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Highly Regio- and Stereoselective Synthesis of *Z* and *E* Enol Esters by an Amine Catalyzed Conjugate Addition-rearrangement Reaction of Ynals with Carboxylic Acids

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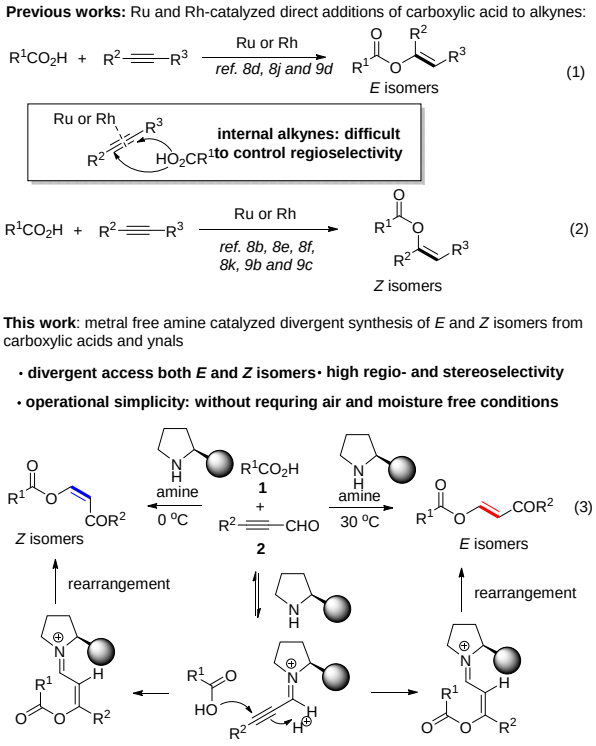
ABSTRACT: The broad synthetic utility of labile enol esters demands efficient methods for the stereo- and regio-selective synthesis of both *Z* and *E* isomers. The available synthetic methods dominated by metal catalysis cannot meet the challenge. We wish to report a metal free organocatalytic divergent approach to both *E* and *Z* isomers of enol esters from the same reactant pools with the same catalytic system. A process involves an amine catalyzed conjugate addition of carboxylic acids to ynals, which triggers a rearrangement leading to enol esters. The reaction proceeds highly regio- and stereoselectivley. Simple manipulation of reaction temperatures enables to produce *Z*-isomers at 0 °C (*Z*:*E* 15:1 - >20:1), whereas at higher 30 °C to give *E*-isomers (*E*:*Z* 15:1 - >20:1). Furthermore, the mild reaction conditions accommodate a broad array of densely functionalized carboxylic acids including complex biologically relevant structures and ynals for the process. Therefore, synthetically valued, structurally diverse enol esters are efficiently synthesized. Preliminary mechanistic studies suggest an amine promoted conjugate addition-rearrangement pathway responsible for the formation of the enol esters.

KEYWORDS: Enol esters / Organocatalysis / Ynals / Carboxylic Acids / Michael additions.

Introduction

Despite the lability of enol esters, the functionality is featured in a number of natural products with intriguing biological properties such as anti-cancer, inhibitory BACE1, and anti-viral activities.[1] Moreover, the lability endows high activity as versatile building blocks in organic synthesis. They have been widely used for a variety of transformations such as aldol and Mannich,[2] asymmetric hydrogenation,[3] cyclization,[4] and cross-coupling[5] reactions. The configuration of products produced highly depend on the geometry of *E* and *Z* isomers of the enol esters employed. Therefore the stereoselective synthesis of *E* and *Z* isomers is critically important for their synthetic applications. The state-of-the-art technologies for their syntheses are dominated by transition metal catalysis.[6-11] One of the attractive approaches involves the direct addition of simple carboxylic acids to alkynes in the presence of transition metal promoters. The pioneering study of Ru promoted addition of carboxylic acids to alkynes by Rotem and Shvo[8a] has triggered significant interests on the development of effective Ru,[8] or Rh[9] complexes as catalysts aimed at improving *E* and *Z* selectivity and/or regioselectivity (Scheme 1, Eq. 1 and 2). However, only a handful of approaches are disclosed for the preparation of *E* by Dixneuf,[8d] Itoh[8j] Cramer[9d] or *Z* by Dixneuf,[8b] Gooßen,[8e] Leong,[8f] Inoue,[8k] and Breit[9b,9c] isomers. In principle, *E* and *Z* isomers can be accessed from the same pool of reactants. Nonetheless, to the best of our knowledge, a strategy capable



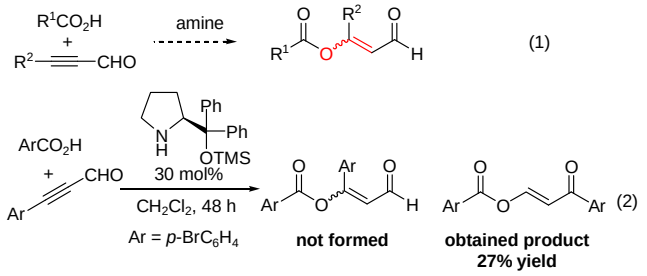
Scheme 1. Methods for Synthesis of Enol Esters.

of producing *E* and *Z* isomers in an efficient divergent fashion remains elusive. Furthermore, it is difficult for the Ru and Rh activation mode to achieve good regioselectivity for internal alkynes (Scheme 1). Finally, in addition to toxicity and cost concerns and the lability of ligand-metal complexes, these transition metals catalyzed reactions are generally performed under restricted air and moisture free conditions.

Herein we wish to report a new alternative catalytic approach to enol esters using amine as a catalyst for the first time under operationally simple ambient conditions.[11] We found that an amine catalyzed conjugate addition of carboxylic acids to ynals triggered an unexpected subsequent rearrangement leading to highly regio- and stereo-controlled *Z* and *E* enol ester products in a divergent manner (Scheme 1, Eq. 3). At lower temperature (0 °C), *Z*-isomers are formed highly stereoselectively (> 15:1 *Z*:*E*), while at higher temperature (30 °C), thermodynamic control *E* products are produced dominantly (> 15:1 *E*:*Z*). The strategy reported in this study is distinct from that of widely studied transition metal Ru and Rh catalysis. An unprecedented amine catalyzed the conjugate addition of carboxylic acid to C≡C triple bonds leads to an unexpected rearrangement process for the enol ester formation.

Results and Discussion

Exploration and optimization Iminium catalysis has enjoyed great success.[12] A diverse array of nucleophiles can participate in conjugate addition processes to form new C-C and C-X bonds. Nonetheless, to the best of our knowledge, carboxylic acids as nucleophiles for the amine promoted conjugate addition reactions with enals have not been developed. We believe that weak nucleophilicity and high leaving tendency of carboxylic acids are difficult to be added into an iminium ion in the reversible process. Inspired by our and other groups' studies with ynals in organocatalysis,[13-15] we proposed the use of ynals instead of enals because of the formation of irreversible adduct due to p-π conjugation of the lone pair electrons with the C=C double bond and higher reactivity of ynals than that of enals (Scheme 2, Eq. 1).



Scheme 2. Amine Catalyzed Conjugate Addition of Carboxylic Acids to Ynals

To validate the feasibility, we performed an exploratory investigation of reacting of 4-bromobenzolic acid with (4-bromophenyl)propynal in the presence of Jorgensen-Hayashi diphenyl prolinol TMS ether (30 mol%) in CH_2Cl_2 (Eq. 2). To our delight but unexpectedly, an *E*-enol ester rather than a conjugate addition adduct was obtained, verified by X-ray single crystal structure (Figure. 1).[16]

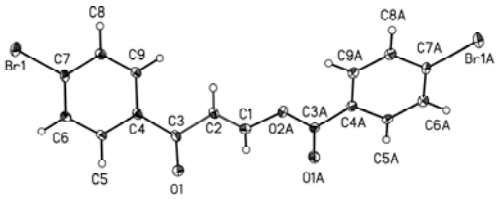
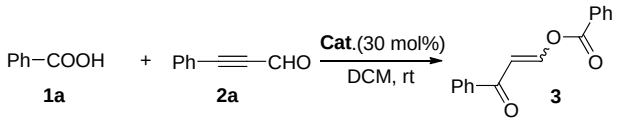


Figure 1. X-ray single crystal structure.

Table 1. Optimization of Amine Catalyzed Synthesis of Enol Esters[a]



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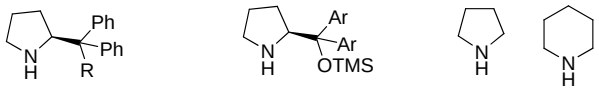


C1 R = OTMS **C4** R = OH
C2 R = OTBS **C5** R = H
C3 R = OTES

C6 Ar=3,5-dimethylphenyl
C7 Ar=3,5-bis(trifluoromethyl)phenyl

C8 **C9**

Entry	Cat.	t (h)	Yield (%)[b]
1	**C1**	24	29
2	**C2**	24	16
3	**C3**	24	24
4	**C4**	24	36
5	**C5**	48	-
6	**C6**	24	32
7	**C7**	24	76
8	**C8**	48	-
9	**C9**	48	-
10[c]	**C7**	24	60
11[d]	**C7**	24	72
12[d,e]	**C7**	24	80
13[d,f]	**C7**	96	72

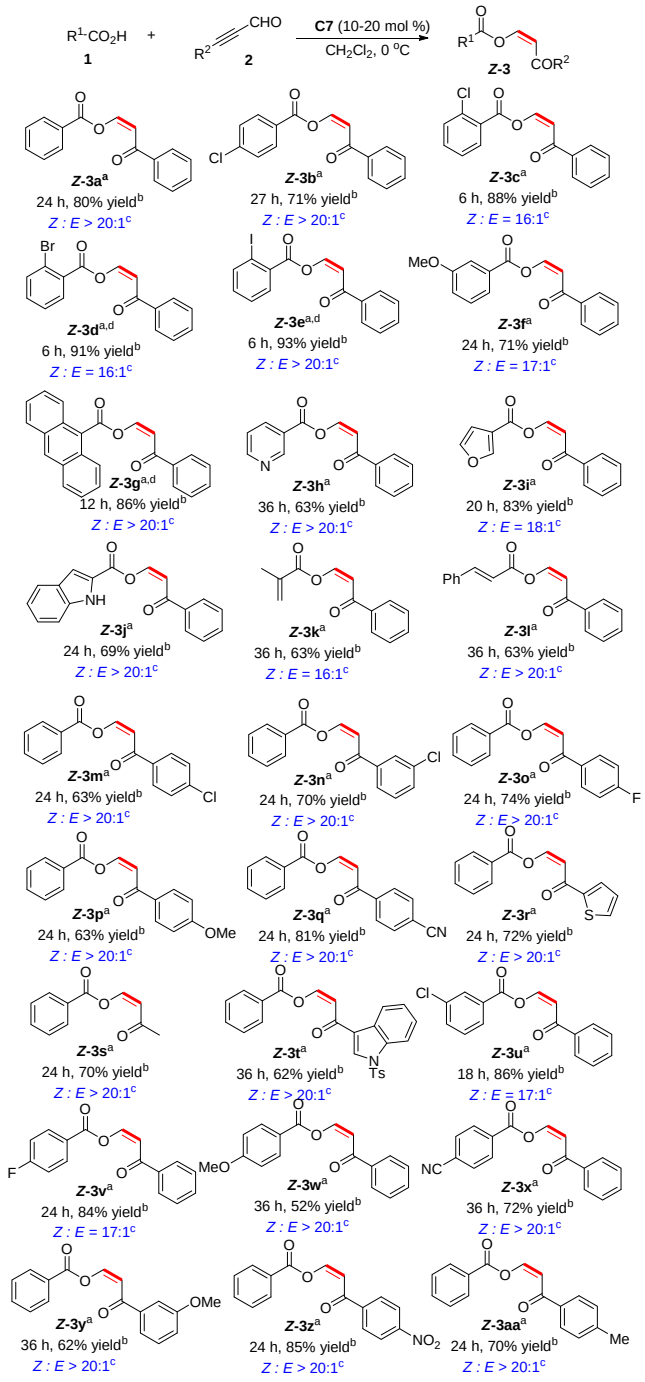
[a] Reaction conditions: unless specified, the reaction was carried out with 0.24 mmol of **1a** and 0.2 mmol of **2a** in 0.8 mL of CH_2Cl_2 with 30 mol% catalyst was stirred at rt for a specified time. Unless specified, see the Experimental Section for reaction conditions. [b] Isolated yields with both isomers. [c]

20% catalyst was used. [d] 20% catalyst was added in three times, each time 1/3 of the total amount catalyst was used, see Methods for details. [e] 0 °C, Z/E > 20/1. [f] 30 °C, *E*/*Z* > 20/1.

The unexpected outcomes prompted us to investigate the interesting process in details. In the initial effort, we attempted to optimize the reaction conditions to improve the reaction yields using benzoic acid **1a** and phenylpropiolaldehyde **2a** as substrates in the present of an amine catalyst (Table 1). Screening of catalysts (entries 1-9) revealed **C7** giving the best results (76% yield, entry 7). It seems that the steric hindrance and side chain acidity of catalysts can facilitate the process by enhancing the formation of iminium ion and facial selectivity and minimizing 1,2-addition reaction. Decreasing the catalyst loading to 20 mol % furnished lower yield (60%, entry 10). We found that the addition of the catalyst in three portions led to improved yield by reducing the catalyst decomposition under the acidic reaction conditions (72%, entry 11). We also noticed that after 24 h at rt the *Z*/*E* ratio of the product **3a** was 5/1 based on ^{1}H NMR analysis of the reaction mixture. This suggests that the process could involve a kinetic/thermodynamic control. Indeed, at lower temperature (0 °C, entry 12), a kinetic control product *Z* isomer (> 20:1 *Z*/*E*) was obtained in 80% yield. Higher temperature was favored for the thermodynamic control *E* isomer. Only *E* isomer was produced in 72% yield at 30 °C after 96 h (entry 13). To the best of our knowledge, this study represents the first example, enabling synthesis of both *E* and *Z* enol esters using the same catalytic system and the same reactants.

Synthesis of *Z* isomers We first probe the scope of the process for the formation of *Z* isomer products. As shown in Scheme 3, clean *Z*-enol esters are produced (*Z*/*E* > 15/1). It appears that the reactions have significant tolerance toward structural variations of both reactants, carboxylic acids **1** and ynals **2**. Therefore, structurally diverse *Z*-enol esters are obtained under the mild reaction conditions. First, the electronic and steric effects of different functional groups on the phenyl ring in acids **1** were examined (***Z*-3a** - ***Z*-3f**). It was found that regardless of the electron-neutral, -donating or -withdrawing groups installed on the substrates, all afford the desired products in good to high yields. In addition to substituted phenyl systems, fused aromatic (e.g., 9-anthracenyl, ***Z*-3g**) and heteroaromatic structures including 3-pyridinyl, 3-furanyl and 2-indolyl (***Z*-3h** - ***Z*-3j**) can effectively engage in the processes. It is interestingly observed that for 2-indolyl carboxylic acid, the CO_2H rather than C_3 position, which is considered more nucleophilic, participated in the reaction (***Z*-3j**). We also found that α, β-unsaturated acids such as methacrylic acid (***Z*-3k**) and *trans*-cinnamic acid (***Z*-3l**) could be tolerated by the process in good yields. Examination of the structural alternation of ynals reveals a similar trend (***Z*-3m** - ***Z*-3q**). Furthermore, heteroaromatic and aliphatic systems could be applied (***Z*-3r** - ***Z*-3t**). It is also realized the limitation of the process. Aliphatic acids can participate in the process, but the reactivity is lower than that of aromatics ones. It takes longer reaction time and it produces a mixture of *Z* and *E* isomers and unrearrangement product. For example, reaction of 3-phenylpropionic acid with phenylpropiolaldehyde **2a** even with 30 mol% **C7** gave 18% enol ester product and direct conjugate unrearrangement adduct in 25% yield. It appears that aliphatic acid adducts are difficult to undergo the subsequent rearrangement process.

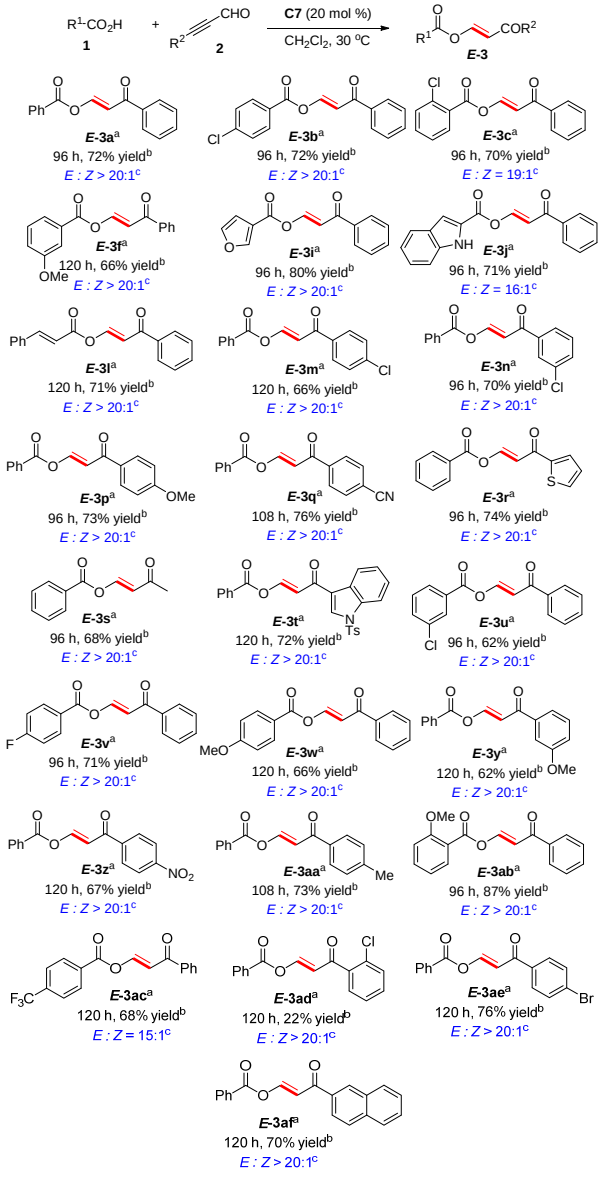
Synthesis of *E* isomers Having established an efficient protocol for the synthesis of *Z*-enol esters, we then turned our attention on the construction of *E*-enol esters. Since the more stable *E*-enol esters are thermodynamically controlled products, we conducted studies by raising the reaction temperature and/or extending the reaction time. To our delight, the desired *E*-enol esters were obtained when the reaction was performed at 30 °C and longer reaction time (96-120 h) (Scheme 4).



[a] Unless stated otherwise, see SI Methods for detail of the reaction conditions. [b] isolated yields. [c] Determined by ^{1}H NMR. [d] 10 mol % **C7** used.

Scheme 3. Substrate scope of C7-catalyzed synthesis of *Z*-enol esters.

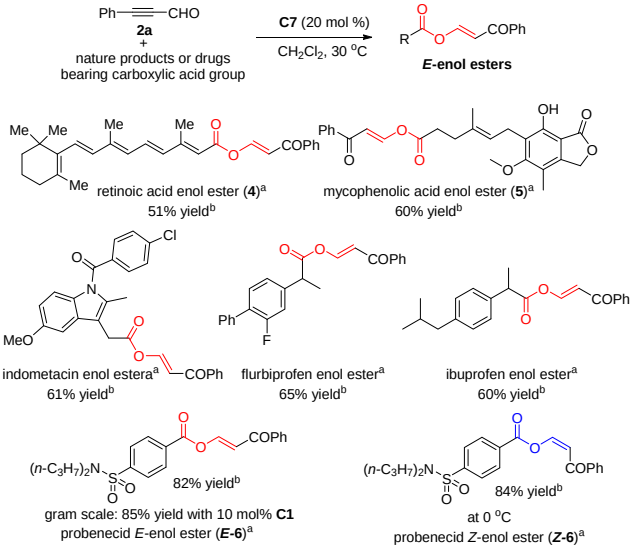
Notably under the reaction conditions, again clean *E*-isomers (15:1 - > 20:1 *E* : *Z* ratio) were attended in good to high yields (62-92%). Again, a variety of acids and ynals as reactants can be applied for this process with a broad substrate scope and therefore this offers a viable approach to *E*-enol esters with various structure features.



[a] Unless stated otherwise, see SI Methods for detail of the reaction conditions. [b] Isolated yield. [c] Determined by ^{1}H NMR.

Scheme 4. Scope of C7-catalyzed synthesis of *E*-enol esters.

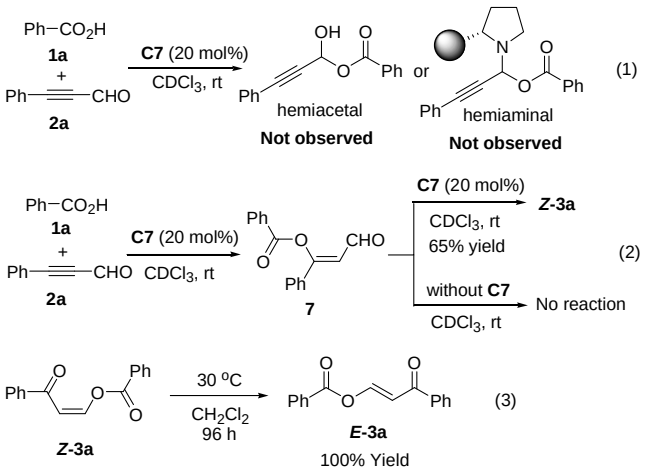
Derivatization of complex carboxylic acids In addition to the relative simple acids, we also demonstrated that the mild reaction conditions enable biologically relevant, more complex carboxylic acids to selectively react with ynals using phenyl propynal as example (Scheme 5). It was found that under the thermodynamically controlled reaction conditions, heavily functionalized acids can effectively participate in the reactions chem-, regio- and stereo-selectively to deliver interesting *E*-enol ester derivatives **4-6** in high yields. They include retinoic acid,[17] mycophenolic acid,[18] an immunosuppressant drug and others (Scheme 5). It is noteworthy that the reaction conditions can tolerate highly acid sensitive polyene and nucleophilic phenol moieties in retinoic acid and mycophenolic acid. Finally, we chose therapeutic probenecid[19] to show divergent synthesis of its *Z* and *E* enol esters. Both cases offered good yields and excellent *Z* and *E* selectivity. Furthermore, this protocol can be conveniently scaled up, as shown in the use of probenecid (5.0 mmol) and phenylpropiolaldehyde (3.6 mmol) with 10 mol% catalyst **C7**, delivering ***E*-6** in 85% yield (Scheme 5).



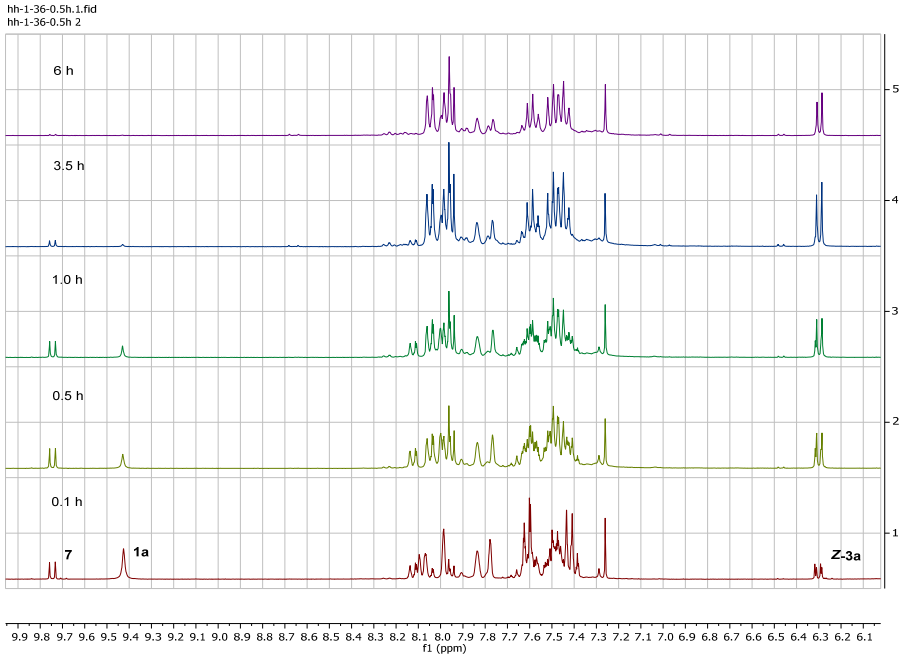
[a] Unless stated otherwise, see SI Methods for detail of the reaction conditions. [b] Isolated yield.

Scheme 5. Synthesis of enol esters derived from natural products and therapeutics.

Preliminary mechanistic studies The unexpected enol ester formation from carboxylic acids and ynals prompted us to conduct preliminary studies of the interesting reaction mechanism. We found that the process involving the Meyer–Schuster type rearrangement[20] was ruled out because the formation of the hemiacetal or hemiaminal was not observed (Scheme 6, Eq. 1), which is an essential precursor for the rearrangement. Instead, a Michael adduct **7** was formed initially, observed by *in situ* ^{1}H NMR (Figure 2). Furthermore, we isolated and characterized the product by reaction of benzoic acid **1a** with ynal **2a**. It was found that only in the presence of **C7**, the adduct was able to converted into enol ester ***Z*-3a** (Eq. 2). Without the catalyst, no reaction occurred. These results suggest that the catalyst is necessary for the initial Michael and subsequent rearrangement reactions.



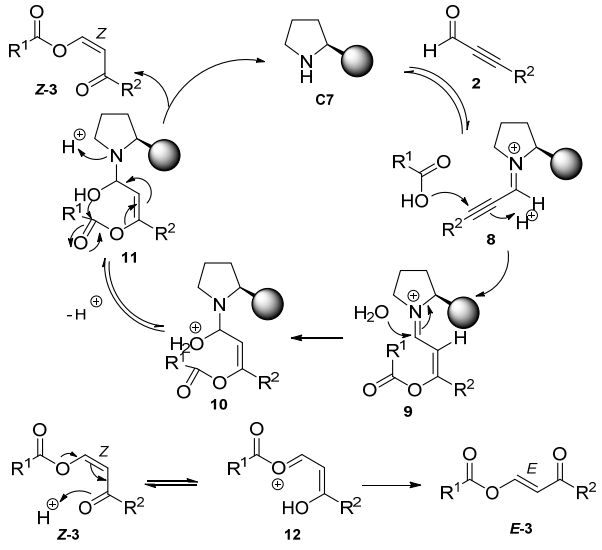
Scheme 6. Reactions designed for study of reaction mechanism.



[a] The *in situ* ^{1}H NMR analysis was carried out with 0.12 mmol of **1a** and 0.1 mmol of **2a** in 2 mL of $CDCl_3$ with 30 mol% catalyst **C7**.

Figure 2. Reaction progress of C7 catalyzed reaction of 1a with 3a.

Based on the above studies, we proposed a catalytic cycle for the formation of enol esters **3** (Scheme 7). Nucleophilic attack of benzoic acid from less hindered side of the iminium ion **8** is followed by protonation of α-carbon gives *cis*-iminium ion **9**. Nucleophilic addition H_2O to the iminium ion leads to hemiaminal **11** after proton transfer with **10**. Hydroxyl group triggers an interesting rearrangement *via* intramolecular transesterification to gives rise to a *Z*-enol ester ***Z*-3** with concomitant release of the catalyst. Under thermodynamic control condition, the kinetic control ***Z*-3** undergoes isomerization *via* intermediated **12** to furnish more stable ***E*-3**, which is confirmed by the transformation of ***Z*-3** to ***E*-3** experiment (Scheme 6, Eq. 3).



Scheme 7. Proposed catalytic cycle.

Conclusions

In conclusion, we have established a new divergent organocalytic protocol for the preparation of both *E*- and *Z*-enol esters from a diverse array of simple carboxylic acids and ynals. Under kinetic control conditions, *Z*-enol esters are produced highly stereoselectively while *E*-isomers are selectively formed by thermodynamic control. Preliminary mechanistic studies suggest an amine catalyzed unprecedented Michael-rearrangement pathway for the formation of the enol esters. Different from transition metal catalysis of carboxylic acids with alkynes, a novel organocatalytic catalysis strategy is implemented for the conjugate addition of carboxylic acid to polarized C≡C triple bonds. Further investigation of the reaction mechanism in detail and the exploration of the chemistry for new transformations are currently pursued in our laboratories.

ASSOCIATED CONTENT

Experiment details and spectroscopic data. 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 interests.

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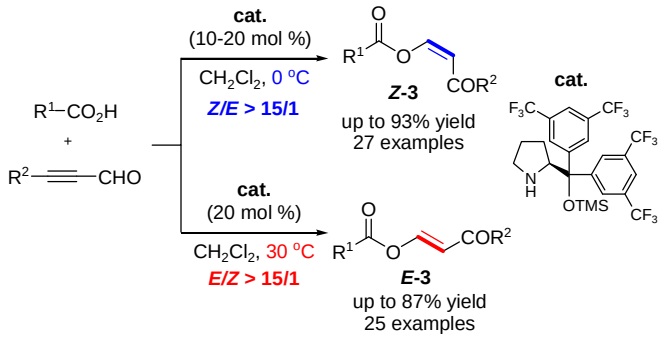
TOC:


cat.
(10-20 mol %)
CH2Cl2, 0 °C
Z/E > 15/1
Z-3
up to 93% yield
27 examples
cat.
(20 mol %)
CH2Cl2, 30 °C
E/Z > 15/1
E-3
up to 87% yield
25 examples
R1–CO2H
+
R2—≡—CHO
COR2
OTMS
F3C
CF3