Communication

Asymmetric Retro-Claisen Reaction by Chiral Primary Amine Catalysis

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Asymmetric Retro-Claisen Reaction by Chiral Primary Amine Catalysis

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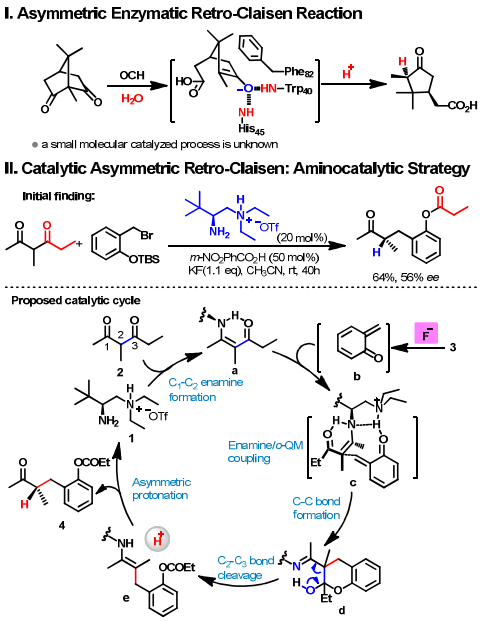
Supporting Information Placeholder

ABSTRACT: The communication describes an enamine-based asymmetric retro-Claisen reaction of β-diketones by primary amine catalysis. The reaction proceeds *via* a sequence of stereoselective C-C formation, C-C cleavage and a highly stereospecific enamine protonation to afford chiral α-alkylated ketones or macrolides with high yields and enantioselectivities. A detailed mechanism was explored on the basis of experimental evidence and computational studies to account for the observed stereocontrol.

Mimicking the enzyme-catalyzed biochemical transformations is an attractive and powerful strategy in synthetic methodology development.[1] The enzyme-catalyzed retro-Claisen reaction，distributing widely in human metabolism, biodegradation and other biocatalysis, provides a prototype for strategic C-C bond cleavage in organic synthesis.[2] A number of these C-C bond hydrolases, such as *α or β*-diketone hydrolase, MCP hydrolase and Friedel-Crafts hydrolase, have been discovered, which catalytically cleave C-C bonds of diketones *via* varied mechanisms. Recently, stereoselective retro-Claisen type enzymes with synthetic potential have also been identified. 6-Oxo camphor hydrolase (OCH) from *Rhodococcus* as well as its orthologue *Anabaena* β-diketone hydrolase (ABDH) from the cyanobacterium *Anabaena* has been found to catalyze an enantioselective transformation of 6-oxocamphor along with the formation of an interesting chiral cyclopentanone (Scheme 1, **I**).[3] Base activated water molecule as well as a well-defined enolate oxyanion hole are the key factors contributing in the effective and stereoselective catalysis in these enzymes. Given the fundamental importance of this process in organic synthesis, an asymmetrically chemical mimic for such a retro-Claisen reaction remains surprisingly unknown.

Retro-Claisen reaction is distinguished by the C-C bond cleavage of β-carbonyl to generate an ester and an enolate-carbanion, serving as a versatile precursor in late-stage synthesis.[4] Unfortunately, the current methods are limited in their applications owing to the use of strong Lewis acid or dependence on stoichiometric strong base. Consequently, the stereocontrol in these processes is extremely challenging. As far as we are aware, asymmetric retro-Claisen reactions with C-C bond activation have not been described in the literature to date. β-Diketones are versatile synthons widely employed in synthetic chemistry.[4] In our pursuit of asymmetric catalysis with 1,3-diketones, we have investigated the reaction with *in-situ* generated *ortho*-quinone methide by chiral primary amine catalysis.[5] Unexpectedly, the reaction delivered a deacylated product with good regioselectivity and

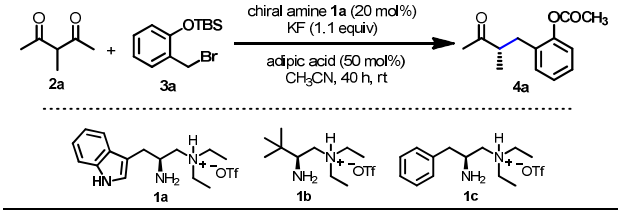
Scheme 1. Catalytic Asymmetric Retro-Claisen Reaction



moderate enantioselectivity (Scheme 1, **II**). Mechanistically, this reaction features a unique sequential enamine-based C-C bond formation and cleavage, formulating an unprecedented stereoselective retro-Claisen process based on the electrophilic nature of *o*-QM in C-C formation[6] as well as the nucleophilic ability of the resulted phenoxide anion to initialize C-C cleavage (Scheme 1, **II**). The observed decent regio- and stereocontrol promoted us to further develop this reaction. The difficulties for such an enamine-based process are multifold: 1) both enzymatic and chemical retro-Claisen processes are enol/enolated-based, enamine-based retro-Claisen reaction is unknown; 2) as a prerequisite, the driving force of regioseleclive C-C cleavage and chiral control required a successful enamine/*o*-QMs coupling avoiding the

background reaction of stabilized enolic form of β-diketones and side reaction of the fleeting *o*-QMs;[7] 3) moreover, manipulating a proton to enamine intermediate is also a challenge differing from protonation of enol in enzyme-catalyzed process (Scheme 1, II).[8] In this context, we demonstrated the first example of an asymmetric retro-Claisen reaction via C-C bond activation by primary amine catalysis and Lewis base activation, providing access to chiral α-tertiary alkylated ketones that are difficult to reach using other methods.

Table 1. Screening and Optimization[a]



entry	variation from standard conditions	yield (%)[b]	ee (%)[c]
1	none	83	93
2	**1b**	76	95
3	**1c**	81	92
4	no aminocatalyst	no	
5	succinic acid	64	91
6	malonic acid	63	90
7	*n*-valeric acid	55	40
8	*n*-valeric acid (1.0 eq.)	59	49
9	**1b** + no acid	27	4
10	**1b** + *m*-MeO_2CPhCO_2H (1.0 eq.)	64	63
11	**1b** + *m*-phthalic acid	86	95
12	**1b** + *p*-phthalic acid	80	85
13	**1b**+ *o*-phthalic acid	56	79
14	THF	30	80
15	CH_2Cl_2	trace	
16	CH_3CN (0.7 mL)	86	95

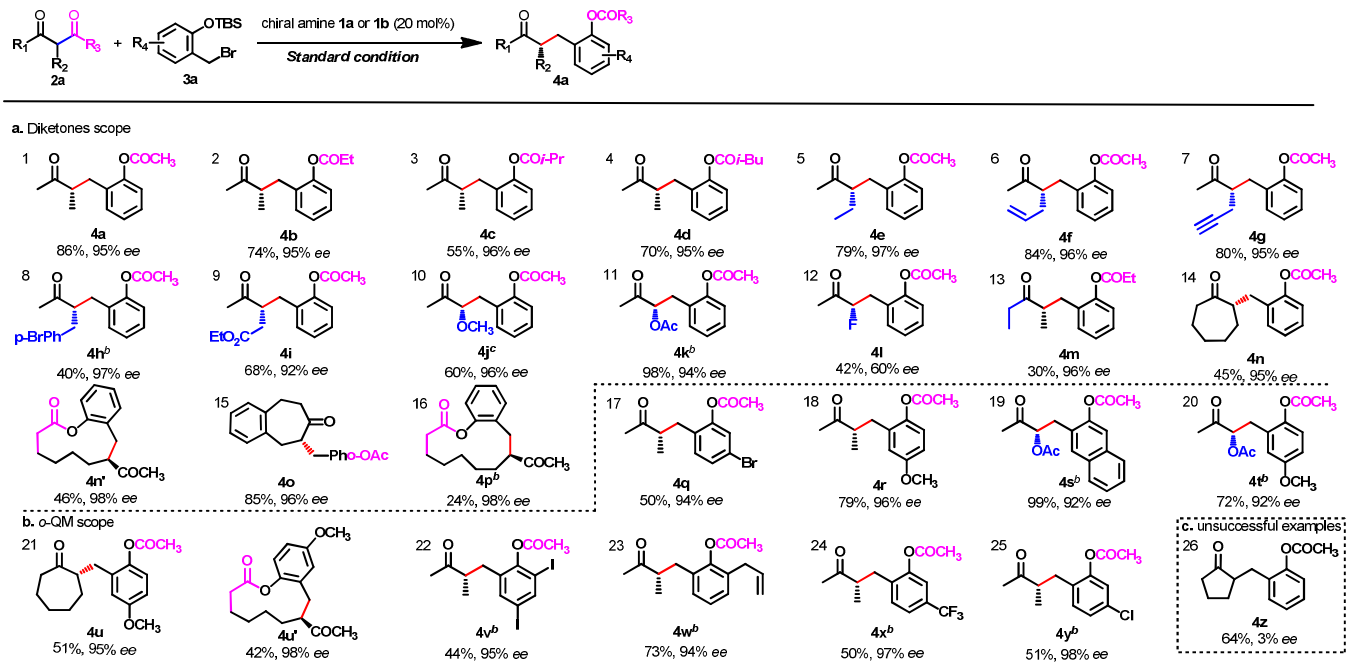
[a]Reactions were performed at room temperature in 0.3 mL CH_3CN, with **2a** (0.1 mmol), **3a** (0.11 mmol), **1a** (20 mol %), KF (0.11 mmol) and adipic acid (50 mol %), 40 h. [b]Yield of isolated product. [c]Determined by HPLC analysis.

We explored this asymmetric retro-Claisen process using 3-methy-2,4-pentanedione **2a** and the *o*-QM precursor **3a** as the coupling partners by our developed chiral primary amine catalyst **1**. Delightfully, the desired C-C bond cleavage product **4a** was acquired in 83% yield and 93% *ee* under the optimized conditions with primary amine **1a** (Table 1, entry 1). Other diamine catalysts **1** derived from different amino acids all performed equally well with comparable yields and enantioselectivities for the retro-Claisen reaction (Table 1, entries 2 and 3). No desired reaction was observed in the absence of aminocatalyst, highlighting the aminocatalytic nature (Table 1, entry 4).[9] KF was identified as the optimal Lewis base and other fluoride additives such as NaF, LiF and KHF_2 led to lower yield. The use of acidic additive was essential for effective stereocontrol, to note that the reaction in absence of weak acid was virtually non-selective (Table 1, entry 9). Dicarboxylic acids were found to favor enantioselective control (Table 1, entries 5, 6 and 11), and monoacids, with varied acidity and loadings, led to poor enantioselectivity (Table 1, entries 7-10). Both adipic acid and *m*-phthalic acid were identified as the optimal additive (entry 11). In the latter case, even the geometry of the diacids has a significant influence on reactivity and stereoselectivity (entries 11-13) and the mono-protected *m*-phthalic acid was also ineffective (entry 10), highlighting the critical diacid effect. Further optimization also revealed noted solvent effect (Table 1, entries 14-16). No reaction occurred when using dichloromethane as reaction media (entry 15), and the reaction worked more effectively in the dilute solution of acetonitrile with higher enantioselectivity (entry 16).

With the optimized conditions in hand, we then examined the scope of the reaction. Asymmetric β-ketoacetones worked well to give the expected reto-Claisen products in good yields and excellent enantioselectivities (Table 2, entries 2-4). The C-C cleavage occurred exclusively on the more bulky keto moiety and no other regioisomer was observed, highlighting the capability of primary amine to differentiating the two keto groups and selectively forming enamine on the smaller aceto side (Scheme 1, II). Acetoacetones bearing different α-substituents such as ethyl (**4e**), allyl (**4f**), propargyl (**4g**), benzyl (**4h**) and carboxylate-containing alkyl (**4i**) could also be incorporated to give desymmetric alkylation products in 40-84% yields and 92-97% *ee* (Table 2, entries 5-9). α-Phenylacetoacetone, dominantly in its enol form, was not a workable substrate in this reaction (not shown). The reaction also worked equally well with α-heteroatom substituted acetoacetones such as α-methoxyl (**4j**)- or acetoxyl (**4k**)- acetoacetones (Table 2, entries 10 and 11) and quantitative conversion to the expected adduct could be achieved in the case of **4k** with 98% yield and 94% *ee* (entry 11). α-Fluoroacetoactone also worked, albeit with low enantioselectivity (60% *ee*, entry 12). A large ethyl ketone has also been examined, giving 96% *ee*, but low yield (30% yield, entry 13).

β-Diketones are mainly to exist as enols, particularly with cyclic diketones. The dominant enol forms might pose problems in exploring the enamine-catalysis with cyclic β-diketones. Indeed, when we examined the reactions with 2-acetylcyclopentanone or 2-acetylcyclohexanone, only racemic product (Table 2, entry 26) or complicated mixture (for cyclohexanone, not shown) was obtained. In contrast, 2-acetylcycloheptanone worked smoothly to afford retro-Claisen type products (Table 2, entry 14). In this case, both keto moieties were amenable to the enamine activation (verified by NMR, SI) and hence two C-C cleavage adducts, **4n** and **4n'**, corresponding to the deactylation pathway and ring-enlarged pathway, were isolated with 95% *ee* and 98% *ee*, respectively. Notably, the latter adduct **4n'** is an 11-membered lactone that was notoriously challenging to synthesize. A benzocycloheptanone was also employed in the reaction to afford interestingly a single deacetyled adduct macrolide **4o** in 85 yield and 96% *ee* (Table 2, entry 15). Cyclooctanone has also been examined, showing lower activity. In this case, the use of chiral primary amine **1b** led to a sole product of macrolide **4p** in 24% yield and 98% *ee* (Table 2, entry 16). The scope of *o*-QM precursors with both electron-withdrawing and electron-donating groups were tolerated to furnish the target retro- Claisen products in moderate to good yields

Table 2. Scope of *β*-Diketones and *o*-QMs of Retro-Claisen Reactions via C-C Bond Cleavage[a]

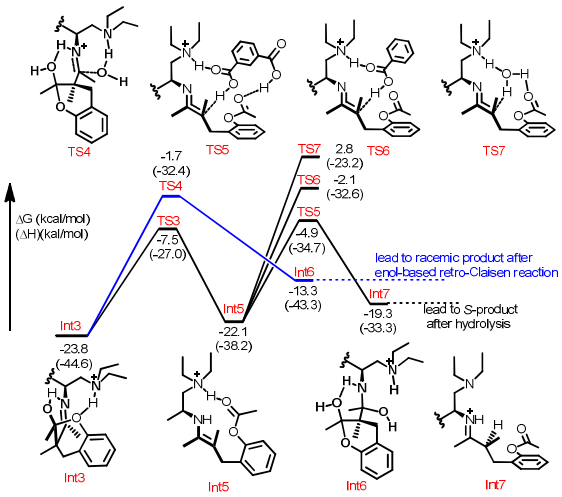


[a]All reactions were performed at room temperature in 0.7 mL CH_3CN, with **2** (0.1 mmol), **3** (0.11 mmol), **1a** (20 mol %), KF (0.11 mmol) and adipic acid (50 mol %), 40 h. Yield of isolated product. Determined by HPLC analysis. [b]Reactions performed with **1b** (20 mol %), **3** (0.15 mmol) and KF (0.15 mmol). [c]With **3** (0.15 mmol) and KF (0.15 mmol).

and high enantioselectivities (entries 17-25).

A number of experimental and theoretical studies were carried out to understand the mechanistic details. The reaction mixture was *in-situ* examined by ESI-MS and key aminocatalytic intermediates (e.g. enamine and catalyst-product adduct, **a** and **e** in Scheme 1) could be identified. In addition, alkylation of aminocatalyst with *ortho*-quinone methide and other side products were also clearly noted in the absence of weak acid additive (See SI), suggesting one role of the weak acid additive is to suppress side reactions leading to catalyst poison or background reactions.

Scheme 2. The Reaction Energy Profile

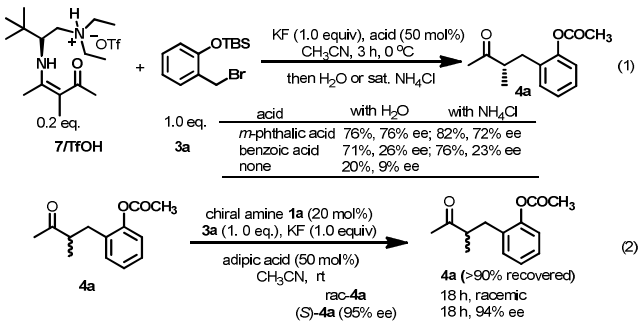


To determine the origin of stereo-induction as well as the dicarboxylic acid effect, we performed detailed DFT calculations of this catalytic multi-step process using Gaussian 09 (Scheme 2 and see SI for the full scheme).[10] It was found that the irreversible nucleophilic addition of the enamine intermediate to the *in-situ* formed *o*-QM was quite facile, leading to a much stable ketal intermediate (**int3**). Next, the enamine-based reversible *retro*-Claisen step occurred with 16.3 kcal/mol of activation energy (**TS3**). Unlike the classic retro-Claisen process, the tertiary amine embedded in the catalyst could facilitate the proton transfer of ketal O-H, which made the C-C bond cleavage much more facile. It should be noted that the reversible retro-Claisen step also proceeded in a highly stereospecific manner and only *E*-enamine was formed (**int5**). Our subsequent exploration on the stereogenic enamine protonation revealed a highly stereospecific shuttled proton transfer leading to only S-product, irrespective of the involving additive (Scheme 2, **TS 5-7**). Similar proton shuttle was previously verified in a conjugate addition-enamine protonation reaction.[8h] After careful examination, we found that a competing reaction pathway was existed for the stable ketal intermediate, where direct hydrolysis of the iminium moiety could occur with activation energy of 22.1 kcal/mol (**TS4**). The so-formed *β*-ketone-ketals would then undergo enol type retro-Claisen/protonation process, resulting in racemic product. Our calculation revealed that the presence of weak acid additive would favor the enamine-protonation pathway over that of the iminium-hydrolysis pathway (Table 1, entries 9-13; Scheme 2, **TS4** *vs* **TS 5-7**), thus facilitating high stereoinduction.

To further look into the acid effect, we separately prepared and characterized the enamine intermediate 7 using our previous procedure (SI).[5b] When **7**/TfOH was employed in reacting with *ortho*-quinone precursor **3a** under otherwise identical acidic conditions, the coupling proceeded quickly to

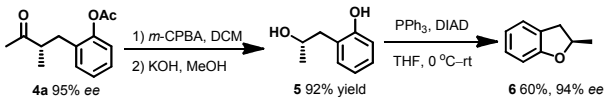
completion in less than 3 hrs and there seemed no obvious diacid effect at this stage. The resulted mixture was then treated with either water or sat. NH_4Cl aqueous solution, and in both case, notable stereoeffect was observed with the dicarboxylic acid showing significantly better enantioselectivity than mono acid and only 9% ee in the absence of weak acid, consistent with those observed under catalytic conditions (Scheme 3, eq. 1).[11] In addition, no enantio-enrichment or deracemization was observed when *rac*-**4a** or (*S*)-**4a** was subjected to the catalytic conditions (Scheme 3, eq. 2). Taken together, these results verified that enamine-protonation was the stereogenerating step in the reaction sequence and that weak acid was directly involved in this key step. The plausible mode of weak acid participation is a proton shuttle as illustrated in **TS 5-7** (Scheme 2).[8h] Besides providing a favorable acid/base buffer media to suppress side reactions, the stereocontrol effect of dicarboxylic acid might also be understood by considering the known recognition effect between diamine and diacid.[12] The observed geometry effect of diacid is in line with this notion (Table 1, entries 11-13).

Scheme 3. Control Experiments



To further demonstrate the utility of this new asymmetric retro-Claisen reaction of *β*-diketones, **4a** was subjected to a Baeyer-Villiger oxidation reaction followed by hydrolysis using KOH to generate diol **5**.[13] Then intramolecular Mitsunobu reaction gave the dihydrobenzofuran **6** (Scheme 4), a class of heterocycles presented in many natural products and biologically active compounds.[14]

Scheme 4. Synthetic Transformations



In summary, we have developed an enamine strategy for asymmetric retro-Claisen C-C bond cleavage of *β*-diketones by merging chiral primary amine catalysis and Lewis base activation. The salient features include the highly stereoselective C-C coupling between enamine and *ortho*-quinone methide, as well as the enamine-mediated C-C cleavage and the highly stereospecific enamine protonation. This retro-Claisen protocol provides accesses to chiral α-tertiary ketones and chiral macrolides that are difficult to synthesize otherwise. Further development of enamine-based Claisen reactions is underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization of new compounds and computational studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) The low enantioselectivity may be rationalized by the enhanced iminium hydrolysis under stoichiometric conditions. Efforts to characterize the *in-situ* generated intermediates (e.g. **int3**, **int5**, Scheme 2) have been in vain due to the heterogeneous nature of the reaction.

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Graphic abstract