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

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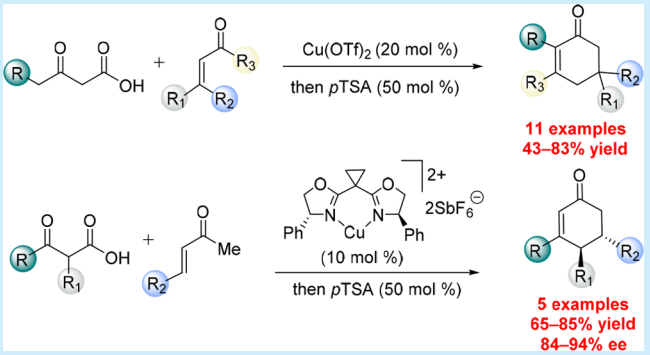
Supporting Information

ABSTRACT: This work describes the development of a new single-pot copper(II)-catalyzed decarboxylative Michael reaction between β-keto acids and enones, followed by in situ aldolization, which results in highly functionalized chiral and achiral cyclohexenones. The achiral version of this Robinson annulation features a hitherto unprecedented Michael reaction of β-keto acids 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 has been devised for preparing chiral cyclohexenones, including some products that contain vicinal stereocenters (5 examples, 65−85% yield, 84−94% ee). This latter protocol has been successfully applied to the enantioselective formation of the oxygenated 10-nor-steroid core from readily available starting materials.



Employed by the nature in polyketide synthesis, decarboxylative reactions of β-keto acids represent a powerful and mild means for constructing new C−C bonds in complex settings. The enolates derived from β-keto acids could serve as versatile nucleophiles compatible with a variety of carbon-based electrophiles.[1] Due to carboxylate acting as a traceless activating group, such reactions can 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 a copper(II)-catalyzed decarboxylative aldol reaction using noticebly mild conditions 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-keto acids,[3−5] including an application in enantioselective Ni(II)-catalyzed Michael reactions 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 do, however, suffer from severe limitations posed by the high sensitivity of Michael reactions to the steric effects exhibited by the substitution pattern on the enones and β-keto acids.

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

Our studies commenced with an investigation of the reaction between β-keto acid **1a** and mesityl oxide **2a** (Table 1). Considering that the intermolecular addition to β,β′-enones

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Scheme 1. Metal-Catalyzed Decarboxylative Additions

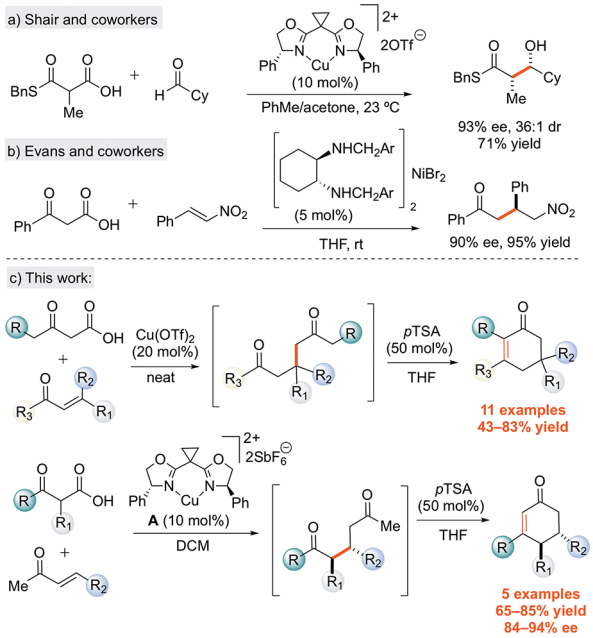
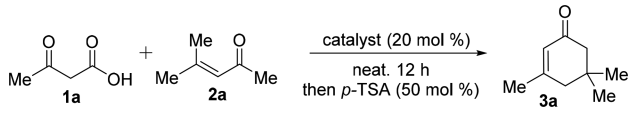


Table 1. Evaluation of the Catalysts for Decarboxylative Robinson Annulation[a]



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 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 the *p*-TSA step; however, introduction of the *p*-TSA step led to the higher yields for entries 11 and 12 (cf. SI for additional details).

such as **2a** is extremely rare[10] and encountered mostly for the Mukaiyama Michael reaction,[11] we investigated various catalytic and stoichiometric promoters.[13] Monitoring these reactions represents a challenge as multiple products are 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. Supporting Information (SI)) resulted in the cleanest formation of **3a** in 45% yield. This yield was further improved by adding a 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 allowed us to conclude that $Cu(OTf)_2$ is an excellent and unique catalyst for the formation of **3a** (entry 12, 83% yield). In addition, $Fe(OTf)_2$ and $Yb(OTf)_3$ were found to possess some activity, but this was 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 it alone did not promote the formation of **3a** to the same extend (entry 3).

With the catalyst and conditions developed, the scope of the decarboxylative Robinson annulation of *β*,*β*′-disubstituted enones to give cyclohexenones with quaternary stereocenters was next explored (Table 2). Consistent 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 the unsaturated 2-decalone **3b** in 57% yield (Table 2, entry 2). This transformation could tolerate modifications in the *β*-keto acid, and in addition to **1a**, *β*-keto acids **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 tolerated changes in the *β*,*β*′-substitution pattern without a significant drop in the overall yield. Importantly, this method provides quick, straightforward, and selective access to highly functionalized cyclohexenones that are not always readily accessible through other transformations such as metal-catalyzed alkyne insertion into cyclobutanones.[14]

Our initial attempts to accomplish the enantioselective formation of cyclohexenones **3** containing quaternary stereocenters by using the chiral bis(oxazoline)-based Cu(II) complexes such as **A**[6,8,9] met with limited success, as the reactions of *β*,*β*′-substituted 2-en-1-ones **2** suffered from 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*-keto acids **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 the 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*-keto acids **4h**, 10-nor-steroid **6e** was directly obtained in 85% yield with 93% ee and 8:1 dr (1 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 via X-ray crystallographic analysis. It is noteworthy that the skeleton present in **6e** is commonly found in various natural 10-nor-cardiotonic steroids.[15]

The plausible mechanism for the copper-catalyzed decarboxylative Michael reaction is proposed in Figure 1. The enol form of *β*-keto acids **4** is proposed to undergo chelation with Cu(II)

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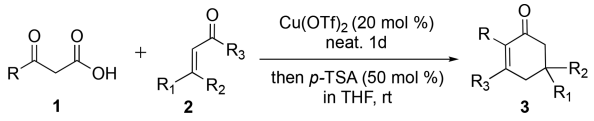
Table 2. Substrate Scope for the Decarboxylative Michael Reaction Leading to Formation of Cyclohexenones with Quaternary Carbon[a]



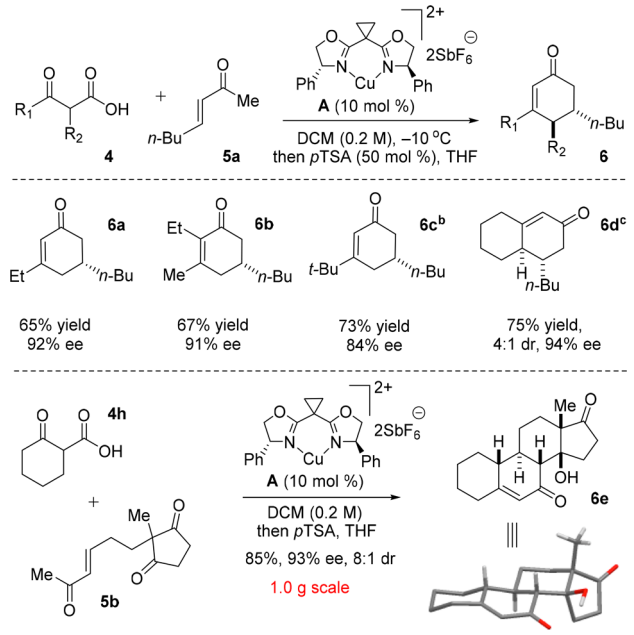
1 2 3

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	36 h	52	3c
4[c]	R = Me	2d	36 h	43	3d
5[c]	R = Me	2e	36 h	60	3e
6[c]	R = Me	2f	36 h	53	3f
7[c]	R = Me	2g	36 h	52	3g
8[c]	R = Me	2h	36 h	59	3h
9	R = Me	2i	12 h	62	3i
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 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.

complex **A**. The complexation to Cu(II) results in enhanced acidity of carboxylate, which is important for the activation of the enones **6** either by protonation or through hydrogen bonding. The activated enone **6** then undergoes a Michael reaction followed by a proton transfer with the enolized β-keto acid. 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

Scheme 2. Enantioselective Copper-Catalyzed Decarboxylative Robinson Annulation[a]



[a]β-Keto acid **1** (1.6 equiv), enone **6a** (1 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** were found to have the same ee values.

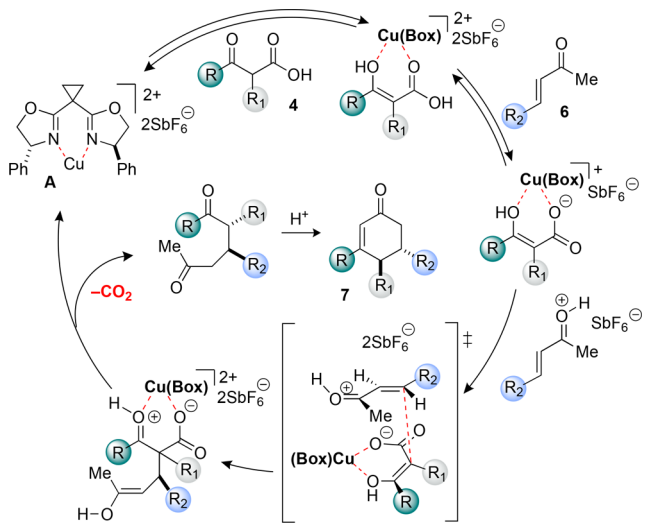


Figure 1. Proposed mechanisms.

and co-workers who proposed that the decarboxylation takes place after the reaction with electrophile.[2,16] 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-keto acids and enones followed by in situ aldolization has been developed that achieves an expedient formation of highly functionalized chiral and achiral cyclohexenones. The achiral version of this Robinson annulation protocol features a previously unprecedented Michael reaction of β-keto acids with sterically hindered β,β′-substituted enones and provides access to all carbon

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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. A 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 (4 examples, 65−85% yield, 84−94% ee). In addition, this latter protocol was successfully applied to accomplish a single-pot enantioselective formation of an 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-nor-steroids[15] is the subject of our ongoing studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00607.

Experimental procedures and ^{1}H and ^{13}C NMR spectra of compounds (PDF)

Accession Codes

CCDC 1586998 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.

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Notes

The authors declare no competing financial interest.

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