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Dynamic Kinetic Resolution of α-Trifluoromethyl Hemiaminals without α-Hydrogen via NHC-Catalyzed *O*-Acylation

Yuan-Yuan Gao, Chun-Lin Zhang, Lei Dai, You-Feng Han, and Song Ye*

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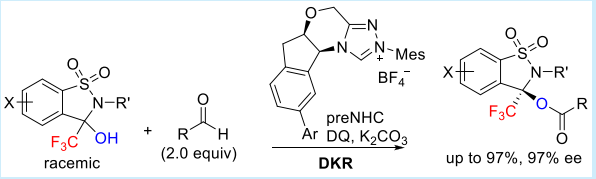
ABSTRACT: Following the well-recognized dynamic kinetic resolution (DKR) of hemiaminals with α-hydrogen under lipase and chiral DMAP catalysis, the unprecedented DKR of hemiaminals without α-hydrogen was developed via N-heterocyclic carbene catalyzed *O*-acylation of 3-hydroxy-3-trifluoromethylbenzosultams. The racemic hemiaminals without α-hydrogen were effectively racemized and differentiated by chiral NHCs under basic conditions. The resulting esters were obtained in high yields with good to high enantioselectivities.

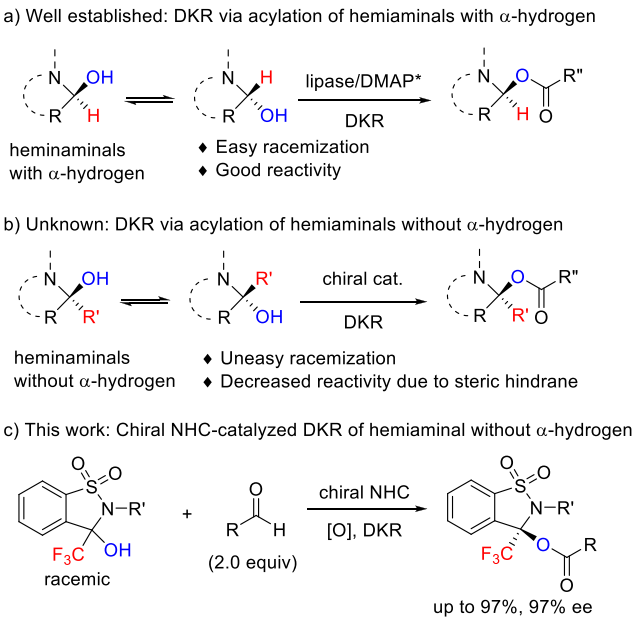


Kinetic resolution (KR) is a useful strategy for the preparation of optically active compounds. More importantly, the dynamic kinetic resolution (DKR), which can transform racemic starting materials into enantiomerically pure products with 100% theoretical yield, is of great interest in asymmetric synthesis.[1] In the meantime, N-heterocyclic carbenes (NHCs) are powerful organocatalysts[2] for various reactions.[3] In recent years, the NHC-catalyzed kinetic resolutions have also been established,[4] which include the KR of secondary[5] and tertiary alcohols,[6] phenols,[7] α-substituted amines,[8] sulfoximines,[9] azomethine imines,[10] oxaziridines,[11] and β-lactams.[12] Furthermore, a few examples of NHC-catalyzed DKR reactions have been reported. In 2012, Scheidt and co-workers pioneered the NHC-catalyzed DKR of racemic β-ketoesters.[13] Subsequently, NHC-catalyzed DKR of β-halo-α-ketoesters,[14] substituted esters,[15] hemiacetals,[16] enamines,[17] and ketoacids[18] have been explored.

The dynamic kinetic resolution of cyclic hemiaminals via *O*-acylation is an efficient method for the synthesis of chiral α-acyloxyl N-heterocycles. Compared with well-established DKR via acylation of hemiaminals with α-hydrogen under lipase[19] and chiral DMAP catalysis (Scheme 1, reaction a),[20] to the best of our knowledge, there is no example reported for the DKR of hemiaminals without α-hydrogen, possibly due to the steric hindrance and the difficulty of its racemization under mild conditions (Scheme 1, reaction b). In 2018, Wang et al. developed an NHC-catalyzed KR of anilides but without success in DKR.[21] Considering the wide application of benzosultams[22] and the trifluoromethyl group[23] in biologically active compounds, in this communication, we report an NHC-catalyzed DKR of 3-hydroxy-3-trifluoromethylbenzosultams (Scheme 1c).

The DKR of benzosultam-derived hemiaminal **1a** via *O*-acylation with benzaldehyde **2a** was explored as the model reaction in the presence of 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (DQ) as the oxidant under NHC catalysis (Table 1).

Scheme 1. Dynamic Kinetic Resolution via Acylation of Hemiaminals



Although the reaction with preNHC catalysts **A** and **B**, derived from L-pyroglutamic acid, gave only a trace of desired oxidative acylation product **3aa** (entries 1 and 2), we were encouraged

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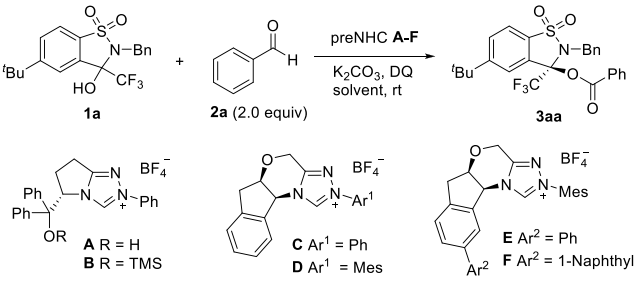
Table 1. Optimization of Reaction Conditions[a]



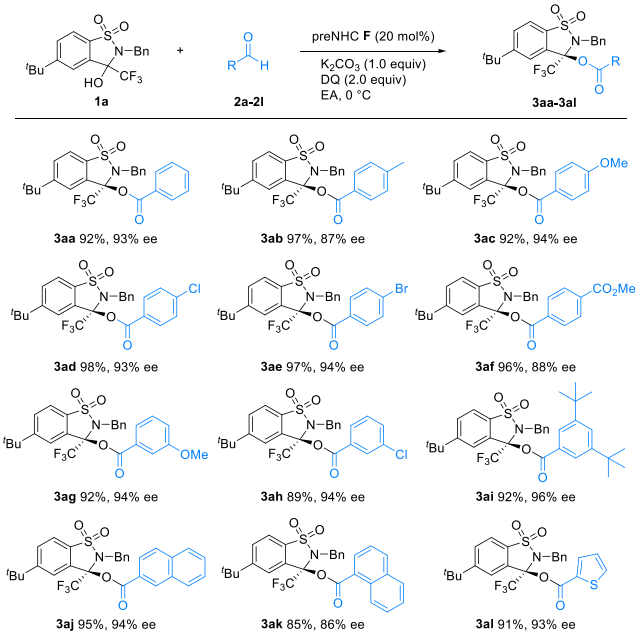
entry	preNHC	solvent	yield[b] (%)	ee[c] (%)
1	**A**	THF	trace	
2	**B**	THF	trace	
3	**C**	THF	34	72
4	**D**	THF	52	69
5	**E**	THF	80	87
6	**F**	THF	92	89
7	**F**	DCE	trace	
8	**F**	Et_2O	29	94
9	**F**	EA	92	92
10[d]	**F**	EA	92	93

[a]General conditions: **1a** (0.2 mmol), **2a** (2.0 equiv), preNHC (20 mol %), base (1.0 equiv), DQ (2.0 equiv), solvent (2 mL), 15 h, rt. [b]Yield of isolated product. [c]Determined by HPLC analysis using a chiral stationary phase. [d]At 0 °C. EA = ethyl acetate, DQ = 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone.

that the reaction catalyzed by tetracyclic aminoindanol-derived *N*-phenyl preNHC **C**[24] afforded the product **3aa** in 34% yield with 72% ee (entry 3). The yield was improved to 52% when *N*-mesityl preNHC **D**[25] was employed (entry 4). The yield (80%) and enantioselectivity (87% ee) were improved dramatically when an additional phenyl group was introduced for the aminoindanol-derived preNHC **E**[16c] (entry 5). The yield was further increased to 92% with 89% ee when α-naphthyl was installed for the preNHC-catalyst **F**[16c] (entry 6). Several solvents were then screened for the reaction. It was found that the reaction proceeded sluggishly in 1,2-dichloroethane (entry 7), and excellent enantioselectivity but low yield was resulted in diethyl ether (entry 8). We were happy to find that both high yield and high enantioselectivity were achieved with ethyl acetate as the solvent (entry 9). Lowering the temperature to 0 °C showed some benefit to the enantioselectivity with high yield kept (entry 10).

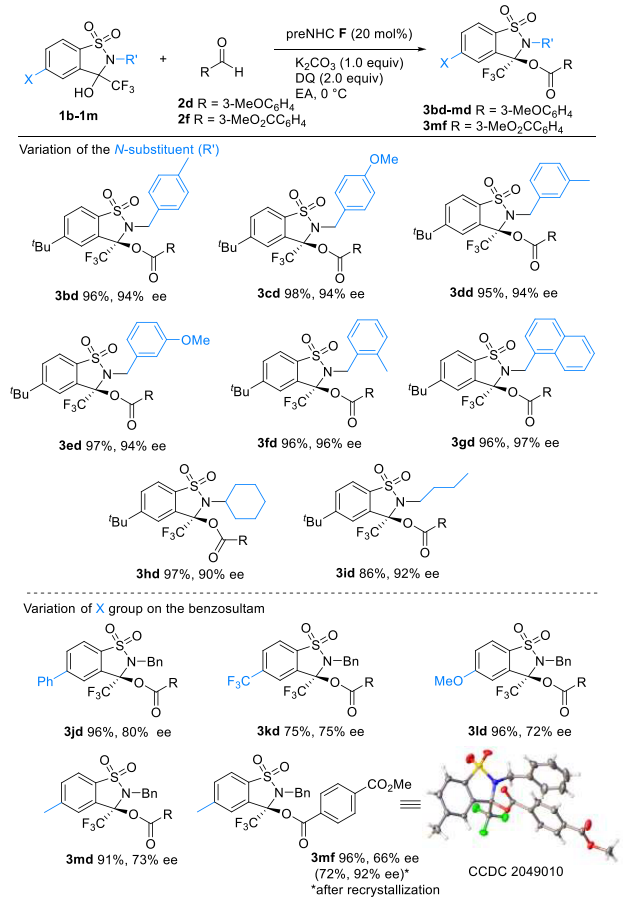
With the optimized conditions in hand, the scope of aldehydes was then investigated (Scheme 2). It was found that benzaldehyde bearing both electron-donating (Ar = 4-MeC_6H_4 and 4-$MeOC_6H_4$) and electron-withdrawing groups (Ar = 4-ClC_6H_4, 4-BrC_6H_4, and 4-$MeO_2CC_6H_4$) at the *para*-position worked well to give products **3aa**−**3af** in excellent yields and enantioselectivities. *Meta*-substituted aryl aldehydes (Ar = 3-$MeOC_6H_4$, 3-ClC_6H_4, and 3,5-$^t Bu_2C_6H_3$) performed well under the standard reaction conditions (**3ag**−**3ai**). High yield and enantioselectivity were achieved for the reaction of β-naphthaldehyde (**3aj**), while α-naphthaldehyde showed some decreased enantioselectivity (**3ak**). The reaction of thiophene-2-carbaldehyde gave the corresponding product (**3al**) in 91% yield with 93% ee. Unfortunately, aliphatic aldehydes did not work for the reaction under the current conditions.

Scheme 2. Scope of Aldehydes



The scope of benzosultam-derived hemiaminals was also explored (Scheme 3). The 3-hydroxybenzosultams with different *N*-benzyl groups worked well for the DKR reaction to give the desired *O*-acyl products **3bd**−**3gd** in high yields

Scheme 3. Scope of the Benzosultam-Derived Hemiaminals



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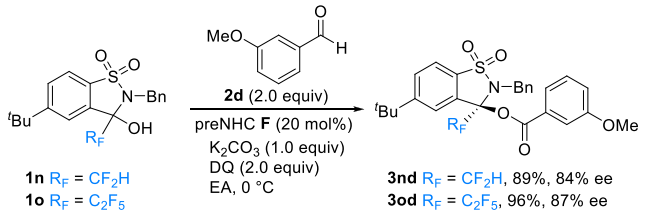
and high enantioselectivities. Notably, the *N*-alkyl benzosultams (*N*-cyclohexyl and *N*-^{n}butyl) worked well for the DKR reaction (**3hd**−**3id**). Both electron-withdrawing groups and electron-donating groups (X = Ph, CF_3, OMe, Me) at the phenyl ring of benzosultams were tolerated but gave the products (**3jd**−**3mf**) with some decreased enantioselectivities, which could be improved to 92% ee after recrystallization (**3mf**). The absolute (*R*)-configuration of product **3mf** was assigned via single-crystal X-ray analysis.

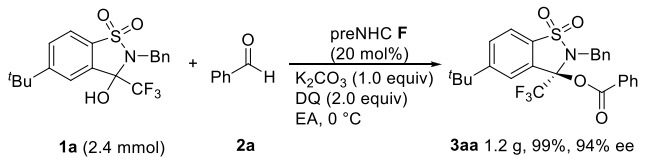
To further expand the scope of the hemiaminals, those with 3-difluoromethyl (**1n**) and 3-pentafluoroethyl (**1o**) instead of trifluoromethyl were also tested for the DKR reaction, which afforded the desired products (**3nd** and **3od**) in high yields with some decreased but still high enantioselectivities (Scheme 4).

Scheme 4. Reaction of α-Difluoromethyl and α-Pentafluoroethyl hemiaminals



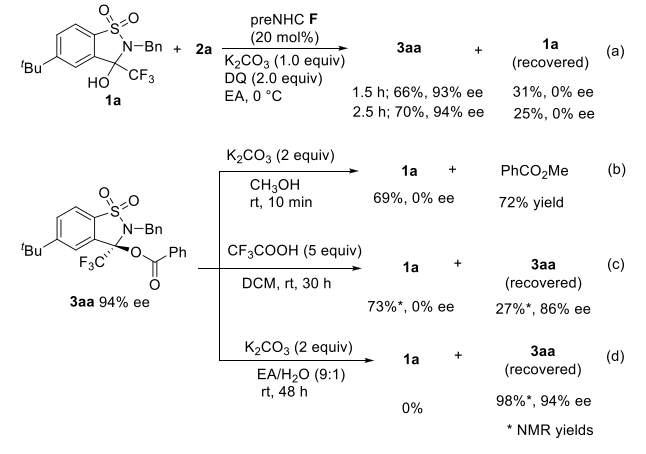
The reaction could be easily scaled up to 2.4 mmol of benzosultam-derived hemiaminal **1a**, giving 1.2 g of the desired product **3aa** in 99% yield with 94% ee under standard conditions (Scheme 5).

Scheme 5. Gram-Scale Synthesis



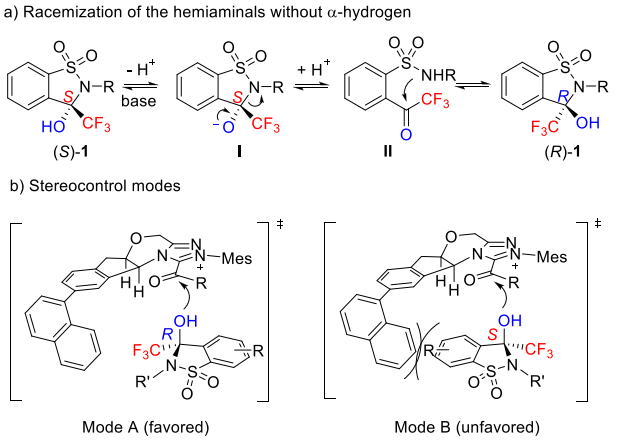
Several control experiments were carried out to clarify the mechanism of the racemization of α-hydroxy-α-trifluoromethylbenzosultams (Scheme 6). When the reaction was quenched before the full consumption of hemiaminal **1a**, the ester **3aa** with high ee was isolated and hemiaminal **1a** without enantioexcess was recovered (reaction a). This result suggests that the racemization of **1a** is much faster than the *O*-acylation reaction under the NHC catalysis conditions. Then we tried to synthesize optically active hemiaminal **1a** by the alcoholysis of its optical active ester **3aa** (94% ee) under basic conditions, which gave hemiaminal **1a** without enantioexcess (reaction b). The hydrolysis of **3aa** under acidic conditions gave the racemic hemiaminal, and some loss of the enantiopurity of the ester **3aa** was observed, which was possibly due to the re-*O*-acylation of the resulted racemic hemiaminal (reaction c). No hydrolysis or racemization of **3aa** was observed in the presence of 2 equiv of K_2CO_3 in the mixed solvent of ethyl acetate/water (9:1) at room temperature (reaction d).

Scheme 6. Investigation on Racemization



Based on the control experiments, we proposed a mechanism for racemization of hemiaminals via ketones **II** under basic conditions (Scheme 7a). The electron-withdrawing *N*-sulfonyl and trifluoromethyl groups can enhance the acidity of the α-hydroxyl in hemiamianls **1**, thus facilitating the racemization. The addition of (*R*)-3-hydroxy-3-trifluoromethyl benzosultams (mode A) are kinetically favored over their (*S*)-enantiomers (mode B) to attack the acyl azolium, which is generated from aldehyde under oxidative NHC catalysis (Scheme 7b). The additional bulky aryl group of the NHC catalyst can increase the repulsion in unfavored stereocontrol mode B and play an important role in differentiating the two enantiomers of the hemiaminals.

Scheme 7. Racemization of the Hemiaminals and Stereocontrol Modes



In summary, a dynamic kinetic resolution of hemiaminals without α-hydrogen was developed via the chiral NHC-catalyzed *O*-acylation of 3-hydroxy-3-trifluoromethylbenzosultams. The racemic hemiaminals without α-hydrogen were effectively racemized and differentiated by chiral NHCs under basic conditions. This protocol provides a wide range of enriched benzosultam derivatives in excellent yields with good to excellent enantioselectivities. Other related NHC-catalyzed dynamic kinetic resolution reactions are underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00024.

Experimental details, crystallographic data and NMR spectra for obtained compounds (PDF)

Accession Codes

CCDC 2049010 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Song Ye − *Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, CAS Research/Education Center for Excellence in Molecular Sciences, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China; University of Chinese Academy of Sciences, Beijing 100049, China;* orcid.org/0000-0002-3962-7738; Email: songye@iccas.ac.cn

Authors

Yuan-Yuan Gao − *Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, CAS Research/Education Center for Excellence in Molecular Sciences, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China; University of Chinese Academy of Sciences, Beijing 100049, China*

Chun-Lin Zhang − *Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, CAS Research/Education Center for Excellence in Molecular Sciences, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China*

Lei Dai − *Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, CAS Research/Education Center for Excellence in Molecular Sciences, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China; University of Chinese Academy of Sciences, Beijing 100049, China;* orcid.org/0000-0002-4225-7408

You-Feng Han − *Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, CAS Research/Education Center for Excellence in Molecular Sciences, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China; University of Chinese Academy of Sciences, Beijing 100049, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00024

Notes

The authors declare no competing financial interest.

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