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Copper(II)-Catalyzed Tandem Decarboxylative Michael/Aldol Reactions Leading to the Formation of Functionalized Cyclohexenones

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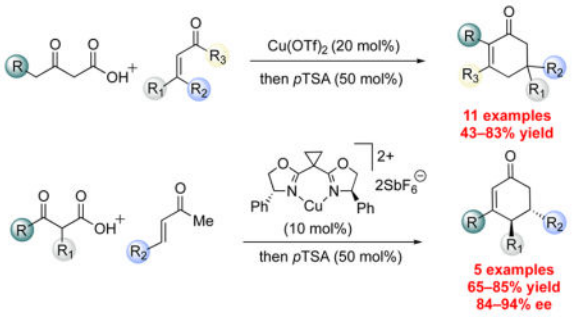
Abstract

This work describes the development of new single-pot protocol involving copper(II)-catalyzed decarboxylative Michael reaction between β-ketoacids and enones followed by in situ aldolization resulting in highly functionalized chiral and achiral cyclohexenones. The achiral version of this Robinson annulation protocol features previously unprecedented Michael reaction of β-ketoacids with sterically hindered β, β′-substituted enones and provides access to all carbon quaternary stereocenter-containing cyclohexenones (11 examples, 43–83% yield). In addition, an asymmetric chiral bis(oxazoline) copper(II)-catalyzed single-pot Robinson annulation is used to generate chiral cyclohexenones including the products containing vicinal stereocenters (5 examples, 65–85% yield, 84–94% ee). This latter protocol is successfully applied to accomplish single-pot enantioselective formation of oxygenated 10-nor- steroid core from readily available starting materials in excellent yield and selectivity (85% yield, 93% ee, 8:1 dr).

Graphical Abstract



Employed by the nature in polyketide synthesis, decarboxylative reactions of β-ketoacids represent powerful and mild means for the construction of new C-C bonds in complex

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, ^{1}H and ^{13}C NMR spectra of compounds (pdf).

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settings. The enolates derived from β-keto acids could serve as versatile nucleophiles compatible with a variety of carbon-based electrophiles.[1] Due to the presence of carboxylate that acts as a traceless activating group, such reactions could be promoted under very mild conditions using the catalysts that otherwise would not be compatible with strongly basic ketone-derived enolates. Thus, in 2003, the Shair group described the first example of copper(II)-catalyzed decarboxylative aldol reaction using noticebly mild condition that resulted in a highly selective formation of aldol adducts in good yields and selectivities (Scheme 1a).[2] Following this report, a number of studies focused on further unraveling the potential of decarboxylative transformations involving β-ketoacids,[3–5] including their application in enantioselective Ni(II)-catalyzed Michael reaction by the Evans group (Scheme 1b).[3a] Subsequently, many examples of decarboxylative Michael additions have been accomplished using different Lewis acidic catalysts,[3] chiral organocatalysts,[4] and photoredox catalysts.[5] These studies, however, suffer from severe limitations posed by high sensitivity of Michael reactions to the steric effects exhibited by the substitution on enones and β-ketoacids.

Recently, our group demonstrated that Cu(II) complexes under solvent-free conditions are among the most active catalysts for the Michael reaction between β-ketoesters and enones.[6] This catalytic in Cu(II) protocol[7–9] enabled previously unprecedented formation of highly strained Michael reaction products containing vicinal quaternary/tertiary and quaternary/quaternary stereocenters[10] under the atmospheric pressure.[6a] Based on these prior results, we envision that Cu(II) salts could promote decarboxylative Michael reactions of unreactive substrates to provide products that are typically inaccessible through previously reported reactions of β-ketoacids. This work demonstrates for the first time that Cu(II) salts are unique catalysts able to promote decarboxylative Michael reactions between β-ketoacids and enones, and the Michael adducts are directly cyclized to form functionalized cyclohexenones *in situ*. The enantioselective variant of this Robinson annulation[12] may provide chiral cyclohexenones with vicinal tertiary centers, the motifs that are frequently present in natural products. The utility of this protocol to natural product synthesis is successfully demonstrated by accomplishing an expedient synthesis of oxygenated 10-nor cardiotonic steroid skeleton **6e** in excellent yield and selectivity.

Our initial studies commenced with investigating the reaction of β-keto acid **1a** and mesityl oxide **2a** (Table 1). Considering that the intermolecualar addition to β, β′-enones such as **2a** is extremely rare[10] and encountered mostly for the Mukaiyama variant of Michael reaction,[11] we investigated various catalytic and stoichiometric promoters.[13] Monitoring these reactions represented a challenge as multiple products were often observed. Interestingly, the preliminary screen identified that the Robinson annulation product **3a** rather than the direct Michael addition product prevailed in the cases when productive reactions were observed. The $Cu(OTf)_2$-catalyzed reaction (*cf.* SI) resulted in the cleanest formation of **3a** in 45% yield. This yield was further improved by adding the solution of *p*-TSA in THF at the end of the reaction to facilitate the cyclization and dehydration of cyclic and acyclic products arising from the Michael reaction of **1a** and **2a**. Re-evaluation of the Lewis acid catalyzed reactions under these modified conditions (entries 5–12, Table 1) further secured the conclusion that $Cu(OTf)_2$ is an excellent and unique catalyst for the formation of **3a** (entry

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12, 83% yield). In addition, $Fe(OTf)_2$ and $Yb(OTf)_3$ were found to possess some activity, albeit significantly lower than for the $Cu(OTf)_2$-catalyzed case (entries 6 and 7). The catalytic activity of $Cu(OTf)_2$ cannot be attributed solely to the *in situ* generation of triflic acid as triflic acid alone did not promote the formation of **3a** to the same extend (entry 3).

With the catalyst and conditions developed above, the scope of the decarboxylative Robinson annulation of β, β′-disubstituted enones leading to cyclohexenones with quaternary stereocenters was explored next (Table 2). Consistently with the observations made for the reaction of **1a** and **2a** (*vide supra*), all of the reactions described in Table 2 provided mixtures of Michael adducts and cyclized products when treated with $Cu(OTf)_2$ (20 mol%) alone. However, clean formation of the cyclohexenones was observed if the Cu(II)-catalyzed reactions were followed by *in situ* treatment with *p*TSA (50 mol%) in THF. Thus, in accord with the results obtained for mesityl oxide **2a**, the reaction of (*R*)-(+)-pulegone **2b** and **1a** resulted in unsaturated 2-decalone **3b** in 57% yield (Table 2. entry 2). This transformation could tolerate modification in β-ketoacid, and in addition to **1a**, β-ketoacids **1b** (entries 3–10) and **1c** (entry 11) were successfully employed to provide cyclohexenes **3c–3k** in good to excellent yields. Finally, the reactions of **1b** with a variety of β, β′-disubstituted enones (**2c–2j**) indicated that this method tolerates changes in the β, β′-substitution without significant drop in the overall yield. Importantly, this method provides a quick, straightforward and selective access to highly functionalized cyclohexenones that are not always readily accessible through other methods such as metal-catalyzed alkyne insertion into cyclobutanones.[14]

Our initial attempts to accomplish enantioselective formation of cyclohexenones **3** containing quaternary stereocenters by using the chiral bis(oxazoline)-based Cu(II) complexes such as **A**[6,8,9] were met with limited success as the reactions of β, β′-substituted enones **2** suffered from the low conversion and enantioselectivity. However, the reactions of β-monosubstituted enones such as **5a** proceeded with excellent yields and enantioselectivities (Scheme 2). Thus, the annulation of **5a** with reactive β-ketoacids **4** lacking the C2-substitution resulted in the formation of chiral cyclohexenones **6a**–**6c** in good yields and excellent enantioselectivities. In addition, the reaction of C2-substituted β-ketoester **4d** and **5a** led to the formation of synthetically valuable functionalized decalin **6d** as a 4:1 mixture of diastereomers at C4 in 75% yield and 94% ee for both diastereomers. The formed diastereomers were found to be epimeric at the C4 position as a result of decarboxylation followed by a moderately selective protonation of the resultant enol. To further demonstrate the utility of this chemistry, the enantioselective decarboxylative Robinson annulation method was also successfully applied to the synthesis of 10-nor-steroid **6e**. Based on our previous study,[6] enone **5b** was generated in two steps from the readily available starting materials. Upon decarboxylative Robinson annulation of **5b** with β-ketoacids **4d**, 10-nor-steroid **6e** was directly obtained in 85% yield with 93% ee and 8:1 d.r. (1.0 g scale). The diastereomers arise at the C10 position as a result of decarboxylation/enol protonation, and the stereochemistry of the major diastereomer **6e** was assigned using X-ray crystallographic analysis. It is noteworthy that the skeleton present in **6e** is commonly found in various natural 10-nor-cardiotonic steroids.[15]

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The plausible mechanism for the copper catalyzed decarboxylative Michael reaction is proposed in Figure 1. The enol form of β-ketoacids **4** is proposed to undergo chelation to the Cu(II) complex **A**. The complexation to Cu(II) results in enhanced acidity of carboxylate, which is important for the activation of enones **6** either by protonation or through hydrogen bond. The activated enone **6** then undergoes a Michael reaction followed by a proton transfer with the enolized β-ketoacid. The Michael reaction is then followed by decarboxylation and aldol condensation leading to **7**. This proposal is consistent with the mechanism for decarboxylative aldol addition by Shair and coworkers who proposed that the decarboxylation takes place after the reaction with electrophile.[2] It is also consistent with the observation that both diastereomers of **6d** are formed with identical enantiopurity, which implies that the enantiodetermining step precedes decarboxylation. In summary, a new single-pot protocol involving copper(II)-catalyzed decarboxylative Michael reaction between β-ketoacids and enones followed by in situ aldolization was developed to achieve expedient formation of highly functionalized chiral and achiral cyclohexenones. The achiral version of this Robinson annulation protocol features previously unprecedented Michael reaction of β-ketoacids with sterically hindered β, β′-substituted enones and provides access to all carbon quaternary stereocenter-containing cyclohexenones (11 examples, 43–83% yield). Copper(II) salts were discovered to be unique catalysts for these Michael reactions as the other Lewis and Brønsted acids evaluated in these studies were inferior to Cu(II) catalysts. Similar protocol could be applied to achieve the formation of cyclohexenes with vicinal tertiary centers (*cf.* SI and Scheme 2). The later substrates were also formed asymmetrically using chiral bis(oxazoline) copper(II) complexes as the catalysts. This single-pot enantioselective Robinson annulation was used to generate chiral cyclohexenones containing vicinal stereocenters (5 examples, 65–85% yield, 84–94% ee). In addition, this latter protocol was successfully applied to accomplish single-pot enantioselective formation of oxygenated 10-nor- steroid core from readily available starting materials in excellent yield and selectivity (85% yield, 93% ee, 8:1 dr). The further application of these methods in the synthesis of natural diterpenes and 10-norsteroids[14] is the subject of our ongoing studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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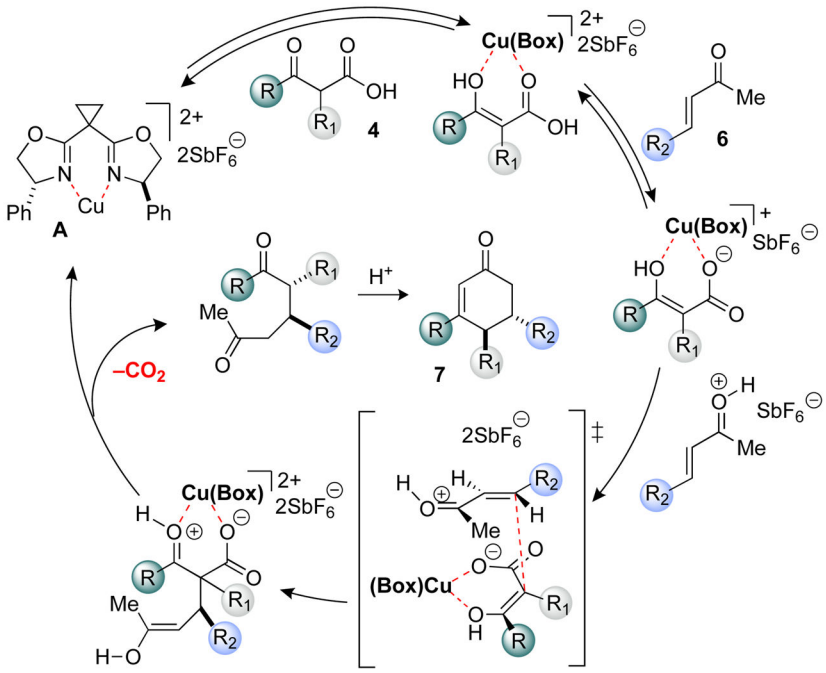

Figure 1.
Proposed Mechanisms

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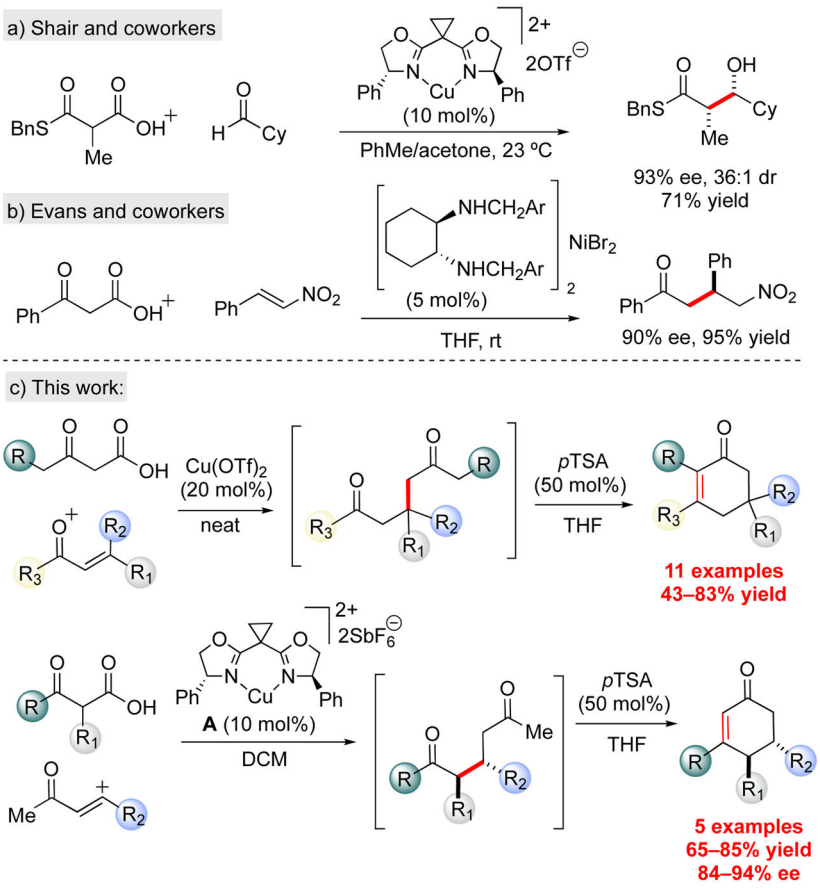

Scheme 1.

Metal catalyzed decarboxylative additions

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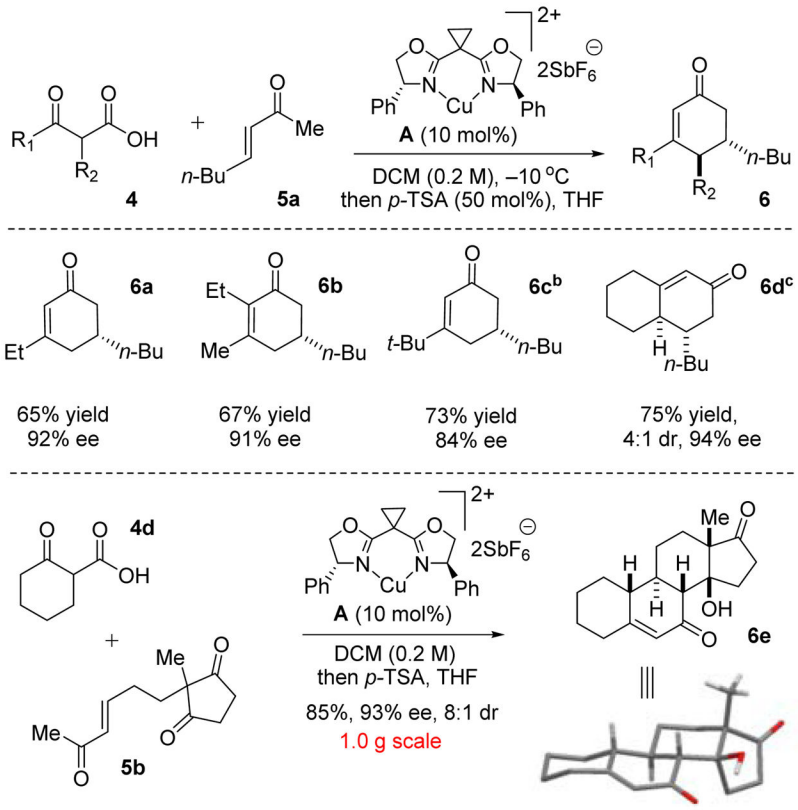

Scheme 2. Enantioselective copper catalyzed decarboxylative Robinson annulation[a]

[a]β-keto acid **1** (1.6 equiv), enone **6a** (1.0 equiv), then add *p*-TSA (50 mol%). Isolated yield (average of 2 trials). [b] *p*-TSA cyclization at 60 °C for 24 h. [c]Diastereomers of **6d** was found to have the same ee values.

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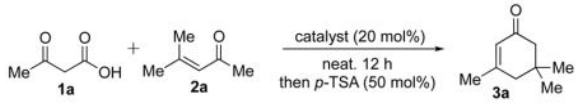
Table 1

Evaluation of the catalysts for decarboxylative Robinson annulation[a]



entry	catalyst	yield (%)	entry	catalyst	yield (%)
1	Et_3N	no reaction[b]	**7**[d]	$Yb(OTf)_3$	17
2	DBU	no reaction[b]	**8**[d]	$Zn(OTf)_2$	no reaction[b]
3	TfOH	15	**9**[d]	$Mn(OTf)_2$	no reaction[b]
4	$BF_3{\cdot}OEt_2$	no reaction[c]	**10**[d]	$Cu(OAc)_2$	no reaction[c]
5[d]	$Ni(OTf)_2$	no reaction[b]	**11**[d]	$CuCl_2$	20
6[d]	$Fe(OTf)_3$	9	**12**[d]	$Cu(OTf)_2$	83

[a]β-keto acid **1a** (1.6 equiv), vinyl ketone **2a** (1.0 equiv), then add *p*-TSA (0.5 equiv), THF, rt, 12 h.

[b]Consumption of both **1a** and **2a** leading to multiple products is observed.

[c]Consumption of **1a** leading to multiple products is observed.

[d]Reactions were conducted with and without *p*-TSA step; however, introduction of *p*-TSA step led to the higher yields for entries 11 and 12 (*cf.* SI for additional details).

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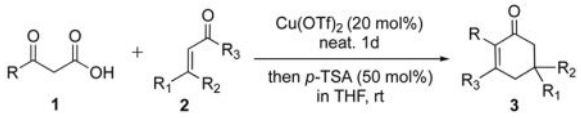
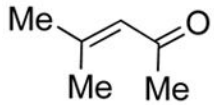
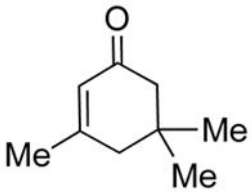
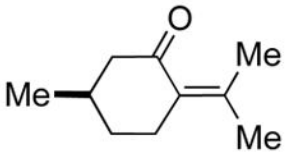
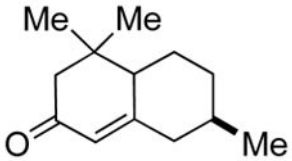
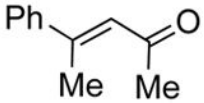
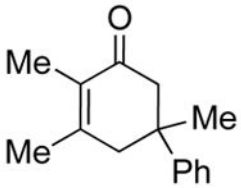
Table 2

Substrate scope for the decarboxylative Michael reaction leading to formation of cyclohexenones with quaternary carbon.[a]



entry	β-keto acid	vinyl ketone	time	yield[b] (%)	product
1	R = H **(1a)**	 **2a**	12 h	83	 **3a**
2	R = H	 **2b**	12 h	57	 **3b**
3[c]	R = Me **(1b)**	 **2c**	3d	52	 **3c**

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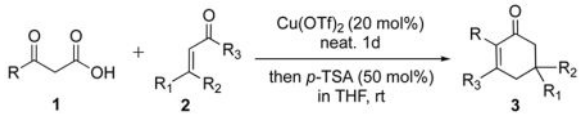
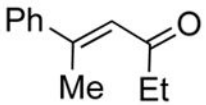
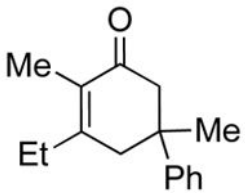
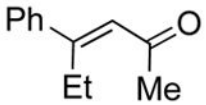
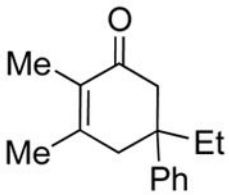
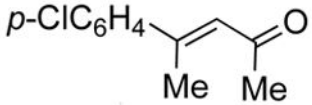
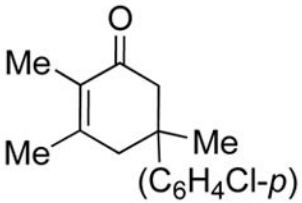


entry	β-keto acid	vinyl ketone	time	yield[b] (%)	product
4[c]	R = Me	 **2d**	3d	43	 **3d**
5[c]	R = Me	 **2e**	3d	60	 **3e**
6[c]	R = Me	 **2f**	3d	53	 **3f**

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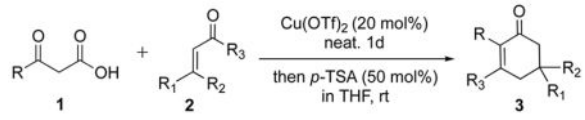
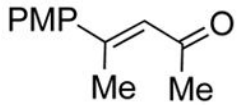
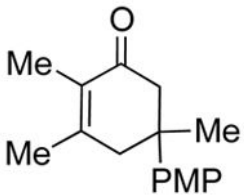
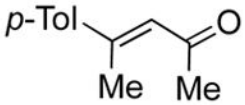
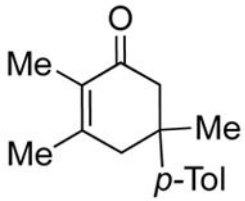
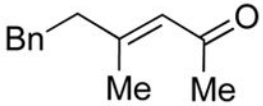
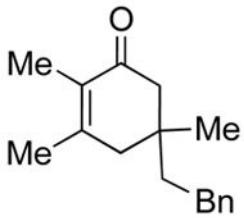


entry	β-keto acid	vinyl ketone	time	yield[b] (%)	product
7[c]	R = Me	 **2g**	3d	52	 **3g**
8[c]	R = Me	 **2h**	3d	59	 **3h**
9	R = Me	 **2i**	12 h	62	 **3i**

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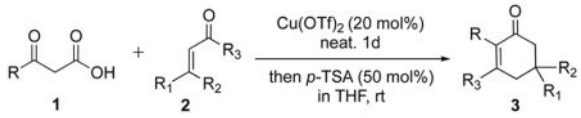
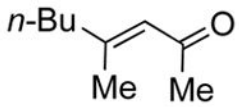
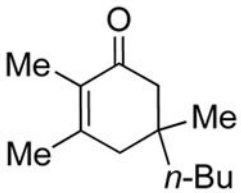
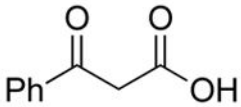
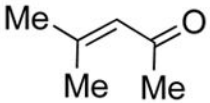
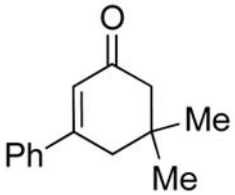


entry	β-keto acid	vinyl ketone	time	yield[b] (%)	product
10	R = Me	 **2j**	12 h	70	 **3j**
11[d]	 **(1c)**	 **2a**	12 h	81	 **3k**

[a]β-keto acid **1** (1.6 equiv), vinyl ketone **2** (1.0 equiv), then add *p*-TSA (0.5 equiv).

[b]Isolated yield (average of 3 trials).

[c]Additional β-keto acid **1** (0.5 equiv) was added every 24 h due to decarboxylation.

[d]*p*-TSA cyclization at 60 °C for 24 h.