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Diastereodivergent Construction of Bicyclic γ-Lactones via Enantioselective Ketone Hydroacylation

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Supporting Information

ABSTRACT: We present a diastereodivergent strategy for constructing bicyclic γ-lactones bearing quaternary carbon centers via ketone hydroacylation. By applying a Rh catalyst and JoSPOphos ligand, either the *anti* or *syn* bicyclic γ-lactones can be accessed with high enantio- and diastereoselectivities, depending on the choice of solvent, temperature, and counterion.

Cyclic architectures comprise a large number of natural products with diverse biological activity.[1] Nature uses enzymes to access both stereoisomers of any bicycle through kinetic control.[2] 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[3] (Figure 1a), we sought an atom-economical strategy[4] to access both the

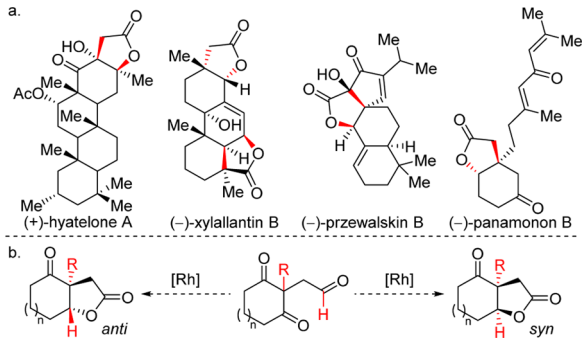
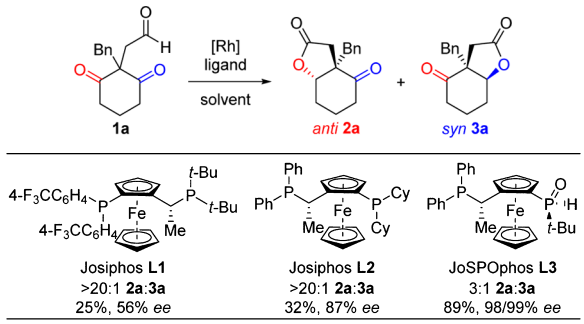


Figure 1. Inspiration for diastereodivergent formation of bicyclic γ-lactones.

syn and *anti* diastereomers by ketone hydroacylation[5−7] (Figure 1b). Toward this goal, we herein report the construction of bicyclic γ-lactones featuring the rare activation of aliphatic aldehydes, without competitive decarbonylation.[7,8]

To begin our studies, we chose 4,4′-diketo aldehyde **1a** bearing a β-quaternary carbon center as the model substrate. This substrate would allow us to address the challenge of preparing quaternary carbon centers with high enantiocontrol using desymmetrization.[9−11] Guided by previous hydroacylations,[6,7] we examined $[Rh(C_2H_4)_2Cl]_2$ with a wide range of bidentate phosphine ligands.[12] The Josiphos family of ligands, which we previously found to promote *intermolecular* hydroacylation with aliphatic aldehydes, proved promising (Table 1).[12] A combination of $[Rh(C_2H_4)_2Cl]_2$ and Josiphos **L1** in toluene afforded the *anti* bicyclic γ-lactone **2a** (25% yield, >20:1 *dr*, 56% *ee*). Using Josiphos **L2** improved the enantioselectivity (32% yield, >20:1 *dr*, 87% *ee*). With JoSPOphos **L3**,[13] both diastereomers were observed with excellent enantioselectivities (98% *ee* for **2a** and 99% *ee* for **3a**) in 89% yield as a 3:1 mixture of **2a:3a**. Developed by Pugin and Pfaltz for asymmetric hydrogenation, this ligand had yet to be explored for hydroacylation.[13]

Table 1. Ligand Effects on Stereoselectivity[a,b]



[a]Isolated yields. The *ee* was determined by chiral SFC analysis, and *dr* was determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b]Conditions: **1a** (0.20 mmol), $[Rh(C_2H_4)_2Cl]_2$ (2.5 mol %), ligand (5 mol %) in toluene (0.4 mL), 21 °C, 24 h.

While methods for making bicyclic γ-lactones have been reported,[14,15] we aimed to develop a complementary and diastereodivergent strategy. Because the JoSPOphos **L3** ligand provided access to both *anti* and *syn* diastereomers with high enantiocontrol, we chose this ligand for further study. Through a solvent study at 21 °C (Table 2a), we found that the *anti* diastereomer was favored in polar aprotic solvents, such as 1,2-dimethoxyethane (DME) (8:1 **2a:3a**). In contrast, the *syn* diastereomer was preferred in polar protic solvents, such as *tert*-amyl alcohol (*t*-AmOH) (1:3 **2a:3a**). By applying these solvents, we discovered a strong temperature dependence (Table 2b). At lower temperatures, the *anti* diastereomer was favored (*e.g.*, 13:1 **2a:3a** at 10 °C in DME), whereas higher temperatures favored the *syn* diastereomer (*e.g.*, 1:10 **2a:3a** at 80 °C in *t*-AmOH). Finally, tuning of the catalyst counterion revealed that those more coordinating (*e.g.*, Cl^-) promote **2a**, whereas those less coordinating (*e.g.*, SbF_6^-) favor **3a** (Table 2c).[16,17] Ultimately, this intramolecular hydroacylation generates the *anti* diaster-

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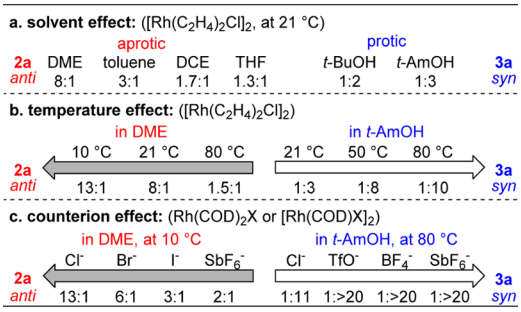
Table 2. Parameters Impacting Diastereocontrol[a,b]

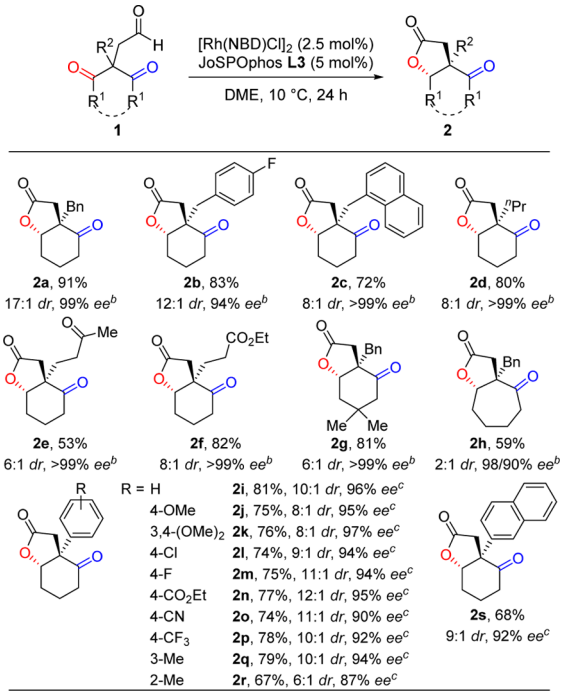


[a]Conditions: **1a** (0.20 mmol), [Rh] (5 mol %), JoSPOphos **L3** (5 mol %) in solvent, 24 h. The diastereomeric ratio (*dr*, **2a**:**3a**) for each case was determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b]For isolated yields and *ee*'s of the products, see Table S2 in SI.

eomer **2a** (91% yield, 17:1 *dr*, 99% *ee*) under $[Rh(NBD)Cl]_2$/**L3** in DME at 10 °C and the *syn* diastereomer **3a** (98% yield, >20:1 *dr*, 97% *ee*) under $Rh(COD)_2SbF_6$/**L3** in *t*-AmOH at 80 °C.

Next, we examined the scope and prepared 19 *anti* bicyclic γ-lactones in high yields and enantioselectivities (Table 3). Keto

Table 3. Enantioselective and *anti*-Diastereoselective Ketone Hydroacylation[a]

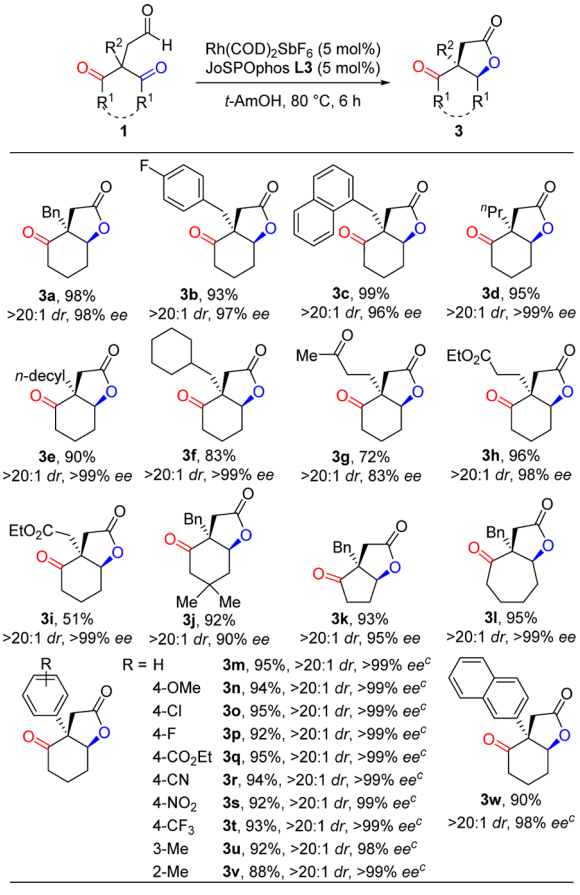


[a]Isolated yields of the major diastereomer **2**. The *ee* was determined by chiral SFC analysis, and *dr* was determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b]Conditions: **1** (0.10 or 0.20 mmol), $[Rh(NBD)Cl]_2$ (2.5 mol %), JoSPOphos **L3** (5 mol %) in DME (0.50 M), 10 °C, 24 h. [c]Conditions: **1** (0.10 mmol), $[Rh(COD)Cl]_2$ (2.5 mol %), Josiphos **L1** (5 mol %) in *n*-BuOAc (0.50 M), 100 °C, 24 h.

aldehydes bearing various alkyl groups cyclized to the corresponding *anti* bicyclic γ-lactones in 53−91% yields with 6−17:1 *dr* and 94−>99% *ee* (**2a**−**f**). Dimethyl substituted bicyclic γ-lactone **2g** was obtained in 81% yield, 6:1 *dr*, >99% *ee*, and its absolute configuration was determined by X-ray crystallography.[12] A keto aldehyde containing a seven-membered ring underwent the intramolecular hydroacylation to afford bicyclic[5.3.0]lactone **2h** in 59% yield and 98% *ee* but with lower diastereoselectivity (2:1 *anti*:*syn*). Under the standard conditions, we found that the 3-phenyl substituted keto aldehyde gave the corresponding *syn* bicyclic γ-lactone **3m** rather than the expected *anti* diastereomer **2i**. By using Josiphos **L1** as the ligand in *n*-BuOAc at 100 °C, however, the *anti* diastereomer **2i** was obtained in 81% yield, 10:1 *dr*, and 96% *ee*. Using Josiphos **L1**, substrates with either electron-donating (**2j**, **2k**, **2q**, **2r**) or electron-withdrawing groups (**2l**−**p**) on the phenyl ring gave the desired bicyclic γ-lactones in 67−78% yields with 6−12:1 *dr* and 87−97% *ee*. Aryl halides (**2b**, **2l**, **2m**), ketones (**2e**), esters (**2f**, **2n**), and nitriles (**2o**) were tolerated.

In a similar fashion, we examined the substrate scope under the *syn* diastereoselective conditions (Table 4). Twenty-three 4,4′-

Table 4. Enantioselective and *syn*-Diastereoselective Ketone Hydroacylation[a,b]



[a]Isolated yields of the major diastereomer **3**. The *ee* was determined by chiral SFC analysis, and *dr* was determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b]Conditions: **1** (0.10 or 0.20 mmol), $Rh(COD)_2SbF_6$ (5 mol %), JoSPOphos **L3** (5 mol %) in *t*-AmOH (0.20 M), 80 °C, 6 h. [c]$[Rh(COD)Cl]_2$ (2.5 mol %) was used.

diketo aldehydes gave the desired *syn* bicyclic γ-lactones (**3a**−**w**) in 51−99% yields with >20:1 *dr* and 83−>99% *ee*. Substrates with five- or seven-membered rings efficiently afforded the corresponding *syn* [3.3.0] and [5.3.0] bicyclic γ-lactones (**3k**, 93% yield, >20:1 *dr*, 95% *ee*; **3l**, 95% yield, >20:1 *dr*, >99% *ee*), respectively.[18] Our hydroacylation conditions tolerated ketone (**3g**), ester (**3h**−**i**, **3q**), halogen (**3b**, **3o**, **3p**, **3t**), nitrile (**3r**), nitro (**3s**), and naphthyl groups (**3c**, **3w**). Some of the aldehydes

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showcased here (**1e**, **1f**, **1i**, and **1k**) were unreactive when tested under the *anti* selective conditions. The *syn* selective protocol shows greater scope most likely due to the higher reaction temperature. The absolute configuration of **3j** was confirmed by X-ray crystallography.[12] In comparison to the *anti* selective hydroacylation, the enantiotopic carbonyl group undergoes reduction to generate the corresponding *syn* diastereomer (see X-ray data for compound **2g** vs **3j**).[12]

To explore the elaboration of these bicycles, we applied this method to achieve an enantioselective formal synthesis of (−)-mesembrine (Figure 2), which is a potent serotonin

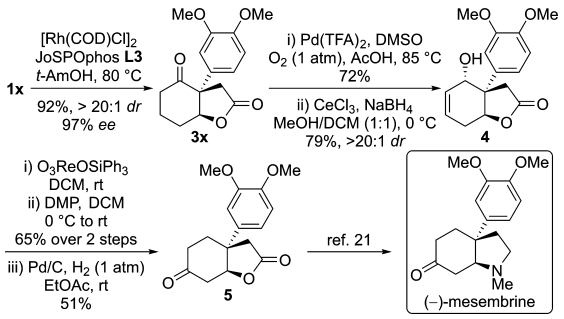

Figure 2. Formal enantioselective synthesis of (−)-mesembrine.

reuptake inhibitor isolated from *Sceletium tortuosum*.[19,20] We chose to intercept a racemic intermediate from Kulkarni's route.[21] Rh-catalyzed desymmetrization of the 4,4′-diketo aldehyde **1x** provided *syn* bicyclic γ-lactone **3x** in 92% yield, >20:1 *dr*, 97% *ee*. The absolute configuration of **3x** was confirmed by X-ray crystallography.[12] Pd-catalyzed aerobic dehydrogenation[22] and subsequent Luche reduction afforded the allylic alcohol **4**. Sequential, 1,3-transposition of **4** with Osborn's rhenium(VII) catalyst,[23] oxidation, and catalytic hydrogenation afforded isomeric *syn* bicyclic γ-lactone **5**, which has been converted to (−)-mesembrine.[21]

To gain insight into the mechanism, we prepared isotopically labeled substrates and performed crossover and KIE experiments. A crossover experiment with **1b** and **D-1a** suggests that Rh−H insertion is intramolecular, rather than intermolecular.[12] We measured kinetic isotope effects by using a mixture of **1a** and **D-1a**; we observed no KIE under *anti* conditions and a KIE near unity under the *syn* conditions (Figure 3). These results suggest that neither aldehyde C−H bond activation nor Rh-hydride insertion are turnover-limiting.[24]

On the basis of our observations and previous reports,[6,7,25] we propose a mechanism in which reductive elimination governs the diastereoselectivity (Figure 4).[26] First, oxidative addition of the aldehydic C−H bond in diketo aldehyde **1** to the Rh(I)-catalyst generates an acyl-Rh(III)-hydride intermediate **I**. Subsequent insertion of the ketone carbonyl group into the Rh−H bond of **I** generates either rhodacycle **II** or **III**. Because the insertion step is reversible, intermediates **II** and **III** are in equilibrium. The turnover-limiting and stereodetermining step is reductive elimination, which delivers the bicyclic γ-lactone (**2** or **3**) and regenerates the Rh(I)-catalyst. Thus, Curtin−Hammett type kinetics may be operative.[26] Based on our X-ray crystallography results, enantiotopic carbonyl groups are selected by the same catalyst, which suggests remarkably different transition states leading to the *syn* versus *anti* isomers. The solvent and coordinating ability of the counterion influences these transition state geometries and energies. Notably, we also observe a strong

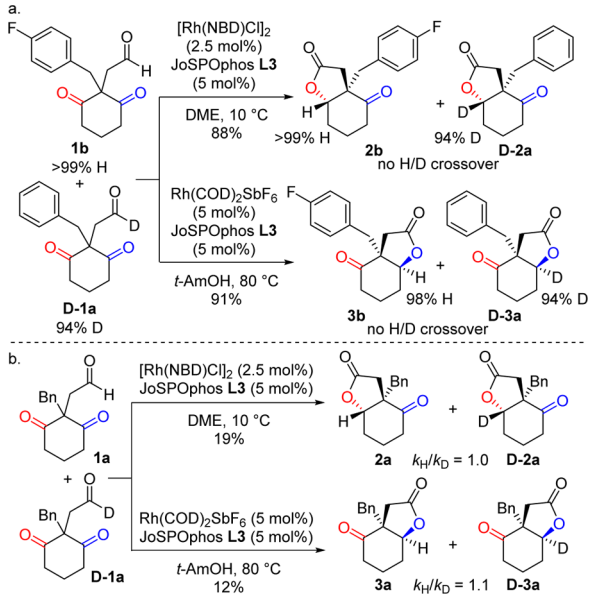

Figure 3. H/D crossover and kinetic isotope effect experiments.

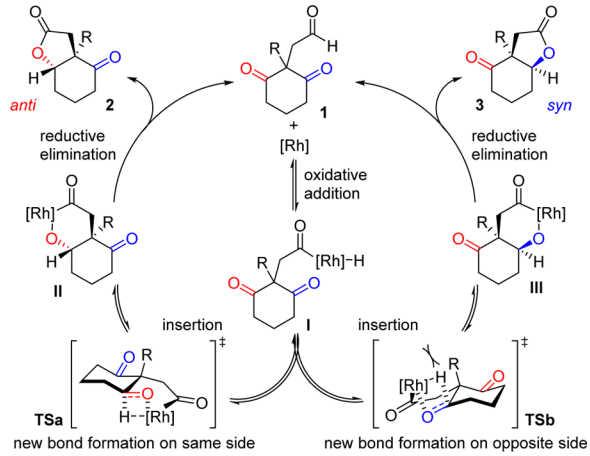

Figure 4. Reductive elimination governs diastereoselectivity.

temperature dependence on diastereoselectivity,[27] which may be due to a marked difference in the entropy of activation for these competing reductive eliminations.

By computational studies,[28] 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.[9b] 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,[12] 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.

■ ASSOCIATED CONTENT

Supporting Information

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Detailed experimental procedures and compound characterization (PDF)
Crystallographic data (CIF, CIF, CIF)

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Notes

The authors declare no competing financial interest.

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(28) DFT calculations shows that the free energy of **2a** is 5.8 kcal/mol higher than **3a**. See SI for more details.

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