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Catalytic decarboxylative alkylation of β-keto acids with sulfonamides *via* the cleavage of carbon–nitrogen and carbon–carbon bonds†

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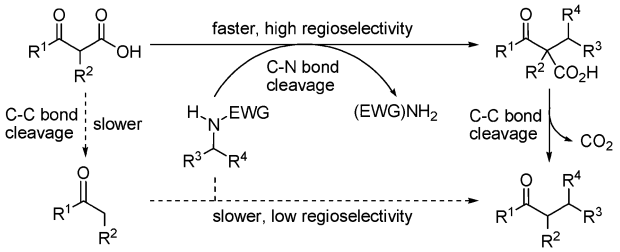
An efficient decarboxylative alkylation reaction of β-keto acids with *N*-benzylic or *N*-allylic sulfonamides has been developed, for the first time, through sequential cleavage of carbon–nitrogen and carbon–carbon bonds in the presence of 10 mol% of $FeCl_3$.

While β-keto esters have been widely employed as carbon nucleophiles to couple with a broad range of carbon electrophiles in carbon–carbon bond-forming reactions, the corresponding β-keto acids have received relatively little attention in this respect. Sporadic examples show that under appropriate conditions β-keto acids are capable of undergoing decarboxylative carbon–carbon bond-forming reactions with carbon electrophiles such as aldehydes,[1] imines,[2] electron-deficient alkenes,[3] allylic acetates,[4] and 1,3-diene monoepoxides.[5] Such biomimetic reactions allow β-keto acids to be employed as attractive surrogates of ketones for α-alkylation in a highly regioselective manner because, in general, direct alkylation of ketones suffers from unsatisfying reactivity and regioselectivity. Nevertheless, for a long time further exploration of the synthetic utility of β-keto acids has been hampered by their instability to heat, acids, and bases.[1c,d] Herein, we wish to disclose an unprecedented decarboxylative alkylation of β-keto acids with sulfonamides *via* catalytic cleavage of carbon–nitrogen and carbon–carbon bonds.

Electron-withdrawing group-activated alkylamines have emerged as useful sp^3 carbon electrophiles to couple with a range of nucleophiles through acid-catalyzed carbon–nitrogen bond cleavage.[6,7] Significantly, the formation of nonacidic byproducts is beneficial to reduce undesired side reactions, such as overalkylation and elimination, when compared to similar reactions with alkyl halides, which are commonly employed as alkylating agents and inevitably leads to the generation of hydrogen halides as strongly acidic byproducts.[8] In this context, we envisioned that it would be possible to develop a decarboxylative alkylation of β-keto acids with electron-withdrawing group-activated alkylamines under appropriate acidic conditions based on the assumption that the formation of neutral byproducts would slow down the decomposition of β-keto acids through decarboxylation (Scheme 1). However, it is a formidable challenge to fine tune reaction conditions for the purpose to cleave the carbon–nitrogen bonds in activated alkylamines prior to the carbon–carbon bonds in β-keto acids.



Scheme 1 Proposed decarboxylative alkylation of β-keto acids with electron-withdrawing group-activated alkylamines.

The decarboxylative alkylation of β-keto acid **1a** with an activated benzhydrylamine was selected as a model reaction to test our hypothesis (Table 1). Initially, the acidity of β-keto acid **1a** itself was attempted to catalyze its reaction with *p*-toluenesulfonyl-activated benzhydrylamine (sulfonamide **2a**) in 1,2-dichloroethane at room temperature (Table 1, entry 1). However, no alkylation product was obtained, and β-keto acid **1a** was found to decompose slowly to give acetophenone. Gratifyingly, the employment of 10 mol% of $FeCl_3$ to catalyze the reaction resulted in the formation of ketone **3a** in 29% yield (Table 1, entry 2). More excitingly, the yield was dramatically improved up to 98% simply by elevating the temperature to 60 °C (Table 1, entry 4). Lowering the catalyst loading to 5 mol% or switching the catalyst to other Lewis acids just led to diminished yields or even no desired product at all (Table 1, entries 5–12). A Brønsted acid such as sulfuric acid was also capable of catalyzing this reaction, but provided a much lower yield (67%, Table 1, entry 13). Replacement of 1,2-dichloroethane with a few other organic solvents dramatically reduced the yield (Table 1, entries 14–18). Moreover, the reaction efficiency was significantly affected by the electron-withdrawing groups on the amine nitrogen atoms, and no better yield was obtained when replacing the *p*-toluenesulfonyl group with another sulfonyl group, a phosphoryl group, an acyl group, or an alkoxycarbonyl group (Table 1, entries 19–24).

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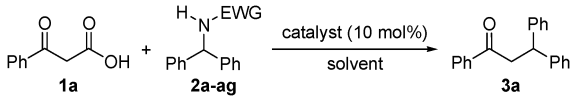
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for products. See DOI: 10.1039/c1cc12790j

Table 1 Optimization of reaction conditions[a]



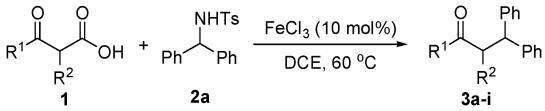
Entry	2a–ah, EWG	Catalyst	Solvent	Temp/°C	Yield[b] (%)
1	**2a**, Ts	None	DCE	25	0
2	**2a**, Ts	$FeCl_3$	DCE	25	29
3	**2a**, Ts	$FeCl_3$	DCE	45	88
4	**2a**, Ts	$FeCl_3$	DCE	60	**98**
5[c]	**2a**, Ts	$FeCl_3$	DCE	60	75
6	**2a**, Ts	$FeCl_3{\cdot}6H_2O$	DCE	60	56
7	**2a**, Ts	$ZnCl_2$	DCE	60	27
8	**2a**, Ts	$Cu(OTf)_2$	DCE	60	0
9	**2a**, Ts	$La(OTf)_3$	DCE	60	0
10	**2a**, Ts	$Bi_2(SO_4)_3$	DCE	60	0
11	**2a**, Ts	$SnCl_4{\cdot}5H_2O$	DCE	60	62
12	**2a**, Ts	TMSCI	DCE	60	0
13	**2a**, Ts	H_2SO_4	DCE	60	67
14	**2a**, Ts	$FeCl_3$	$CHCl_3$	60	64
15	**2a**, Ts	$FeCl_3$	EtOAc	60	33
16	**2a**, Ts	$FeCl_3$	THF	60	12
17	**2a**, Ts	$FeCl_3$	$MeNO_2$	60	66
18	**2a**, Ts	$FeCl_3$	MeCN	60	21
19	**2ab**, 4-$O_2NC_6H_4SO_2$	$FeCl_3$	DCE	60	94
20	**2ac**, 2-$O_2NC_6H_4SO_2$	$FeCl_3$	DCE	60	67
21	**2ad**, *n*-$C_8H_{17}SO_2$	$FeCl_3$	DCE	60	91
22	**2ae**, $(PhO)_2PO$	$FeCl_3$	DCE	60	0
23	**2af**, PhCO	$FeCl_3$	DCE	60	0
24	**2ag**, BnOCO	$FeCl_3$	DCE	60	52

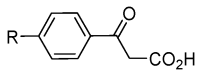
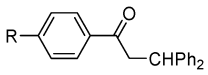
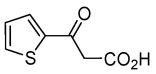
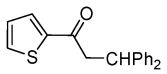
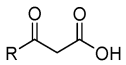
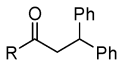
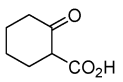
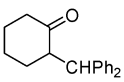
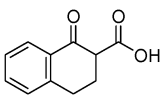
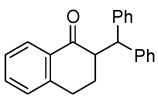
[a] Reaction conditions: β-keto acid **1a** (0.24 mmol), activated benzhydrylamine **2a–ag** (0.20 mmol), catalyst (if any, 10 mol%), solvent (1.0 mL), 1.5 h. [b] Isolated yield. [c] 5 mol% of $FeCl_3$ was used.

In the presence of 10 mol% of $FeCl_3$, a range of β-keto acids smoothly underwent decarboxylative alkylation with sulfonamide **2a** to afford structurally diverse unsymmetric ketones in good to excellent yields (Table 2, entries 1–7). This reaction well tolerated electron-rich aromatic moieties (Table 2, entries 2 and 3), and moreover, no regioisomeric alkylation product was obtained from the reaction with β-keto acids **1e** and **1f** (Table 2, entries 5 and 6). α-Alkyl β-keto acids were also examined in the iron-catalyzed decarboxylative alkylation reaction, and the corresponding unsymmetric ketones were obtained in moderate yields (Table 2, entries 8 and 9).

A variety of *N*-bisbenzylic sulfonamides were smoothly reacted with β-keto acid **1a** in the presence of 10 mol% of $FeCl_3$ to afford the corresponding 2,2-diarylethyl phenyl ketones in good yields (Table 3, entries 1–5). It is noteworthy that both electron-withdrawing and electron-donating groups were successfully introduced into the ketone products by employing the sulfonamides bearing such groups on the aromatic rings. The carbon–nitrogen bonds of *N*-monobenzylic sulfonamides were successfully cleaved under the same reaction conditions and coupled with β-keto acid **1a** to afford the desired ketones in moderate to good yields (Table 3, entries 6–9). To our delight, no rearrangement was observed for the carbon–carbon multiple bonds in the reaction with *N*-(α-alkynylbenzyl)- or *N*-(α-alkenylbenzyl)-*p*-toluenesulfonamides (Table 3, entries 10–12). Moreover, *N*-allylic sulfonamides served as suitable substrates to couple with β-keto acid

Table 2 Decarboxylative alkylation of β-keto acids with sulfonamide **2a**[a]

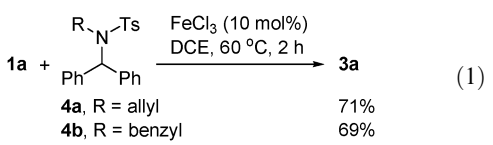


Entry	β-Keto acids	Product	Time/h	Yield[b] (%)
				
1	**1a**, R = H	**3a**, R = H	1.5	98
2	**1b**, R = OMe	**3b**, R = OMe	2	92
				
3	**1c**	**3c**	2	74
				
4	**1d**, R = Me	**3d**, R = Me	2	77
5	**1e**, R = $(CH_2)_2Me$	**3e**, R = $(CH_2)_2Me$	2	92
6	**1f**, R = $CHMe_2$	**3f**, R = $CHMe_2$	2	90
7	**1g**, R = CMe_3	**3g**, R = CMe_3	1.5	79
				
8	**1h**	**3h**	2	56
				
9	**1i**	**3i**	2	39

[a] Reaction conditions: β-keto acid **1** (0.24 mmol), sulfonamide **2a** (0.20 mmol), $FeCl_3$ (10 mol%), DCE (1.0 mL), 60 °C. [b] Isolated yield.

1a (Table 3, entries 13 and 14).[9] Nevertheless, this reaction was not applicable to less reactive sulfonamides such as *N*-benzyl-*p*-toluenesulfonamide, *N*-allyl-*p*-toluenesulfonamide and *N*-(1-adamantyl)-*p*-toluenesulfonamide.

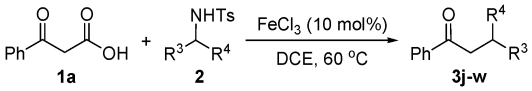
The decarboxylative alkylation reaction was found to work well with a *p*-toluenesulfonyl-activated secondary benzylic amine. For example, ketone **3a** was obtained in a good yield from the reaction of β-keto acid **1a** with sulfonamide **4a** or **4b** in the presence of 10 mol% of $FeCl_3$ (eqn (1)). It is noteworthy that the other carbon–nitrogen bond of sulfonamide **4a** or **4b** was not cleaved at all.

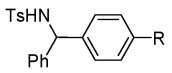
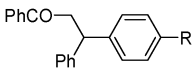
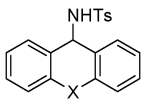
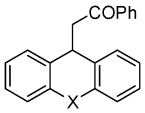
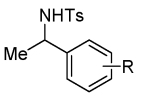
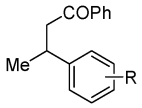
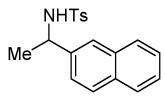
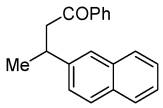
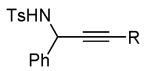
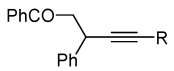
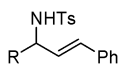
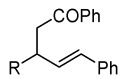
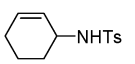
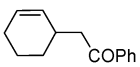


(1)

The reaction of β-keto acid **1a** with optically active sulfonamide (*R*)-**2h** (93% ee) proceeded smoothly in the presence of 10 mol% of $FeCl_3$ to afford ketone **3p** in nearly racemic form (1% ee) (Table 3, entry 7). This result suggests that a benzyl cation intermediate is involved in the reaction.[6d,g,7e,f] To gain

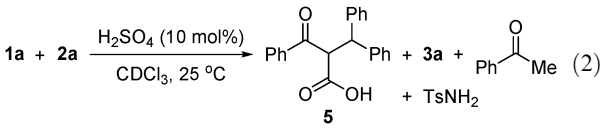
Table 3 Decarboxylative alkylation of β-keto acid **1a** with sulfonamides[a]

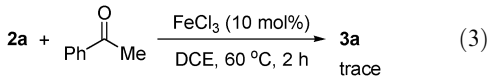


Entry	Sulfonamides	Product	Time/h	Yield[b] (%)
				
1[c]	**2b**, R = OMe	**3j**, R = OMe	6	87
2	**2c**, R = Cl	**3k**, R = Cl	1.5	83
				
3[d]	**2d**, X = CH_2CH_2	**3l**, X = CH_2CH_2	1	83
4	**2e**, X = S	**3m**, X = S	1.5	65
5	**2f**, X = O	**3n**, X = O	2	72
				
6	**2g**, R = H	**3o**, R = H	3	52
7	**2h**, R = 4-OMe	**3p**, R = 4-OMe	1.5	59
8	**2i**, R = 2-Me	**3q**, R = 2-Me	1.5	65
				
9	**2j**	**3r**	2	58
				
10	**2k**, R = Ph	**3s**, R = Ph	2	83
11	**2l**, R = *n*-Bu	**3t**, R = *n*-Bu	1	71
				
12	**2m**, R = Ph	**3u**, R = Ph	1	73
13	**2n**, R = Me	**3v**, R = Me	1.5	54
				
14	**2o**	**3w**	3	45

[a] Reaction conditions: β-keto acid **1a** (0.24 mmol), sulfonamide **2** (0.20 mmol), $FeCl_3$ (10 mol%), 1,2-dichloroethane (1.0 mL), 60 °C. [b] Isolated yield. [c] The reaction was run at room temperature. [d] 0.30 mmol of β-keto acid **1a** was used.

more insights into the reaction mechanism, we carried out ^{1}H NMR spectroscopic analysis of a mixture of β-keto acid **1a**, sulfonamide **2a**, and 10 mol% of sulfuric acid in deuterated chloroform at room temperature and identified β-keto acid **5** as an intermediate, which was confirmed by ESI-HRMS spectroscopic analysis (eqn (2)). Although acetophenone was detected in a significant amount in this mixture, it could not be effectively alkylated with sulfonamide **2a** under the conditions as illustrated in eqn (3). These experiments substantially supported the reaction pathway proposed in Scheme 1, and the sequential S_N1 alkylation/decarboxylation accounts for the extremely high regioselectivity observed in the reaction (Table 2, entries 5 and 6).





In summary, a range of β-keto acids smoothly undergo decarboxylative alkylation with *N*-benzylic or *N*-allylic sulfonamides in the presence of 10 mol% of $FeCl_3$ to afford structurally diverse unsymmetric ketones in good to excellent yields and with extremely high regioselectivity. Preliminary mechanistic studies indicate that the reaction proceeds through S_N1 alkylation followed by decarboxylation.

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Notes and references

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