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Functionalized Cyclopentenones Through a Tandem NHC-Catalyzed Dynamic Kinetic Resolution and Ambient Temperature Decarboxylation: Mechanistic Insight and Synthetic Application

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Abstract

An unusual room temperature β -lactone decarboxylation facilitated a five-step enantioselective formal synthesis of the cyclopentane core of an estrogen receptor β -agonist. A computational study probed the underlying factors facilitating unprecedented, rapid decarboxylation. Aryl substitution promotes faster reaction in the retro-[2+2] as a result of conjugative stabilization with the forming olefin. Additionally, the configuration of the α -ester in these fused β -lactones leads to differential decarboxylation rates resulting in enantioselectivity.

Catalytic methods to assemble bioactive molecules and privileged motifs are on-going pursuits in synthesis. Many have sought to achieve this goal by employing organic catalysts, which allows for a greener approach.¹ *N*-Heterocyclic carbenes (NHC) have emerged as powerful class of organic catalysts that can be used to construct important structural motifs, bioactive molecules, and natural products.² Our group and others have shown that NHCs react with aldehydes to generate catalytically competent enolate,³ homoenolate,⁴ and acyl anion intermediates,⁵ which have been trapped with various electrophiles. In 2012, we reported the first NHC-catalyzed dynamic kinetic resolution (DKR) of α -substituted- β -ketoesters (1) to furnish bicyclic β -lactones (2) and cyclopentenones (3) (Scheme 1 eq. 1).⁶ Computational studies⁷ shed light on the rare, non-classical nature of this specific organocatalytic DKR and on the origins of stereoselectivity in the β -lactone formation. While examining this NHC-DKR process we determined that aryl ketones with electron-donating substitution or heteroaromatic ketones normally resulted in complete spontaneous decarboxylation to the cyclopentene (3) under the reaction conditions (eq. 2). Unfortunately, this rapid decarboxylation led to cyclopentenones with diminished enantioselectivity, due the moderate diastereoselectivity (5–7:1 d.r.) for the lactone forming process. However,

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substrates possessing an *ortho*-substitution on the aryl ring of the ketone furnished the respective products in 20:1 dr. Therefore, the rapid decarboxylation before the separation of the diastereomer lactones is inconsequential, allowing for the isolation of the desired cyclopentene in high yield while maintaining the high enantioselectivity (90% *ee*). In this communication, we apply this DKR to construct the cyclopentane ring of known bioactive benzopyrans. This report demonstrates that this DKR can be applied to the enantioselective synthesis of different analogues of these bioactive benzopyrans. Additionally, we delve into the mechanism of the rapid decarboxylation for this DKR process using computational methods and explain why certain substrates are more prone to rapid decarboxylation, even under these mild conditions.

(1)

(2)

In 2006, Eli Lilly disclosed a new class of hydroxylated benzopyrans that were highly potent and selective estrogen receptor β -agonist with nanomolar activity in models of benign prostatic hyperplasia, otherwise known as enlarged prostate (Figure 1).⁸ A subsequent structure-activity relationship study revealed that the cyclopentane ring was essential to provide nanomolar activity while maintaining the great selectivity.^{8e} Previous reported syntheses to these enantioenriched benzopyrans relied on an eight-step linear reaction sequence and a subsequent preparative chiral HPLC separation of the final benzopyran to obtain enantiopure products. To the best of our knowledge, a general catalytic asymmetric variant to these compounds has not been reported. The formal synthesis began with the treatment of literature known⁹ acetophenone 4 with dimethyl carbonate and sodium hydride in toluene afforded β -keto ester 5. A Tsuji-Trost allylation of β -ketoester and with allyl carbonate 6 and subsequent PCC oxidation provided aldehyde 7 in 36% yield over three steps. In the key enantioselective, catalytic DKR step, the exposure of aldehyde 7 to 7 mol % of azolium 8 with 30 mol % of Cs_2CO_3 gave cyclopentene 9 in 86% yield with excellent enantioselectivity (92% *ee*). A subsequent hydrogenation (Pd/C) gave cyclopentane 10 in 48% yield as a sole diastereomer based on comparison with reported structures.¹⁰ This cyclopentane (10) in racemic form has previously been converted to selective estrogen

receptor benzopyran 11 in three steps by scientists at Eli Lilly.^{8e} Thus we have been able to employ our NHC-DKR-decarboxylation strategy toward an efficient, asymmetric route to these valuable benzopyrans and related structures. Most notably this synthetic sequence avoids the previously described chiral separation approach and provides a stereocontrolled and efficient method to rapidly assemble a diverse library of these bioactive benzopyrans.

β -lactones with an electron-rich aryl ring, such as 4-MeOPh (**2a**, Table 1, entry 1), synthesized under Scheme 1 conditions undergo unprecedented and rapid decarboxylation to the cyclopentene, often leaving no trace of the lactone.⁶ This outcome is in sharp contrast to the thermolytic conditions (>60 °C) typically required for decarboxylative [2+2]-cycloreversion of β -lactones (Scheme 3).¹¹ Reduced temperatures have traditionally only been achieved through radical decarboxylation.¹² Electron-neutral (**2b**) and -poor (**2c**) β -lactones are stable to Scheme 1 conditions; decarboxylation only occurs after heating in SiO₂ (Scheme 3), as previously observed.

To probe the apparent electronic effects controlling this unusual decarboxylation and the origins of enantioselectivity, we conducted a computational study using quantum mechanical computations (SCS-MP2¹³/def2TZVP¹⁴//B3LYP¹⁵/6-31G(d)¹⁶ with B3LYP/6-31+G(d,p)/PCM(DCE)**Error! Hyperlink reference not valid.** solvation corrections).¹⁸ The computed retro-[2+2] transition state structures (TSs) are shown in Figure 1. The *anti* and *syn* refer to the diastereomeric relationship between the lactone and the loss of CO₂. All transition structures are concerted asynchronous,¹⁹ and our computed barriers match the observed relative rates of decarboxylation. The *anti* configuration reacts faster than the *syn* (Scheme 3).

CO₂ ejection is accelerated by conjugation to the planar aryl group. The configuration of the α -ester affects the conjugation by affecting the degree of planarity of the aryl group with the forming olefin. In the *anti* TS, the aryl groups are planar to the forming olefin, facilitating the ejection. This is in contrast to the *syn* TS, where the aryl group is slightly twisted out of the plane, costing an energetic penalty of 0.3 kcal mol⁻¹.

As a consequence of the conjugation, *the electronic nature of the aryl group has a direct effect on the reactivity*. Initial cleavage of the C–O bond leads to a transient benzylic carbocation character, which is sensitive to the electronics of the aryl group. Electron-donating *para* and/or *ortho* substituted aryl groups dramatically lowers the decarboxylation TS barriers, for example, *p*-OMe aryl substitution (Table 1) reacts rapidly *anti* at 19.1 kcal mol⁻¹. This is in contrast to electron-neutral and electron-poor substituted aryl lactones that have higher barriers of 27.5 and 31.4 kcal mol⁻¹, respectively, in agreement with experimentally observed higher reaction temperatures. In all aryl cases, the *syn* barriers are higher, but still follow the general trend. This trend echoes limited reports on the decarboxylation in a series of related β -lactones at ambient and cryogenic temperatures, with rapid decarboxylation for electron-donating (*p*-OMePh) substituents and none for electron-neutral or -poor substituents.²¹ In the absence of conjugating aryl groups, e.g., aliphatic ($G^\ddagger = 33.3$, $G^\ddagger = 0.1$) and hydro ($G^\ddagger = 38.2$, $G^\ddagger = -1.0$), barriers are higher and the enantioselectivity is diminished and reversed, respectively.

Enantioselectivity is inherent to the molecule by virtue of the α -group configuration. We modulated the size and electronics of the α -group to probe whether steric or electronic factors (measured in A values²² and σ_p^+ ,²³ respectively) give rise to the different *anti/syn* barriers. To test for steric control, the ester ($\sigma_p^+ = 0.49$, $A = 1.27$) was replaced by the similarly electron-withdrawing but smaller cyano group ($\sigma_p^+ = 0.66$, $A = 0.17$). CN α -substitution led to a loss of selectivity. Electronic control was investigated by replacement with the equivalently sized, but electron donating methyl group ($\sigma_p^+ = -0.31$, $A = 1.7$). Retention of selectivity was observed computationally with methyl α -substitution and loss with cyano, indicating that the ester controls selectivity through its steric component. This observed steric effect originates from the strain afforded by decarboxylation *syn* to the α group (Figure 1). The pseudo-equatorial (*R*)-ester in the minor *syn*-**TS12** diastereomer leads to a repulsive interaction (2.9 Å) with the departing CO₂. The absence of this repulsion in the favored *anti*-**TS12** lowers the barrier by ~2–3 kcal/mol.

In conclusion, we have demonstrated the NHC-catalyzed DKR/decarboxylation process can be utilized as the key step in the enantioselective formal synthesis of a benzopyran estrogen receptor β -agonist. Using an *ortho*-substituted aryl ketone allowed us to achieve high enantioselectivity (92% *ee*) without prior separation of the diastereomers. This process alleviates the need for chiral HPLC as previously used in a Lilly campaign to separate the enantiomers of the benzopyrans. Utilizing computational studies we uncovered the principles controlling the concerted retro-[2+2] decarboxylation mechanism from this DKR, including the electronic effects on rate. Aryl ketones with electron rich substitution likely decarboxylate through *ortho/para*-quinone methide resonance like intermediates. The *anti*-selective decarboxylation observed for aryl ketones is the result of steric interactions between the α group and the carboxylate groups in the *syn*-TSs.

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Supplementary Material

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Scheme 1.
NHC-Catalyzed Dynamic Kinetic Resolution

Scheme 2.

Enantioselective formal synthesis of estrogen receptor β-agonist 11.

Scheme 3.
 β -Lactone decarboxylation to cyclopentene.²⁰

Table 1

Electronic effects on decarboxylation rate and selectivity.

Entry	R	Yield (% ee) ^a	<i>anti</i> -TS12 G ^{‡b}	<i>syn</i> -TS12 G [‡] (G ^{‡b})
1	2a 4-OMePh	71 (70)	19.1	22.1 (3.0)
2	2b Ph	95 (98) ^{c,d}	24.7	27.5 (2.8)
3	2c 4-CNPh	64 (99) ^c	29.1	31.4 (2.3)
4	2d Me	– ^e	33.3	33.4 (0.1)
5	2e H	– ^e	38.2	37.2 (–1.0)

^a Scheme 1 conditions, (*S*)-**3** major product.^b Energies reported in kcal mol^{–1}.^c No decarboxylation observed under Scheme 1 conditions.^d Scheme 2 conditions.^e Theoretical values only. Substrates not accessible through Scheme 1.

Table 2

Test for origins of selectivity by α group modulation.

Entry	R	R'	<i>anti</i> -TS12 $G^\ddagger$ ^a	<i>syn</i> -TS12 $G^\ddagger$ ($G^\ddagger$) ^a
1	2f CN	4-OMePh	33.9	34.3 (0.4)
2	2g CN	H	30.5	29.7 (-0.8)
3	2h Me	4-OMePh	18.4	21.0 (2.6)
4	2i Me	H	35.8	34.6 (-1.2)

^aEnergies reported in kcal mol⁻¹.