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Carbene-Catalyzed Dynamic Kinetic Resolution of Carboxylic Esters

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Supporting Information

ABSTRACT: Carbene-catalyzed reaction of carboxylic esters has the potential to offer effective synthetic solutions that cannot be readily achieved by using the more conventional aldehyde-type substrates. Here we report the first carbene-catalyzed dynamic kinetic resolution of α,α-disubstituted carboxylic esters with up to 99:1 er and 99% yield. The present study clearly illustrates the unique power of carbene-catalyzed reactions of readily available and easy to handle carboxylic esters.

Carboxylic acids and the related carbonyl compounds bearing two or more substituents at the α-carbons are important functional molecules. For example, ibuprofen and ketoprofen, derivatives of propionic acid bearing a stereogenic α-carbon center, are widely used as nonsteroidal anti-inflammatory drugs[1] (Figure 1a). Thus, the synthesis and transformation of

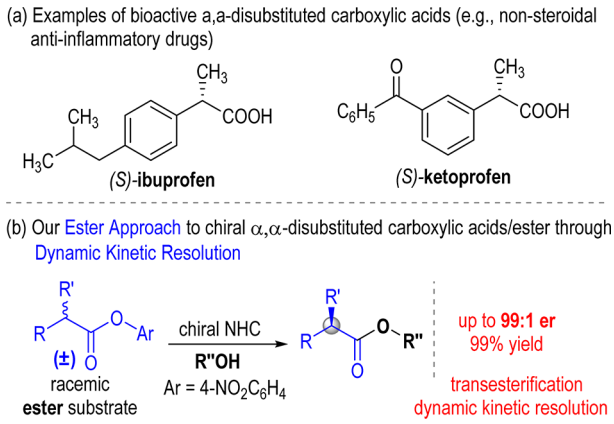

Figure 1. Enantiomerically enriched α,α-disubstituted carboxylic acids/esters and our synthetic strategy.

such α,α-disubstituted carbonyl compounds is of profound importance. N-Heterocyclic carbene (abbreviated as NHC or carbene in this article) organic catalysts have been successfully used to activate aldehydes and α,β-unsaturated aldehydes (enals) for a diverse set of asymmetric reactions.[2] However, when an additional alkyl or aryl substituent is placed at the α-carbon of the aldehydes or enals, the reaction efficiency is dramatically reduced.[3a] This restriction on the enal/aldehyde α-carbon substitutents has limited the application of carbene catalysis to prepare some of the most important molecules such as bioactive α,α-disubstituted carboxylic acids. It remains underdeveloped at this point in using carbene-catalyzed aldehyde reactions to prepare α,α-disubstituted carboxylic acids asymmetrically.[3,4] On the other hand, researchers have focused on the more reactive ketene substrates via organic catalysis to prepare enantiomerically enriched α,α-disubstituted carboxylic esters/acids. Fu has pioneered asymmetric protonation reactions by using planar-chiral DMAP-type organic catalysts with excellent enantioselectivities;[5] Smith and Ye have pioneered the asymmetric protonation reactions of ketenes to give α,α-disubstituted carboxylic ester products with moderate to good enantioselectivities.[6] The instability of ketene substrates and the challenges in selective asymmetric protonation have limited the wide applications of these otherwise elegant approaches using ketene substrates.

We are interested in using carbene catalysts to activate readily available and stable carboxylic esters for effective transformations.[7] In particular, the use of carboxylic esters as substrates can induce useful transformations that cannot be easily achieved by using the related aldehyde and enal substrates, as demonstrated by Lupton[8] and us.[7] Here we report the first carbene-catalyzed reaction to effectively prepare enantiomerically enriched α,α-disubstituted carboxylic esters via a dynamic kinetic resolution process (Figure 1b). Our reaction starts with racemic carboxylic ester substrates and gives transesterified products with excellent er (up to 99:1) and yield (up to 99%). There are no previous reports for the preparation of such chiral product by using the related enal or aldehyde substrates under (oxidative) carbene catalysis.

Notably, carbene organic catalysts have been previously used in two types of kinetic resolution. First, kinetic resolution of racemic alcohols and related binols with up to 50% yields has been reported by Suzuki,[9a] Maruoka,[9b] Studer,[9c] Yamada,[9d] and Zhao.[9e,f] Additionally, (dynamic) kinetic resolution of ketones or imines (bearing a chiral center) via NHC-bound Breslow intermediates[10] or dienolate intermediates has been reported by Scheidt, Johnson, Wang, and us.[11]

Key results of initial reaction optimization using ester **1a** as the model substrate are summarized in Table 1. Alcohol **2** was found to be optimal after screening (e.g., the use of methanol, benzyl alcohol led to product with <69:31 er under various conditions,

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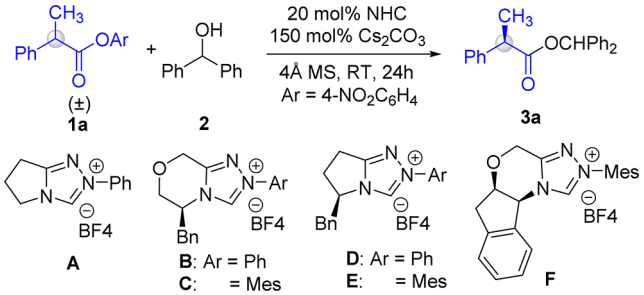
Table 1. Condition Optimization[a]



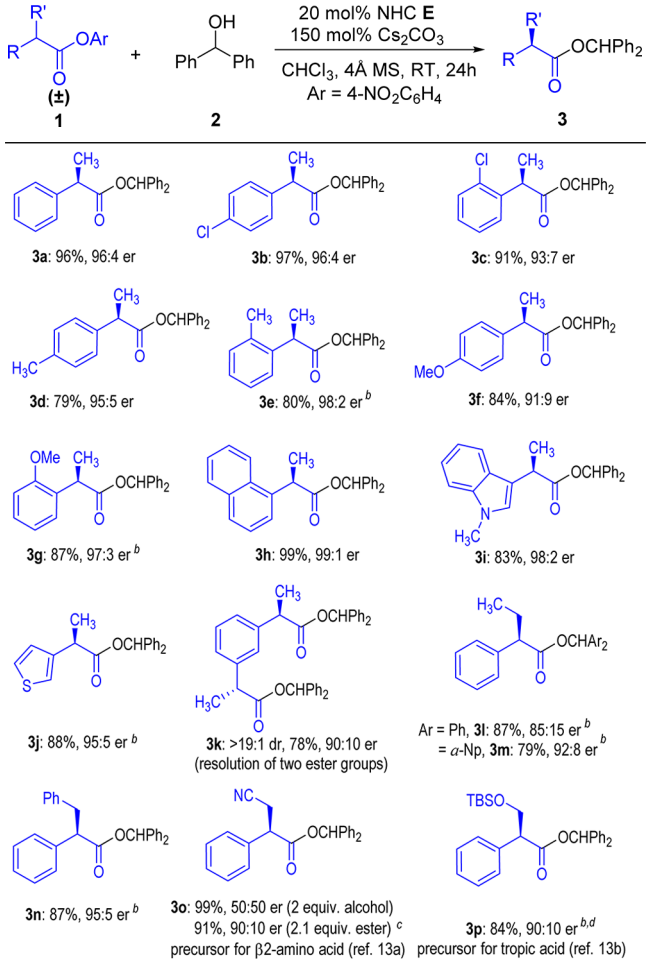
entry	NHC	solvent	yield (%)[b]	er[c]
1	–	THF	<5	–
2	**A**	THF	99	–
3	**B**	THF	99	67:33
4	**B**	solvents[d]	45–99	62:38–75:25
5	**B**	$CHCl_3$	99	80:20
6	**C**	$CHCl_3$	80	88:12
7	**D**	$CHCl_3$	99	85:15
8	**E**	$CHCl_3$	99(96)	96:4
9	**F**	$CHCl_3$	70	91:9

[a]Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), solvent (1 mL), rt, 24 h. [b]Yield determined by NMR analysis with an internal standard. Isolated yield in parentheses based on **1a**. [c]Enantiomeric ratio of **3a**, determined via chiral phase HPLC analysis. Mes = 2,4,6-trimethylphenyl. [d]See SI.

see SI). We were pleased to first find that the background ester exchange reaction (in the absence of carbene catalyst) was minimal (<5% conversion after 24 h, entry 1) and also that the addition of achiral triazolium NHC precatalyst **A**, first reported by Rovis,[12a] led to **3a** with quantitative yield (entry 2). Having thus proven the efficiency of the carbene-catalyzed ester exchange reaction in our system, we next moved to screening chiral carbene catalysts. Amino alcohol-derived chiral NHC precatalyst **B**, first reported by Leeper,[12b] could mediate this reaction to give **3a** with excellent yield and encouraging er of 67:33 (entry 3). Solvent was found to affect both yields and er values (entry 4, and see SI), the best of which were obtained with $CHCl_3$ (99% yield, 80:20 er, entry 5). Additional studies found that the use of *N*-Mes-substituted triazolium catalysts offered product **3a** with higher er values (e.g., compared entry 6 with 5, 8 with 7). We finally discovered that the use of precatalyst **E**, first explored by Bode,[12c] gave **3a** with optimal 96% isolated yield and acceptable (96:4) er (entry 8). Catalyst **F** could mediate this reaction to give **3a** with 70% yield and 91:9 er (entry 9).

With an acceptable reaction condition in hand (Table 1, entry 8), we next examined the scope of the esters (Table 2). Different substituents and substitution patterns on the α-phenyl ring of the ester substrates were all tolerated (product **3a**–**g**). The phenyl substituent of substrate **1a** could be replaced with 1-naphthyl and heteroaryl substituent without obviously affecting the reaction yields and er values (**3h**–**j**). In the cases where the reaction was slow at rt (**3e**, **3g**, **3j**, **3l**–**p**), the reaction mixture was heated to 40 °C, and acceptable er values were still achieved. Diester (**3k**) could be resolved as well with excellent dr and er. When the α-methyl unit of **1a** was replaced with an ethyl substituent (**3l**), a decreased er (85:15 er) was observed under the standard condition. The drop in er could be solved by using a different alcohol reacting partner (e.g., $(\alpha\text{-Np})_2CHOH$, gave **3m** with 92:8 er). The methyl group in **1a** could also be replaced by a benzyl substituent (**3n**) negligible change on reaction outcomes.

Table 2. Scope of Reactions[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), $CHCl_3$ (1 mL). [b]40 °C. [c]**1** (0.21 mmol), **2** (0.1 mmol), 40 °C. [d]20 mol % NHC **D**.

When a cyanomethyl-substituted ester was used under the standard condition, the corresponding transesterification product (**3o**) was obtained in quantitative yield but with close to 50:50 er. We then found that by using 0.5 equiv of the alcohol substrate (to achieve kinetic resolution; rather than dynamic kinetic resolution in this case), the corresponding ester product **3o** could be obtained with 90:10 er and 91% yield (based on alcohol substrate, or 43% yield based on ester substrate). A TBS-protected hydroxylmethyl unit (**3p**) could also be used to replace the methyl group of substrate **1a**, here the use of less bulky *N*-phenyl-substituted catalyst **D** gave better results. The products from our reactions and their closely related derivatives are useful functional molecules. For example, product **3o** could be readily converted to β^2-amino acid,[13a] and TBS-protected hydroxylmethyl product (**3p**) could be converted to natural products such as chiral tropic acid and its analogues.[13b]

Optically enriched α-aryl propionic acid and their derivatives are bioactive molecules and medicines.[1,14] Our method offers very effective access to many of these medicines and their derivatives, as illustrated in Table 3. Our method is also amenable for scale-up synthesis, as illustrated by a gram-scale preparation of naproxen ester (**3v**, 1.1 g). The ester group of our product (e.g., **3v**) can be easily removed by using well-established method.

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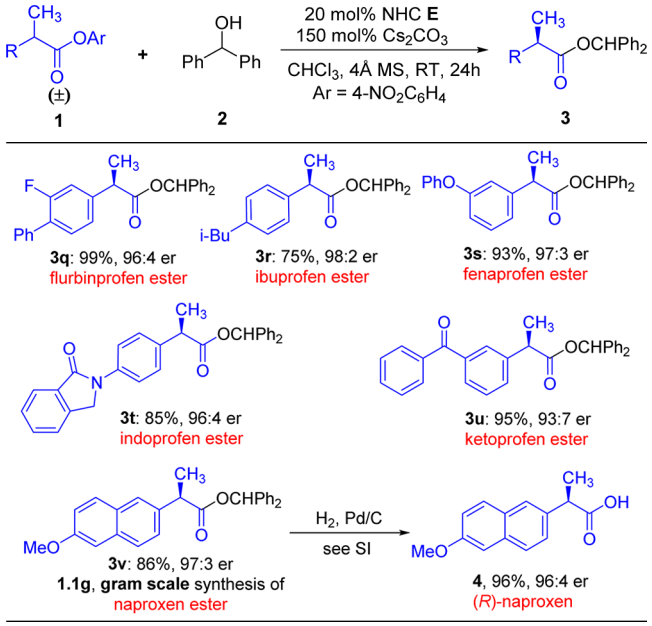
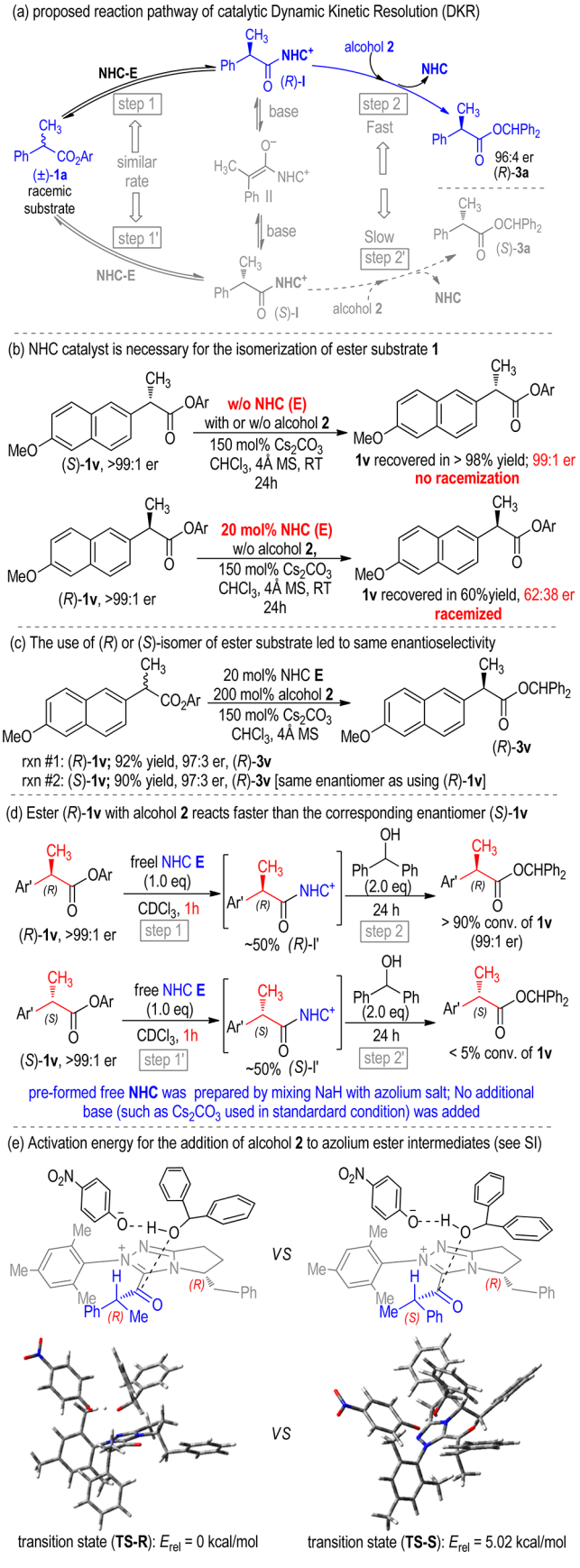
Table 3. Medicinal Molecules Prepared Using Our Method[a]



[a]Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), NHC **E** (0.02 mmol), $CHCl_3$ (1 mL), 24 h.

A postulated reaction pathway is briefly illustrated in Scheme 1a. The addition of chiral carbene catalyst **E** to racemic ester substrate **1a** gives diastereomeric intermediate (*R*)-**I** and (*S*)-**I**. Intermediate (*R*)-**I** preferentially reacts with alcohol substrate **2** to give **3a** with high enantiomeric ratio. To further understand the mechanism, we performed the reaction by using enantiomerically pure (*S*)-**1v** as the substrate in the absence of carbene catalyst (Scheme 1b). Neither background transesterification reaction nor racemization of (*S*)-**1v** was observed. In contrast, when enantiomerically pure (*R*)-**1v** was mixed with carbene **E**, the recovered **1v** was partially racemized. Thus, the carbene catalyst is required for the racemization of the ester substrate (isomerization between (*R*)-**I** and (*S*)-**I**) and the transesterification reaction (**1v** to **3v**). In addition, the use of either (*R*) or (*S*)-enantiomer of the ester substrate under our catalytic conditions gave the transesterification product with the same enanioselectivities and similar yields (Scheme 1c). When preformed free NHC catalyst was used in the absence of additional base, racemization of the ester substrate was not observed (Scheme 1d), suggesting that both NHC and base were required for the isomerization of the ester substrate. It was also found that the addition of (preformed) NHC catalysts to either enantiomer of the ester substrate **1v** had similar reaction rate (Scheme 1d, steps 1 and 1′) in forming the acylazolium ester intermediate (*R*)-**I**′ and (*S*)-**I**′ (~50% conversion in both cases after 1 h). In the subsequent addition of alcohol **2** to the azolium ester intermediates, the intermediate (*R*)-**I**′ reacted much faster than (*S*)-**I**′ (Scheme 1d, steps 2 and 2′). These studies (Scheme 1d) suggest that the final step of ester formation is the asymmetric step, and the overall process is a dynamic kinetic resolution. The key step of alcohol addition to the acylazolium ester intermediate was also evaluated via DFT calculation (Scheme 1e). The calculation revealed that the energy of the addition of alcohol **2** to intermediate (*S*)-**I** is 5.02 kcal/mol higher than that of alcohol **2** adding to the intermediate (*R*)-**I**, which is consistent with our experimental observations.

Scheme 1. Proposed Pathway and Mechanistic Studies



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In summary, we have developed a carbene-catalyzed reaction of esters that offers useful synthetic solutions which are not readily accessible from the conventional reactions based on aldehyde substrates. Our approach, through dynamic kinetic resolution of carboxylic esters, allows for effective access to the broadly useful α,α-disubstituted carboxylic esters with up to 99:1 er and 99% yield. The present study clearly illustrates the unique power of carbene-catalyzed activation and reaction of carboxylic esters and shall encourage further development of new activation modes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00406.

Experimental details and data (PDF)

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Notes

The authors declare no competing financial interest.

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