En Route to Diastereopure Polycyclic γ-Lactones by Iridium-Catalyzed Hydride Transfer

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Abstract

The reductive lactonization strategy provides an efficient access to stereoenriched polycyclic γ-lactones. However, it is still a formidable challenge to develop an efficient and versatile protocol with excellent levels of diastereocontrol. Herein we provide a highly diastereoselective and efficient route to diastereopure bi- and polycyclic γ-lactones, by means of an iridium-catalyzed hy-dride transfer strategy. This method features high levels of stereocontrol, broad substrate scope, and high catalyst efficiency (S/C = up to 5000). Mechanistic studies suggested that the iridium hydride formation be the rate-determining step, and that the hydride transfer step be the diastereo-determining step. The large steric hindrance of the iridium hydride species and intramolecular hydro-gen bonding are critically key to the diastereocontrol of the hydride transfer process. From the perspectives of configurational anal-ysis and Duniz angles of attack, the nature of diastereocontrol is well rationalized. A more general empirical rule based on facial se-lectivity analysis for explaining and predicting the stereochemistry is also proposed.

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En Route to Diastereopure Polycyclic γ-Lactones by Iridium-Catalyzed Hydride Transfer

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Keywords

Iridium catalysis | hydride transfer | reductive lactonization | diastereoselectivity control | polycyclic γ-Lactones

Comprehensive Summary

The reductive lactonization strategy provides an efficient access to stereoenriched polycyclic γ-lactones. However, it is still a

Background and Originality Content

Stereoenriched polycyclic γ-lactones display a wide spectrum of biological activities, and are important lead molecules for the development of physiological and therapeutic agents. Representative bioactive compunds containing *cis* -γ-lactone substructures are listed in Figure 1, including*Longilactone* ,[1] *Merrilactone*

A ,[2]Ineleganolide,[3]*(+)- Strigol,* [4]*Artemisin A* ,[5]and *Mitchellene C.* [6] The 2,3-*cis* -bicyclic γ-lactones were also used as key intermediates in the total synthesis of natural products Mitchellenes B-H.[7]

The importance of stereoenriched polycyclic γ-lactones has triggered numerous efforts for their chemical synthesis.[8,9]Specifically, the reductive lactonization of 2,3-fused 4-oxo-butanoic acids, with two stereocenters pre-installed, represents a step-economic and diastereo-controllable stragegy. However, very limited efforts have been made in this area.[10] In 1983 Eisenbraun and coworkers investigated the diastereocontrol, using*cis* -2-benzoylcyclohexane-1-carboxylic acid (R = Ph, (±)-*cis* -**1a**) as the model substrate (Scheme 1a, i).[10a] They found that the diastereochemical outcomes were dependent on the reducing agents. With strongly basic metal hydrides, *anti* -selectivity (*syn:anti* = 21:79 to 5:95) was favored. Notably, with sterically large hydrides, the*anti* -selectivity was highly enhanced (5:95 or 6:94). They also evaluated the platinum oxide catalyzed hydrogenation, and a moderate*syn* -selectivity was observed (*syn* :*anti* = 74:26). In 2005, Rovis and coworkers achived a good *syn* -selectivity by means of an acid-promoted transfer hydrogenation process ($PhMe_2SiH$/TFA) (Scheme 1a, ii).[10b]This protocol was limited to a variety of (±)-*cis* -2-propionylcycloalkane-1-carboxylic acid (*syn* :*anti* = 90:10 to >95:5). For example, the reaction of 2-propionylcyclohexane-1-carboxylic acid (R = Et, (±)-*cis* -**1b**) yielded a *syn* :*anti* ratio of 93:7. However, their protocol was not applicable to the 2-aroyl counterparts, as exemplified by the unselective reaction of (±)-*cis* -**1a**(*syn* :*anti* = 50:50). Even now, controlling the diastereochemistry of the reductive γ-lactonization still remains a formidable challenge, and an efficient and versatile protocol with excellent diastereocontrol is in high demand.

Figure 1 Bioactive structures with polycyclic*cis* -γ-lactone substructures.

Scheme 1 Previous and our reductive γ-lactonization strategies.

The past several years have witnessed our efforts on developing new synthetic methodologies by virtue of catalytic hydride transfer processes catalyzed by a novel series of half-sandwiched $[Cp^*Ir^{III}Cl/PyIm]^+Cl^-$complexes [PyIm = 2-(4,5-dihydro-1*H* -imidazol-2-yl)pyridine, Cp* = pentamethylcyclopentadiene]. With those complexes, a series of reactions were realized under acidic conditions by our group, including transfer hydrogenation of aldehydes,[11]ketones,[12] nitroalkenes,[13]imines,[14] deoxygenation of alcohols,[15] and other reactions.[16]The reduction of oximes and reductive amination and beyond were also reported by Luo's group. [17] The key intermediates were identified as iridium hydrides [Ir]–H, of which the hydride atom comes from the formyl hydrogen of formic acid (Scheme 1b). Our systematic studies have disclosed the special properties of the iridium hydride species: They were mild hydride donors with weak Lewis basicity and nucleophilicity and large steric hindrance. These properties rendered them as acid-tolerant and stereo-discriminating transient reducing agents, as evidenced by our previous highly diastereoselective hydride transfer reductions of endocyclic sp^2-hybridized carbon centers of cyclohexyl/cyclopentyl carbocations[15b] and 1,5-benzodiazepines[14] (Scheme 1b). Out of our expertise, we envision to try our $[Cp^*Ir^{III}Cl/PyIm]^+Cl^-$catalysts in solving the diastereocontrol challenge of reductive γ-lactonization. The key to the diastereocontrol lies on the sterically governed hydride transfer to the exocyclic sp^2-hybridized carbon of carbonyl group. Gratifyingly, our catalysts, even at *S/C* = 5000 (*S/C* = substrate/ catalyst molar ratio), showed good performance in inducing the diastereocontrol, yielding (±)-*syn* -**2** in 99:1 dr in most cases. What is more, the substrate scope limitation in previous studies was well overcome (Scheme 1c, R = aryl and alkyl). Herein, we report our iridium-catalyzed highly diastereoselective reductive lactonization strategy, and provide an efficient access to diastereopure bicyclic γ-lactones with three continuous sterecenters.

Results and Discussion

Using (±)-*cis* -**1a** as the model substrate, we optimized the reaction conditions, using ethanol and water as the green solvent (Table 1).[18] The relative configuration of*syn* -**2a** was assigned by analyzing the coupling constants of the proton at the newly formed stereocenters and by comparing the NMR spectra of *syn* -**2a** with those reported. Catalysts were first screened (entries 1-8). At *S/C* = 1000, the catalysts**C1** –**C7** gave 83-99% yields (entries 1-7), while N-Ts catalyst **C8** only resulted in a 39% yield (entry 8). The substituents on pyridine rings and the N-substituent on the imidazoline ring imposed different effects on the yields,

presumably by affecting the basicity and nucleophilicy of the corresponding iridium hydride intermediates. **C1** was selected as the optimal catalyst. Decreasing its loadings to 2000 and 5000 *S/C* ratios still gave (±)-*syn* -**2a** in >99 and 87% yields (entry 9-10). Shortening the reaction time to 1 hour, the yield of (±)-*syn* -**2a** slightly decreased under the condition of 2000 *S/C* ratio (entry 11). Upon lengthening time to 4 hours at 5000 *S/C* ratio, 90% yield of (±)-*cis* -**1a** was obtained (entry 12). Optimization of the equivalents of formic acid revealed that 8 equivalents of formic acid or more was necessary for a complete conversion (entries 9, 13, and 14).

Table 1 Optimization of reaction conditons

entry	cat.	*S/C* [a]	time (h)	Yield (%)[b]	*syn*:*anti*[c]
1	**C1**	1000	2	>99	99:1
2	**C2**	1000	2	83	99:1
3	**C3**	1000	2	96	99:1
4	**C4**	1000	2	96	99:1
5	**C5**	1000	2	95	99:1
6	**C6**	1000	2	90	99:1
7	**C7**	1000	2	94	99:1
8	**C8**	1000	2	39	99:1
9	**C1**	2000	2	>99	99:1
10	**C1**	5000	2	87	99:1
11	**C1**	2000	1	98	99:1
12	**C1**	5000	4	90	99:1
13[d]	**C1**	2000	2	76	99:1
14[e]	**C1**	2000	2	>99	99:1

[a] Molar ratio of substrate to catalyst.[b] ^{1}H NMR yield with 1,3,5-trimethoxybenzene as an internal standard. [c] Determined by^{1}H NMR.[d] HCO_2H (4 equiv).[e] HCO_2H (12 equiv).

A number of *cis* -2-acyl cycloalkane-1-carboxylic acids were synthesized via either $AlCl_3$-catalyzed Friedel-Crafts acylation[19] or Ni-catalyzed cross-coupling of anhydrides with organozinc reagents,[20] followed by submitting them to the optimal conditions (Table 2). The stereochemistry of products was further demonstrated by the one-dimensional NOE (Nuclear Overhauser Effects) spectra of four randomly selected representative compounds (**2c** ,**2x** , **2aa** , and **2b**). We focused our substrate scope on 2-aroyl substrates (R = aryl, *cis* -**1**), to which previously established *syn* -selective reductive lactonization protocols were not applicable.[10b] In addition to*cis* -**1a** , other 2-aroyl substituted substrates were converted to the desired diastereopure products in 60-99% yields and 98:2 to >99:1 diastereoselectivity, strongly favoring the formation of *syn* -isomers (**2a** -**2u**). The substituents, for instance, alkyls, phenyl, phenyloxyl, benzenesulfenyl, and halogen atoms, on phenyl rings, whether electron-donating or withdrawing, all uniformly gave [?] 98:2 dr (**2a** -**2n**), although the yields varied. Substrates bearing more complex arene rings such as 5,6,7,8-tetrahydronaphthalen-2-yl (**2o**), 4-methylnaphthalen-2-yl (**2p**), naphthalen-2-yl and naphthalen-1-yl (**2q**), pyren-4-yl (**2r**), 9*H* -fluoren-3-yl (**2s**), and dibenzo[*b* ,*d*]thiophen-2-yl (**2u**) also transformed in >99:1 dr. The ketoacid with dibenzo[*b* ,*d*]furan-2-yl (**2t**) was reductively lactonized in [?] 98:2 dr values. Oxidation of the sulfur atom of*syn* -**2u** did not reduce its diastereopurity.

We next examined the effects of backbone architectures on the stereochemial results. Introduction of an endocyclic disubtituted (**2w**) or tetrasubstituted alkene moiety (**2x**), being fused with a bridged bicyclic [2.2.1] or [2.2.2] scaffold (**2y** and **2z**), or contraction of the cyclohexane ring to cyclopentane (**2aa**) or cyclobutane (**2ab**), did not affect the stereochemical outcomes. All products were produced in >99:1 dr values, and *syn* -products were formed exclusively.

Substrates with alkanoyls (R = alkyl, *cis* -**1**) were also amenable to the diastereocontrol. The reactions

of*cis* -**1b** and *cis* -**1ac** both gave > 99:1 dr values and reasonable yields.

Table 2 Substrate scope[a]

[a] *cis* -**2a** , **2c** –**2h** ,**2k** –**2o** , **2q, 2w, 2ab** were isolated by extraction. [b] The regioselective ratio (rr) of ketoacid was 94:6 (*para* :*ortho*), and it was inherited to the next step. [c] The *rr* of ketoacid and product was 50:50. [d] 0.1 mmol of ketoacid was used. [e] HCO_2H (16 equiv.),**C1** (S/C = 500), H_2O/EtOH (1:1), 80°C, 6 h. [f] The *rr* of ketoacid and product was 96:4.[g] HCO_2H (12 equiv.), **C1**(S/C = 500), H_2O/EtOH (1:1), 80°C, 6 h.

Mechanistic studies were performed (Scheme 2). The isotope tracing experiments with HCO_2D, DCO_2D, and D_2O (Scheme 2a) demonstrated that (1) the transfered hydride originated from the formyl group of formic acid, and (2) that H–D exchange, both between iridium hydride ([Ir]–H) and D_2O and between iridium deteride ([Ir]–D) and H_2O, occurred before the hydride or deuteride transfer.[12, 15a, 21] The H–D exchange between [Ir]–D and solvent was dramatically suppressed by using DCO_2D and D_2O-EtOH as the respective deteride source and solvent, and thereby a 95% D-incorporation was obtained. We also measured the kinetic isotope effect (KIE), and ak_H /k_D = 4.8 was observed (Scheme 2b). The primary KIE implied that the rate-determining step should involve a C–H cleavage event.

The key intermediate during the reductive lactonization was observed by^{1}H NMR of the crude reaction mixture (Scheme 2c). It turned out to be an alcohol (**3a**), which was generated from the diastereospecific reduction of the ketone moiety. Treatment of this alcohol under acidic conditions (AcOH) yielded lactone*syn* -**2a** with >99:1 *syn* :*anti*ratio. We also found that the reduction of 4-ketoester*cis* -**1m'** did not occur (Scheme 2d), which indicated the important role of the carboxylic acid group in facilitating the reduction. Similar carboxylic acid effect was also observed by Rovis and coworkers.[10b]

Scheme 2 Isotope labelling, KIE, and other mechanistic expecriments.

Scheme 3 Proposed mechanism and diastereocontrol models

On the basis of the mechanistic studies, a plausible mechanism was proposed (Scheme 3a). In light of the KIE studies, the generation of iridium hydride **B** via β-hydride elimination was suggested to be the rate-determining step.[22] Subsequent hydride transfer to the carbonyl group, which was activated by the carboxylic group, served as the diastereo-determining step. Considering the experimental results in Scheme 2d, we proposed that the hydrogen bonding between the carboxylic acid and ketone moiety accounted for the activation. In detail, protonation of the C=O bond of carboxylic acid**1a** increased its acidity, and an intramolecular hydrogen bonding between O–H and carbonyl C=O occurred, as designated by the structure **C** . Although **C** could resonate with**D** , it was suggested as the major contributor for explaining the carboxylic effect. On the other hand, the intramolecular hydrogen bonding, to some extent, fixed the configuration by connecting the ketone and carboxylic acid moieties. The fixed and somewhat rigid configuration of the molecule rendered the hydride transfer more stereoselective. In this regard, it is the intramolecular hydrogen bonding that holds responsibility for the excellent diastereocontrol in the hydride transfer step. Once diastereospecifically formed,**3a** immediately undergoes intramolecular esterification, following classic acid-catalyzed addition-elimination mechanism, to form lactone *syn* -**2a** , without eroding the stereochemistry of the newly generated stereocenter.

To better understand the diastereocontrol of the hydride transfer, we performed the DFT calculations. The calculated fixed configurations and Bürgi-Dunitz angles of attack for hydride delivery to carbonyl were shown in Scheme 3b and 3c.[23] In the case that the carboxylic assumes axial position and benzoyl equatorial position (Scheme 3b), the frontside attack will encounter severe steric repulsion against two axial hydrogen atoms and one axial carboxylic group. However, the backside attack faces very little steric retardation. Consequently, the hydride delivery in this direction kinetically preferentially gave *syn* -**2a** . Similar stereocontrol is also applicable in the other configuration bearing an equatorial carboxylic and an axial benzoyl (Scheme 3c). In one word, it is the steric repulsion between sterically bulky iridium hydride and the cycloalkyl ring that governs the diastereoselectivity.

To explain the backbone architecture effects in Table 2 and also to predict the stereochemical outcomes of the potential reactions of substrates with similar stereochemistry, we proposed a rule of thumb (Scheme 3d). The hypothesis that the hydrogen bond form an additional ring (ring B) leads to a *cis* -fused bicyclic system, and thereby the hydride reduction of the "pseudo-endocyclic" carbonyl was endowed with facial selectivity—the hydride can attack from either convex or concave face.[24] Owing to the large steric hindrance of the iridium hydride, it would preferentially donate its hydride from the sterically much more accessible convex face, in this way generating a configuration with all the hydrogen atoms on the three tertiary stereocenters residing in the same convex face.

Scheme 4 Gram-scale reactions and synthetic applications

In the two gram-scale reactions, **2a** and **2m** were both isolated in excellent yields and > 99:1 dr (Scheme 4a). The purification was very convenient. Column chromatography was not required. Extraction with ethyl acetate followed by drying and concentration afforded desired products in good NMR purities (see Supporting Information). The 4-bromophenyl group in **2m** acted a handle for further chemical manipulations (Scheme 4b). For examples, the Suzuki coupling of **2m** with three aryl boric acids carrying electron-withdrawing or electron-donating substituents delivered more functionalized products **4a** -**4c** in 56-96% yields, and the stereochemistry of the three stereocenters was not affected.

trans -2-Benzoylcyclohexane-1-carboxylic acid (*trans* -**1a**) did not undergo the reductive lactonization (Scheme 4c), highlighting the importance of the configurational effect of the substrate. In other words, our iridium catalysts showed excellent capability in discriminating the *cis* - and*trans* -substrates, and highly selectively catalyzed the reactions of *cis* -substrates, leaving the *trans* -ones intact. This selectivity provides an easy procedure to separate the *cis* - and*trans* -2-acylcycloalkane-1-carboxylic acids, which were generated as a diasteremeric mixture in some cases and were difficult to be separated due to their almost identical polarity. As shown in Scheme 4d, subjection of equimolar *cis* -**1a** and*trans* -**1a** to standard reductive latonization conditions produced *cis* -**2b** in 94% yield and*trans* -**1a** in 92% recovery. Due to the largely different polarities and water solubility of *cis* -**2b** and*trans* -**1a** , they were easily separated.

Conclusions

We have developed a highly diastereoselective method for efficient synthesis of diastereopure bi- and polycyclic γ-lactones, using*cis* -2,3-fused 4-oxo-butanoic acids as the starting materials. This method features the use of a $[Cp^*Ir^{III}Cl/PyIm]^+Cl^-$catalyst with formic acid as the hydride source. Advantages of this method include excellent diastereoselectivity control, use of water-ethanol as solvent, broad substrate scope, and high catalyst efficiency (*S/C* up to 5000). The gram-scale reactions take place efficiently in excellent yields and diastereocontrol. Mechanistic studies suggested that the iridium hydride formation be the rate-determining step, and that the hydride transfer step be the diastereo-determining step. The large steric hindrance of the iridium hydride species underlies the success of diastereocontrol. The carboxylic acid group of substrates plays important roles in activating the substrates and in rendering a relatively rigid configuration to highly diastereoselectively receive the hydride. DFT calculations provide detailed insights into the nature of diastereocontrol, from the perspectives of configurational analysis and Duniz angles of attack. An empirical rule based on facial selectivity analysis for explaining and predicting the stereochemistry is also proposed. Our iridium catalysts only work on *cis* -2,3-fused 4-oxo-butanoic acids, showing excellent level of molecular recognization. This selectivity can be harnessed to separate the diastereomeric mixtures of *cis* - and*trans* -2-acylcycloalkane-1-carboxylic acids. Compared with previous methods, our method shows superiority in terms of substrate scope, degree of diastereocontrol, and sustainability.

Experimental

To a 10-mL reaction tube was sequentially added *cis* -2-acyl cycloalkane-1-carboxylic acids**1** (0.2 mmol), ethanol (0.5 mL), 1 mL of **C1** solution in deionized water (0.0001 mol/L, *S/C* = 2000). The tube was then sealed with a rubber cap. A syringe needle was inserted into the cap to connect the inner to outer atmosphere. The mixture was stirred for 3 minutes in an 80 °C heating block, followed by addition of formic acid (60 μL, 1.6 mmol, 8 equiv) in one portion via a microsyringe. After stirring for 2 h, the reaction mixture

was cooled to room temperature, diluted with saturated brine (2 mL), and extracted with ethyl acetate (2 mL × 3). The organic phase was dried with anhydrous Na_2SO_4 and then removed under reduced pressure. ^{1}H NMR pure *syn* -**2a** ,**2c** –**2h** , **2k** –**2o** , **2q** ,**2w** , **2ab** were obtained without further purification. Other products were purified by silica gel column chromatography.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

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Εν Ρουτε το Διαστερεοπυρε Πολψςψςλις γ-Λαςτονες βψ Ιριδιυμ-ἀταλψζεδ Ηψδριδε Τρανσφερ Yang
An iridium-catalyzed highly diastereoselective and efficient route to diastereopure bi- and polycyclic γ-lactones is achieved,