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Enantioselective Ketone Hydroacylation Using Noyori's Transfer Hydrogenation Catalyst

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Supporting Information

ABSTRACT: An enantioselective ketone hydroacylation enables the direct preparation of lactones from keto alcohols. The alcohol is oxidized in situ to an aldehyde, obviating the need to prepare sensitive keto aldehyde substrates. Noyori's asymmetric transfer hydrogenation catalyst was applied to address challenges of reactivity, chemoselectivity, and enantioselectivity.

The γ-butyrolactone core occurs in more than 15,000 natural products,[1] including antibiotic and antitumor agents, and it is a useful building block in organic synthesis.[2] To prepare enantioenriched lactones, our laboratory has been developing rhodium-catalyzed hydroacylation.[3] These rhodium catalysts, however, fail to cyclize 1,4-keto aldehydes such as **3** to generate the corresponding γ-butyrolactones (Figure 1a).[4,5] Instead, significant decarbonylation occurs, presumably due to the conformational flexibility of these substrates. Poor reactivity and chemoselectivity have limited the use of other catalysts in this transformation, including N-heterocyclic carbenes (NHCs),[6a,b] ruthenium hydrides such as $RuHCl(CO)(PPh_3)_3$,[6c] and iridium hydrides.[6d] Enantioselectivity is difficult to achieve, and only one moderately enantioselective (43−84% ee) Tishchenko-type cyclization of related 1,5-keto aldehydes, which uses stoichiometric SmI_2 and a chiral auxiliary, has been reported.[6e] These results highlight a need for hydroacylation catalysts that operate by alternative mechanisms. To address these challenges, we considered that a bifunctional ruthenium hydride catalyst could be applied to achieve a novel chemo- and enantioselective hydroacylation of 1,4-dioxygenated substrates (Figure 1b).[7]

Applying an asymmetric transfer hydrogenation (ATH) catalyst[8] allows the 1,4-keto aldehyde substrate, which is sensitive to decomposition via aldol-type pathways, to be replaced with a stable 1,4-keto *alcohol* that undergoes in situ oxidation to the requisite aldehyde (Figure 1b).[9] Krische and co-workers have demonstrated diene and alkyne hydroacylation from the alcohol oxidation state by applying transfer hydrogenation conditions.[10] We envisioned that hydroacylation of 1,4-keto alcohol **4** could occur by initial asymmetric reduction of the ketone to afford diol **5**. Oxidation of the primary alcohol[11] would generate 1,4-hydroxy aldehyde **6**, which could cyclize to hemiacetal **7**. Finally, irreversible oxidation of **7** would yield the desired γ-butyrolactone **8**.[12,13] In contrast to our reported rhodium-catalyzed hydroacylations,[3] this mechanistic scenario circumvents activation of the aldehyde C−H bond and therefore avoids competing aldehyde decarbonylation.[14]

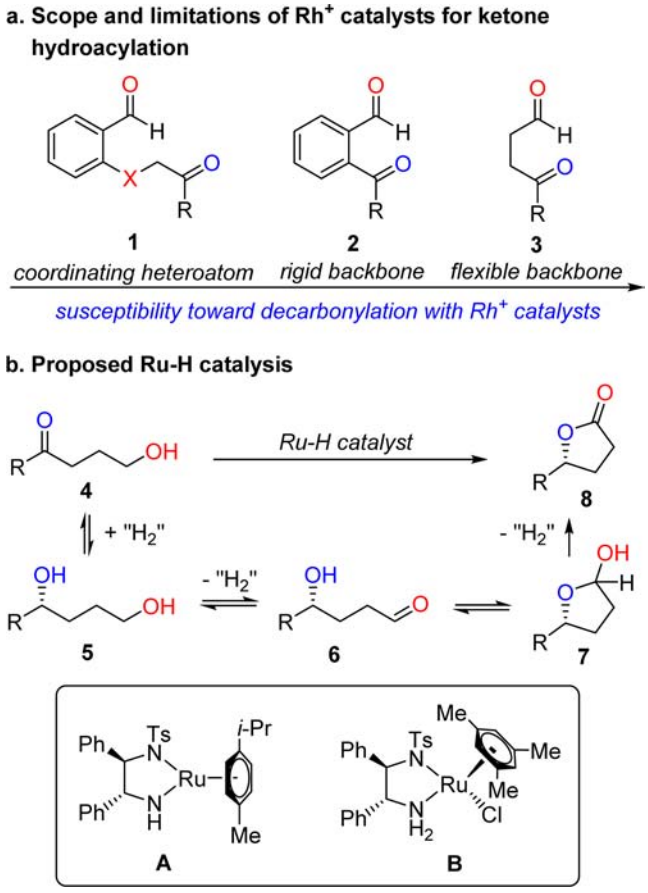

Figure 1. Strategies for intramolecular ketone hydroacylation.

With this mechanism in mind, we chose to apply Noyori's ATH catalyst[8] in ketone hydroacylation. To test our hypothesis, we combined 4-hydroxybutyrophenone with 5 mol % **A** and 1.2 equiv of acetone as a hydrogen acceptor (Scheme 1). We evaluated a number of solvents[15] and found that when ethyl acetate (EtOAc) was used, γ-phenyl-γ-butyrolactone was isolated in 92% yield with 91% ee in favor of the *R* stereoisomer.[16] In contrast to reports on the use of $RuHCl(CO)(PPh_3)_3$[6c] and iridium hydrides[6d] in ketone hydro-

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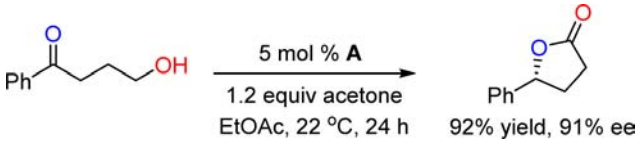
Scheme 1. Enantioselective Hydroacylation of 4-Hydroxybutyrophenone



acylation, this transformation proceeded at room temperature and no aldehyde dimerization or overoxidation products were observed.

We monitored this transformation by ^{1}H NMR spectroscopy and observed a sigmoidal reaction profile (Figure 2).[17] When

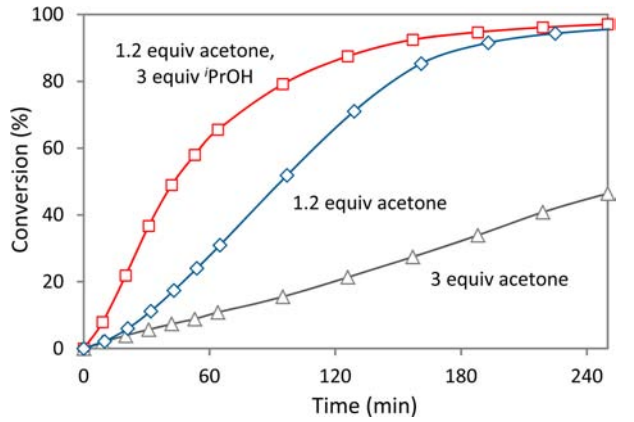


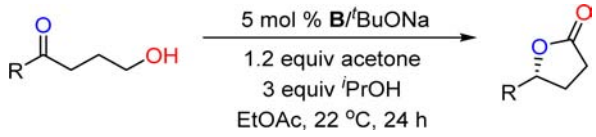
Figure 2. Kinetic profiles for hydroacylation of 4-hydroxybutyrophenone with 5% **A** and different amounts of ^{i}PrOH and acetone in C_6D_6.

the reaction was initiated with 3 equiv of the coproduct isopropyl alcohol (^{i}PrOH), we observed an increased rate and no significant induction period. To explain this autocatalytic behavior,[18] we propose that ^{i}PrOH, which is generated via reduction of acetone during the hydroacylation, promotes the formation of the ruthenium hydride catalyst and accelerates the ATH step. A larger excess of ^{i}PrOH resulted in the formation of a reductive cyclization product (2-phenyltetrahydrofuran), while excess acetone inhibited the reaction.

Rather than independently preparing catalyst **A**, we aimed to generate the active catalyst in situ by dehydrochlorination of the commercially available ruthenium salt [(*R*,*R*)-TsDPEN]-(arene)RuCl]. Although the aldehyde intermediate **6** is likely sensitive to base-induced decomposition via aldol pathways, in situ NMR monitoring of the reaction (vide supra) with **A** indicated that this aldehyde accounts for less than 1% of the substrate distribution during catalysis. We thus tested a catalyst mixture of **B** and sodium *tert*-butoxide (^{t}BuONa) and found that the desired γ-butyrolactone could be isolated in 90% yield with 93% ee (Table 1, entry 1). Increasing the reaction scale to 3 mmol (0.5 g) gave similar results.

With this convenient protocol, a range of 4-hydroxybutyrophenone derivatives[19a] can be oxidized to the corresponding chiral lactones (Table 1). Substitution at the 3- and 4-positions of the phenyl group with electron-donating or -withdrawing groups (entries 2−6) resulted in yields and ee's of 70−91% and 87−92%, respectively. Substrates with low oxidation potentials, such as 4-methoxyacetophenone, typically undergo ATH with moderate enantioselectivity when ^{i}PrOH is used as a hydrogen donor because of partial racemization of the product via reversible dehydrogenation.[8,19a] In contrast, we observed that a

Table 1. Enantioselective Hydroacylation of 1,4-Keto Alcohols[a]



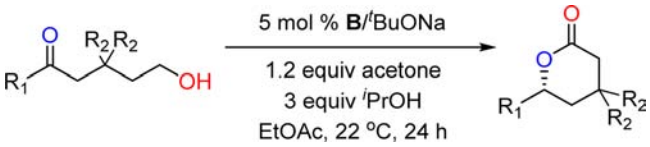
entry	R	isolated yield (%)	ee (%)
1	Ph	90 (92[b])	93 (93[b])
2	3-Cl-C_6H_4	83	90
3	3-MeO-C_6H_4	82	91
4[c]	4-Br-C_6H_4	91	87
5[b]	4-F-C_6H_4	84	87
6[c,d]	4-MeO-C_6H_4	70	92
7[d]	2-naphthyl	78	90
8[c]	2-furyl	77	87
9[c,d,e]	Ph−C≡C	65	91
10[c,d,e]	^{n}Bu−C≡C	79	90

[a]0.3 mmol scale. [b]3 mmol scale (0.5 g). [c]0 °C. [d]3 days. [e]10 mol % **B**/^{t}BuONa

4-methoxy-substituted hydroxy ketone (entry 6) underwent hydroacylation with relatively high enantioselectivity (92% ee). This result suggests that either the lactol formation or lactonization enforces greater kinetic control on the stereodetermining hydrogenation than in conventional ATH.[20] Other substituents capable of forming π interactions with the catalyst,[21] such as 2-naphthyl, 2-furyl, and alkynyl[19b] (entries 7−10), gave good results as well (65−79% yield with 87−91% ee). In general, performing the reaction at 0 °C led to higher enantioselectivity, and **B** furnished products in similar yields but with 2−16% higher ee than **A**.[22]

Our method can also be applied to cyclize 1,5-hydroxy ketones to δ-valerolactones (Table 2), despite the greater ring strain in six-membered lactones than in five-membered lactones (by approximately 2.4 kcal/mol[23]). Substrates with aryl substituents performed similarly to their five-membered-ring analogues and gave excellent results (entries 1−4). The yields ranged from 65 to 81%, and high levels of enantioselectivity

Table 2. Enantioselective Hydroacylation of 1,5-Keto Alcohols[a]



entry	R_1	R_2	isolated yield (%)	ee (%)
1	Ph	H	81	90
2	4-Cl-C_6H_4	H	65	96
3[b,c]	3-MeO-C_6H_4	H	70	95
4[b]	4-Me-C_6H_4	H	73	91
5	2-benzofuryl	H	65	90
6	2-furyl	H	<10[e]	n.d.
7[d]	^{n}Bu−C≡C	H	42[e]	86
8	Ph−C≡C	H	32[e]	86
9	2-furyl	Me	98	90
10[d]	^{n}Hex−C≡C	Me	55	90
11	Ph−C≡C	Me	87	90

[a]0.3 mmol scale. [b]0 °C. [c]3 days. [d]10 mol % **B**/^{t}BuONa. [e]NMR yield.

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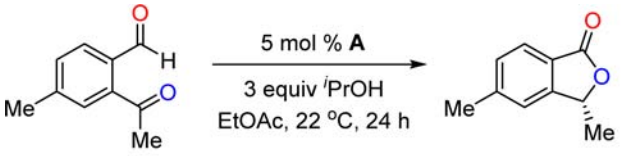
were obtained for both electron-rich and -deficient substrates (96 and 95% ee, respectively; entries 2 and 3). While a benzofuryl-substituted ketone was cyclized in good yield (entry 5), furyl and alkynyl substrates (entries 6−8) were transformed with poor efficiency.[24] However, introducing a *gem*-dimethyl group on the backbone (entries 9−11) promoted cyclization of these otherwise challenging substrates (55−98% yield, 90% ee).

Finally, we wondered how the ruthenium catalysts would compare to the cationic rhodium catalysts that our laboratory previously used to cyclize seven-membered-ring precursors **1** and 2-keto benzaldehydes **2**.[3a,c] For this study, **A** was chosen as the catalyst to avoid base-induced aldol reactions, and acetone was not added because **1** and **2** were already in the aldehyde oxidation state. While derivatives of **1** and other seven- or eight-membered-ring precursors were resistant to hydroacylation,[25] a 2-keto benzaldehyde derivative underwent efficient hydroacylation to generate the corresponding phthalide in 85% yield with 90% ee (Scheme 2). Thus, the rhodium and ruthenium catalysts provide complementary scope and mechanistic pathways for asymmetric ketone hydroacylation.

Scheme 2. Hydroacylation of a 2-Keto Benzaldehyde



85% yield, 90% ee

In summary, we have reported a novel strategy for the asymmetric hydroacylation of 1,4- and 1,5-keto alcohols. The use of a bifunctional ATH catalyst was crucial to obtain reactivity at room temperature, chemoselectivity for ketone hydroacylation over aldehyde dimerization, and high enantioselectivity. Although this transformation is oxidative overall, the reaction was found to be autocatalytic in a reductant (^{i}PrOH) and inhibited by excess oxidant (acetone). γ-Butyrolactones, δ-valerolactones, and phthalides are accessible by this method.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(4) Applying [Rh((*S*,*S*,*R*,*R*)-Duanphos)NO_3] (the catalyst in ref 3c) for hydroacylation of 4-oxobutyrophenone yielded only the decarbonylation product (unpublished result).

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(12) For selected examples of diol oxidation to lactones using metal hydride catalysts, see: (a) Ito, M.; Osaku, A.; Siibashi, A.; Ikariya, T. *Org. Lett.* **2007**, *9*, 1821. (b) Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *Org. Lett.* **2002**, *4*, 2361. (c) Suzuki, T.; Morita, K.; Matsuo, Y.; Hiroi, K. *Tetrahedron Lett.* **2003**, *44*, 2003. (d) Endo, Y.; Bäckvall, J.-E. *Chem.—Eur. J.* **2011**, *17*, 12596. (e) Maytum, H. C.; Tavassoli, B.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 4387.

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(15) EtOAc gave the highest enantioselectivity among the various solvents that were examined. Benzene, toluene, 1,2-dichloroethane, and acetonitrile gave good reactivity but slightly lower enantioselectivity. Tetrahydrofuran, 1,4-dioxane, and dichloromethane showed lower reactivity. See the Supporting Information (SI) for details.

(16) The absolute configuration of the lactone was determined by correlation of the optical rotation with literature data and was the same as that expected for ATH of the same ketone. See the SI for details.

(17) See the SI for plots of reaction rate vs time.
(18) For some recent examples of autocatalytic reactions, see: (a) Giri, R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 15860. (b) Sewell, L. J.; Lloyd-Jones, G. C.; Weller, A. S. *J. Am. Chem. Soc.* **2012**, *134*, 3598. (c) Flegeau, F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161.
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(20) Deuterium labeling studies indicated that lactonization of 1,4-diols, where one alcohol is primary and the other is secondary, is faster than oxidation of the secondary alcohol (see ref 12a), supporting a mechanism in which ATH of the ketone is rate-limiting.
(21) Attractive interactions between the π system of the aryl or alkynyl ketone with the C−H bonds of the mesitylene ligand in the major diastereomeric pathway and repulsive interactions between the π system and the SO_2 moiety on the diamine ligand in the minor diastereomeric pathway are thought to contribute to the high enantioselectivity. See: (a) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818. (b) Dub, P. A.; Ikariya, T. *J. Am. Chem. Soc.* **2013**, *135*, 2604.
(22) See the SI for a comparison of the ee's obtained using **A** and **B**.
(23) Bierenstiel, M.; Schlaf, M. *Eur. J. Org. Chem.* **2004**, 1474.
(24) The δ-valerolactone products with alkynyl substituents and no substitution on the backbone (Table 2, entries 7 and 8) decomposed on silica and could not be isolated in pure form. The reaction was repeated several times for these substrates, and the isolated yields varied from 20 to 66%. Because of these difficulties in product isolation, NMR yields are reported in entries 6−8 of Table 2. In these instances, the ee values were determined by derivatization of the products with excess phenyllithium to form a diol, followed by purification and chiral HPLC analysis.
(25) Tested substrates included 6-oxo-6-phenylhexan-1-ol, 7-oxo-7-phenylheptan-1-ol, and **1a** (X = O, R = Ph).