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Catalyst-free Formation of 1,4-Diketones by Addition of Silyl Enolates to Oxyallyl Zwitterions *in situ* Generated from α-Haloketones

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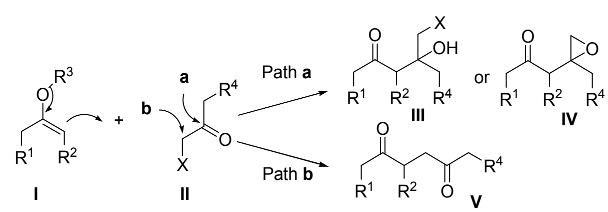
Reported here is the exclusive formation of 1,4-diketones by the uncatalyzed reaction of silyl enolates and α-haloketones. Enolates **I** inherently are more likely to react with *α*-haloketones **II** at the carbonyl carbon to produce halohydrin derivatives **III** or 2-(2-oxoethyl)-oxiranes **IV**. Thus, a variety of metal-catalyzed coupling reactions have been developed to avoid the undesired reaction in attempting the preparation of 1,4-diketones. We found that the oxyallyl zwitterions *in situ* generated from α-haloketones enabled the addition of silyl enolates to the *α*-carbonyl position to exclusively form 1,4-diketones in weakly basic conditions. Various types of silyl enolates and α-haloketones were applied to the catalyst-free coupling.

Introduction

1,4-Diketones are common substructures of natural products and pharmaceuticals,[1] like Maoecrystal V[1a] and Herquline,[1d] as well as highly useful synthetic building blocks of various carbocyclic and heterocyclic compounds, such as cyclopentenones,[2] furans,[3] thiophenes,[4] pyrroles[5] and pyridazine derivatives.[6] Therefore, significant efforts have been directed toward the synthesis of those highly valuable synthons.[7] The most straightforward method for their preparation would be the C-C bond formation between carbonylmethyl anion and cation equivalents.[8] Although versatile enolates have been developed as carbonylmethyl anions, selecting appropriate candidates as carbonylmethyl cation units is still a challenging problem. *α*-Haloketones might be used as carbonylmethyl cation equivalents, but there is a regioselectivity problem resulting from the two reactive sites respectively located at the carbonyl carbon and the *α*-carbonyl position.[9] Without metal catalysts, enolates **I** inherently are more likely to react with *α*-haloketones **II** at the carbonyl carbon to produce halohydrin derivatives **III** or 2-(2-oxoethyl)-oxiranes **IV** (Scheme 1, Path **a**).[10] Thus, a variety of metal-catalyzed coupling reactions have been developed to avoid the undesired reaction for the preparation of 1,4-diketones **V** (Scheme 1, Path **b**).[11]

Our interest in this chemistry stems from our work on the interrupted cycloadditions of oxyallyl zwitterions.[12] We have recently reported that the direct coupling of unprotected indoles and α-halo ketones via *in situ* generated oxyallyl zwitterions provides *α*-indolylketones.[13] Upon further exploration, we have also found an efficient catalytic-free method for the coupling of naphthols with oxyallyl zwitterions to produce *α*-naphtholylketones.[14] Additionally, MacMillan's report has also demonstrated that oxyallyl zwitterions allow the addition of *π*-nucleophiles or even neutral heteroatoms to the *α*-carbonyl position under mild, weakly basic conditions.[15]



Scheme 1. Reaction approaches of enolates with *α*-haloketones.

It is notable that the Harmata group has reported an efficient ene-like reaction between alkyl enol ethers **VII** and a special oxyallyl zwitterion **VI** yielded from a specific *α*-chloroketone (Scheme 2).[12b] It demonstrates that the leaving group, the Me_2PhSi moiety substituted on the oxyallyl zwitterion **VI**, takes part in a crucial role in the hydride shifting process and finally benefits the reaction efficiency.

Based on the above findings, we hypothesized that the course of the reaction might be changed if the leaving group is located on enolates **XI**, and that simple oxyallyl zwitterion **X** generated in weakly basic conditions might allow the exclusive addition of silyl enolates **XI** to the *α*-carbonyl position of **X** and finally form 1,4-diketones **XIII** after desilylation (Scheme 2). With the merits of the mildness of the desilylation process, the ease of preparation and the cleanliness of reactions, silyl enolates have long been known as weak nucleophiles in the

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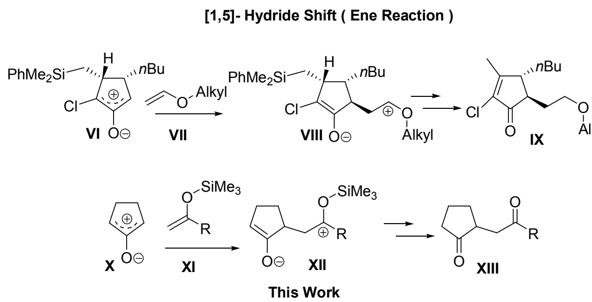
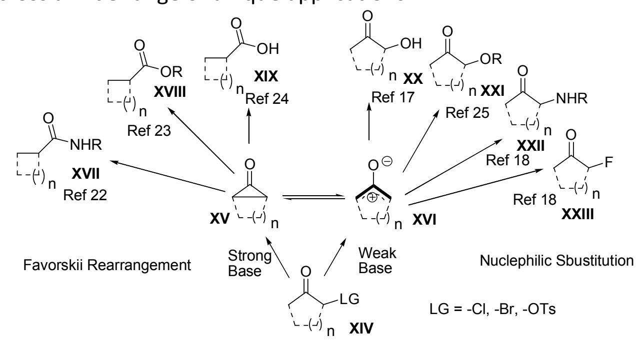
Mukaiyama aldol addition, Michael addition, and alkylation reaction.[16] However, to our knowledge, this is the first report on their application in the synthesis of 1,4-diketones without any catalyst.[17]



Scheme 2. Reaction approaches of enolates with Oxyallyl zwitterions.

and their derivatives after bond migration.[19] Furthermore, the oxyallyl zwitterions have also been known as dienophiles in [4+3] cycloadditions to construct seven-membered carbocycles across a wide range of unique applications.[20]

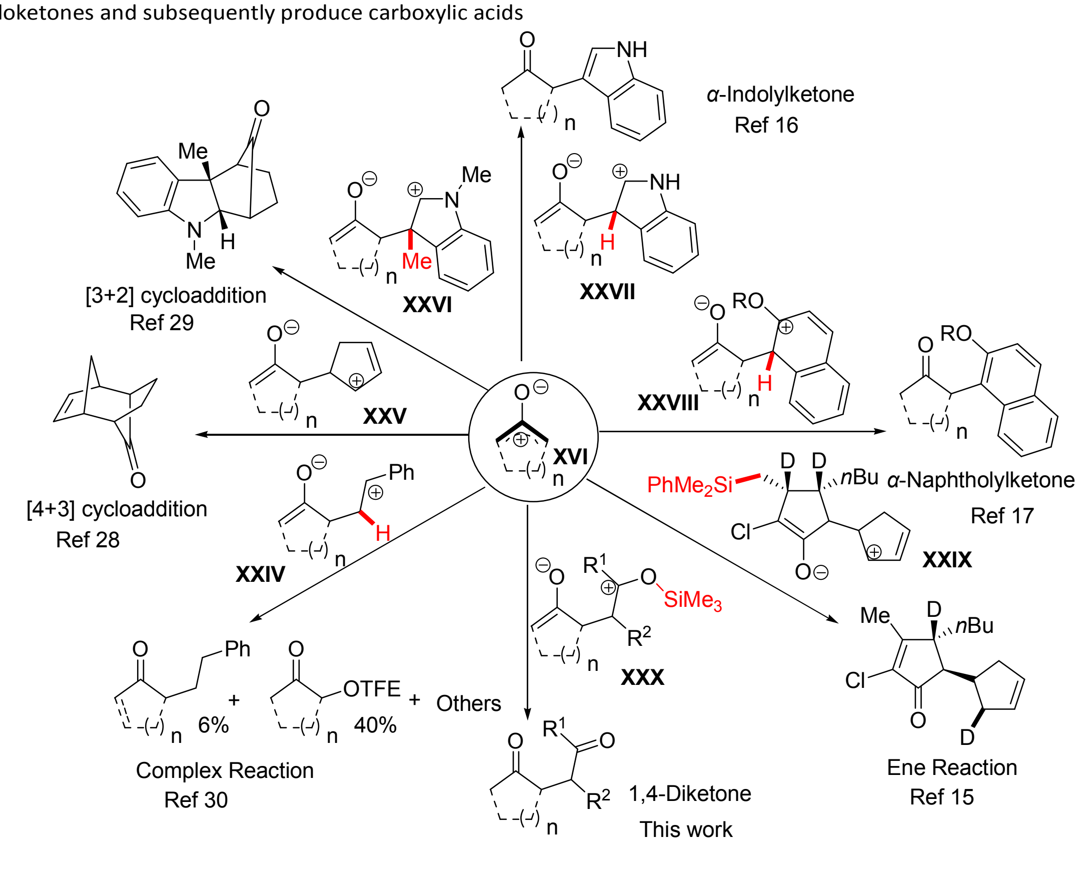


Scheme 3. The reaction of oxyallyls with *p*-nucleophiles

Background

Oxyallyl zwitterions and cyclopentanone intermediates, which can be transformed to each other, were first proposed as transient electrophilic intermediates in the Favorskii rearrangement in 1894.[18] More specifically, under strongly basic conditions, a variety of nucleophiles add to the carbonyl carbon of the incipient cyclopentanone intermediates induced from α-haloketones and subsequently produce carboxylic acids

To shed light on the reaction mechanism of nucleophiles with oxyallyls (cyclopentanone intermediates and oxyallyl zwitterions), different types of reactions are summarized in Scheme **3** and 4. Under typical Favorskii rearrangement conditions (Scheme **3**),[21] strong bases induce the formation of cyclopentanone intermediates **XV** from α-haloketones and



Scheme 4. The reaction of oxyallyl zwitterions with π-nucleophiles using TFE or HFIP as solvent

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then 2-chlorocyclopentanone reacts with water to afford the ring-contracted product **XIX** accompanied with other compounds.[24] Remarkably, treatment of 2-chlorocyclopentanone with the weak base (sodium carbonate) instead of the strong base (sodium hydroxide) affords an excellent yield of the substituted product XX. However, in the presence of a weaker base, such as sodium bicarbonate, or without any bases, most of the starting material remains unreacted, and only a trace of the substituted product **XX** is detected.[14] Based on those observations, we proposed that the generation of oxyallyl zwitterions **XVI** (the valence tautomers of the cyclopropane intermediates **XV**) under the weakly basic conditions is the key step, which permits the subsequent addition of the p-nucleophiles to render the substituted products (**XX**-**XXIII**).[25]

It should be noted that both oxallyl zwitterions and cyclopentanone intermediates are formed in the reaction of α-haloketones with furan using sodium 2,2,2-trifluoroethoxide as a base in 2,2,2-trifluoroethanol (NaTFE/TFE), and that the two corresponding types of products, the ring-contracted products (**XVIII**, Scheme 3) and the [4+3] cycloadducts (Scheme 4) are eventually generated.[26]

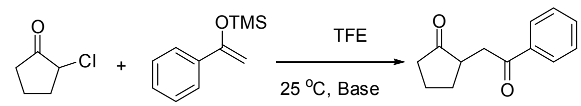
It is well known that oxyallyl zwitterions[27] tend to react with enes either in a stepwise or a concerted fashion so as to generate the [4+3][28] or [3+2][29] cycloadducts (Scheme 4). However, several valuable interrupted cycloadditions of oxyallyl zwitterions have been reported in recent years. The mechanism of the interrupted cycloadditions depends on (i) the nucleophilicity of π-nucleophiles, (ii) the positions of the leaving groups on the intermediates **XXIV** – **XXX** and (iii) the difficulty of removing the leaving groups from the intermediates **XXIV** – **XXX**. Compared with indole or silyl enolate, the low nucleophilicity of styrene and the difficult deprotonation of the intermediate **XXIV** (denoted in red color) result in the complexity of the reaction of styrene with 2-chlorocyclopentanone in TFE.[30] Whereas, an efficient reaction takes place when the leaving groups become easy to release from the intermediates **XXVII** – **XXX**. Moreover, the course of the reaction is changed just by changing the positions of the leaving groups (the silyl group) on the intermediates, and thus the product of the intermediate **XXX** is 1,4-diketone, entirely different from the product of the intermediate **XXIX**.

Results and Discussion

Optimization of Reaction Conditions.

The proposed transformation was first examined using 1-phenyl-1-trimethylsiloxyethylene **2a** and 2-chlorocyclopentanone **1a** in the presence of sodium carbonate as a base, and trifluoroethanol (TFE) as a solvent (Table 1). To our delight, the desired 1,4-diketone **3a** was obtained efficiently in one step without halohydrin **III** or cycloaddition compound being detected, thereby demonstrating the feasibility of our proposal (The structure of 3a was characterized by 2D NMR spectroscopy). However, an excess amount of silyl enolate was needed because of its instability in TFE (Table 1, entry 2). Moreover, three equivalents of silyl enolate were eventually found to be optimal in terms of yield (Table 1, entry 4), as a higher amount of silyl enolate could lead to the generation of quite a few byproducts containing the silyl group. Remarkably, we discovered that the basicity of bases showes a significant effect on the reaction cleanliness and yield. In fact, an organic base Et_3N, could also effectively initiate the reaction (Table 1, entries 8). However, when employing a relatively weak base, i.e. sodium bicarbonate, only a trace of the desired product was detected (Table 1, entry 6). On the contrary, when a strong base, i.e. NaOH, was used, the reaction became messy (Table 1, entry 7).

Table 1. Model Reaction Optimization.



1a 2a 3a

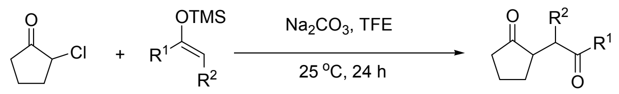
Entry	Base [1.2 eq]	**1a** [equiv]	**2a** [equiv]	Time [h]	Yield [%][b]
1	Na_2CO_3	1	1	6	42
2	Na_2CO_3	0	1	12	--[c]
3	Na_2CO_3	1	2	12	61
4	Na_2CO_3	1	3	12	70
5	Na_2CO_3	1	4	12	65
6	$NaHCO_3$	1	3	24	trace
7	NaOH	1	3	3	complex
8	Et_3N	1	3	12	60

[a] Reaction conditions: **1a** (1.0 mmol), 2a (1.0-4.0 mmol), Base (1.2 mmol) in TFE (2 mL) at 25 °C; [b] Isolated yield. [c] Silyl enolate was not detected by TLC after twelve hours.

Scope and Generality of the Substrates.

With the optimized conditions in hand, we next examined other silyl enolates in this new synthetic protocol. Gratifyingly, a variety of silyl enolates functioned well in this nucleophilic reaction. In general, since alkyl enol ethers (Table 2, entries 7-12) are more stable than aryl enol ethers (Table 2, entries 1-6) in TFE, a little excess amount of alkyl enol ethers led to better yields in the reaction system. No steric effect was observed for theterminal enol ethers (Table 2, entries 1-4 and 7-9) and the disubstituted enol ethers (Table 2, entries 5-6 and 10-12) showed nearly the same reaction efficiency as the monosubstituted enol ethers.

Table 2. Coupling Reaction: Scope of Silyl Enolates[a]



1a 2 3

Entry	Enolate	Product	Yield[%][b]
1	2a	3a	70
2	2b	3b	65
3	2c	3c	78
4	2d	3d	69
5	2e	3e	73(1:1 dr)
6	2f	3f	67(5:2 dr)
7	2g	3g	72
8	2h	3h	73
9	2i	3i	76
10	2j	3j	81(1:1 dr)
11	2k	3k	80(1:1 dr)
12	2l	3l	71(1:1 dr)

[a] Reaction conditions: **1a** (1.0 mmol), silicon enolates (3.0 mmol in entries 1-3, 2.0 mmol in entries 4-11), Na_2CO_3 (1.2 mmol) in TFE (2 mL) at 25 °C; [b] Isolated yield; [c] The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude material.

In addition, we found that the electron density of silyl enolates plays an important role in the reaction efficiency. As a matter of fact, the reaction with silyl enolate (**2c**) bearing an electron-donating substitutent proceeded efficiently by this uncatalyzed system (Table 2, entry 3). On the contrary, no desired product was isolated for this reaction of 2-chlorocyclopentanone with silyl enolates bearing a strong electron-withdrawing substitutent, such as trimethyl((1-(4-nitrophenyl)vinyl)oxy)silane and 4-(1-((trimethylsilyl)oxy)vinyl)benzonitrile. Silyl enolates generated from aldehydes, such as trimethylsiloxyethylene, 2-phenyl-1-trimethylsiloxyethylene and 2-benzyl-1-trimethylsiloxyethyl-ene, yielded complicated reaction mixtures that were not studied further.

Table 3. Coupling Reaction: Scope of *α*-haloketones[a]

Entry	Haloketone	Enolate	Product	Yield[%][b,c]
1	1b	2a	3m	62
2	1c	2a	3m	60
3	1d	2a	3m	56
4	1b	2k	3j	71(1:1 dr)
5	1e	2k	3l	63(1:1 dr)
6	1f	2j	3n	39 (5:1 dr)
7	1g	2j	3o	51(10:1 dr)
8	1h	2a	3p	32(10:1 dr)
9	1i	2f	3q	31

[a] Reaction conditions: α-haloketones (1.0 mmol), silicon enolates (3.0 mmol in entries 1,2,7,8; 2.0 mmol in entries 3-6), Na_2CO_3 (1.2 mmol) in TFE (2 mL) at 25 °C; [b] Isolated yield; [c] The diastereomer ratio was determined by ^{1}H NMR spectroscopic analysis of the crude material.

We next examined the scope of *α*-haloketones in the catalyst-free formation of 1,4-diketones. This transformation is not limited to five-membered rings since both six-membered rings and seven-membered rings are competent substrates (Table 3, entries 1-5). Additionally, both *α*-chloro- and *α*-bromocyclohexanones gave the same products with similar reaction rate and efficiency (Table 3, entries 1 and 2). For the reaction of *α*-iodocyclohexanone, the reaction rate was faster but the yield was lower in comparison with the other two halocyclohexanones. Use of acyclic *α*-haloketones afforded the corresponding 1,4-diketones in comparable yields (Table 3, entries 6-7). Furthermore, the reaction of dibromoketones (**1h-**

1i) with an equimolar or excess molar amount of silyl enolates gave the monosubstituted products (Table 3, entries 8-9). The coupling reaction showes a high regioselectivity, as only one regioisomer (**3q**) was obtained, whose structure was confirmed by 2D NMR.

Experimental Section

General Information

Nuclear magnetic resonance spectra (^{1}H and ^{13}C) were recorded on 300, 400, and 500 MHz spectrometers with tertramethylsilane (TMS) as an internal standard. The splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). High resolution mass spectral analysis (HRMS) was performed on ESI-QTOP mass spectrometer. Visualization was performed using a UV lamp or chemical stains like $KMnO_4$ and 2,4-dinitrophenyl hydrazine solutions.

Commercially available materials were used as received, except α-haloketones that were further purified via distillation or column chromatography over silica gel prior to use. Some of the α-chloroketones (2-bromocyclohexanone, 2-chlorocycloheptanone and 1,3-dibromo-3-methylbutan-2-one) were prepared using literature method.[31]

Typical procedure for catalyst-free coupling of silyl enolates with α-haloketones.

A 4 mL vial equipped with a magnetic stir bar was charged with freshly distilled α-haloketone **1** (0.5 mmol), anhydrous Na_2CO_3 (0.6 mmol) and TFE (1.0 mL). Silyl enolate **2** (1.0-1.5 mmol) was added in portionwise to the reaction mixture at 25 ^oC. After completion of the reaction (about 12-24h, monitored by TLC or crude ^{1}H NMR analysis), the reaction was quenched with water (1.0 mL) and stirred for 30 min. Extraction with CH_2Cl_2 (3 × 10 mL), drying of the combined organic layers with Na_2SO_4, filtration, and evaporation of the solvent in vacuum gave a residue which was purified by column chromatography on silica gel with petroleum ether and ethyl acetate (v/v = 10:1 to 1:1) as the eluent to afford the desired product.

2-(2-oxo-2-phenylethyl)cyclopentanone (3a):[32] The title compound was prepared as colorless oil in 70% yield according to the general procedure as described above. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 5.2, 3.4 Hz, 2H), 7.61 – 7.52 (m, 1H), 7.45 (dd, J = 10.5, 4.7 Hz, 2H), 3.53 (dd, J = 18.1, 3.3 Hz, 1H), 3.04 (dd, J = 18.1, 8.0 Hz, 1H), 2.69 – 2.60 (m, 1H), 2.47 – 2.20 (m, 3H), 2.09 (ddd, J = 6.4, 4.0, 2.0 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.71 – 1.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.4, 198.0, 136.6, 133.2, 128.6, 128.0, 45.1, 38.6, 37.5, 29.7, 20.8; IR (KBr, cm^{-1}): 2962, 2879, 1738, 1684, 1596, 1448, 1263, 1001, 753, 690; HRMS (ESI) calcd for $C_{13}H_{15}O_2$ $(M+1)^+$: 203.1067, Found: 203.1070.

2-(2-(3-bromophenyl)-2-oxoethyl)cyclopentanone (3b): The title compound was prepared as light brown solid in 65% yield according to the general procedure as described above; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (t, J = 1.7 Hz, 1H), 7.91 – 7.85 (m, 1H), 7.69 (ddd, J = 7.9, 1.9, 0.9 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 3.49 (dd, J = 18.2, 3.4 Hz, 1H), 3.01 (dd, J = 18.2, 7.9 Hz, 1H), 2.68 – 2.61 (m, 1H), 2.46 – 2.32 (m, 2H), 2.32 – 2.21 (m, 1H), 2.16 – 2.05 (m, 1H), 1.92 – 1.82 (m, 1H), 1.61 (td, J = 12.0, 6.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.0, 196.6, 138.3, 136.0, 131.1, 130.2, 126.5, 123.0, 45.0, 38.7, 37.4, 29.6, 20.8; HRMS (ESI) calcd for $C_{13}H_{14}BrO_2$ $(M+1)^+$: 281.0172, Found: 281.0179.

2-(2-(4-methoxyphenyl)-2-oxoethyl)cyclopentan-1-one (3c): The title compound was prepared as colorless oil in 78% yield according to the general procedure as described above; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.83 (m, 2H), 7.01 – 6.82 (m, 2H), 3.86 (s, 3H), 3.47(dd, J = 20.0, 4.0 Hz, 1H), 2.99 (dd, J = 17.8, 8.0 Hz, 1H), 2.73 – 2.50 (m, 1H), 2.48 – 2.18 (m, 3H), 2.12 – 2.02 (m, 1H), 1.88-1.72 (m, 1H), 1.66-1.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.5, 196.5, 163.5, 130.3, 129.7, 113.7, 55.4, 45.2, 38.3, 37.6, 29.7, 20.8; IR (KBr, cm^{-1}): 2971, 2897, 1738, 1670, 1603, 1260, 1177, 811, 562, 497; HRMS (ESI) calcd for $C_{14}H_{17}O_3$ $(M+1)^+$: 233.1172, Found: 233.1175.

2-(2-(naphthalen-1-yl)-2-oxoethyl)cyclopentanone (3d): The title compound was prepared as white solid in 69% yield according to the general procedure as described above; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.93 – 7.85 (m, 2H), 7.64 – 7.46 (m, 3H), 3.59 (dd, J = 17.7, 3.8 Hz, 1H), 3.12 (dd, J = 17.7, 7.8 Hz, 1H), 2.73 (d, J = 8.1 Hz, 1H), 2.42 (ddd, J = 18.8, 10.3, 4.8 Hz, 2H), 2.36 – 2.24 (m, 1H), 2.15 – 2.08 (m, 1H), 1.92 – 1.85 (m, 1H), 1.75 – 1.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.2, 202.3, 135.5, 133.9, 132.7, 130.1, 128.4, 127.9, 127.5, 126.5, 125.7, 124.3, 45.6, 42.0, 37.5, 29.6, 20.8; HRMS (ESI) calcd for $C_{17}H_{17}O_2$ $(M+1)^+$: 253.1223, Found: 253.1225.

2-(2-oxocyclopentyl)-3,4-dihydronaphthalen-1(2H)-one (3e): Two diastereomers were prepared as white solid in 73% total yield according to the general procedure as described above. **The upper isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.8 Hz, 1H), 7.46 (dd, J = 10.8, 4.1 Hz, 1H), 7.41 – 7.15 (m, 2H), 3.27 – 3.06 (m, 2H), 3.06 – 2.86 (m, 2H), 2.40 (dd, J = 17.6, 7.8 Hz, 1H), 2.29 – 1.98 (m, 4H), 1.87 (dddd, J = 18.5, 11.6, 8.1, 5.2 Hz, 2H), 1.70 (ddd, J = 18.2, 11.8, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.6, 198.5, 144.1, 133.4, 132.4, 128.7, 127., 126.6, 49.6, 47.7, 38.5, 29.6, 26.1, 25.5, 20.8; IR (KBr, cm^{-1}): 3447, 2961, 1737, 1714, 1162, 1020, 802, 472, 418; HRMS (ESI) calcd for $C_{15}H_{17}O_2$ $(M+1)^+$: 229.1223, Found: 229.1233; **The lower isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.34 – 7.20 (m, 2H), 3.36 – 3.26 (m, 1H), 3.13 (ddd, J = 17.0, 12.0, 5.3 Hz, 1H), 3.00 (dt, J = 16.6, 3.5 Hz, 1H), 2.72 – 2.57 (m, 1H), 2.35 (dd, J = 17.5, 6.7 Hz, 1H), 2.24 (dd, J = 14.0, 5.8 Hz, 1H), 2.21 – 2.01 (m, 4H), 1.89 – 1.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.5, 197.4, 144.0, 133.4, 132.4, 128.7, 127.4, 126.6, 50.4, 49.3, 37.8, 29.6, 28.3, 25.1, 21.1; IR (KBr, cm^{-1}): 3447, 2924, 1733, 1716, 1162, 761, 418; HRMS (ESI) calcd for $C_{15}H_{17}O_2$ $(M+1)^+$: 229.1223, Found: 229.1231.

2-(1-oxo-1-phenylpentan-2-yl)cyclopentanone (3f): The title compound was prepared as a brown mixture of two diastereomers in 67% yield according to the general procedure as described above; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.4 Hz, 2H), 7.64 – 7.52 (m, 1H), 7.46 (dd, J = 15.2, 7.7 Hz, 2H), 3.87 (dt, J = 9.3, 4.7 Hz, 1H), 2.69 – 2.50 (m, 1H), 2.39 – 2.21 (m, 1H), 2.09 (tdd, J = 11.5, 10.0, 5.9 Hz, 3H), 1.91 – 1.59 (m, 4H), 1.47 – 1.28 (m, 1H), 1.28 – 1.08 (m, 1H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.8, 202.7, 136.9, 132.9, 128.7, 128.3, 51.7, 45.4, 37.9, 31.0, 25.9, 21.0, 20.8, 14.2; IR (KBr, cm^{-1}): 3746, 3396, 2962, 2877, 1816, 1733, 1164, 1051, 1010, 418; HRMS (ESI) calcd for $C_{16}H_{21}O_2$ (M+1)$^+$: 245.1536, Found: 245.1540.

2-(2-oxo-4-phenylbutyl)cyclopentanone (3g): The title compound was prepared as colorless oil in 72% yield according to the general procedure as described above; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, J = 10.3, 4.6 Hz, 2H), 7.26 – 7.13 (m, 3H), 2.90 (t, J = 7.7 Hz, 3H), 2.75 (dd, J = 16.0, 8.1 Hz, 2H), 2.55 – 2.40 (m, 2H), 2.40 – 2.30 (m, 1H), 2.27 – 2.13 (m, 2H), 2.10 – 2.00 (m, 1H), 1.89 – 1.74 (m, 1H), 1.49 (dd, J = 11.9, 6.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.1, 207.9, 140.8, 128.5, 128.3, 126.1, 44.8, 44.3, 42.5, 37.4, 29.7, 29.4, 20.7; HRMS (ESI) calcd for $C_{15}H_{19}O_2$ (M+1)$^+$: 31.1380, Found: :231.1381.

2-(4-methyl-2-oxopentyl)cyclopentanone (3h):[33] The title compound was prepared as colorless oil in 73% yield according to the general procedure as described above; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (d, J = 16.6 Hz, 1H), 2.43 (ddd, J = 61.0, 21.5, 8.9 Hz, 2H), 2.38 – 2.10 (m, 6H), 2.10 – 2.00 (m, 1H),1.81 (d, J = 11.2 Hz, 1H), 1.53 (dd, J = 11.5, 6.9 Hz, 1H), 0.92 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.2, 208.7, 51.8, 44.8, 42.9, 37.4, 29.4, 24.7, 22.5, 22.5, 20.7; HRMS (ESI) calcd for $C_{11}H_{19}O_2$ (M+1)$^+$: 183.1385, Found: 183.1386.

2-(2-oxotridecyl)cyclopentanone (3i): The title compound was prepared as brown oil in 76% yield according to the general procedure as described above; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.87 (d, J = 16.7 Hz, 1H), 2.57 – 2.13 (m, 7H), 2.12 – 1.98 (m, 1H), 1.98 – 1.70 (m, 1H), 1.61 – 1.39 (m, 3H), 1.25 (s, 16H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.3, 209.1, 44.8, 42.9, 42.3, 37.4, 31.9, 29.6, 29.5, 29.4, 29.3, 29.3, 29.1, 23.8, 22.6, 20.7, 14.1; HRMS (ESI) calcd for $C_{18}H_{33}O_2$ (M+1)$^+$: 281.2475, Found: 281.2484.

2-(2-oxocyclopentyl)cyclohexanone (3j):[34] Two diastereomers were prepared as white solid in 81% total yield according to the general procedure as described above. **The upper isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85 (dd, J = 7.7, 3.8 Hz, 1H), 2.60 – 2.47 (m, 1H), 2.42 (dd, J = 14.0, 1.7 Hz, 1H), 2.39 – 2.25 (m, 2H), 2.25 – 2.10 (m, 2H), 2.10 – 1.97 (m, 2H), 1.96 – 1.74 (m, 3H), 1.73 – 1.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.7, 211.0, 50.5, 48.7, 42.0, 38.4, 30.3, 27.4, 26.2, 25.3, 20.9; IR (KBr, cm^{-1}): 2938, 2863, 1734, 1706, 1465, 1316, 1141, 502, 463; HRMS (ESI) calcd for $C_{11}H_{17}O_2$ (M+1)$^+$: 181.1223, Found: 181.1226; **The lower isomer:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 – 2.94 (m, 1H), 2.54 (ddd, J = 18.2, 11.9, 9.1 Hz, 1H), 2.45 – 2.21 (m, 3H), 2.16 – 1.95 (m, 5H), 1.89 (dddd, J = 18.0, 14.9, 7.4, 4.0 Hz, 2H), 1.79 – 1.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.3, 210.0, 51.2, 49.9, 41.9, 38.0, 31.8, 27.1, 25.4, 25.2, 21.2; IR (KBr, cm^{-1}): 3735,2951, 2874, 1734, 1706, 1506, 1148, 418, 408; HRMS (ESI) calcd for $C_{11}H_{17}O_2$ (M+1)$^+$: 181.1223, Found: 181.1232.

[1,1'-bi(cyclopentane)]-2,2'-dione (3k):[35] Two diastereomers were prepared as white solid in 80% total yield according to the general procedure as described above. **The upper isomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.73 – 2.59 (m, 2H), 2.41 – 2.29 (m, 2H), 2.13 – 1.98 (m, 6H), 1.86 – 1.74 (m, 2H), 1.72 – 1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.0, 48.5, 38.0, 25.3, 20.7; IR (KBr, cm^{-1}): 3447, 2963, 2878, 1734, 1405, 1145, 821, 488; HRMS (ESI) calcd for $C_{10}H_{15}O_2$ (M+1)$^+$: 167.1067, Found: 167.1071; **The lower isomer:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 – 2.48 (m, 2H), 2.32 (ddd, J = 18.6, 8.4, 1.1 Hz, 2H), 2.25 – 2.10 (m, 4H), 2.09 – 1.96 (m, 2H), 1.86 – 1.66 (m, 2H), 1.59 (qd, J = 12.0, 6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.0, 49.2, 38.2, 26.7, 20.9; IR (KBr, cm^{-1}): 3446, 2962, 2873, 1733, 1449, 1133, 1000, 599, 418; HRMS (ESI) calcd for $C_{10}H_{15}O_2$ (M+1)$^+$: 167.1067, Found: 167.1070.

2-(2-oxocyclopentyl)cycloheptanone (3l): The title compound was prepared as a white mixture of two diastereomers in 71% yield according to the general procedure as described above; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (dt, J = 7.6, 4.3 Hz, 1H), 2.92 (ddd, J = 12.9, 9.5, 6.5 Hz, 1H), 2.69 – 2.58 (m, 2H), 2.52 (ddd, J = 16.2, 6.5, 2.8 Hz, 1H), 2.47 – 2.30 (m, 3H), 2.30 – 2.23 (m, 1H), 2.23 – 2.09 (m, 2H), 2.09 – 1.95 (m, 4H), 1.81 (qdd, J = 25.2, 11.4, 6.2 Hz, 10H), 1.71 – 1.47 (m, 6H), 1.47 – 1.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.0, 220.0, 214.5, 213.7, 52.4, 52.2, 51.7, 51.2, 43.9, 43.7, 37.9, 37.9, 30.1, 29.8, 29.7, 29.2, 29.1, 28.8, 26.3, 25.7, 23.9, 23.6, 21.0, 20.7; IR (KBr, cm^{-1}): 3447, 2930, 2874, 1733, 1696, 1453, 1148, 502, 418; HRMS (ESI) calcd for $C_{12}H_{19}O_2$ (M+1)$^+$: 195.1380, Found: 195.1388.

2-(2-oxo-2-phenylethyl)cyclohexanone (3m):[36] The title compound was prepared as white solid in 62% yield according to the general procedure as described above; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 5.2, 3.3 Hz, 2H), 7.61 – 7.52 (m, 1H), 7.52 – 7.41 (m, 2H), 3.61 (dd, J = 17.7, 6.6 Hz, 1H), 3.17 (dd, J = 12.7, 6.3 Hz, 1H), 2.69 (dd, J = 17.7, 5.7 Hz, 1H), 2.49 – 2.39 (m, 2H), 2.33 – 2.07 (m, 2H), 1.89 (dd, J = 9.9, 6.4 Hz, 1H), 1.79 (dt, J = 12.7, 3.4 Hz, 1H), 1.73 – 1.64 (m, 1H), 1.46 (qd, J = 12.8, 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 198.6, 137.0, 133.0, 128.5, 128.0, 46.4, 41.9, 38.3, 34.3, 27.9, 25.3; HRMS (ESI) calcd for $C_{14}H_{17}O_2$ (M+1)$^+$: 217.1223, Found: 217.1226.

2-(3-oxopentan-2-yl)cyclohexanone (3n):[37] The title compound was prepared as brown oil in 39% yield according to the general procedure as described above; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (p, J = 7.0 Hz, 1H), 2.65 (dd, J = 13.0, 6.4 Hz, 1H), 2.61 – 2.54 (m, 1H), 2.48 (dt, J = 10.8, 7.2 Hz, 1H), 2.42 – 2.25 (m, 2H), 2.09 – 1.98 (m, 2H), 1.91 – 1.84 (m, 1H), 1.77 – 1.54 (m, 3H), 1.13 (d, J = 7.1 Hz, 3H), 1.10 – 0.96 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 211.7, 53.8, 44.8, 42.2, 35.4, 30.8, 27.7, 25.1, 14.8, 7.5; IR (KBr, cm^{-1}): 2938, 2864, 1759, 1708, 1450, 1281, 1167, 1019, 974, 890; HRMS (ESI) calcd for $C_{11}H_{19}O_2$ (M+1)$^+$: 183.1380, Found: 183.1387.

2-(2-oxo-1,3-diphenylpropyl)cyclohexanone (3o): The title compound was prepared as brown oil in 51% yield according to the general procedure as described above; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.15 (m, 8H), 7.11 – 7.04 (m, 2H), 4.34 (d, J = 7.3 Hz, 1H), 3.71 (q, J = 15.9 Hz, 2H), 2.96 – 2.71 (m, 1H), 2.38 – 2.19 (m, 2H), 2.03 – 1.81 (m, 2H), 1.81 – 1.62 (m, 3H), 1.60 – 1.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 206.9, 136.6, 134.0, 129.7, 129.3, 128.7, 128.5, 127.3, 126.9, 56.3, 54.4, 49.6, 42.1, 30.4, 27.5, 25.0; IR (KBr, cm^{-1}): 3059, 3028, 2924, 2852, 1768, 1717, 1496, 1426, 1154, 1072, 736, 698, 521; HRMS (ESI) calcd for $C_{21}H_{23}O_2$ $(M+1)^+$: 307.1693, Found: 307.1695.

5-bromo-3-methyl-1-phenylhexane-1,4-dione (3p): The title compound was prepared as white solid in 32% yield according to the general procedure as described above; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.93 (m, 2H), 7.57 (dd, J = 10.4, 4.3 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 4.73 (q, J = 6.8 Hz, 1H), 3.92 – 3.60 (m, 2H), 3.52 (dd, J = 17.8, 7.0 Hz, 1H), 3.12 (dd, J = 17.8, 5.8 Hz, 1H), 1.83 (d, J = 6.9 Hz, 2H), 1.29 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 197.9, 136.5, 133.2, 128.6, 128.0, 45.8, 42.0, 38.1, 20.5, 17.6; HRMS (ESI) calcd for $C_{13}H_{16}BrO_2$ $(M+1)^+$: 283.0328, Found: 283.0337.

5-bromo-3,3-dimethyl-1-phenyl-2-propylpentane-1,4-dione (3q): The title compound was prepared as brown solid in 31% yield according to the general procedure as described above; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.7 Hz, 2H), 4.19 (q, J = 13.6 Hz, 2H), 3.98 (dd, J = 10.6, 3.2 Hz, 1H), 1.76 (ddd, J = 18.2, 10.1, 5.4 Hz, 1H), 1.43 (d, J = 5.6 Hz, 1H), 1.38 (d, J = 18.1 Hz, 3H), 1.25 (d, J = 7.0 Hz, 3H), 1.22 – 1.08 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.5, 204.6, 139.0, 133.2, 128.7, 128.3, 51.5, 50.3, 32.9, 31.9, 24.3, 22.3, 21.9, 14.2; IR (KBr, cm^{-1}): 2960, 2873, 1719, 1466, 1447, 1164, 1042, 713, 690; HRMS (ESI) calcd for $C_{16}H_{22}BrO_2$ $(M+1)^+$: 325.0798, Found: 325.0801.

Conclusions

In conclusion, we have detailed a catalyst-free coupling reaction of silyl enolates with α-haloketones via *in situ* generated oxyallyl zwitterions in basic TFE. The reaction took place regioselectively at the α-carbonyl position and finally produced the useful 1,4-diketones. Further studies to define the enolate scope and the optimal catalyst are currently being pursued in our laboratory.

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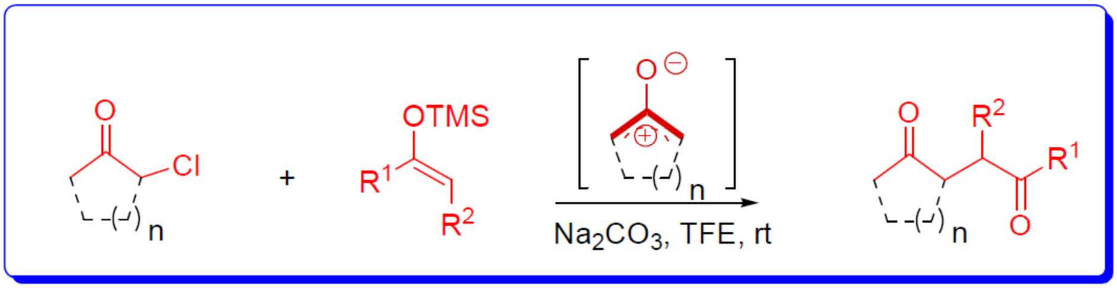
Graphical Abstract



Here we report an efficient and practical method for the preparation of 1,4-diketones by direct coupling of α-haloketones with silyl enolates at room temperature. No catalysts were required in our protocol. Various types of silyl enolates and α-haloketones were applicable to the catalyst-free coupling.