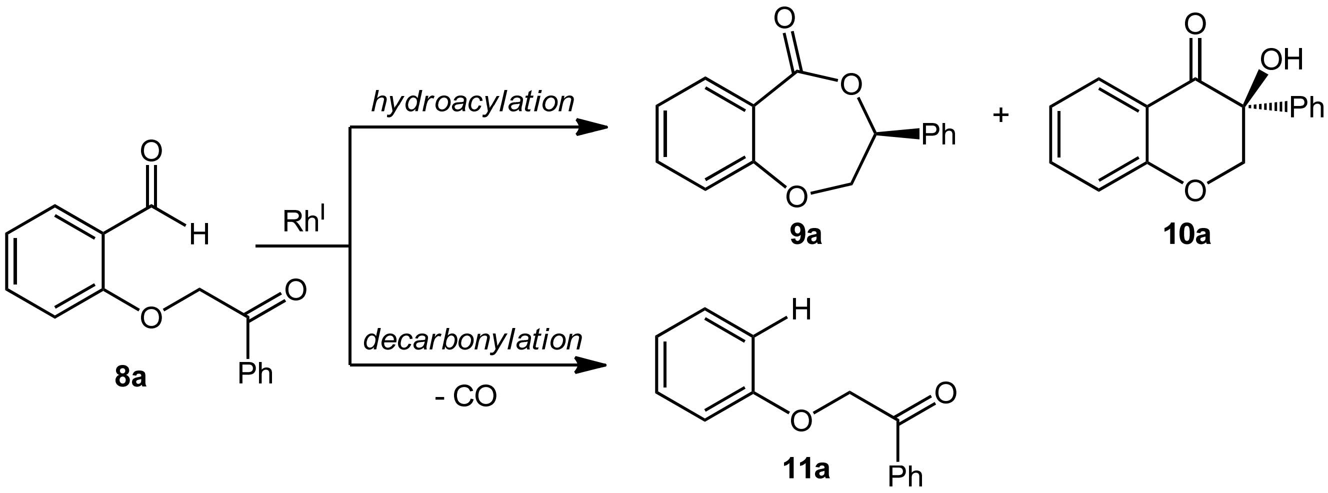


Dong, V. M. *et al. J. Am. Chem. Soc.* **2008**, *130*, 2916.

Rh-Catalyzed Enantioselective Hydroacylation of Ketones

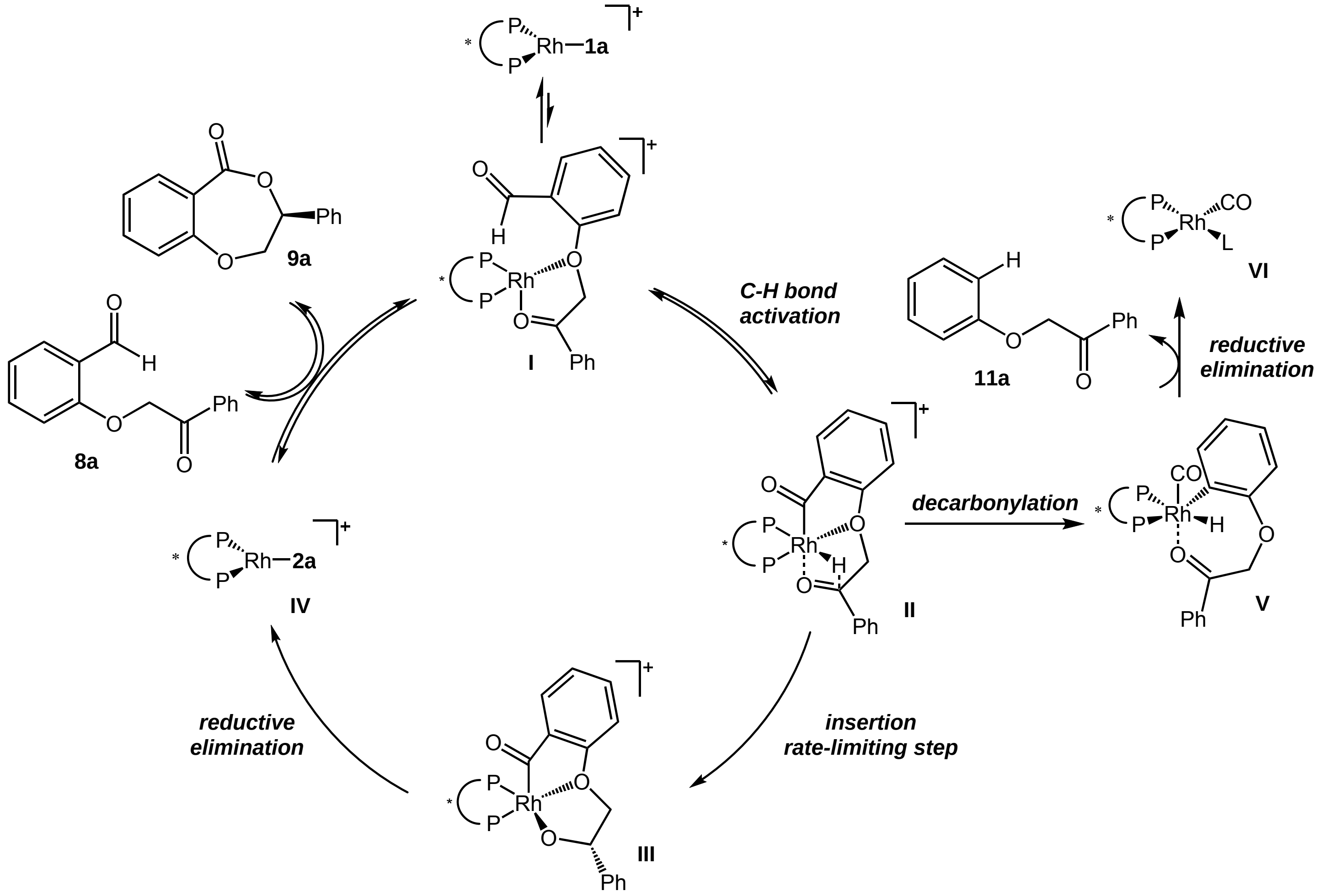


Competing transformations for model substrate



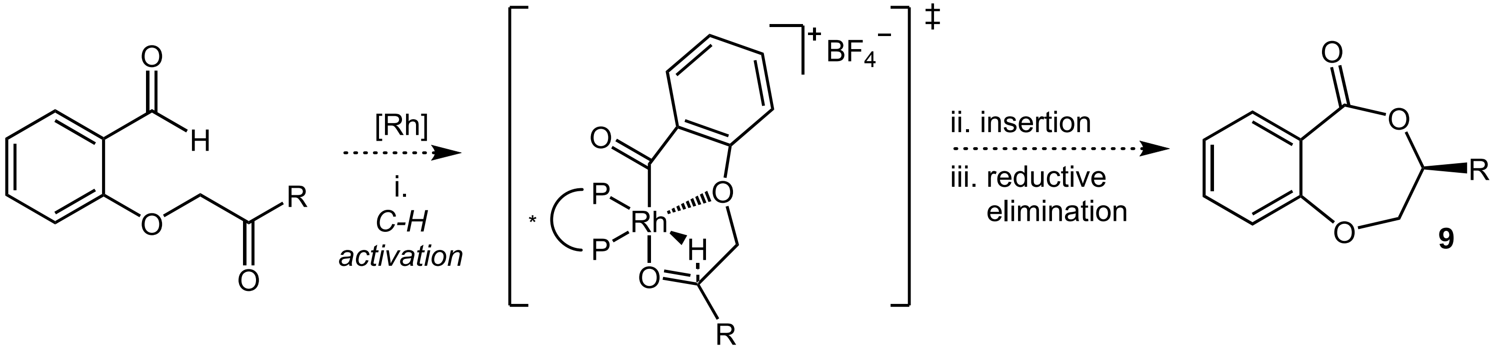
Dong, V. M. *et al. J. Am. Chem. Soc.* **2008**, *130,* 2916.
Tsuji, J. *et al. Tetrahedron Lett.* **1965**, *44,* 3969.

Rh-Catalyzed Enantioselective Hydroacylation of Ketones

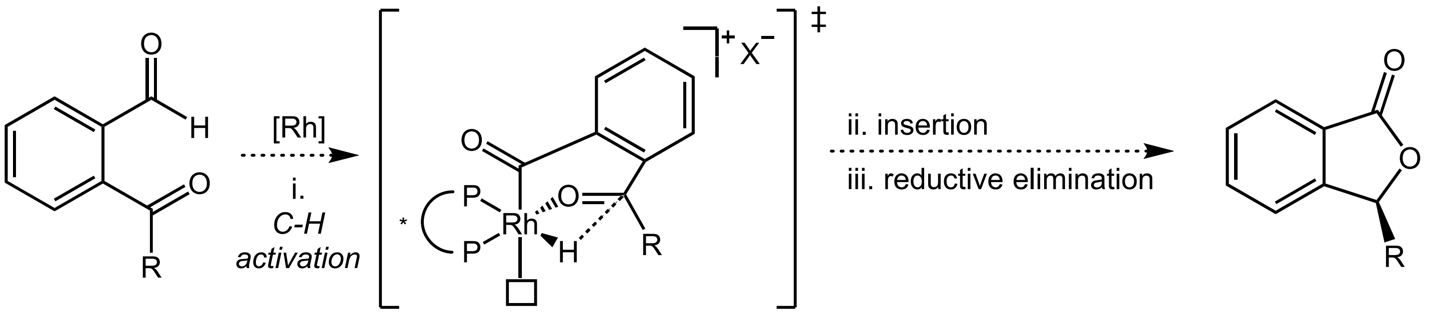


Dong, V. M. *et al. J. Am. Chem. Soc.* **2009**, *131*, 1077.

Rh-Catalyzed Enantioselective Hydroacylation of Ketones



insertion TS ***A***
ether coordination key

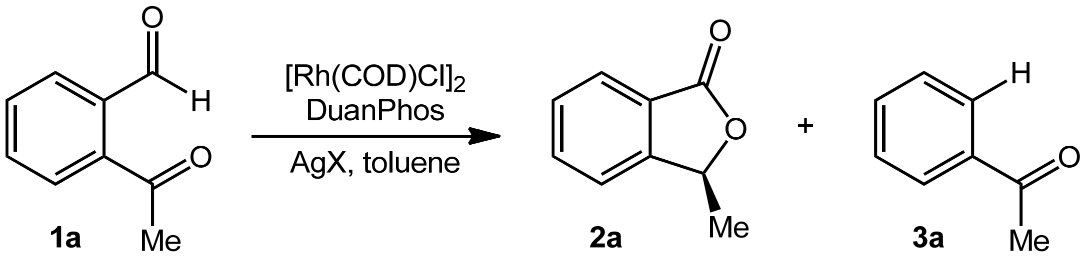


insertion TS ***B***
counter-ion interactions key

Dong, V. M. *et al*. *J. Am. Chem. Soc.* **2009**, *131*, 15608.

Rh-Catalyzed Enantioselective Hydroacylation of Ketones

Counterion effects on reactivity



entry	X	**2a** (%)	ee (%)	**3a** (%)	time
1	SbF_6	30	40	52	1 d
2	BF_4	76	29	24	1 d
3	OTf	> 95	81	< 5	0.5 h
4	OMs	> 95	91	trace	10 h
5	**NO_3**	**> 95**	**97**	**trace**	**7 h**
6	Cl	92	97	trace	3 d

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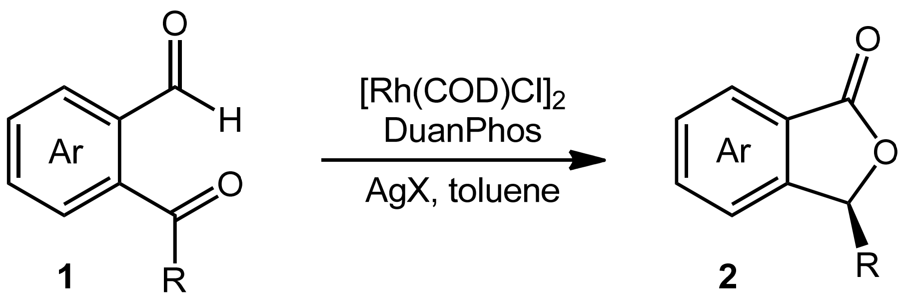
Rh-Catalyzed Enantioselective Hydroacylation of Ketones



R	X	result
alkyl	NO_3	up to 97% yield, 98% ee
aryl	OMs or OTf	up to 93% yield, 96% ee

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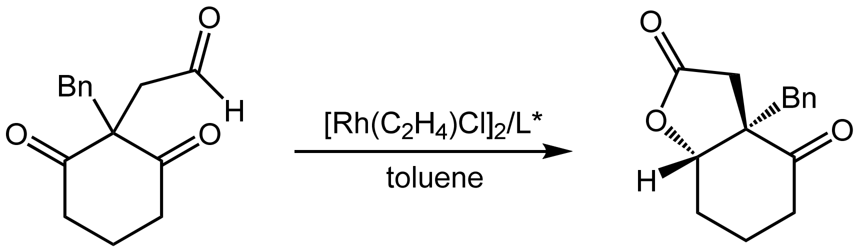
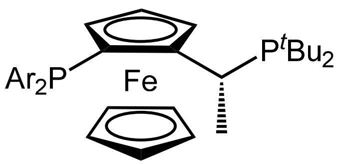
Rh-Catalyzed Enantioselective Hydroacylation of Ketones

Ligand effect



1a   ***anti*-2a**   ***syn*-3a**

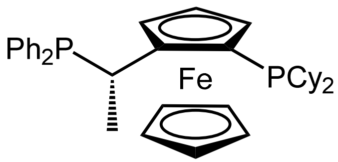


Ar = 4-$CF_3C_6H_4$

Josiphos **L1**

> 20:1 **2a:3a**

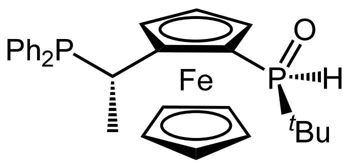
25%, 56% ee



Josiphos **L2**

> 20:1 **2a:3a**

32%, 87% ee



JoSPOphos **L3**

3:1 **2a:3a**

89%, 98% ee/99% ee

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Rh-Catalyzed Enantioselective Hydroacylation of Ketones

Parameters impacting diastereocontrol

a. Solvent effect: ([Rh(C_2H_4)Cl]$_2$, 21 ^oC)

	aprotic				protic		
2a *anti*	DME 8:1	toluene 3:1	DCE 1.7:1	THF 1.3:1	^{t}BuOH 1:2	^{t}AmOH 1:3	**3a** *Syn*

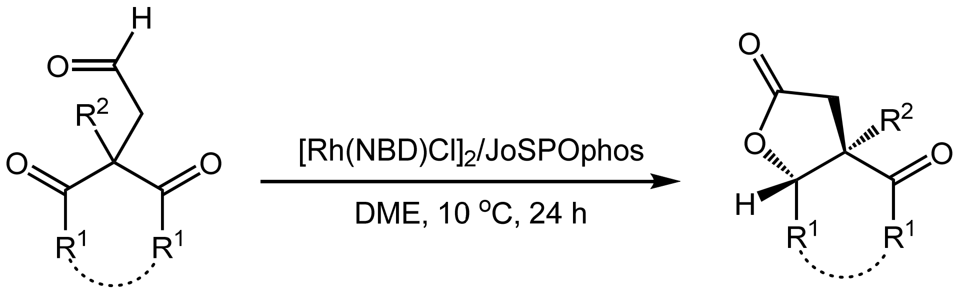
b. Temperature effect: [Rh(C_2H_4)$_2$Cl]$_2$

	in DME (← **2a**)			in ^{t}AmOH (→ **3a**)			
2a *anti*	10 ^oC	21 ^oC	80 ^oC	21 ^oC	50 ^oC	80 ^oC	**3a** *Syn*
	13:1	8:1	1.5:1	1:3	1:8	1:10	

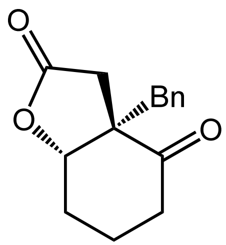
c. Counterion effect: [Rh(COD)$_2$X] or [Rh(COD)X]$_2$

	in DME, at 10 ^oC (← **2a**)				in ^{t}AmOH, at 80 ^oC (→ **3a**)				
2a *anti*	Cl^-	Br^-	I^-	SbF_6^-	Cl^-	OTf^-	BF_4^-	SbF_6^-	**3a** *Syn*
	13:1	6:1	3:1	2:1	1:11	1:>20	1:>20	1:>20	

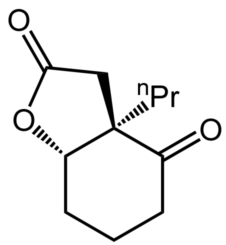
Rh-Catalyzed Enantioselective Hydroacylation of Ketones



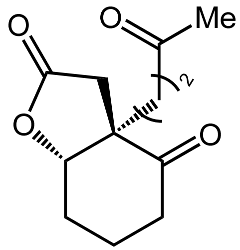
1 → **2**



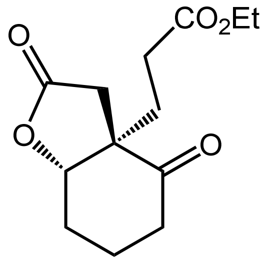
2a, 91%
17:1 dr, 99% ee



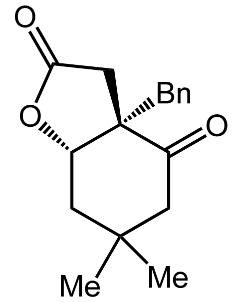
2b, 80%
8:1 dr, >99% ee



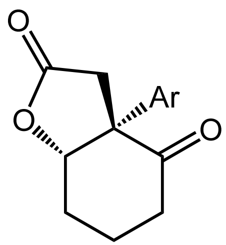
2c, 53%
6:1 dr, >99% ee



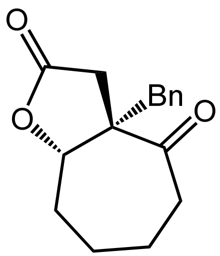
2d, 82%
8:1 dr, >99% ee



2e, 81%
6:1 dr, >99% ee

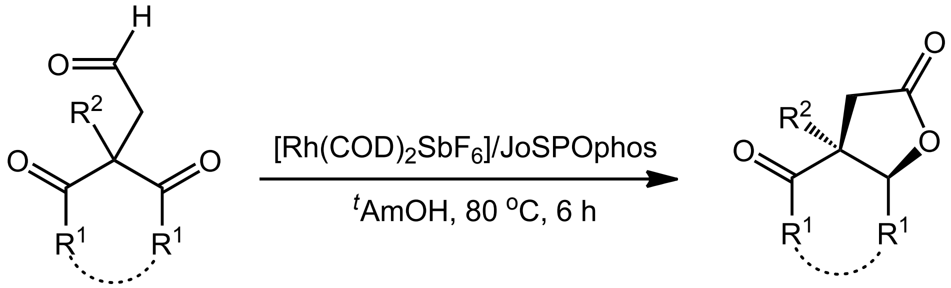


Ar = C_6H_5 **2f** 81%, 10:1 dr, 96% ee
Ar = 4-$MeOC_6H_4$ **2g** 75%, 8:1 dr, 95% ee
Ar = 4-ClC_6H_4 **2h** 74%, 9:1 dr, 94% ee
Ar = 2-MeC_6H_4 **2i** 67%, 6:1 dr, 87% ee
Ar = 3-MeC_6H_4 **2j** 79%, 10:1 dr, 94% ee

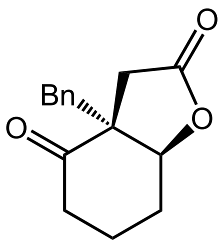


2k, 59%, 2:1 dr
98% ee/90% ee

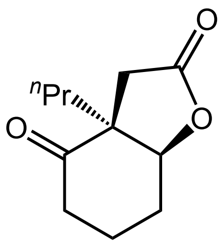
Rh-Catalyzed Enantioselective Hydroacylation of Ketones



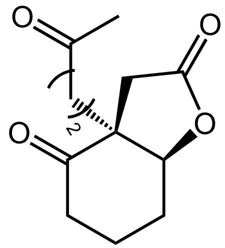
1 → **3**



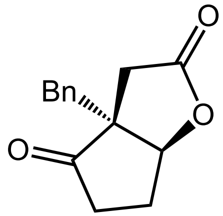
3a, 98%
>20:1 dr, 98% ee



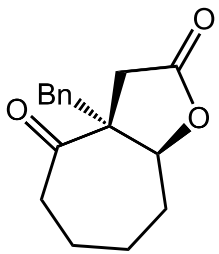
3b, 95%
>20:1 dr, >99% ee



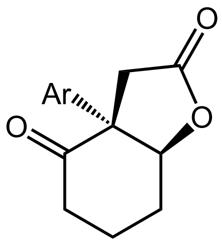
3c, 72%
>20:1 dr, 83% ee



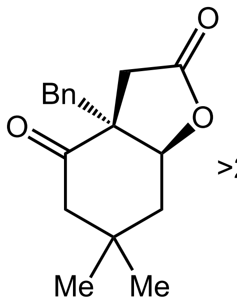
3d, 93%
>20:1 dr, 95% ee



3e, 95%
>20:1 dr, >99% ee



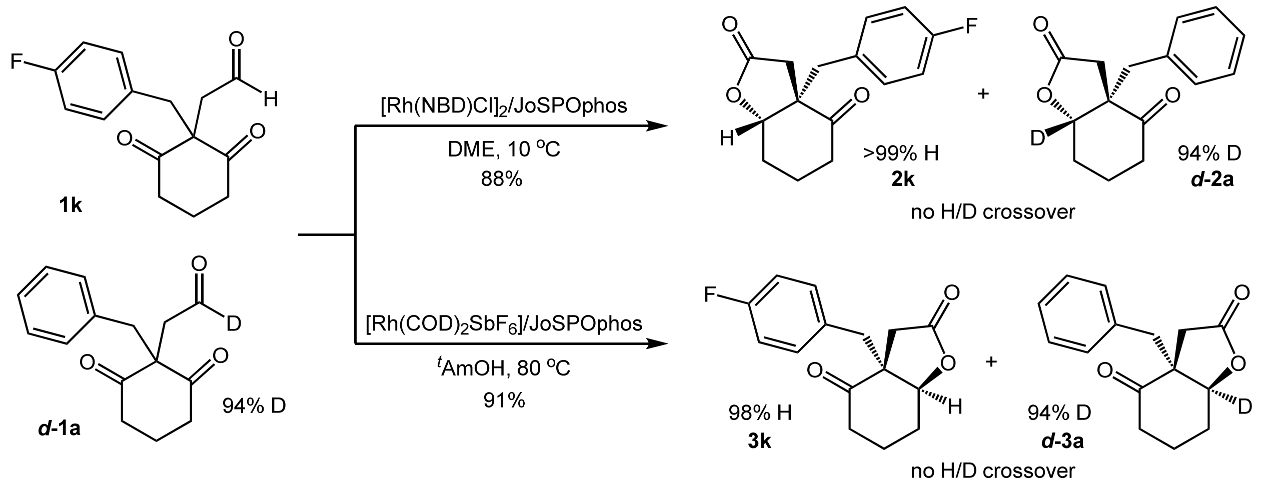
Ar = C_6H_5 **3f** 95%, >20:1 dr, >99% ee
Ar = 4-MeOC_6H_4 **3g** 94%, >20: dr, >99% ee
Ar = 4-ClC_6H_4 **3h** 95%, >20:1 dr, 94% ee
Ar = 3-MeC_6H_4 **3i** 92%, >20:1 dr, 98% ee
Ar = 2-MeC_6H_4 **3j** 88%, >20:1 dr, >99% ee

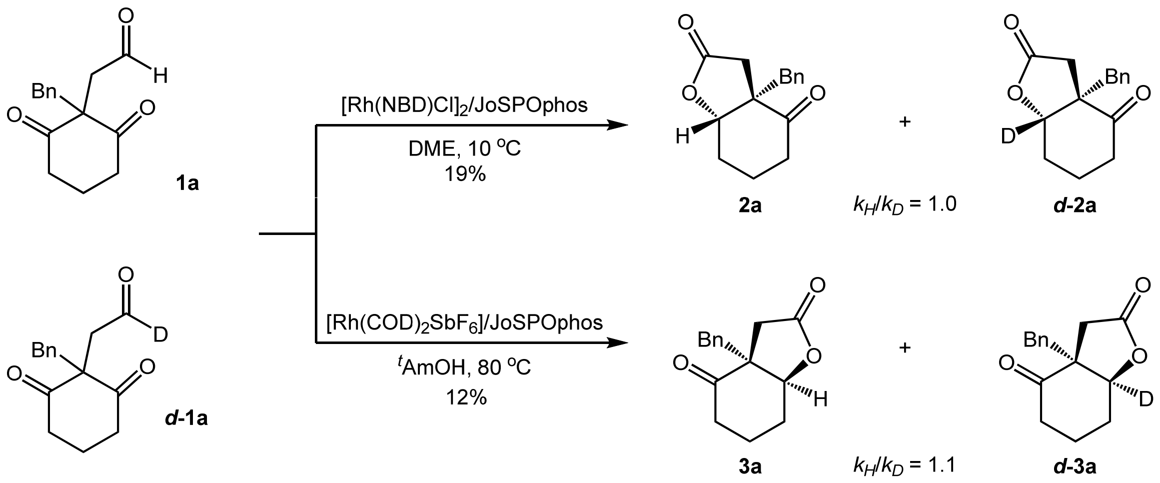


3k, 92%
>20:1 dr, 90% ee

Rh-Catalyzed Enantioselective Hydroacylation of Ketones

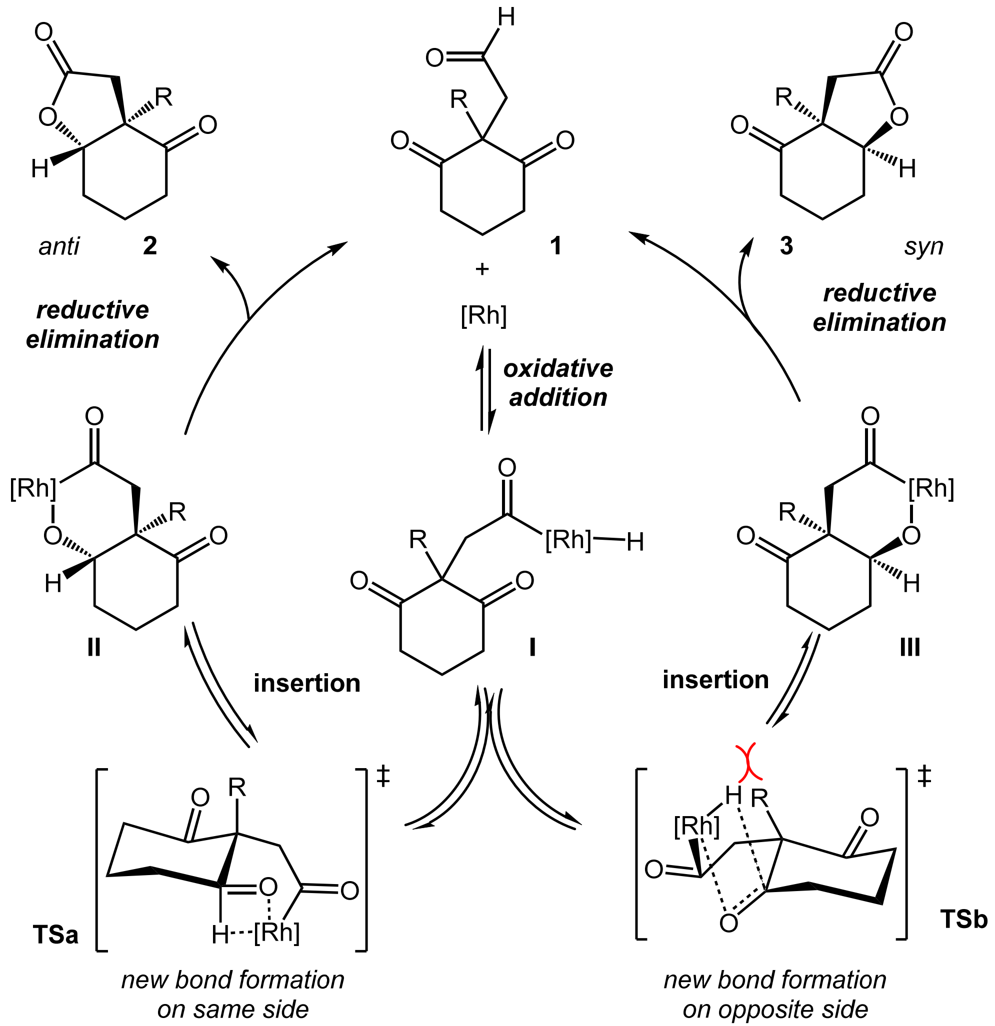
H/D crossover and kinetic isotope effect experiments





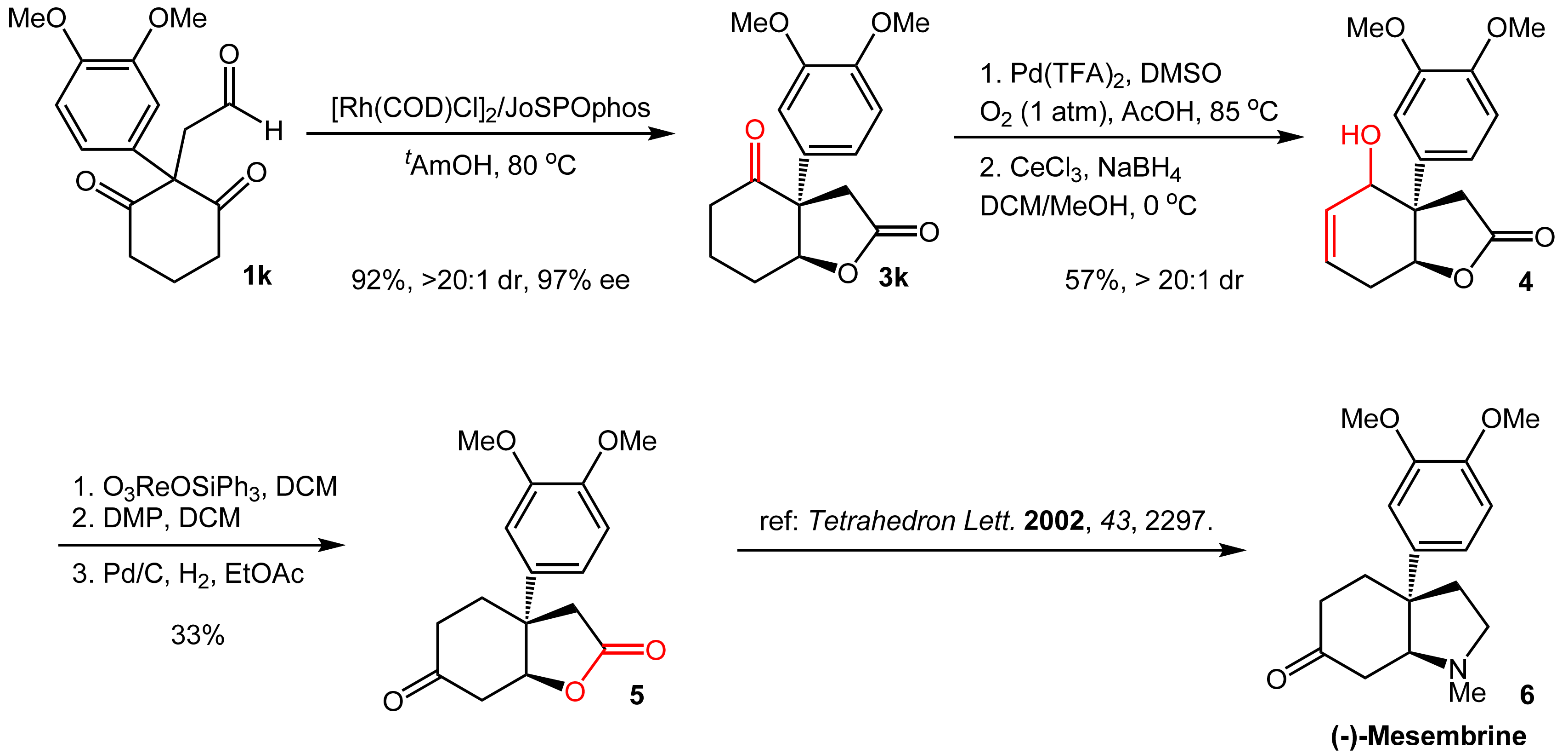
Rh-Catalyzed Enantioselective Hydroacylation of Ketones

Mechanism

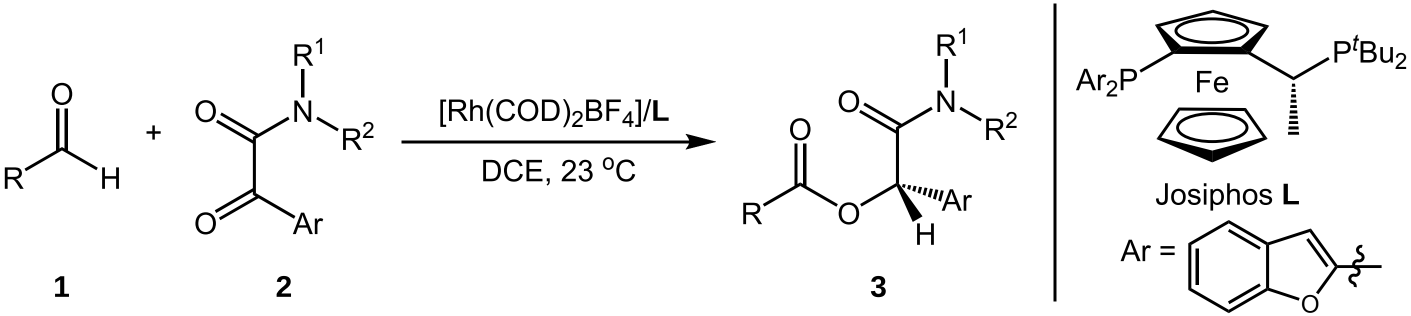


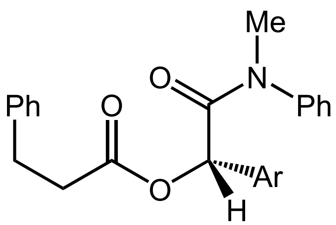
Rh-Catalyzed Enantioselective Hydroacylation of Ketones

Transformations

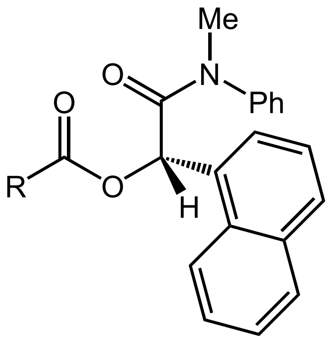


Rh-Catalyzed Enantioselective Hydroacylation of Ketones

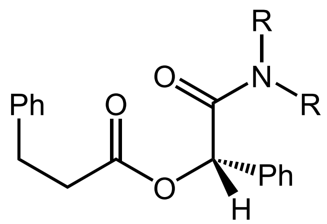




Ar = C_6H_5 **3a** 65%, 87% ee
Ar = 2-MeC_6H_4 **3b** 88%, 95% ee
Ar = 3-MeC_6H_4 **3c** 62%, 86% ee
Ar = Mes **3d** 82%, 96% ee
Ar = 1-naphthyl **3e** 86%, 95% ee



R = ^{i}Bu **3f** 91%, 94% ee
R = Neopentyl **3g** 91%, 93% ee
R = Cy **3h** 57%, 90% ee



R = Ph **3i** 47%, 78% ee
R = Bn **3j** 46%, 81% ee

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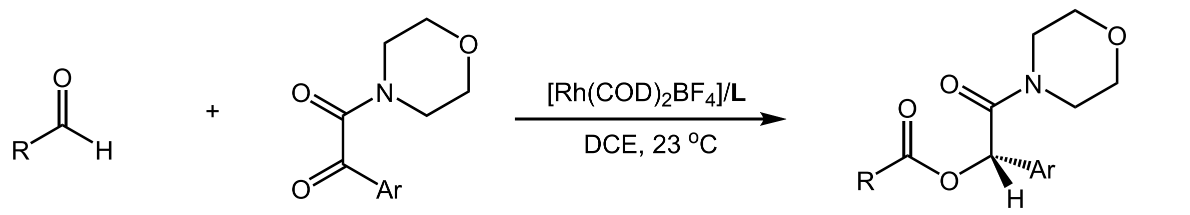
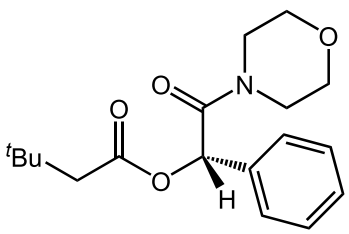
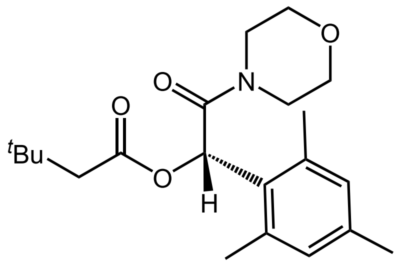
Rh-Catalyzed Enantioselective Hydroacylation of Ketones

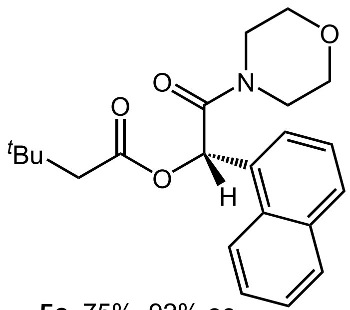




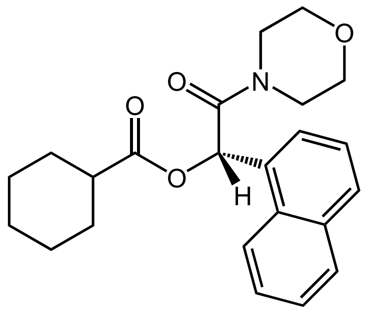
5a, 67%, 80% ee



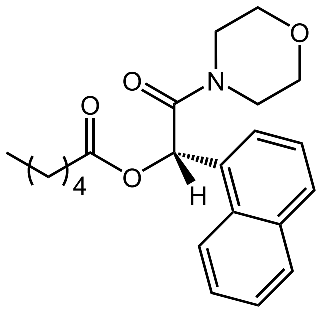
5b, 94%, 95% ee



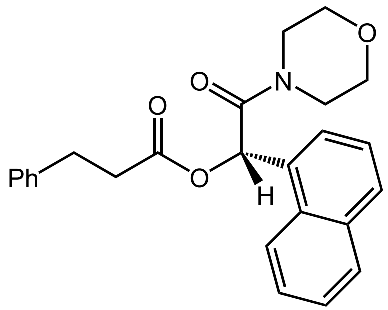
5c, 75%, 92% ee



5d, 59%, 92% ee



5e, 71%, 95% ee



5f, 90%, 94% ee

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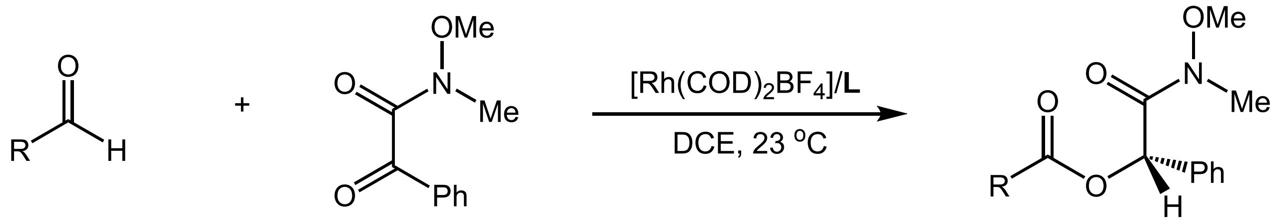
Rh-Catalyzed Enantioselective Hydroacylation of Ketones



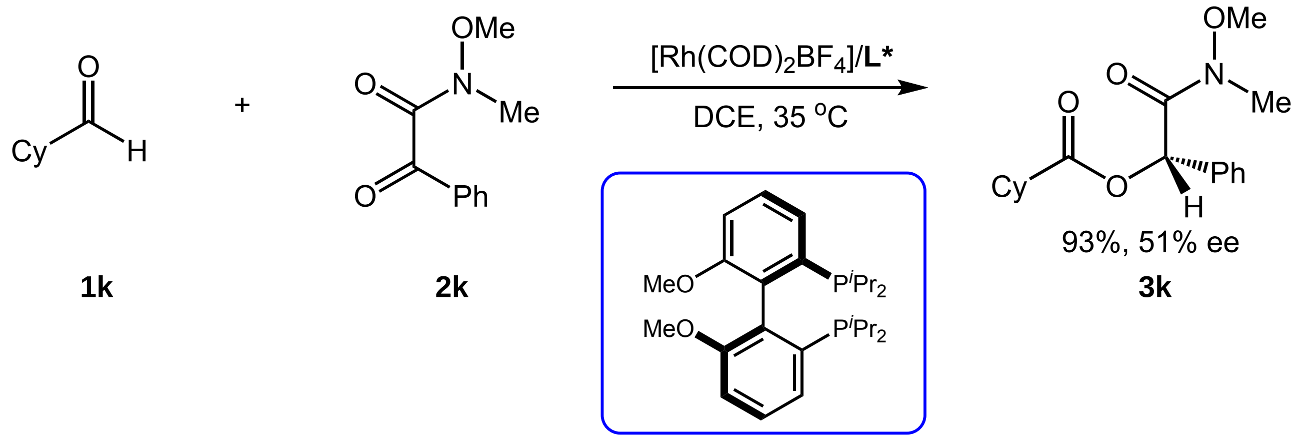
R = alkyl, Ph

1

2

<5% conv.

3



1k

2k

93%, 51% ee

3k

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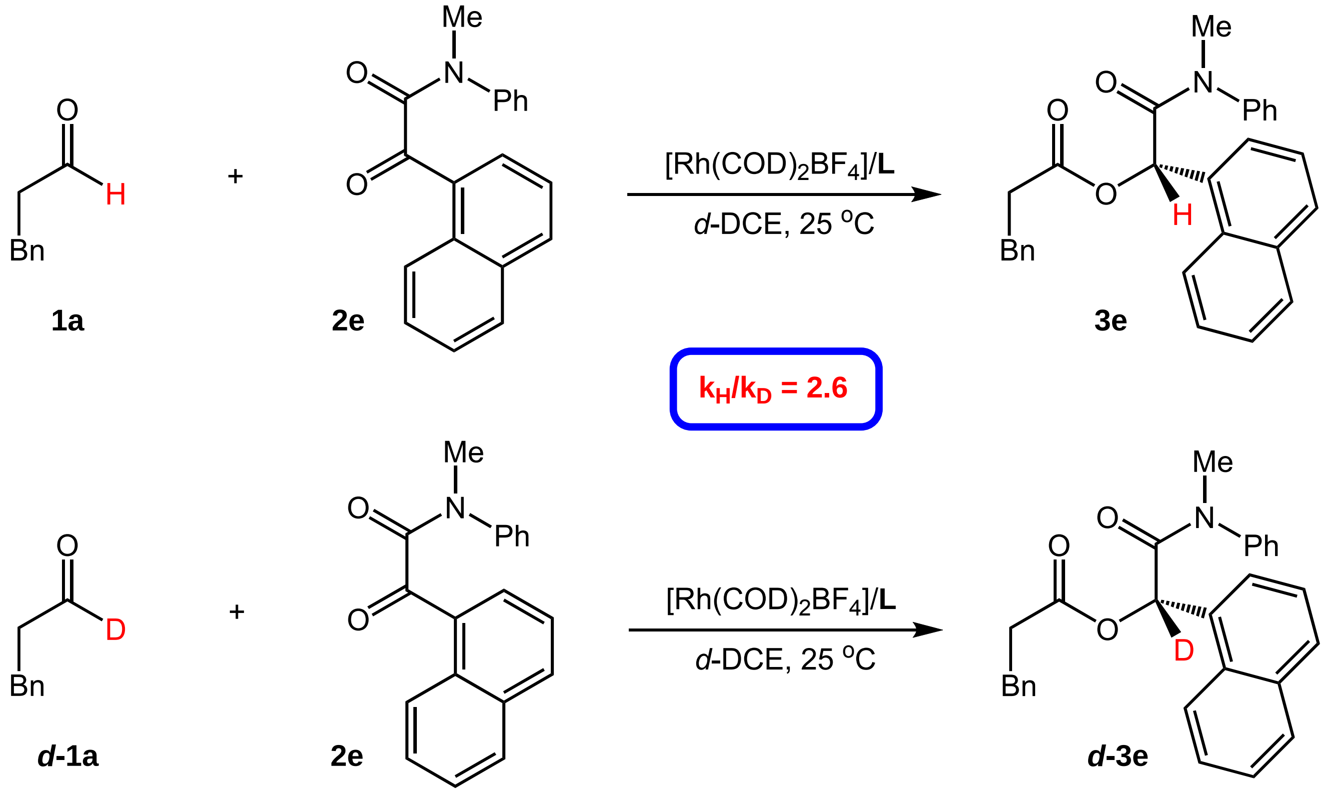
Rh-Catalyzed Enantioselective Hydroacylation of Ketones

KIE experiments



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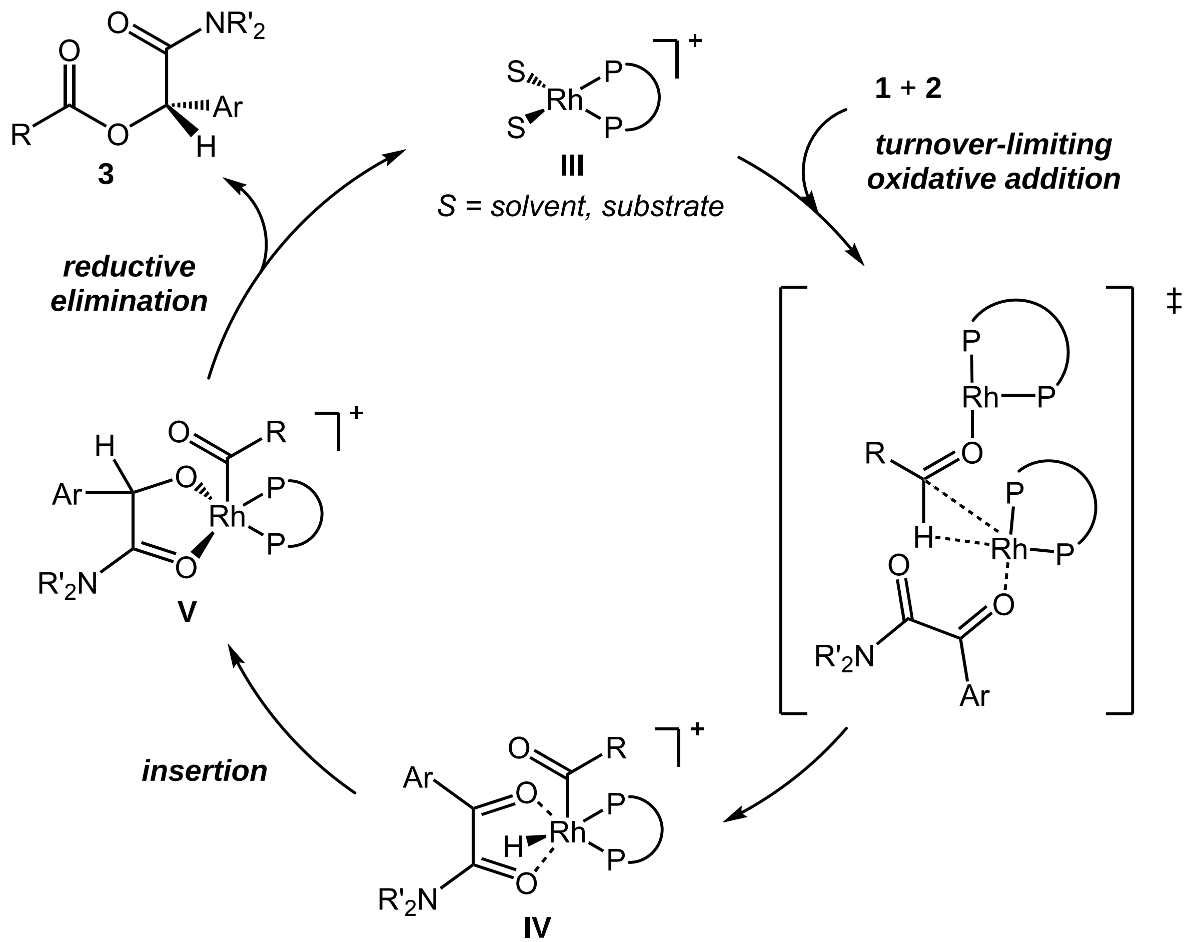
Rh-Catalyzed Enantioselective Hydroacylation of Ketones

Mechanism



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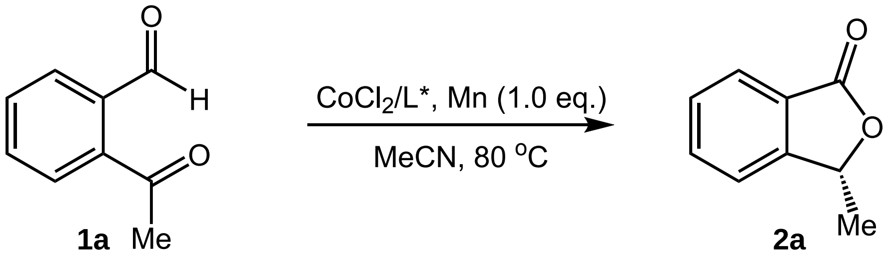
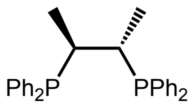
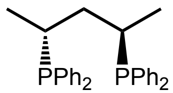
Co-Catalyzed Enantioselective Hydroacylation of Ketones

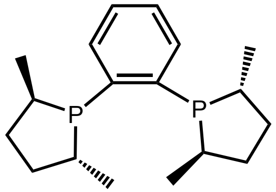




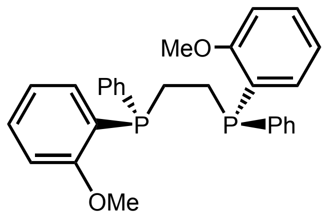
(*S*,*S*)-Chiraphos
No reaction



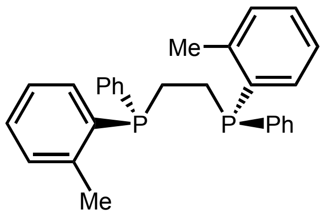
(*R*,*R*)-BDPP
15%, --% ee



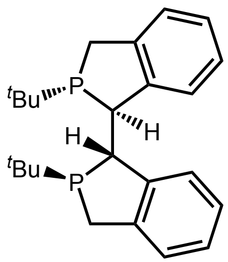
(*R*,*R*)-Me-DuPhos
12%, --% ee



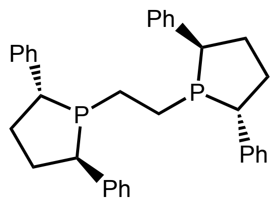
(*R*,*R*)-DIPAMP
4%, --% ee



(*R*,*R*)-Tol-DIPAMP
73%, 79% ee



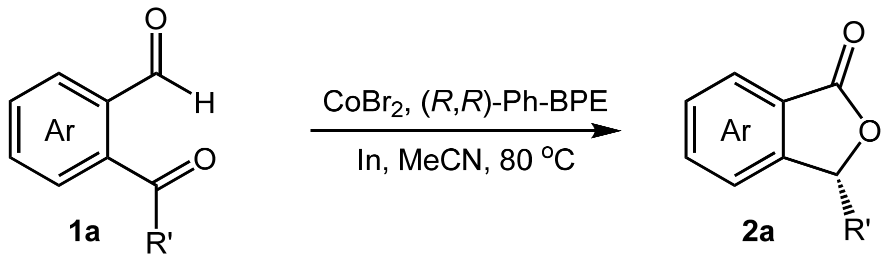
(*S*,*S*,*R*,*R*)-DuanPhos
37%, 85% ee

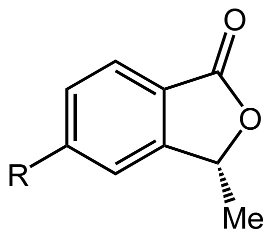


(*R*,*R*)-Ph-BPE
Mn (1.0 eq.), 70%, 95% ee
In (0.2 eq.), 92%, 95% ee ($CoBr_2$)

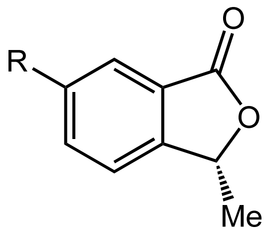
Yoshikai, N. *et al. J. Am. Chem. Soc.* **2014**, *136*, 16748.

Co-Catalyzed Enantioselective Hydroacylation of Ketones

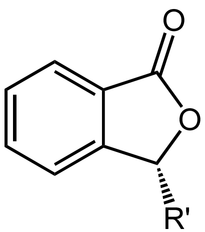




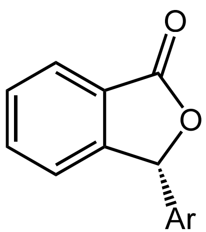
2a R = H, 88%, 95% ee
2b R = MeO, 97%, 93% ee
2c R = Me, 82%, 94% ee



2d R = Me, 84%, 97% ee
2e R = Cl, 75%, 92% ee
2f R = Br, 61%, 90% ee
2g R = CO_2Et, 91%, 93% ee



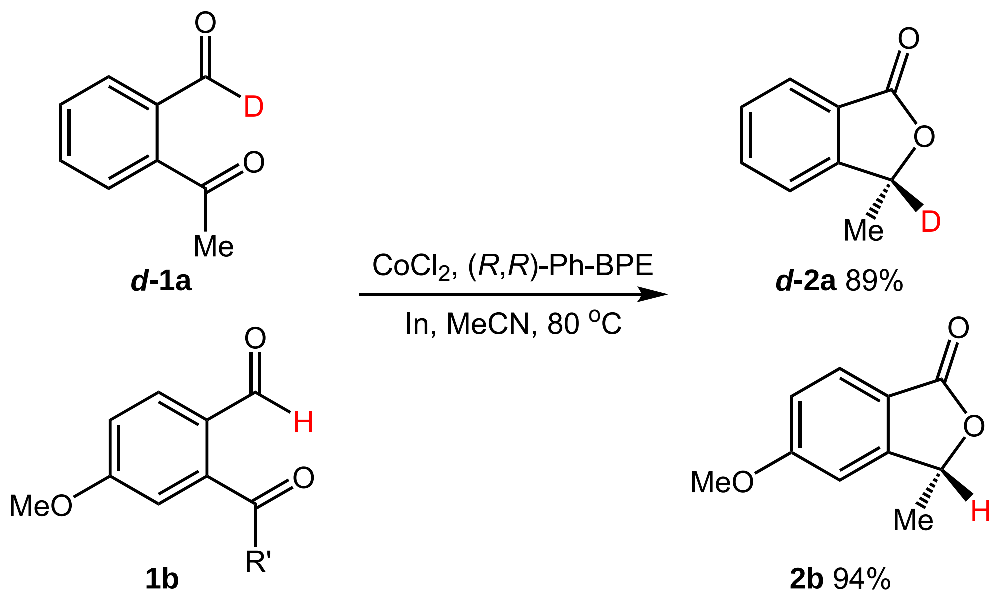
2h R' = Et, 93%, 91% ee
2i R' = ^{i}Pr, 91%, 95% ee

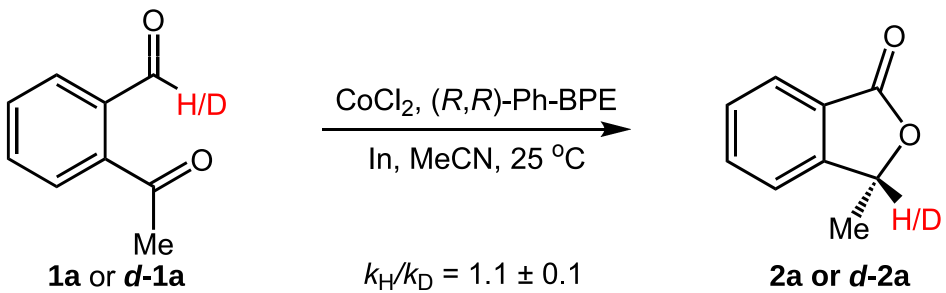


2j Ar = C_6H_5, 92%, 91% ee
2k Ar = 4-$MeOC_6H_4$, 90%, 98% ee
2l Ar = 4-MeC_6H_4, 86%, 92% ee
2m Ar = 4-ClC_6H_4, 83%, 88% ee
2n Ar = 3-MeC_6H_4, 86%, 90% ee
2o Ar = 2-MeC_6H_4, 54%, 82% ee

Co-Catalyzed Enantioselective Hydroacylation of Ketones

Deuterium-labeling experiments

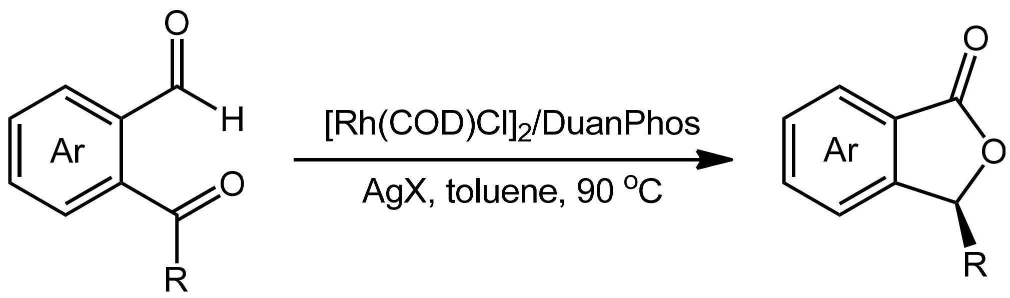




Summary

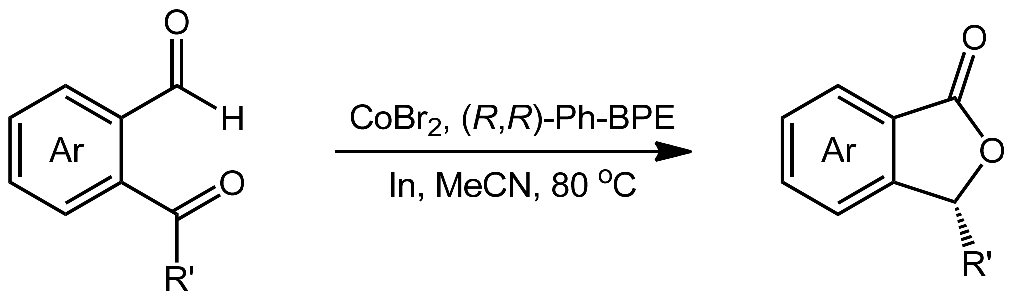
V. M. Dong

Rh-Catalyzed Enantioselective Hydroacylation of Ketones



N. Yoshikai

Co-Catalyzed Enantioselective Hydroacylation of Ketones



Cyclic architectures comprise a large number of natural products with diverse biological activity. Nature uses enzymes to access both stereoisomers of any bicycle through kinetic control. The use of metal catalysis to construct bicyclic motifs with high enantio- and diastereocontrol thus represents a modern challenge for organic synthesis. Inspired by the occurrence of bicyclic *γ*-lactones in natural products, we sought an atom-economical strategy to access both the *syn* and *anti* diastereoisomers by ketone hydroacylation. Toward this goal, we herein report the construction of bicyclic γ-lactones featuring the rare activation of aliphatic aldehydes, without competitive decarbonylation.

By computational studies, we find that the syn bicycle **3a** is thermodynamically more stable than the anti isomer **2a**. We recognize that the syn isomer can undergo a chair flip and thus has more conformational degrees of freedom than its *anti* counterpart. A survey of literature reveals that bond formation to generate related fused bicycles typically occurs to the carbonyl *via* the same side of the reactive tether, suggesting that such additions are rapid and irreversible. In contrast, our hydroacylation strategy enables access to both stereoisomers *via* kinetic control. Under our standard conditions, the *anti* and *syn* products do not interconvert, further supporting the idea that reductive elimination is irreversible. Further kinetic and computational studies are underway to better understand these effects to guide development of future stereodivergent strategies.