Asymmetric Catalysis

Carbene-Catalyzed Enantioselective Aldol Reaction: Post-Aldol Stereochemistry Control and Formation of Quaternary Stereogenic Centers

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Abstract: The dominated approaches for asymmetric aldol reactions have primarily focused on the aldol carbon–carbon bond-forming events. Here we postulate and develop a new catalytic strategy that seeks to modulate the reaction thermodynamics and control the product enantioselectivities via post-aldol processes. Specifically, an NHC catalyst is used to activate a masked enolate substrate (vinyl carbonate) to promote the aldol reaction in a non-enantioselective manner. This reversible aldol event is subsequently followed by an enantioselective acylative kinetic resolution that is mediated by the same (chiral) NHC catalyst without introducing any additional substance. This post-aldol process takes care of the enantioselectivity issues and drives the otherwise reversible aldol reaction toward a complete conversion. The acylated aldol products bearing quaternary/tetrasubstituted carbon stereogenic centers are formed in good yields and high optical purities.

Introduction

The aldol reaction is a basic transformation in forming new carbon–carbon bonds and *b*-hydroxyl carbonyl compounds.[1] Given the proven wide applications, the development of new approaches for aldol reactions continue to be an active research topic of great values. Three main challenges are being addressed in the last several decades. One deals with asymmetric reactions and stereoselectivity controls. Enzymes,[2] enzymatic mimics such as short peptides,[3] chiral Lewis acids,[4] and organic[5] catalysts have all been developed. For example, chiral amines have been shown to promote asymmetric aldol reactions using aldehydes and ketones as the substrates.[6] A second challenge deals with sensitive chemoselectivity issues, such as those involving highly reactive acetaldehyde or its precursors in the reactions.[7] In this regard, List and co-workers have recently found that confined Brønsted acids can behave as highly chemo- and enantioselective catalysts.[8] The third challenge concerns aldol reactions that form (vicinal) quaternary/tetrasubstituted stereogenic centers.[9] Apart from the usual stereoselectivity issues, such reactions are particularly challenging for both kinetic and thermodynamic reasons. The steric bulkiness brings high kinetic barriers in the aldol addition steps;[10] the (substrate-dependent) thermodynamic instability of the aldol product can lead to low conversions owing to the retro-aldol processes.[11] To address these three challenges, nearly all approaches reported to date focus on controlling carbon–carbon bond forming step itself (Figure 1 a). This means that in these approaches the catalysts are primarily used to interact with the substrates (covalently or non-covalently) for substrate activation and chemo/stereo-selectivity control during the aldol carbon-carbon bond formation.

Herein we postulate a new approach for asymmetric aldol reactions, with the focus shifted to post-aldol reaction controls (Figure 1 b). In particular, we propose to activate a masked enolate (vinyl carbonate) by a N-heterocyclic carbene (NHC) catalyst to initiate a reversible aldol reaction to form aldol adduct in a non-enantioselective manner. This reversible aldol reaction is then followed by an enantioselective acylative kinetic resolution catalyzed by the same chiral NHC catalyst to form carbonate protected *b*-hydroxyl carbonyl products with high optical purities. A specific model reaction is shown in Figure 1 c. Activation of an *O*-acylated benzofuranone (1) by a NHC catalyst generates an ester enolate intermediate (I) and a catalyst-bound azolium carbonate intermediate (II). Subsequent aldol addition of I to a dicarbonyl ketone substrate (2) leads to aldol adduct III. This aldol addition step (from I and 2 to III) is highly diastereoselective and substrate-controlled. The unprotected aldol adduct (protonated version of III) is unstable and thus achieving high conversion and clean reaction is unrealistic. Remarkably, in our approach it does not matter much how the aldol process proceeds, as far as the process is reversible and a tiny amount of III can be formed. This is because our subsequent step of acylation can drive the equilibrium of the

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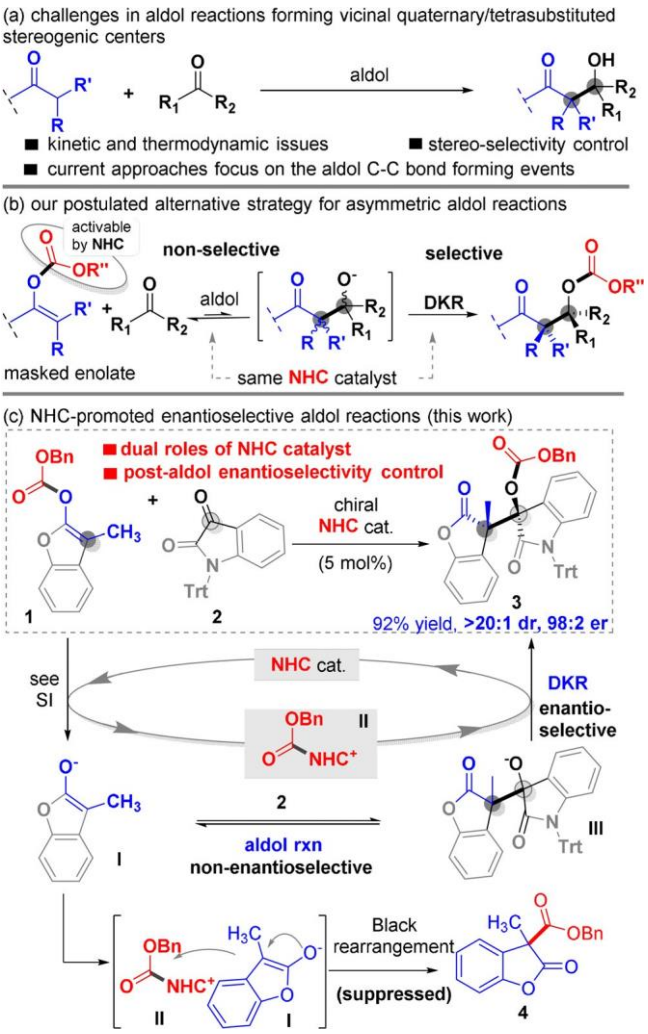


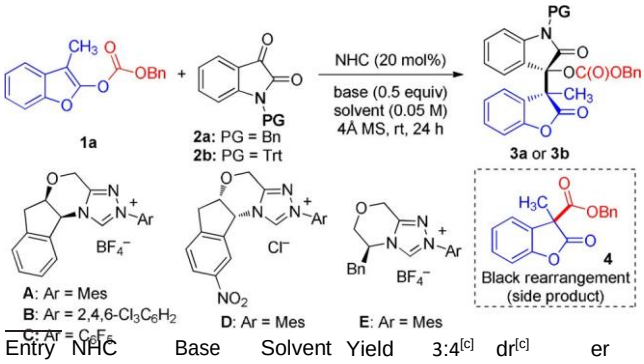
Figure 1. New strategy for challenging aldol reactions.

reversible aldol process toward complete formation of protected aldol product (3). This dynamic kinetic resolution (DKR) process uses the same chiral azolium carbonate intermediate (II, generated in the earlier step) for selective acylation with regeneration of the NHC catalyst. In our approach, the NHC catalyst plays dual roles in two catalytic steps, with the enantioselectivity controlled in a post-aldol DKR process. The aldol products bearing vicinal quaternary/tetrasubstituted stereogenic centers are obtained with excellent diastereo- and enantio-selectivities. Our design fully takes advantage of NHC's capacity in activation of carboxylic esters[12] and promoting dynamic kinetic resolutions.[13] Compared with the classic approaches that focus on the aldol reaction step itself, post-aldol stereoselectivity control (without introducing additional substrates, reagents or catalysts) is nearly undeveloped.[14] Perhaps the most relevant study is Shibasaki's elegant approach of post-aldol isomerization (to amplify the otherwise existed albeit low enantioselectivity) of the aldol adduct.[15] We expect our study to inspire unprecedented catalytic strategies for aldol reactions. In particular, our strategy should be valuable for aldol reactions that are thermodynamically unfavorable, chemoselectively challenging, or sterically and stereo-selectively difficult with the formation of quaternary/tetrasubstituted centers.

Results and Discussion

A first problem to overcome in our approach is to suppress the potential Steglich and Black rearrangements[16] involving the masked enolate (the vinyl carbonate) substrate (Figure 1c). The undesired competing reaction path involved a direct acyl transfer process via a Black rearrangement process between intermediate I and II, leading to adduct 4 as a side product. Initial studies showed that in the presence of azolium salt A[17a] as the NHC pre-catalyst, *N*,*N*-diisopropyl- ethylamin (DIEA) as a base, the reaction of 1a and 2a in tetrahydrofuran (THF) proceeded at room temperature to give a mixture of 3a and 4 in about 1:1 ratio and around 45 % overall yield (Table 1, entry 1).[18] We were encouraged to see the desired aldol product formed in 5:1 dr and 80:20 er. We next searched for conditions that could suppress the Black rearrangement reaction and favor the formation of the aldol product with effective DKR. The postulated DKR step and the Black rearrangement both involve azolium carbonate intermediate II. We thus expect the structure of NHC catalysts to have profound impacts on the reaction out- comes.[17b–d] Studies on the effects of NHC catalysts (entries 1–

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



Entry	NHC	Base	Solvent	Yield [%][b]	3:4[c]	dr[c]	er [%][d]
1	A	DIEA	THF	45	1:1	5:1	80:20
2	B	DIEA	THF	42	1:1	5:1	82:18
3	C	DIEA	THF	40	1:1	5:1	60:40
4	D	DIEA	THF	81	8:1	9:1	92:8
5	E	DIEA	THF	42	1:1	5:1	88:12
6	D	Cs_2CO_3	THF	65	5:1	9:1	88:12
7	D	K_2CO_3	THF	68	6:1	8:1	89:11
8	D	DBU	THF	66	5:1	9:1	88:12
9	D	DIEA	CH_2Cl_2	70	4:1	9:1	90:10
10	D	DIEA	MTBE	90	> 20:1	12:1	92:8
11	D (2 b)[e]	DIEA	MTBE	95	> 20:1	> 20:1	98:2
12	D (2 b)[f]	DIEA	MTBE	94 (92)	> 20:1	> 20:1	98:2

[a] Reaction conditions: 1a (0.1 mmol), 2a (0.15 mmol), base (0.5 equiv), NHC (20 mol%), and 4 A MS (100 mg) in solvent (2.0 mL) at rt. [b] Combined yield of 3 and 4 was calculated by ^{1}H NMR analysis. The data in parenthesis is yield of isolated product. [c] The ratios were determined by ^{1}H NMR analysis of crude product. [d] Enantiomeric ratio of 3 was determined via HPLC on a chiral stationary phase. [e] Substrate 2b was used. [f] 5 mol% of catalyst loading.

5)[17e–h] eventually found that the use of triazolium D[17f] could lead to predominated formation of 3a (3a:4 around 8:1, entry 4). It was also fortunate to see 3a was formed in a good yield with 9:1 dr and 92:8 er (entry 4). The use of bases such as Cs_2CO_3, K_2CO_3, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave slightly deteriorated results (entries 6–8). Examination on solvent effects (entries 9–10) revealed that methyl tert-butyl ether (MTBE) performed the best, giving 3a as essentially the only product (3a:4 > 20:1) in 90 % yield with 12:1 dr and 92:8 er. Control experiments showed that the Black rearrangement was suppressed nearly completely by using MTBE as the solvent under our condition. Replacing the *N*-benzyl (Bn) substituent of 2a with a *N*-trityl (trt) unit (substrate 2b) led to the corresponding aldol product 3b with excellent yield and further improved dr and er values (entry 11). Finally, the NHC catalyst loading could be reduced to 5 mol% with the formation of 3b in 92 % isolated yield, > 20:1 dr, and 98:2 er (entry 12).

With acceptable conditions on hand, we next evaluated the scope of the benzofuranone-derived vinyl carbonate (1) and isatin-based ketone substrate (2) to form the corresponding aldol products (Scheme 1). At first we examined the generality of isatins (2) by using 1a as a model vinyl carbonate (product 3b to 3 q). When the trityl protecting group was replaced by a methyl unit, a longer reaction time (48 h) was necessary and the product 3c was obtained in good yield and stereoselectivity. Both electron-donating and electron-withdrawing substituents at the 5-position of trityl-protected isatins were all tolerated (3 d–3 k). The absolute configuration of 3e was confirmed by X-ray analysis.[19] Introducing a chloride atom or a trifluoromethyl group at the 6-position of isatins did not affect the reaction outcomes, with 3l and 3m formed in high yields, excellent diastereo- and enantio-selectivities. Isatins bearing a fluoride atom or a methyl unit at the 7-position reacted effectively to give 3n and 3o with similar results. The use of 5,7-dimethyl substituted isatins gave 3p in 82 % yield with 97:3 er and >20:1 dr. Additionally, 4,7-dicholoro substituted isatin also proceeded smoothly in this reaction to form the desired product 3q in good yield with high stereoselectivity.

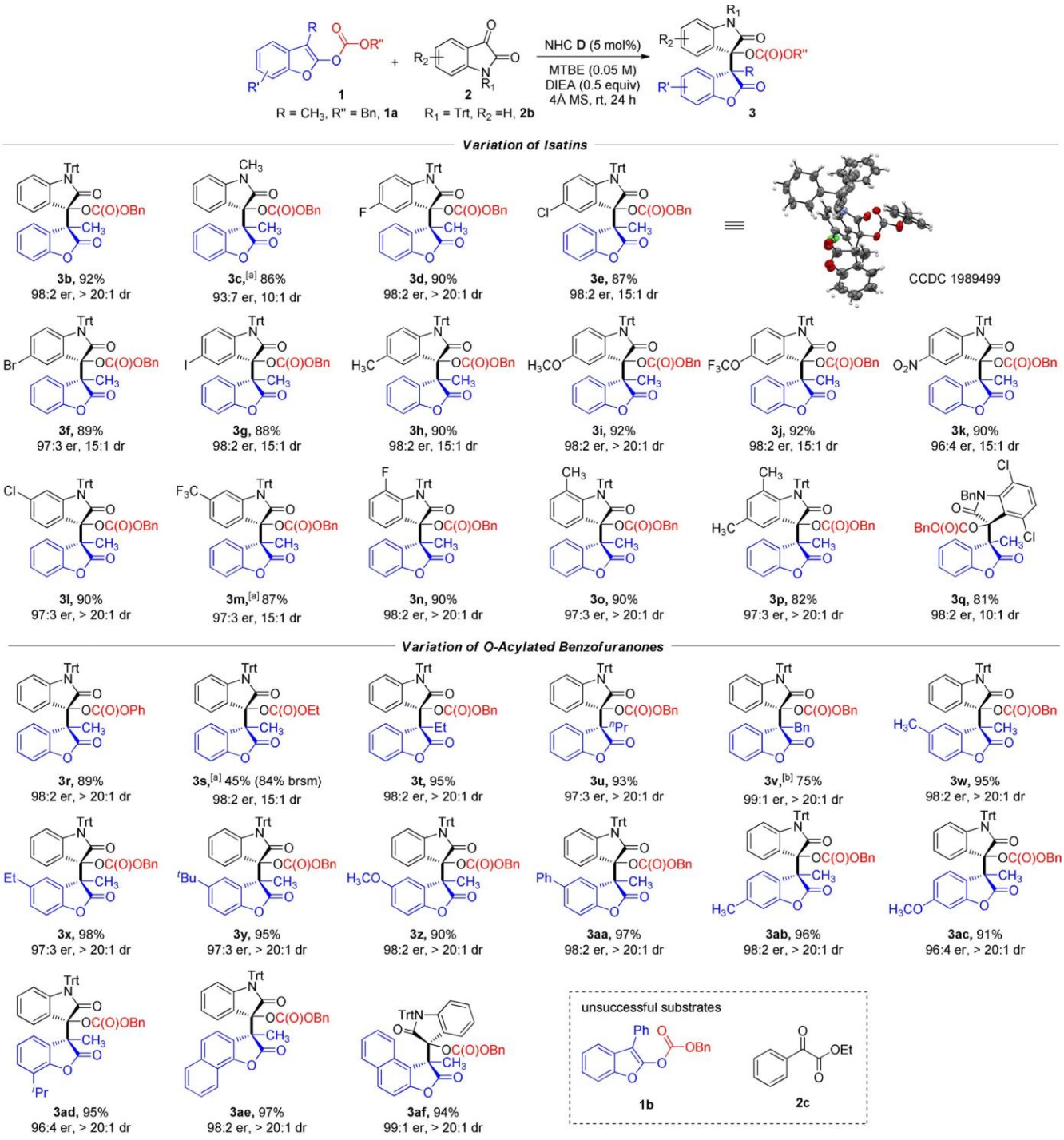
We next examined the scope of *O*-acylated benzofuranones (the enolate reaction partners, 1) with isatin 2b as the model ketone substrate. The *O*-acylation group (R'') of compound 1 was first investigated. Replacing the benzyloxycarbonyl with a benzoyl unit on substrate 1 had little effects on the reaction outcomes: product 3r was formed with similar results as those of 3 b. Using an ethoxycarbonyl unit as the acylation group led to product 3s with excellent diastereo- and enantio-selectivity, albeit with a decreased yield (45 %). The low yield was due to incomplete conversion of the benzofuranone substrate (82 % yield brsm) under the standard condition without further optimizations. The enolate α-substituents (R) of substrate 1 were then studied. Alky substituents (such as ethyl, propanyl, and benzyl units) other than methyl group (3 a) were all well tolerated (3 t–3 v). Installing various substituents (R') on (the different carbons of) the benzene ring of substrate 1 has little influence on the reactions. In all the cases, the products (3w to 3 ad) were obtained with excellent yields, dr and er values. The fused benzene ring of benzofuranones could also be replaced with naphthyl units (3 ae and 3 af). However, 3-phenyl substituted *O*-acylated benzofuranone (1 b) and electron-deficient ketoester (2 c) could not give the desired aldol product (Scheme 1). Notably, in all our reactions under the optimized condition the Black rearrangement were completely suppressed.

To further demonstrate the generality of our new strategy, we next explored the reaction of *O*-acylated azlactones (5) and isatins (2). Under the standard reaction condition as stated above, the trityl-protected isatin as the ketone substrate reacted with azalactones to give the corresponding aldol product 6a in 84 % yield with moderate stereoselectivity (1.3:1 dr, 75:25 er). To our delight and a bit surprise, a high level of diastereo- and enantio-selectivities were restored by switching the *N*-trityl substituent of the isatin to a *N*-methyl unit. Specifically, the aldol product with a *N*-methyl substituent (6 b) was obtained in 82 % yield, 5:1 dr and 95:5 er values. Several methyl-protected isatin substrates were then smoothly converted into the aldol products (6c to 6 g) with good to excellent yields and stereoselectivities. Furthermore, *O*-acylated azlactones bearing various substituents (6h to 6 l) were tolerant under our standard condition without any further optimization (Scheme 2).

Our reaction conditions are mild and the operational protocols are simple. The aldol products could be prepared in larger scales (for example, 3 b, 1.20 gram) without loss on reaction yields or selectivities (Scheme 3 a). The trityl group on the isatin nitrogen atom could be removed in the presence of acetic acid to give 7 in 70 % yield without any erosion on the er value. It turned out a direct use of the corresponding benzofuranone (8) in the presence of benzyl chloroformate (9) to react with isatin (2 a) could successfully give the corresponding aldol product (3 b) with only a slight loss on reaction yield under the current condition (74 % yield, vs. 92 % yield in using pre-formed masked enolate 1 a). The diastereo- and enantio-selectivity remained unchanged (> 20:1 dr, 98:2 er; Scheme 3 b).[20]

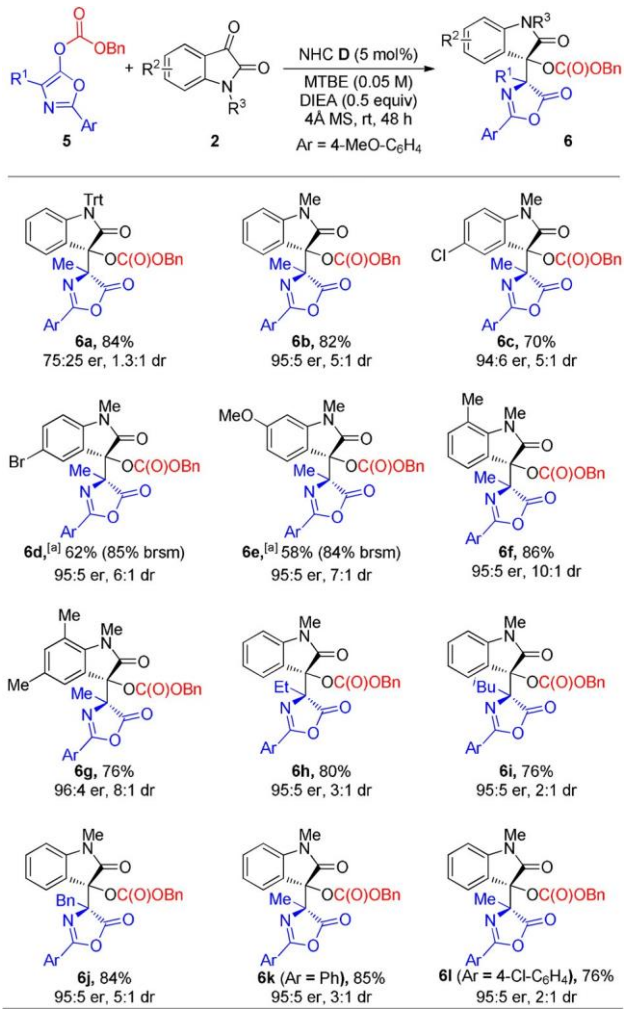
The products of our catalytic reactions contain 3,3-disubstituted oxindole and benzofuranone scaffolds that are widely found in natural products and bioactive molecules.[21] Our laboratories are interested in the antiviral and antibacterial activities of new scaffolds for agricultural use.[22] We evaluated the in vitro bioactivities of our products against *X. oryzae* by the turbidimeter test (Table 2). The commercially available and commonly applied bactericide bismerthiazol and thiodiazole–copper were used as the positive control. Preliminary studies found that a number of our products exhibited inhibitory rates comparable to the commercially available bactericide.

To gain additional insights into the reaction mechanism, multiple control experiments were carried out. First, DIEA as a base could efficiently promote the reversible aldol reaction between benzofuranone (8) and isatin (2d; Scheme 4 a). This aldol reaction reached equilibrium in about 10 minutes (with or without the presence of NHC pre-catalyst) to give aldol adduct (10) with around 53 % conversion and high diastereoselectivity (Scheme 4 a). This unprotected aldol adduct (10) is unstable upon purification on silica gel column chromatog-

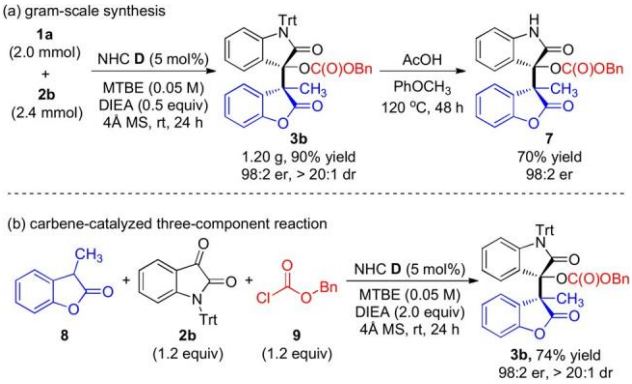


Scheme 1. Scope of the reactions between *O*-acylated benzofuranones and isatins. Reaction conditions: 1a (0.1 mmol), 2 (0.15 mmol), DIEA (0.5 equiv), and NHC (5 mol%) in MTBE (2.0 mL) at rt for 24 h. [a] Reaction was performed at rt for 48 h. [b] Reaction was performed at rt for 36 h.

raphy. A crude reaction mixture of benzofuranone (8) and isatin (2d) containing in situ-formed racemic aldol adduct was subsequently subjected to a NHC-catalyzed acylation (Scheme 4b). The corresponding protected aldol product (3d) was obtained in 80 % yield with 98:2 er and > 20:1 dr (Scheme 4 b). Only trace amount of *O*-acylated benzofuranone (1 a) was formed during this process (see the Supporting Information for details). These results (Scheme 4a and b) suggest that the enantioselectivity of our product is controlled during the NHC-catalyzed DKR acylation process. The presence of NHC pre-catalyst was critical for the acylation step to proceed, as little protected aldol product (3 d) was obtained when the NHC catalyst was absent (Scheme 4 c). The use of masked enol precursor (1 a) or ketone (8) as the enol reaction partner gave comparable results (Scheme 4 b and d).



Scheme 2. Scope of the reactions between *O*-acylated azlactones and isatins. Reaction conditions: 5 (0.1 mmol), 2 (0.12 mmol), DIEA (0.5 equiv), and NHC (5 mol%) in MTBE (2.0 mL) at rt for 48 h. [a] 10 mol% of NHC precatalyst D was used.



Scheme 3. Practical utilities of our new strategy.

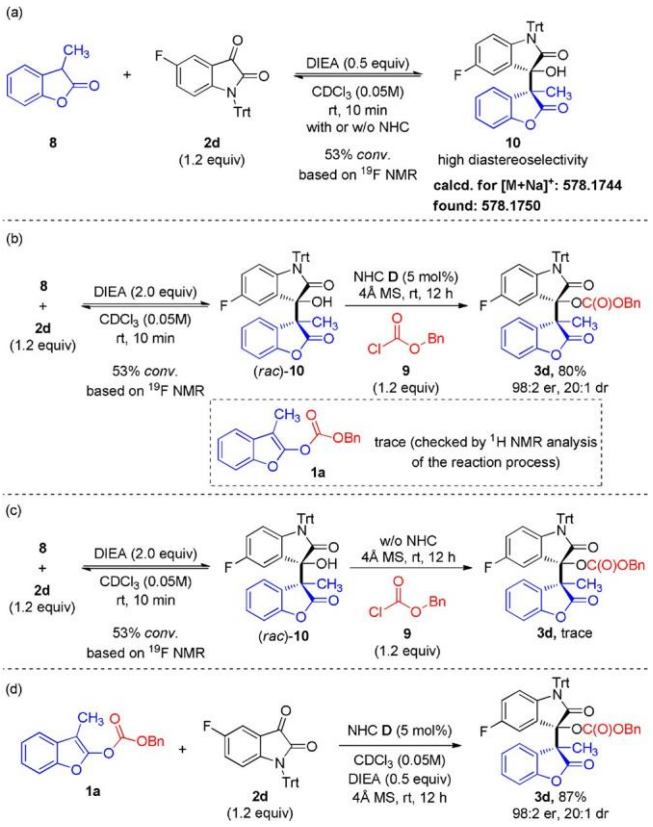
Conclusion

We have launched a new approach for catalytic asymmetric aldol reactions. With our new strategy, the enantioselectivities are controlled after the aldol adducts are formed.

Table 2: The antibacterial activity of the products.[a]

Compound	*X. oryzae* inhibition rate [%]	
	100 μg mL^{-1}	50 μg mL^{-1}
3b	32.7±4.7	17.2±1.8
3d	37.4±1.2	29.2±5.3
3h	39.7±1.8	32.6±1.9
3i	39.9±4.6	39.2±1.5
3k	42.5±2.6	39.2±2.3
3m	34.8±5.8	33.9±2.5
bismerthiazol	49.9±1.7	40.3±3.5
thiodiazole–copper	33.2±3.2	23.6±2.9

[a] Each data point is the average of three replicates. Commercial bacteriocide bismerthiazol and thiodiazole–copper were used as the positive control.



Scheme 4. Control experiments.

The post-aldol process also drives the thermodynamic equilibrium of the reversible aldol process toward complete formation of the acylated *b*-hydroxyl carbonyl products. The NHC catalysts play dual roles in our reactions: one is to activate the masked enolate substrate for aldol reaction, another is to promote the post-aldol dynamic kinetic resolution and acylation. The aldol adducts bearing vicinal quaternary/tetrasubstituted stereogenic centers are formed as essentially single diastereomers with high optical purities. We expect our study to offer alternative solutions for challenging aldol reactions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: acylation · aldol reaction · asymmetric catalysis · dynamic kinetic resolution · N-heterocyclic carbene

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[19] Deposition Number 1989499 (3e) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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