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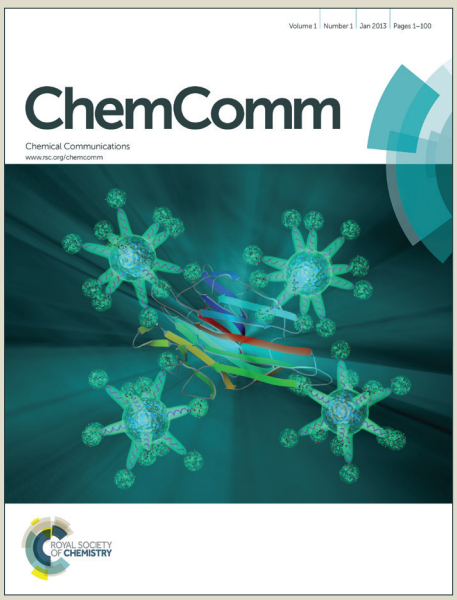

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Iridium-catalyzed regioselective decarboxylative allylation of β-ketoacids: efficient construction of γ, δ-unsaturated ketones

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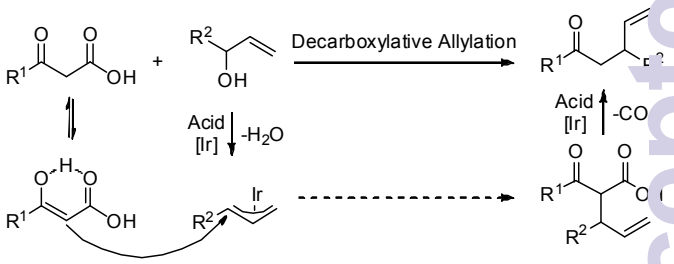
A highly regioselective protocol for the direct synthesis of γ, δ-unsaturated ketones from β-ketoacids and allylic alcohols was proposed and accomplished relying on the combination of $[Ir(cod)Cl]_2$ and 10-camphorsulfonic acid *via* decarboxylative allylation.

Transition-metal-catalyzed allylic alkylation is one of the most efficient tools for constructing *C–C* bonds in natural products synthesis and medicinal chemistry.[1] Although high regioselective and enantioselective allylic alkylation has been realized with a wide range of soft *C*-nucleophiles including both stabilized (malonates, β-ketoesters etc.) and unstabilized ketone enolates (simple ketone enolates), the allylation of methyl ketone enolates with allylic substrates remains challenging because the allylation product must resist a second allylation with another allylic substrate.[2] So far, only a handful of protocols have been developed to meet these challenges. For example, Hartwig and coworkers realized an iridium-catalyzed highly regio- and enantioselective allylation of silyl enol ethers and enamines with allylic carbonates through combination of stoichiometric amount of CsF and ZnF_2.[3] Thus, the development of more readily accessible approach for the pre-activation of such less reactive methyl ketones is still in high demand.

As the precursors of methyl ketones, β-ketoacids could act as stabilized ketone enolates and react with suitable electrophilic substrates. In fact, a series of electrophiles, such as imines,[4] aldehydes,[5] ketones,[6] alcohol,[7] sulfonamide,[8] allylic acetates,[9] isatins,[10] and activated alkenes[11] has been proved to be good reaction partners under certain conditions. Very recently, the Breit's group reported a rhodium-catalyzed regioselective decarboxylative addition between β-ketoacids and terminal allenes to generate a series of γ,δ-unsaturated ketones.[12] The reaction is thought to occur through the intermediacy of π-allyl rhodium intermediate which undergoes nucleophilic attack by β-ketoacid *via* its enol form. In our previous work, we have demonstrated the direct allylation of indoles with allylic alcohol *via* a π-allyl iridium intermediate in the presence of Bronsted acids, which exhibited excellent regioselectivity for branched products.[13] Thus, we envisaged that highly regioselective allylation of methyl ketone might be achieved through decarboxylative allylation of β-ketoacids with allylic alcohols *via* catalytic cleavage of C-O and C-C bonds in the presence of $[Ir(cod)Cl]_2$ and appropriate acid (Scheme 1, for more details see SI).

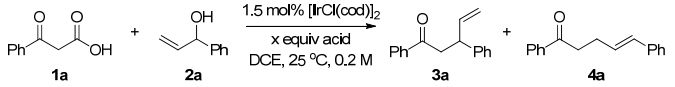


Scheme 1. Proposed iridium-catalyzed decarboxylative allylation of β-ketoacids with allylic alcohols.

To test our hypothesis, the reaction of β-ketoacid **1a** and allylic alcohol **2a** in 1,2-dichloroethane was carried out at room temperature with $[Ir(cod)Cl]_2$ and acid (Table 1). In the presence of 10 mol% of $Fe(OTf)_3$, the reaction gave a 29% yield of the branched product **3a** with a 46:54 ratio of **3a** to the linear product **4a** (entry 1). The investigation of several metal triflate salts gave the desired product **3a** in moderate yield but still with unsatisfactory regioselectivity (<80:20) (entries 2-7). To our delight, when the Lewis acid was replaced with Brønsted acid, the regioselectivity was dramatically improved. The acidity and subtle structural effects on reaction yield and regioselectivity were observed.

Weak acids resulted in low yields (entries 5-8), while stronger acid gave better results (entries 9-11). Camphorsulfonic acid (CSA) (pK_a 1.2) was found to be the best acid in terms of both yield and regioselectivity (entry 9). Stronger acids CF_3COOH (pK_a 0.3) and $TsOH{\cdot}H_2O$ (pK_a -2.8) led to a drop in yield and regioselectivity (entries 10 and 11). Increasing the loading of CSA showed that 0.5 equiv was enough to achieve a satisfactory result (entries 12-13). Lowering the catalyst loading to 0.5 mol% led to diminished yield and regioselectivity (entry 14). In the absence of $[Ir(cod)Cl]_2$, only 24% of **3a** was obtained with a low regioselcetivity (entry 15). Surprisingly, the acidity of *β*-ketoacid **1a** itself could activate the allylic alcohol **2a** slowly, delivering **3a** in 27% yield with excellent regioselcetivity (entry 16).

Table 1 Optimization of reaction conditions[a]



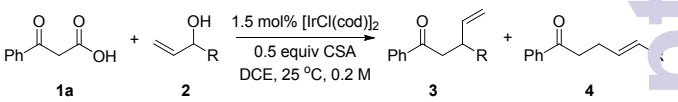
1a **2a** **3a** **4a**

Entry	Acid	x	Yield **3a** (%)[b]	**3a**:**4a**[c]
1	$FeCl_3$	0.1	29	46:54
2	$Cu(OTf)_2$	0.1	43	69:31
3	$Zn(OTf)_2$	0.1	55	72:28
4	$Sc(OTf)_3$	0.1	46	74:26
5	HCOOH	0.1	5	95:5
6	PhCOOH	0.1	11	91:9
7	H_3PO_4	0.1	4	97:3
8	$(PhSO_2)_2NH$	0.1	9	90:10
9	CSA[d]	0.1	80	95:5
10	CF_3COOH	0.1	50	94:6
11	$TsOH{\cdot}H_2O$	0.1	68	80:20
12	CSA	0.5	92 (84)[e]	98:2
13	CSA	1	93	99:1
14[f]	CSA	0.5	78	90:10
15[g]	CSA	0.5	24	43:57
16[h]	-	-	27	99:1

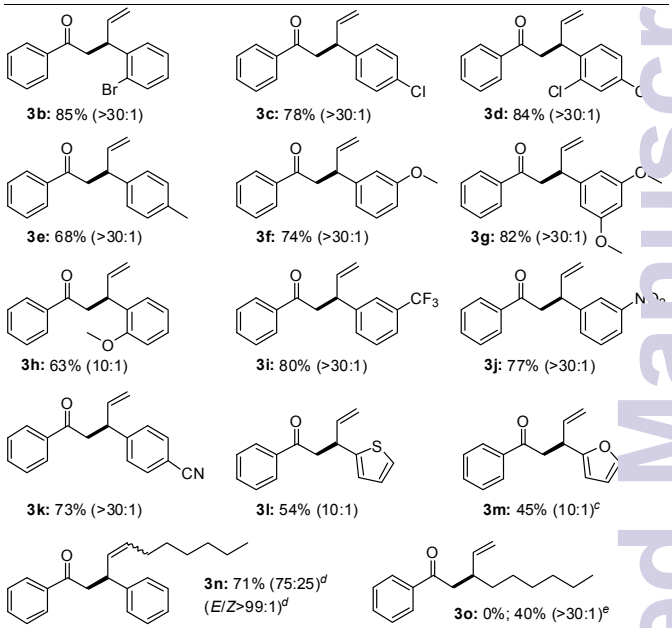
[a] Reaction conditions: *β*-ketoacid **1a** (0.39 mmol), allylic alcohol **2a** (0.30 mmol), $[Ir(cod)Cl]_2$ (1.5 mol%), acid, 1,2-dichloroethane (1.5 mL), N_2, 25 °C, 10 h. [b] GC yield. [c] The ratio of branched and linear isomers (**3a**:**4a**) was determined by ^1H NMR analysis of the crude reaction mixtures. [d] CSA = (±)-10-Camphorsulfonic Acid. [e] Isolated yield. [f] 0.5 mol% $[Ir(cod)Cl]_2$ was used. [g] Without $[Ir(cod)Cl]_2$. [h] 24 h.

With the optimized conditions in hand (Table 1, entry 12), the substrate scope of the reaction with regard to the allylic alcohol component was explored (Table 2). A number of halo- (**3b**-**3d**), alkyl- (**3e**), and alkoxy-substituted aromatic alcohols (**3f** and **3g**) all afforded corresponding products in good yields and regioselectivities. The tolerance of this reaction toward more sterically hindered substrate was also demonstrated in the successful conversion of the *o*-MeO-substituted aryl allylic alcohol (**3h**), although a decrease in regioselectivity was observed. More electron-deficient molecules, such as *m*-CF_3-, *m*-NO_2, and *p*-CN-substituted aryl allylic alcohols were

Table 2 Decarboxylative allylation of β-ketoacid **1a** with allylic alcohols[a,b]



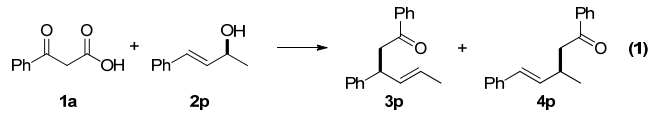
1a **2** **3** **4**



[a] Reaction conditions: *β*-ketoacid **1a** (0.39 mmol), allylic alcohol **2** (0.3 mmol), $[Ir(cod)Cl]_2$ (1.5 mol%), CSA (0.15 mmol), 1,2-dichloroethane (1.5 mL), N_2, 25 °C, 10 h; regioselectivity (reported in brackets) was determined by ^1H NMR analysis of the crude reaction mixtures. [b] Isolated yields. [c] Under CSA-free condition, *β*-ketoacid **1a** (0.6 mmol), 24 h. [d] Regioselectivity and stereoselectivity was determined by ^1H NMR analysis of the isolated product. [e] $TsOH{\cdot}H_2O$ (0.15 mmol) was used instead of CSA.

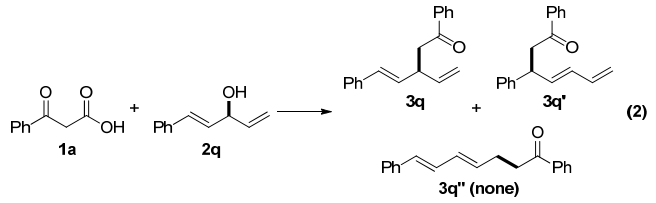
also suitable substrates for the present condition (**3i**-**3k**). Furthermore, heteroaromatic systems could also be employed successfully, albeit with lower regioselectivity (**3l** and **3m**). It should be noted that **3m** was obtained under the CSA-free conditions, since the furyl-substituted allylic alcohol was unstable under strong acid condition. In the case of 1,3-disubstituted allylic alcohols , the regioselectivity was dramatically decreased while an excellent *E*-selectivity was observed for both two isomers (**3n**). Aliphatic allylic alcohol was proved to be sluggish substrate due to the poor leaving ability of the hydroxy group, and the use of a stronger promoter was required to give a moderate yield (**3o**).

To gain further insight into the regioselectivity of this reaction, more challenging and special allylic alcohols were investigated, as showcased with the example of **2p** and **2q**. The α-alkyl allylic alcohol **2p** was also proved to be suitable substrate, and the regioselectivity was similar to that of **3n** [Eq. (1)]. Replacement of the methyl group with a vinyl also resulted in a mixture consisting of isomers **3q** and **3q'**, while linear product **3q''** was not observed. Likewise, both the product **3q** and **3q'** have an excellent *E*-selectivity (up to 20:1) [Eq. (2)].



Reaction conditions: Table 1, entry 12; regioselectivity and stereoselectivity was determined by ^{1}H NMR analysis of the isolated product.

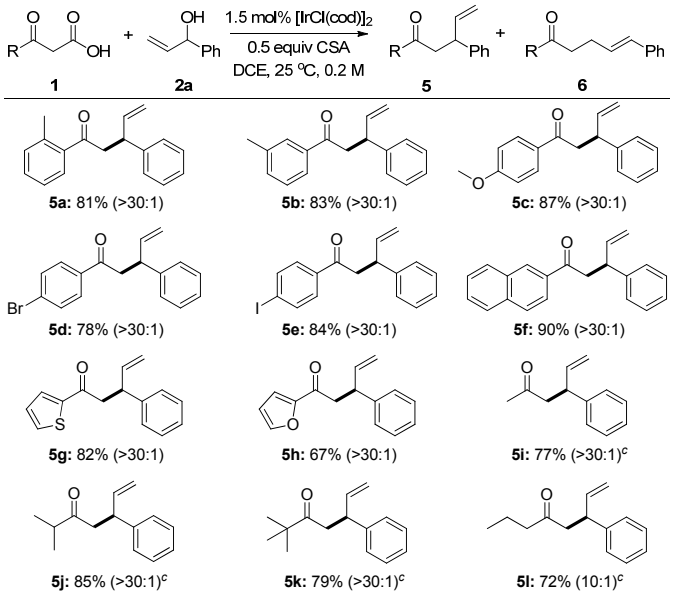
78% yield (**3p+4p**); **3p/4p** = 60:40; only *E* for both **3p** and **4p**



Reaction conditions: Table 1, entry 12; regioselectivity was determined by ^{1}H NMR analysis of crude reaction mixtures; stereoselectivity was determined by GC-MS of crude reaction mixture.

21% yield (**3q**); **3q/3q'** = 55:45; *E*/*Z*> 20:1 for both **3q** and **3q'**

Table 3 Decarboxylative allylation of *β*-ketoacid with allylic alcohol **2a**[a,b]



[a] Reaction conditions: *β*-ketoacid **1a** (0.39 mmol), allylic alcohol **2** (0.30 mmol), $[Ir(cod)Cl]_2$ (1.5 mol%), CSA (0.15 mmol), 1,2-dichloroethane (1.5 mL), N_2, 25 °C, 10 h; regioselectivity (reported in brackets) was determined by ^{1}H NMR analysis of the crude reaction mixtures. [b] Isolated yields. [c] 0.6 mmol *β*-ketoacid was used.

Additionally, a variety of *β*-ketoacids were tested with allylic alcohol **1a** （Table 3）. *β*-Ketoacids substituted with electron-rich (**5a**-**5c**) and halogenated (**5d** and **5e**) arenes underwent the decarboxylative allylation smoothly, delivering corresponding *γ,δ*-unsaturated ketones in good yields with excellent regioselectivities. Naphthyl (**5f**) and heterocycles such as thiophene (**5g**) and furan (**5h**) were also compatible with the reaction condition. Furthermore, aliphatic *β*-ketoacids possessing alkyl groups, including methyl (**5i**), isopropyl (**5j**), *tert*-butyl (**5k**)，and *n*-propyl (**5l**), furnished products in comparable yields，although a modest decrease in regioselectivity was observed for **5l**.

In summary, we have developed an iridium-catalyzed decarboxylative allylic substitution which employs allylic alcohols and readily accessible *β*-ketoacids as nucleophiles to afford bifunctional *γ,δ*-unsaturated ketones. Branched isomers were obtained as the major product under mild conditions with commercially avail[a]ble $[Ir(cod)Cl]_2$ and CSA. This decarboxylative allylation represents an atom economical method that directly using allylic alcohols as substrates without prior activation. Further investigations on the asymmetric version of this reaction is ongoing and will be reported as the results become available.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures and analytical data for products. See DOI: 10.1039/c000000[x]

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