Lactone Synthesis

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Intermolecular Dynamic Kinetic Resolution Cooperatively Catalyzed by an N-Heterocyclic Carbene and a Lewis Acid**

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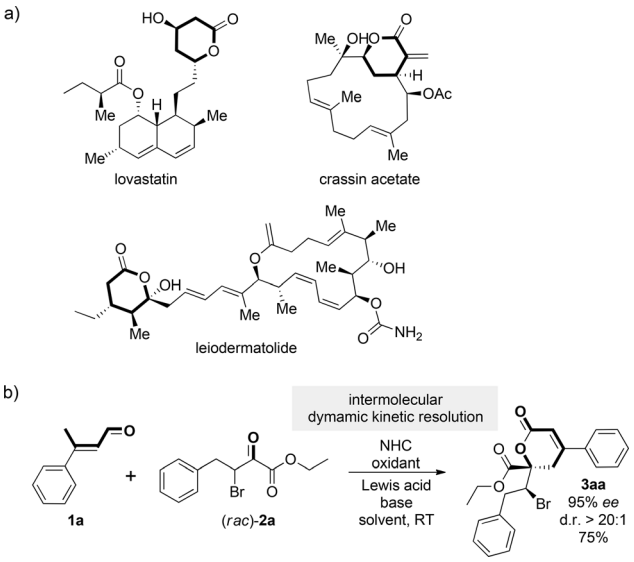
Abstract: *The ubiquitous structure of δ-lactones makes the development of new methods for their enantioselective and stereoselective synthesis an important ongoing challenge. The intermolecular dynamic kinetic resolution (DKR) of β-halo-α-ketoesters cooperatively catalyzed by an N-heterocyclic carbene and a Lewis acid generates two contiguous stereocenters with remarkable diastereoselectivity through an oxidation/lactonization sequence.*

Driven by the demand to enhance the economic balance of chemical processes, there has been an increased interest in the transformation of racemates into a single stereoisomeric product without the occurrence of the undesired stereoisomer. Within this context, dynamic kinetic resolution (DKR) has proven to be a powerful strategy in asymmetric synthesis, allowing the stereoconvergent transformation of both enantiomers of a racemic substrate into a single enantiomer of a target molecule.[1] This approach thus overcomes the limitation of traditional kinetic resolutions,[2] which provide a maximum chemical yield of 50% for a particular enantiomer. In contrast, the theoretical yield of an efficient DKR is up to 99%.[3]

Organocatalytic DKR processes are emerging as significant complementary methods for the conversion of racemic starting materials to products with excellent enantio- and/or diastereocontrol.[4–6] Recently, Chi and co-workers reported an example of the kinetic resolution of azomethine imines through an NHC-catalyzed [3+4] cycloaddition.[7] Zhao and co-workers developed two simple kinetic resolutions through an NHC-catalyzed atroposelective acylation or NHC-catalyzed esterification.[8] To date, only Scheidt and co-workers reported intramolecular NHC-catalyzed DKR transformations for the preparation of β-lactones.[9] However, to the best of our knowledge, the NHC-catalyzed enantioselective intermolecular DKR reaction has not yet been reported.[10] Our present work constitutes the first study of an enantioselective intermolecular dynamic kinetic resolution through oxidative NHC catalysis,[11,12] which leads to enantioenriched δ-lactones. Several examples of biologically important chiral δ-lactones are highlighted in Scheme 1 a.[13]



Scheme 1. a) Representative chiral δ-lactones and b) our preparation method.

The results of the search for and optimization of reaction conditions are summarized in Table 1. The reaction between enal **1a** (0.12 mmol) and α-ketoesters **2a** (0.1 mmol) was chosen as a model reaction and quinone **K** (DQ) was used as the oxidant. Studies on chiral NHC catalysts showed that when indanol-derived catalyst **E** with an *N*-2,6-diethylphenyl substituent was used, the desired cycloaddition product **3aa** was formed, albeit with moderate enantioselectivity and excellent diastereoselectivity (Table 1, entry 5, 71% *ee*, d.r. > 20:1, 81% yield). A switch of the base from K_2CO_3 to CsOAc led to a slightly increased *ee* value, and comparable yield and d.r. (entry 9, 74% *ee*, d.r. > 20:1, 87% yield). Very recently, Scheidt and co-workers reported a significant enhancement of the *ee* value when a mild Lewis acid (e.g. LiCl, $Ti(OiPr)_4$, or $Mg(OtBu)_2$) was used as an additive in NHC-catalyzed additions.[14] In 2011, You and co-workers found that the use of a sodium salt ($NaBF_4$) could significantly improve the enantioselectivity of an NHC-catalyzed redox-Michael reaction.[11f] Later, Chi and co-workers reported the improved control of the enantioselectivity of an NHC-catalyzed cycloaddition by the addition of a Lewis acid, $Sc(OTf)_3$ or $Mg(OTf)_2$.[12a] Inspired by these pioneering results, we investigated several Lewis acids as a potential second catalyst to interact with either one or both of the reaction partners (the vinyl enolate intermediate and the α-ketoesters, Scheme 5). When $Sc(OTf)_3$ was used as a Lewis acid co-catalyst, the results were encouraging; for example, the *ee* value of the product improved from 77% to 81% (entry 14). During the

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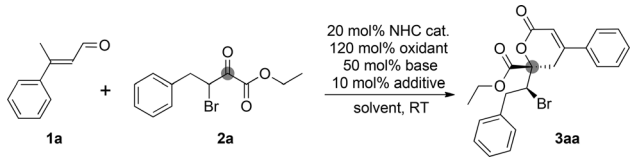
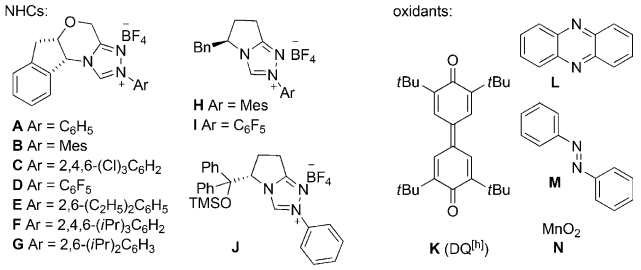
Table 1: Optimization of the reaction conditions.[a]

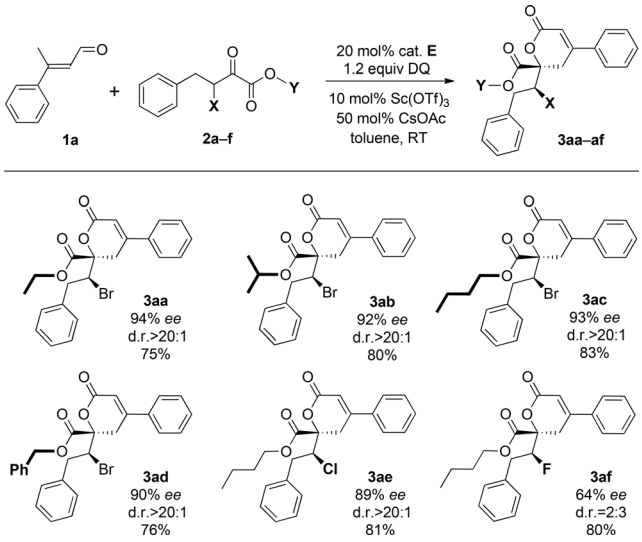


Entry	NHC Cat.	Solvent	Base	Additive	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**A**	THF	K_2CO_3	–	<10	–	–
2	**B**	THF	K_2CO_3	–	82	>20:1	53
3	**C**	THF	K_2CO_3	–	80	>20:1	17
4	**D**	THF	K_2CO_3	–	<10	–	–
5	**E**	THF	K_2CO_3	–	81	>20:1	71
6	**H**	THF	K_2CO_3	–	78	>20:1	25
7	**I**	THF	K_2CO_3	–	<10	–	–
8	**J**	THF	K_2CO_3	–	NR[g]	–	–
9	**E**	THF	CsOAc	–	77	>20:1	74
10	**E**	THF	CsOAc	LiCl[e]	78	2:1	–
11	**E**	THF	CsOAc	$In(OTf)_3$	NR[g]	–	–
12	**E**	THF	CsOAc	$Zn(OTf)_2$	NR[g]	–	–
13	**E**	THF	CsOAc	$Mg(OTf)_2$	80	>20:1	75
14	**E**	THF	CsOAc	$Sc(OTf)_3$	81	>20:1	81
15[h]	**E**	**toluene**	**CsOAc**	**$Sc(OTf)_3$**	**75**	**>20:1**	**94**
16[i]	**E**	toluene	CsOAc	–	76	>20:1	79
17[j]	**E**	toluene	CsOAc	$Sc(OTf)_3$	73	>20:1	94
18	**E**	CH_2Cl_2	CsOAc	$Sc(OTf)_3$	81	>20:1	85
19	**F**	toluene	CsOAc	$Sc(OTf)_3$	77	>20:1	89
20	**G**	toluene	CsOAc	$Sc(OTf)_3$	78	>20:1	93

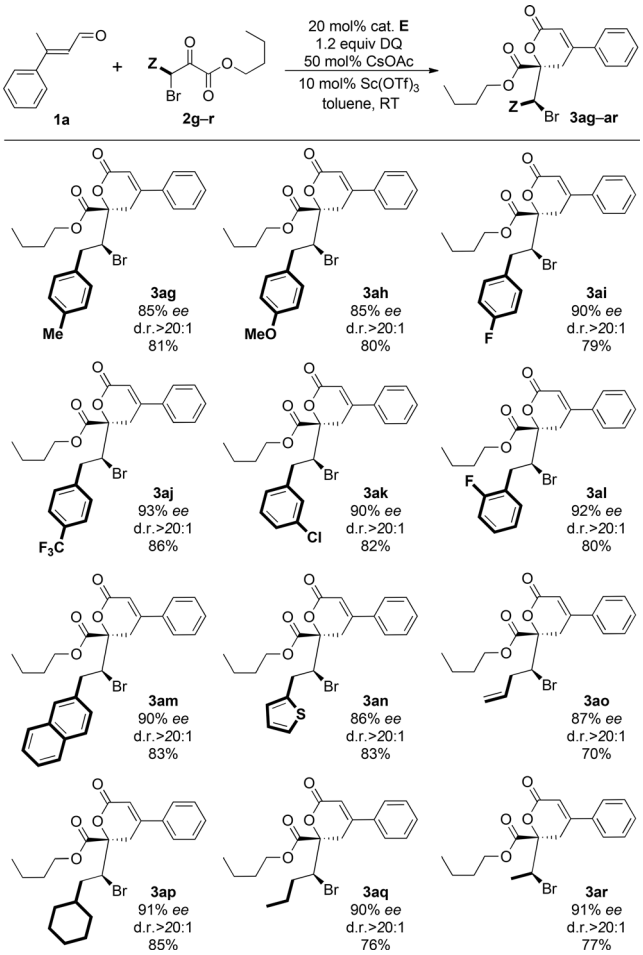
[a] Reaction conditions: aldehyde **1a** (0.12 mmol, 1.2 equiv), α-ketoester **2a** (0.10 mmol, 1.0 equiv), NHC cat. (0.02 mmol), K_2CO_3 (0.05 mmol), oxidant **K** (0.12 mmol, 1.2 equiv), THF (1.0 mL), 24 h, RT. [b] Yields of isolated products after column chromatography. [c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [d] The *ee* values were determined by HPLC using a chiral stationary phase. [e] 20 mol% of LiCl. [f] 100 mol% of CsOAc. [g] No reaction. [h] DQ = 3,3′,5,5′-Tetra-*tert*-butyldiphenoquinone. [i] When the oxidant **K** was replaced by **L**, **M**, or **N**, chemical yields are all <5%. [j] 10 mol% cat. **E**, t = 55 h. The entry in bold marks optimized reaction conditions.



screening of other Lewis acids (LiCl, $In(OTf)_3$, $Zn(OTf)_2$, $Mg(OTf)_2$), we found that the use of $In(OTf)_3$ and $Zn(OTf)_2$ resulted in no conversion. The use of LiCl resulted in a good conversion, but led to low enantio- and diastereoselectivity (entry 10). $Mg(OTf)_2$ was the only other Lewis acid co-catalyst that offered similar benefits in the control of the enantioselectivity (entry 13). At last, we found that the use of toluene as solvent consistently afforded the cycloaddition product with a good yield and excellent *ee* value and d.r. (entry 15, 94% *ee*, d.r. > 20:1, 75% yield). We also tested the feasibility of reducing the loading of the NHC catalyst **E** from 20 mol% to 10 mol%, and still obtained the product in 77%



Scheme 2. Scope of β-halo-α-ketoesters. Reaction conditions: **1a** (0.12 mmol), **2a–f** (0.1 mmol), cat. **E** (0.02 mmol), CsOAc (0.05 mmol), DQ (0.12 mmol), $Sc(OTf)_3$ (0.01 mmol), toluene (1 mL), 24 h, RT.

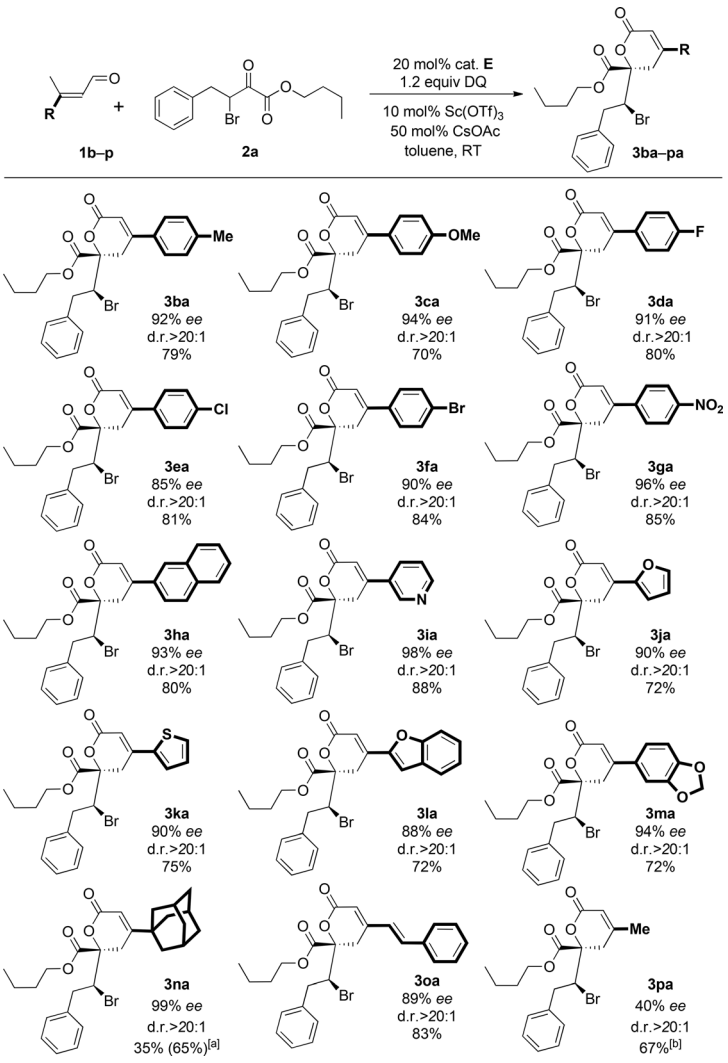


Scheme 3. Scope of other β-halo-α-ketoesters. Reaction conditions: **1a** (0.12 mmol), **2g-r** (0.1 mmol), cat. **E** (0.02 mmol), CsOAc (0.05 mmol), DQ (0.12 mmol), $Sc(OTf)_3$ (0.01 mmol), toluene (1 mL), 24 h, RT.

yield and 94% *ee*, albeit after a prolonged reaction time (entry 17, 55 h vs. 24 h).

With the optimized reaction conditions in hand, the substrate scope of the β-halo-α-ketoesters was evaluated, beginning with the size of ester groups (Scheme 2). A change of the ester group from ethyl (**3aa**, Y = Et) to isopropyl (**3ab**, Y = *i*Pr), *n*-butyl (**3ac**, Y = *n*Bu), or benzyl (**3ad**, Y = Bn) did not encumber the reaction, and the corresponding products were obtained with high enantio- and diastereoselectivity. To further understand the effect of the β-stereogenic center of the side chain on the reaction, we examined α-ketoesters with different β-halo substituents (X = halogen). Replacement of the Br substituent with Cl had little effect on the enantioselectivity of the reaction (**3ae**, 89% *ee*, d.r. > 20:1), however, replacement with F dramatically decreased the enantio- and diastereoselectivity of the reaction (**3af**, 64% *ee*, d.r. = 2:3). With regard to the above-mentioned results, we suspect that the size of the β-halo substituent may be the critical factor for enantio- and diastereocontrol.

In addition to a phenyl group (see Scheme 2), the reaction also tolerated *ortho*-, *meta*-, and *para*-substituted aryl groups at the γ-position of the β-halo-α-ketoesters (Scheme 3) and provided δ-lactones **3ag–al** in high yields and with excellent enantioselectivities (79–86% yield, 85–93% *ee*, all d.r. > 20:1). Naphthyl- (**2m**) and heteroaryl-substituted (**2n**) β-halo-α-ketoesters also reacted efficiently under the reaction conditions to provide **3am** and **3an** (90% *ee* and 86% *ee*, respectively). Several β-halo-α-ketoesters with alkyl groups at the γ-position underwent annulation without a loss of selectivity to provide **3ao–ar** with similarly high efficiency, thus indicating that aromatic interactions between the substrate and the catalyst are not required for high levels of selectivity. The increased steric hindrance of a cyclohexyl substituent in γ-position did not effect the selectivity in the formation of **3ap** (91% *ee*, d.r. > 20:1).

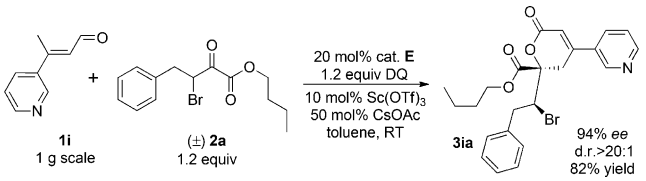


Scheme 4. Scope of α,β-unsaturated aldehydes. Reaction conditions: **1b–p** (0.12 mmol), **2a** (0.1 mmol), cat. **E** (0.02 mmol), CsOAc (0.05 mmol), DQ (0.12 mmol), $Sc(OTf)_3$ (0.01 mmol), toluene (1 mL), 24 h, RT. [a] The number in parentheses is the isolated yield after the recovery of starting material **1n**. [b] 50 °C.

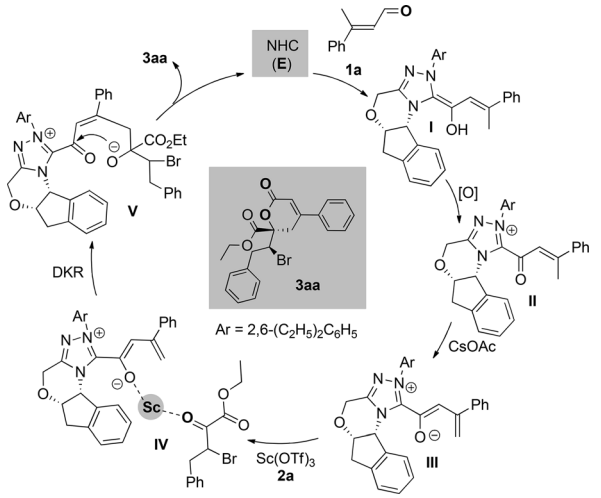
We next examined the scope of the reaction of compound **2a** with differently substituted enal substrates (Scheme 4). Both electron-donating (**3ba**, **3ca**, and **3ma**) and electron-withdrawing (**3da–ga**) substituents on the β-aryl unit were tolerated. Replacement of the β-phenyl substituent of the enal moiety with a naphthyl (**3ha**) or a heteroaryl (**3ia–la**) unit did not have a significant impact on the outcome of the reaction with regard to the yield or *ee* value. Replacement of the β-aryl group by a vinyl substituent gave product **3oa** with 89% *ee* and d.r. > 20: 1. Replacement with a bulky carbon unit gave product **3na** with a decreased yield, but with excellent enantio- and diastereoselectivity (99% *ee*, d.r. > 20:1). Replacement with a shorter carbon unit (e.g., a methyl group) resulted in a slow conversion and moderate enantiocontrol (δ-lactone product **3pa**, at 23 °C: < 10% yield after 24 h; at 50 °C: 67% yield, 40% *ee*).

The coupling of **1i** with **2a** on a gram scale gave product **3ia** in 82% yield without loss of stereoselectivity (Scheme 5). The absolute configuration of **3ad** was determined by X-ray crystallography, and the other products were assigned by analogy.[15]

A postulated reaction pathway for this reaction is depicted in Scheme 6. The vinyl enolate intermediate **III** likely arises from γ-deprotonation of the oxidatively generated unsaturated ester intermediate **II**, although direct oxidation of the γ-carbon atom of the enal moiety in homoenolate intermediate **I**, which would also lead to **III**, cannot be ruled out completely. Vinyl enolate **III** then



Scheme 5. Reaction of **1i** and **2a** on a gram scale.



Scheme 6. Postulated mechanism.

undergoes nucleophilic addition to β-bromo α-ketoester **2a**, eventually affording product **3aa**.[16] During the nucleophilic addition, the Lewis acid $Sc(OTf)_3$ is likely involved in the multisite coordination to bring the ketone electrophile into close proximity with intermediate **III**, as illustrated by **IV**.[17] This coordination may amplify the otherwise weak chiral induction by the chiral NHC catalyst.[18]

In conclusion, we have developed the first intermolecular dynamic kinetic resolution of α-ketoesters through cooperative catalysis by an N-heterocyclic carbene and a Lewis acid. The present process provides efficient access to enantioenriched δ-lactones in good to high yields with excellent diastereoselectivity. Further studies to understand the origin of the selectivity are ongoing in our laboratory.

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Keywords: annulation · dynamic kinetic resolution · lactones · N-heterocyclic carbene · oxidative addition

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[15] CCDC 1019722 (**3ad**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] A concerted pathway for this transformation (from **IV** to **3a**) cannot be ruled out.

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[18] To confirm this statement, a background reaction was conducted without $Sc(OTf)_3$ and with toluene as solvent. As indicated in Table 1, entry 16, the *ee* value of 79% demonstrated that the potential coordination of $Sc(OTf)_3$ played a vital role in the chiral induction.

