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Stereoselective Synthesis of Diverse Lactones through a Cascade Reaction of Rhodium Carbenoids with Ketoacids

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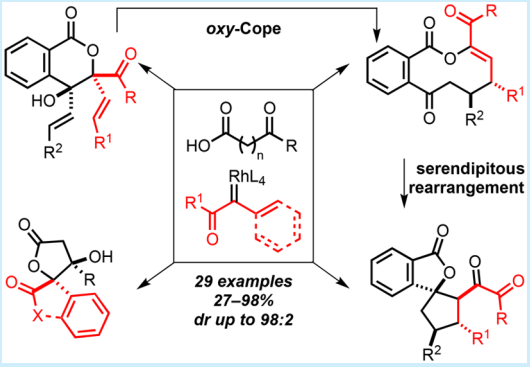
Supporting Information

ABSTRACT: A convergent cascade approach for the stereoselective synthesis of diverse lactones is described. The $Rh_2(TFA)_4$-catalyzed cascade reaction proceeds via a carboxylic acid O−H insertion/aldol cyclization with high chemo-, regio-, and diastereoselectivity. The cascade reaction provides quick access to highly functionalized γ-butyro- and δ-valerolactones from readily accessible ketoacid and diazo synthons. To demonstrate the utility of this approach, a thermally induced oxy-Cope ring-expansion strategy has been incorporated in the cascade sequence to access medium-sized lactones, which can undergo a serendipitous rearrangement to form spiro-lactones through an intramolecular aldol/trans-lactonization sequence. The reaction has proven to be general, with a range of ketoacids and diazo carbonyls to provide functionalized lactones of varying ring sizes.



Spanning the realm of complexity that exists within natural and synthetic organic frameworks, the lactone motif is unquestionably prominent, useful, and attractive to the scientific community.[1] With ring sizes ranging from 4 to 60, the lactone ring is present in food additives,[2a] perfumes,[2b,c] pharmaceuticals,[2d] and bioactive natural products (Figure 1).[2e−g] In addition, these compounds are also valuable synthons, as 3-hydroxybutyrolactone has been utilized as an enantiopure precursor for both Pfizer's Lipitor and AstraZeneca's Crestor.[3]

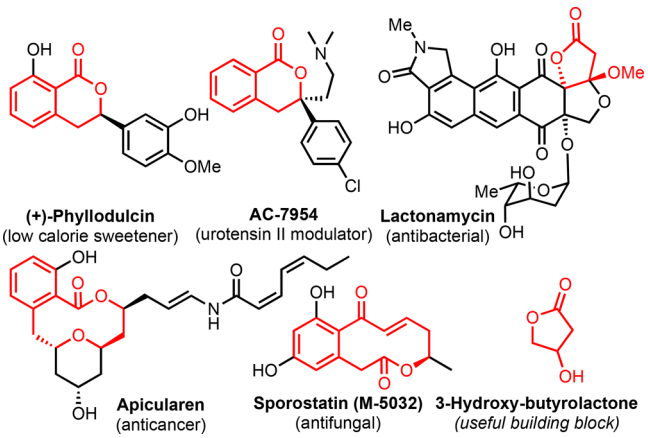


Figure 1. Lactone-based natural products and building blocks.

Because of the importance of the lactone motif, their synthesis remains an area of current interest to the chemical community. Most of the methods for the synthesis of lactones rely on intramolecular cyclization reactions of an appropriate linear precursor.[4] The ring cyclization reactions work fine for small-sized rings (5−7-membered) but often pose challenges for the synthesis of medium-sized rings (8−12-membered) due to their high entropic and enthalpic barriers.[5] Ring-expansion reactions that are insensitive to substrate conformational effects provide an alternative to the conventional cyclization approach.[6] However, the synthesis of appropriate precursors for ring-expansion reactions often requires multiple steps and limits the synthetic utility.[7]

To overcome this synthetic challenge, we envision a carbene cascade approach that utilizes readily accessible ketoacids and diazo carbonyls as starting materials. Our hypothesis is inspired from our recently developed carbene cascade reaction, which proceeds through a carbene O−H insertion/aldol cyclization sequence to provide a substituted tetrahydrofuran intermediate that undergoes a thermally induced oxy-Cope rearrangement to yield functionalized oxacycles.[8] There have also been reports of alcohol O−H insertion/aldol cyclization in the literature for the synthesis of tetrahydrofurans (Scheme 1, eq 1);[9] however, there is no example in the literature of a ketoacid insertion/aldol cyclization for the synthesis of the corresponding γ-butyrolactones, which are common structural motifs found in about 10% of all natural products.[10] The incompatibility of carboxylic acids in carbene cascade reactions may be attributed to the competing insertion reaction via a proton transfer resulting from low pK_a values of protonated carboxylic acids in the zwitterionic intermediate (Scheme 1, eq 2).[11] In this work, we have demonstrated that proton transfer could be delayed to facilitate

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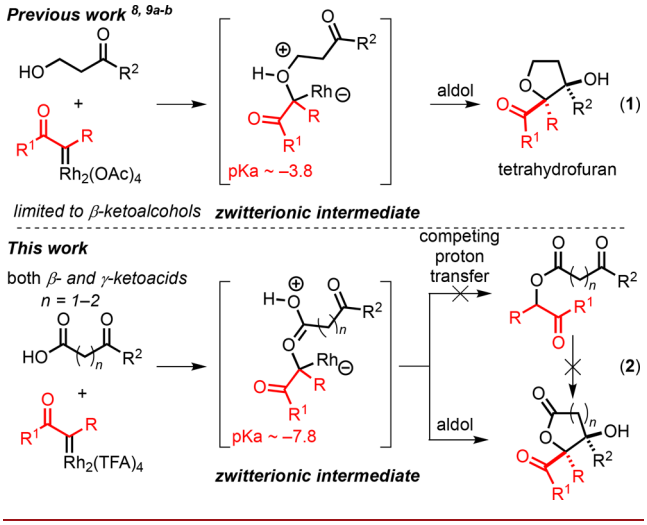
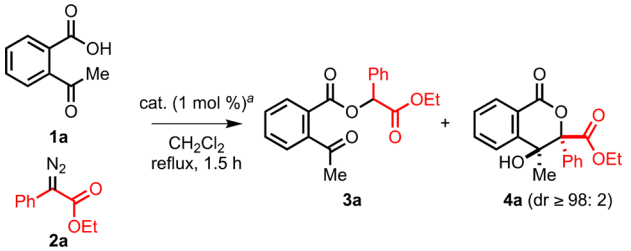
Scheme 1. Recent Applications of O−H Insertion/Aldol Cyclization



the aldol cyclization by simply changing the electronics of the diazo-derived rhodium carbenoid (Scheme 1, eq 2).

As β-ketoacids are prone to decarboxylation,[12] we decided to initiate our optimization reaction with γ-ketoacids. For the initial optimization, commercially available 2-acylbenzoic acid **1a** and diazo **2a** were selected as model substrates and exposed to our previously developed conditions for ketoalcohol O−H insertion/aldol cyclization (Table 1, entry 1).[8] As anticipated, $Rh_2(OAc)_4$ in refluxing CH_2Cl_2 exclusively provided insertion product **3a**. In order to obtain the cascade reaction, we then examined different dirhodium carboxylates known to decompose diazoacetates (Table 1, entries 2−5).[13] Among them, $Rh_2(TFA)_4$ bearing electron-deficient trifluoroacetate ligands was found to be the most efficient and provided the corresponding aldol product **4a** in good yield as a single diastereomer (entry 4). We also achieved some success with $Rh_2(HFB)_4$ (entry 5). With hope of achieving the cascade sequence with earth-abundant transition-metal catalysts known to effectively decompose diazo compounds, we also screened copper and iron salts but did not achieve any success (entries 6−8).[14] Finally, the cascade was attempted under metal-free conditions in refluxing CH_2Cl_2,[15] which led to diazo decomposition to exclusively provide insertion product **3a** (entry 9).

Table 1. Efficiency of Metal Salts in Carbene-Initiated Ketoacid O−H Insertion/Aldol Cyclization



entry	catalyst	3a/4a[b]	4a yield[c] (%)
1	$Rh_2(OAc)_4$	100:0	0
2	$Rh_2(esp)_2$	100:0	0
3	$Rh_2(TPA)_4$	100:0	0
4	**$Rh_2(TFA)_4$**	**37:63**	**60**
5	$Rh_2(HFB)_4$	50:50	46
6	$(CuOTf)_2$benzene	100:0	0
7	$Cu(acac)_2$	100:0	0
8	Fe(TPP)Cl	100:0	0
9		100:0	0

[a]All optimization reactions were performed by adding a 0.24 M solution of **2a** (24.0 mg, 0.12 mmol, 2.0 equiv) to a 0.12 M solution of **1a** (15.0 mg, 0.06 mmol, 1.0 equiv) with catalysts via a syringe pump for 1.5 h. After the addition of diazo compound, all reactions were refluxed for an additional 30 min. [b]The percent ratio of **3a** and **4a** was determined by crude ^{1}H NMR. [c]Isolated yields of **4a** obtained after column chromatography. TPA = triphenylacetate; TFA = trifluoroacetate; HFB = heptafluorobutyrate; acac = acetylacetonate; TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine.

With the optimized conditions in hand, we then investigated the scope of the carbene cascade sequence using $Rh_2(TFA)_4$ as a catalyst (Figure 2). Interestingly, the cascade proceeded in excellent yield with the cinnamoyl derivative (**4b**, Figure 2) presumably due to the lower steric interference of the styryl substituent compared to the methyl group.[16] Both the electron-withdrawing and -donating groups were tolerated on the aromatic ring of diazoacetates (**4c**,**d**, Figure 2). Notably, the cascade reaction also accommodated diazoketones, which are prone to undergo Wolff rearrangement (**4e**, Figure 2).[17] The cascade reaction also proceeded in good yield with isatin diazo to provide the corresponding spirocyclic oxindole (**4f**, Figure 2).[18] The relative stereochemistry of spirooxindole **4f** was determined using single-crystal X-ray crystallography. As expected, the resulting hydroxyl group and carbonyl moiety of the diazo were found to be in a *cis* configuration as reported previously in the literature, including our own work on the carbene−heteroatom insertion/aldol cyclizations.[8,9] We also attempted a reaction with acceptor and acceptor/acceptor diazo compounds ethyl diazoacetate and benzyl diazoacetoacetate, respectively, but we only observed the insertion product without any aldol cyclization product.

With an underlying goal of accessing medium-sized rings, we then turned our attention to vinyldiazoacetates,[19] which will result in aldol products having the divinyl functionality necessary for the thermally induced oxy-Cope ring expansion[8,20] to provide access to 10-membered benzannulated lactones. To our delight, the cascade proceeded in good yield with high diastereoselectivity to provide the corresponding δ-lactones bearing two vinyl substituents. A variety of aryl substituents on ketoacids were also tolerated, bearing electron-withdrawing and electron-donating groups (**4g−l**, Figure 2). The compounds **4g−l** were then subjected to the thermally induced oxy−Cope ring expansion reaction in refluxing toluene (boiling point 110 °C) as previously reported for the synthesis of medium-sized oxacycyles.[8,20] To our surprise, the reaction was found to be sluggish in refluxing toluene.

Therefore, we decided to increase the reaction temperature and switched the solvent to chlorobenzene (boiling point 131 °C). As expected, the oxy-Cope ring expansion proceeded cleanly in good yield to their corresponding benzannulated decanolides (**5a−e**, Figure 3). To our surprise, when the aldol product **4l** was subjected to the same reaction conditions, we obtained a spirophthalolactone bearing a highly functionalized cyclopentane ring (**6a**, Figure 3). The structure of **6a** was determined on the basis of the nuclear Overhauser effect (NOE) correlations and was further confirmed by single-crystal X-ray crystallography.[21]

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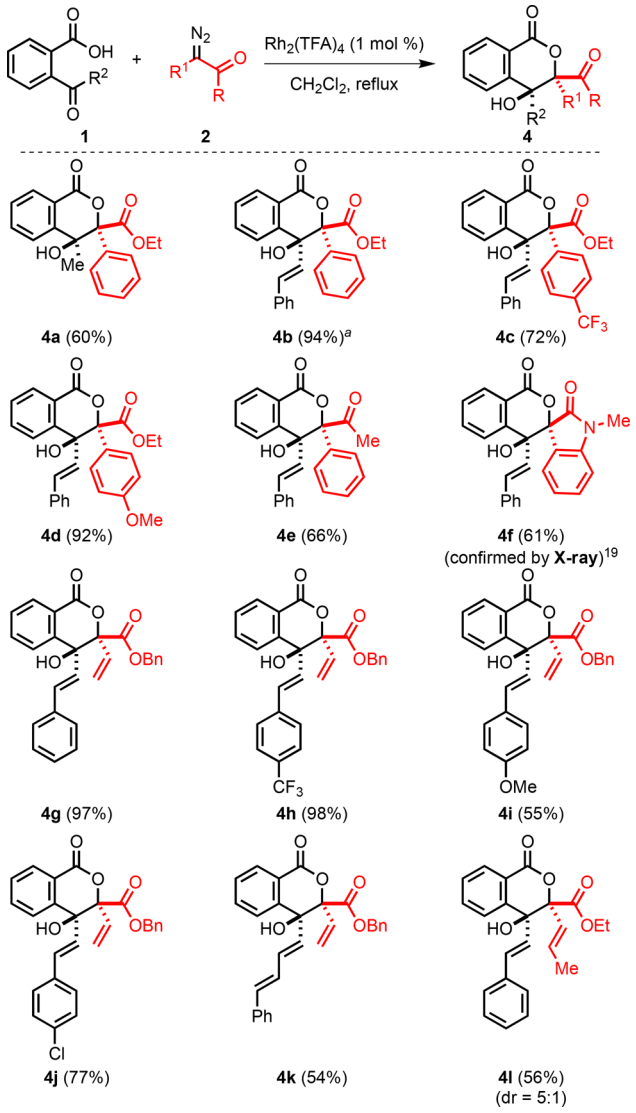

Figure 2. Scope of $Rh_2(TFA)_4$-catalyzed carbene carboxylic acid O−H insertion/aldol cascade sequence; all reactions were performed by adding a 0.24 M solution of **2** (2.0 equiv) to a 0.12 M solution of **1** (1 equiv) over 1.5 h via a syring pump. After the addition of a diazo compound, all reactions were refluxed for an additional 30 min. (a) The reaction was also performed on a 1 mmol scale with an isolated yield of 83%.

As the functionalized cyclopentanes are present in numerous bioactive natural products,[22] we decided to test the substrate scope of this serendipitous cascade. We synthesized aldol products **4m**−**o** with high diastereoselectivity using a methyl-substituted vinyldiazoacetate. As expected, the corresponding δ-lactones **4m**−**o** underwent the serendipitous cascade in good yield as single diastereomers (**6b**−**d**, Figure 4), but at a higher reaction temperature with prolonged reaction time.

We rationalized that the additional methyl substituent on the vinyldiazoacetate might be the cause of this unexpected serendipitous cascade reaction. The product **6a** is presumably formed through the ring-rearrangement reaction of the corresponding decanolide, which will have a significant Prelog strain[23] due to the additional methyl group causing the decanolide to undergo an intramolecular aldol cyclization followed by the translactonization to provide the spirophthalolactone **6** (Scheme 2). Both the methyl and aryl substituents

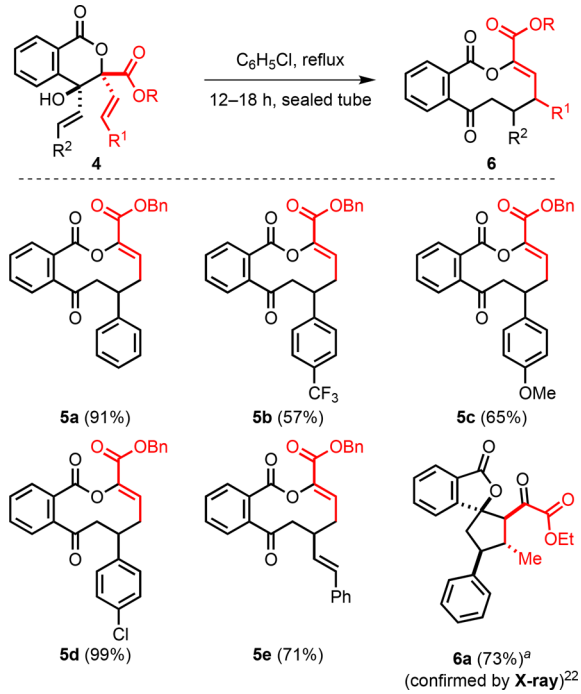

Figure 3. Scope of thermal oxy-Cope ring expansion strategy; all reactions were performed by heating a 0.01 M solution of **4** in chlorobenzene for 12−18 h at 140 °C in a sealed tube. (a) The reaction was heated at 200 °C for 24 h.

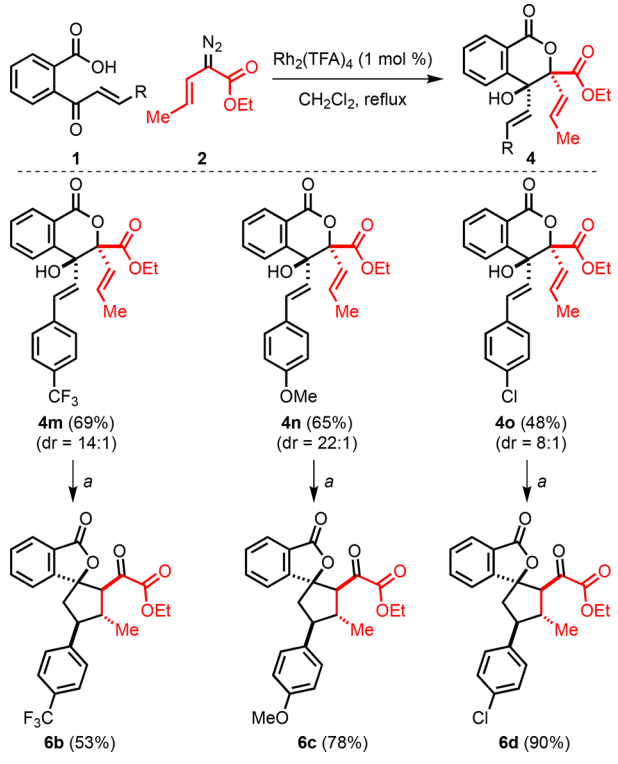

Figure 4. Scope of cascade sequence to access spirocyclic fused phthalolactones; all reactions were performed by adding a 0.24 M solution of **2** (4.0 equiv) to a 0.12 M solution of **1** (1 equiv) over 1.5 h via a syring pump. After the addition of a diazo compound, all reactions were refluxed for an additional 30 min. (a) The reaction was performed by heating a 0.01 M solution of **4** in chlorobenzene for 1−3 d at 200 °C until full conversion of starting material.

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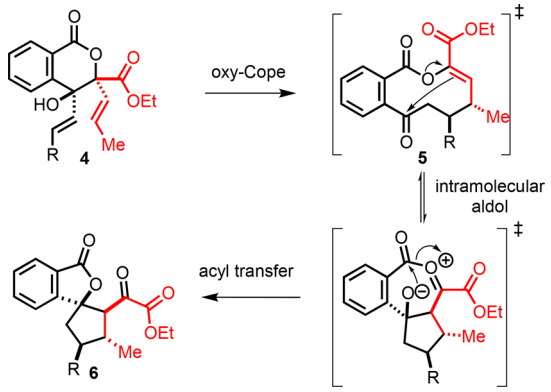
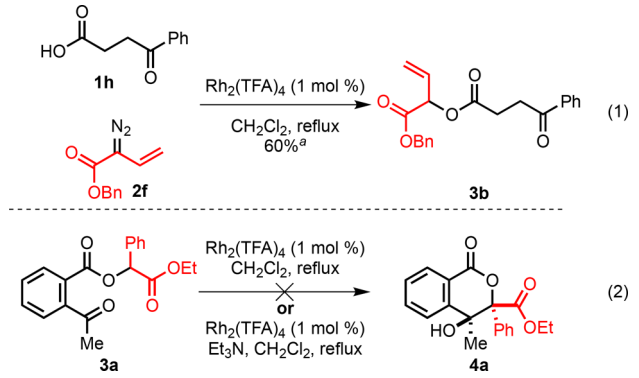
Scheme 2. Plausible Mechanism of Spirophthalolactone-Fused Cyclopentanes



were found to be *anti* to each other in spirophthalolactones, suggesting that the oxy-Cope rearrangement may proceed via a chair-type transition state.[24]

To gain further insight into the reaction mechanism of the ketoacid insertion/aldol cyclization, additional experiments were carried out (Scheme 3). We attempted the same O−H

Scheme 3. Control Experiments

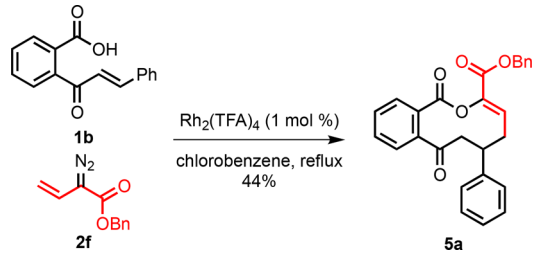


[a]Reagents and conditions: reaction was performed by adding a 0.24 M solution of **2f** (2.0 equiv) into a 0.12 M solution of **1h** (1 equiv) over 1.5 h via a syringe pump. After the addition of **2f**, the reaction was refluxed for an additional 30 min.

insertion/aldol cascade with 3-benzoylpropionic acid, exclusively yielding the insertion product **3b** (Scheme 3, eq 1). This result suggests that the aromatic ring constraint is necessary for a 6-membered aldol cyclization. The aromatic ring brings the electrophilic ketone moiety in closer proximity to rhoda-enolate in the zwitterionic intermediate, lowering the entropic barrier of ring cyclization associated with the corresponding linear alternatives.[25] Next, we performed two experiments with the corresponding insertion product **3a** (Scheme 3, eq 2). We refluxed the insertion product in CH_2Cl_2 with $Rh_2(TFA)_4$ alone and with the addition of excess triethylamine. We did not observe any conversion of insertion product **3a** to aldol product **4a**, suggesting that a rhodium-bound zwitterionic intermediate is necessary for the aldol cyclization.[8,9,20]

Finally, we attempted the synthesis of decanolides as a one-pot cascade by performing the reaction in refluxing chlorobenzene. The synthesis of decanolide **5a** was successful, but the yield was diminished as compared to our two-step protocol (Scheme 4).

Scheme 4. One-Pot Synthesis of Decanolides[a]



[a]The reaction was performed by adding a 0.24 M solution of **2** (2.0 equiv) in chlorobenzene into a 0.12 M solution of **1** (1 equiv) at 60 °C over 1.5 h via a syring pump. After the addition of a diazo compound, the reaction was refluxed for an additional 24 h.

To further demonstrate the utility of this cascade, we also attempted the reaction with β-ketoacids, which are prone to decarboxylation.[12] To our delight, the cascade accommodates β-ketoacids with a wide range of diazo compounds to provide functionalized γ-butyrolactones (Figure 5).[26] As anticipated, the

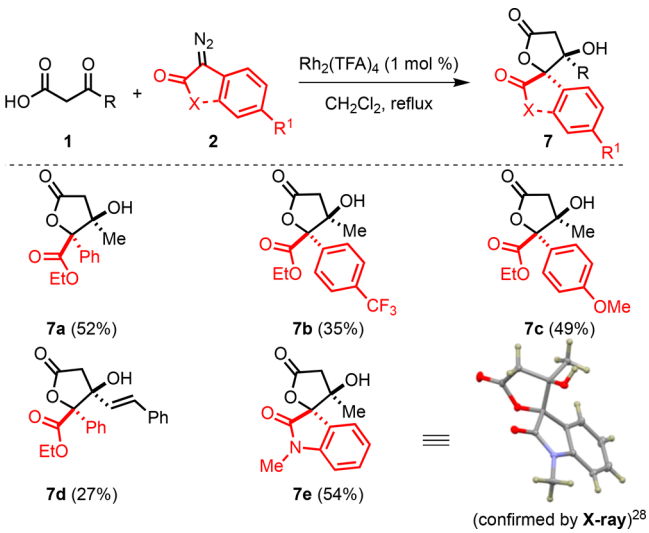


Figure 5. Scope of $Rh_2(TFA)_4$-catalyzed carbene carboxylic acid O−H insertion/aldol cascade sequence for the synthesis of 3-hydroxy-γ-lactones; all reactions were performed by adding a 0.24 M solution of **2** (2.0 equiv) into a 0.12 M solution of **1** (1 equiv) over 1.5 h via a syringe pump. After the addition of a diazo compound, all reactions were refluxed for an additional 30 min.

cascade reaction proceeded in lower yield due to the instability of the ketoacid starting materials under the reaction conditions. The cascade reaction also proceeded in good yield with isatin diazo to provide the corresponding spirocyclic oxindole (**7e**, Figure 5). The relative stereochemistry of the spirocyclic oxindole **7e** was determined using single-crystal X-ray crystallography.[27] As expected, the resulting hydroxyl group and the carbonyl moiety of diazo were found to be in a *cis* configuration as reported previously in the literature, including our own work on the carbene−heteroatom insertion/aldol cyclizations.[8] With an underlying goal to access 9-membered lactones, we also attempted a reaction of β-ketoacids with vinyldiazoacetates; unfortunately, the reaction gave a complex mixture without any trace of aldol product.

In conclusion, the reported rhodium carbenoid initiated carboxylic O−H insertion/aldol cascade sequence is convergent

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in nature and uses readily accessible ketoacids and diazocarbonyls as starting materials to access highly functionalized lactones of a variety of ring sizes. An important feature of this transformation is its high chemo-, regio-, and stereoselectivity. Applications of this cascade reaction to the corresponding lactams are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03327.

Complete experimental details and relevant spectra for all important compounds (PDF)

Accession Codes

CCDC 1844114, 1844116, and 1860137 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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