

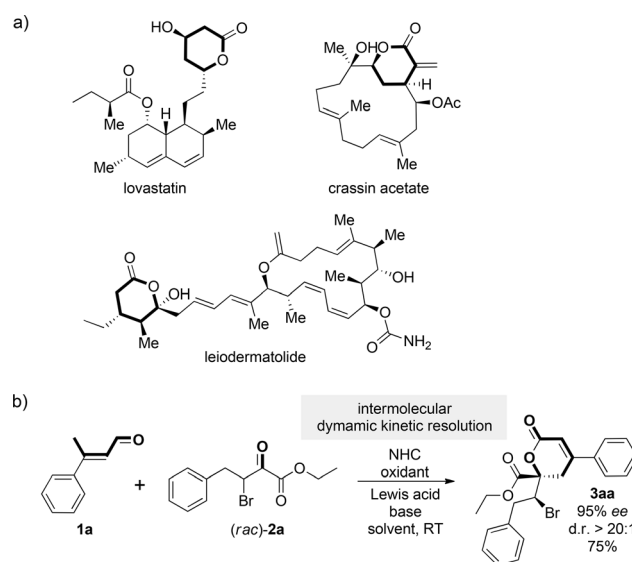
Intermolecular Dynamic Kinetic Resolution Cooperatively Catalyzed by an N-Heterocyclic Carbene and a Lewis Acid**

Zijun Wu, Fangyi Li, and Jian Wang*

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** (DO) 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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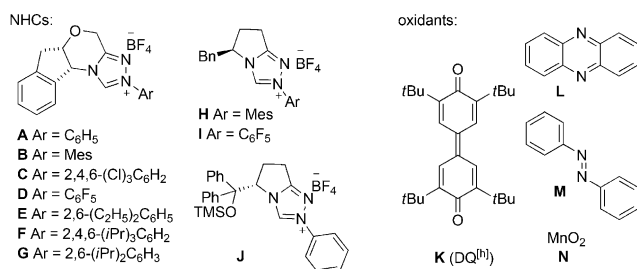
[**] The project described was supported by a grant from the Tsinghua University and the "Thousand Plan" Youth program of China.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201410030>.

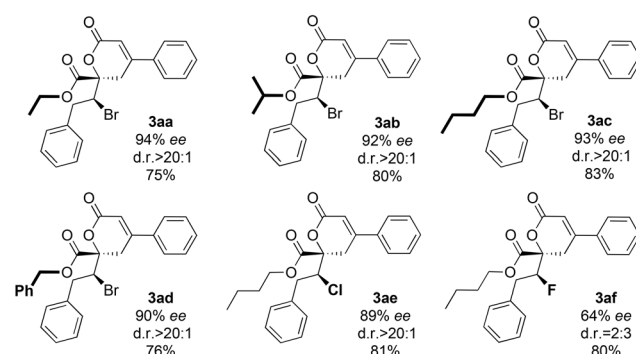
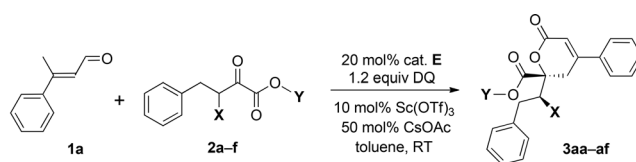
Table 1: Optimization of the reaction conditions.^[a]

Entry	NHC Cat.	Solvent	Base	Additive	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	A	THF	K ₂ CO ₃	—	< 10	—	—
2	B	THF	K ₂ CO ₃	—	82	> 20:1	53
3	C	THF	K ₂ CO ₃	—	80	> 20:1	17
4	D	THF	K ₂ CO ₃	—	< 10	—	—
5	E	THF	K ₂ CO ₃	—	81	> 20:1	71
6	H	THF	K ₂ CO ₃	—	78	> 20:1	25
7	I	THF	K ₂ CO ₃	—	< 10	—	—
8	J	THF	K ₂ CO 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 ^[i]	E	toluene	CsOAc	Sc(OTf)₃	75	> 20:1	94
16 ^[j]	E	toluene	CsOAc	—	76	> 20:1	79
17 ^[j]	E	toluene	CsOAc	Sc(OTf) ₃	73	> 20:1	94
18	E	CH ₂ Cl 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

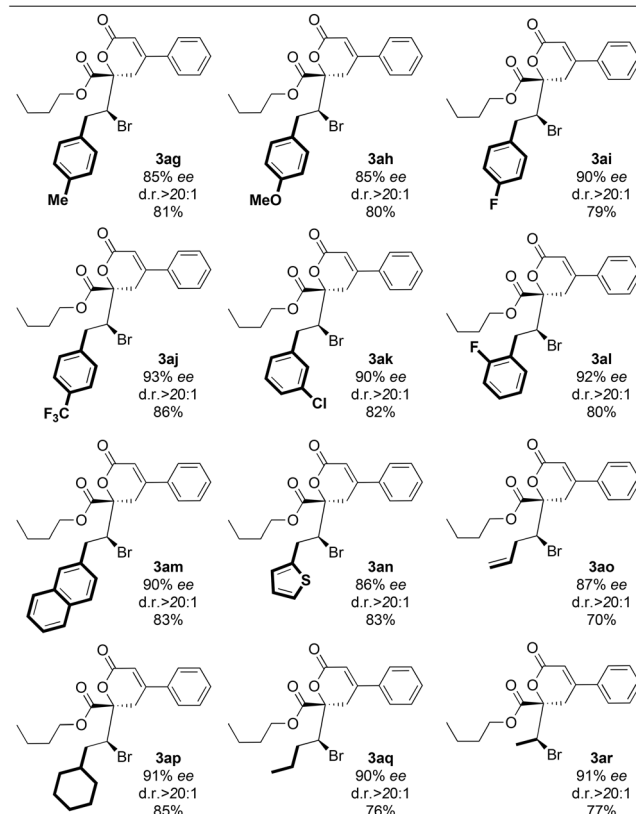
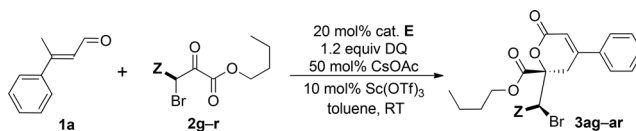
[a] Reaction conditions: aldehyde **1a** (0.12 mmol, 1.2 equiv), α -ketoester **2a** (0.10 mmol, 1.0 equiv), NHC cat. (0.02 mmol), K₂CO₃ (0.05 mmol), oxidant **K** (0.12 mmol, 1.2 equiv), THF (1.0 mL), 24 h, RT. [b] Yields of isolated products after column chromatography. [c] Diastereomeric ratio determined by ¹H 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*-butyldiphenylquinone. [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.

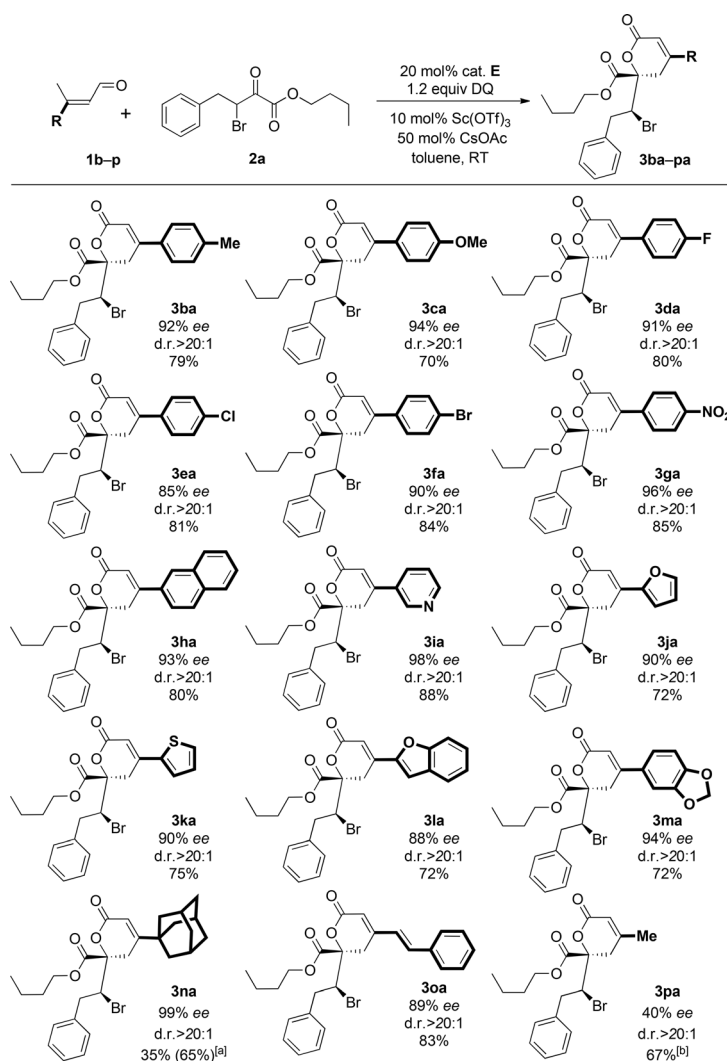
yield and 94% *ee*, albeit after a prolonged reaction time (entry 17, 55 h vs. 24 h).

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).

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*).

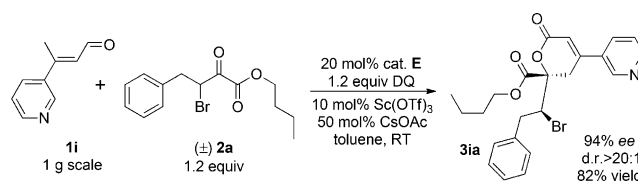
The coupling of **1i** with **2a** on a gram scale gave product **3ia** in 82% yield without loss of stereoselectivity (Scheme 5). The absolute configuration of **3ad** was determined by X-ray



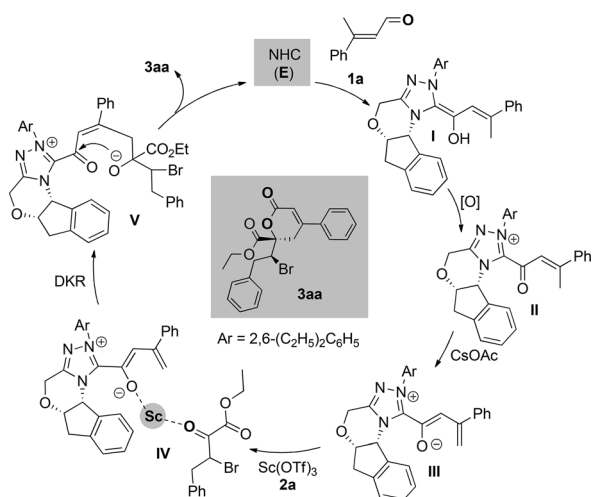
Scheme 4. Scope of α,β -unsaturated aldehydes. Reaction conditions: **1b–p** (0.12 mmol), **2a** (0.1 mmol), cat. **E** (0.02 mmol), CsOAc (0.05 mmol), DQ (0.12 mmol), Sc(OTf)₃ (0.01 mmol), toluene (1 mL), 24 h, RT. [a] The number in parentheses is the isolated yield after the recovery of starting material **1n**. [b] 50°C.

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 $\text{Sc}(\text{OTf})_3$ 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.

Received: October 13, 2014

Published online: November 28, 2014

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

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