The cascade carbo-carbonylation of unactivated alkenes catalyzed by an organocatalyst and a transition metal catalyst: a facile approach to γ -diketones and γ -carbonyl aldehydes from arylalkenes under air[†]

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A novel cascade carbo-carbonylation reaction of unactivated arylalkenes with ketones or aldehydes was catalyzed by an organocatalyst and a transition metal catalyst *via* a SOMOenamine under air, affording a simple approach to γ -diketones and γ -carbonyl aldehydes.

With the great development of organocatalysis in recent years, a new activation methodology regarded as SOMO (single occupied molecular orbital)-enamine activation was developed by MacMillan in 2007.¹ In the same year, Sibi et al. revealed that using a MacMillan-type catalyst and FeCl₃ as a single electron transfer (SET) catalyst, aldehydes reacted with TEMPO via an electron-deficient enamine radical intermediate, giving α-oxyamination products of aldehydes in satisfactory yields with high enantioselectivities.² In the recent three years, MacMillan's research group developed highly stereoselective α -allylation, a^{3a} α -enolation, a^{3b} α -alkylation, a^{3c} α -vinylation, a^{3d} α -arylation, a^{3g} and α -chlorination^{3h} of aldehydes, and carbo-oxidation of styrene³ⁱ via SOMO enamine of aldehydes. In 2009, Nicolaou et al. reported that in the presence of a MacMillantype catalyst and cerium ammonium nitrate (CAN), aldehydes bearing electron-donating groups on aromatic rings underwent an intramolecular Friedel-Crafts type arylation with excellent enantioselectivities.⁴ It is noteworthy that almost all the above SOMO-enamines are from aldehydes, only a few literature reports revealed reactions via SOMO-enamines of ketones. This prompted us to start our study on the reaction of styrenes with SOMO-enamines of ketones in the presence of water. Instead of the expected alcohols, we unexpectedly obtained γ -diketones, which are important synthetic building blocks for many biologically significant compounds and useful heterocyclic motifs such as cyclopentenone, furans, pyrroles and thiophene derivatives.5 Herein, we wish to present a new reaction regarded as the cascade carbo-carbonylation of unactivated alkenes via SOMO-enamine under air, which affords a simple approach to γ -diketones or γ -carbonyl aldehydes.

To screen the conditions for reaction *via* a SOMO-enamine intermediate, the reaction of cyclohexanone with styrene was

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Scheme 1 Organocatalysts 1-4

chosen as a model reaction. It was found that using 1.0 equiv. of FeCl₃ as a SET reagent, 0.3 equiv. of MacMillan-type catalyst salt **1** (Scheme 1) could initiate the carbo-carbonylation reaction of styrene under air in DMF–H₂O at 70 °C, giving a trace amount of γ -diketone **7a** [entry 1, Table 1, also ESI† for details]. Under the same conditions, no **7a** was obtained using proline **2** as organocatalyst, and using piperidine salt **3** and pyrrolidine salt **4a** resulted in **7a** with 8% and 16% yield, respectively (entry 1–2, Table 1). After **4a** was chosen as an optimal organocatalyst, we screened the SET salts, and it was found that using Cu(OTf)₂, CuSO₄ or Cu(ClO₄)₂·6H₂O resulted in the increased yields of 30%, 32% or 40%,

Table 1 Screening of reaction conditions for the reaction of cyclo-
hexanone with styrene mediated by organocatalyst 1–4 and transition
metal salt^a



SET reagent (mol%)	Organocat. (30 mol%)	Time/h	$\operatorname{Yield}^{b}(\%)$
FeCl ₃ (100%)	1–3	60	0-8
FeCl ₃ (100%)	4a	48	16
Cu(OTf) ₂ (100%)	4a	48	30
$CuSO_4$ (100%)	4a	48	32
$Cu(ClO_4)_2 \cdot 6H_2O(100\%)$	4a	48	40
$Cu(ClO_4)_2 \cdot 6H_2O(100\%)$	1–3	60	0-25
$Cu(ClO_4)_2 \cdot 6H_2O(100\%)$	4b-e	48	21-30
$Cu(ClO_4)_2 \cdot 6H_2O(100\%)$		60	0
_	4a	60	0
Cu(ClO ₄) ₂ ·6H ₂ O (100%)	4a	60	0
FeCl ₃ (100%)	4a	60	0
$Cu(ClO_4)_2 \cdot 6H_2O(50\%)$	4a	48	10
$Cu(ClO_4)_2 \cdot 6H_2O(50\%)$	4 a	48	61
	$\begin{array}{c} \text{SET reagent (mol\%)} \\ \hline FeCl_3 (100\%) \\ FeCl_3 (100\%) \\ Cu(OTf)_2 (100\%) \\ CuSO_4 (100\%) \\ Cu(ClO_4)_2 \cdot 6H_2O (100\%) \\ \hline \\ \hline \\ Cu(ClO_4)_2 \cdot 6H_2O (100\%) \\ FeCl_3 (100\%) \\ Cu(ClO_4)_2 \cdot 6H_2O (50\%) \\ Cu(ClO_4)_2 \cdot 6H_2O (50\%) \\ \end{array}$	$\begin{array}{c} & Organocat.\\ (30 \text{ mol}\%) \end{array} \\ \hline FeCl_3 (100\%) & 1-3 \\ FeCl_3 (100\%) & 4a \\ Cu(OTf)_2 (100\%) & 4a \\ CuSO_4 (100\%) & 4a \\ Cu(ClO_4)_2 \cdot 6H_2O (100\%) & 4a \\ Cu(ClO_4)_2 \cdot 6H_2O (100\%) & 1-3 \\ Cu(ClO_4)_2 \cdot 6H_2O (100\%) & 4b-e \\ Cu(ClO_4)_2 \cdot 6H_2O (100\%) & 4b-e \\ Cu(ClO_4)_2 \cdot 6H_2O (100\%) & 4a \\ Cu(ClO_4)_2 \cdot 6H_2O (100\%) & 4a \\ FeCl_3 (100\%) & 4a \\ Cu(ClO_4)_2 \cdot 6H_2O (50\%) & 4a \\ Cu(ClO_4)_2 \cdot 6H_2O (50\%) & 4a \\ Cu(ClO_4)_2 \cdot 6H_2O (50\%) & 4a \\ \end{array}$	$\begin{array}{cccc} & & & & & & & & & & & & & & & & & $

^{*a*} The reaction of styrene (0.5 mmol), cyclohexanone (3.0 mmol), organocatalyst (30 mol%) and SET reagent in DMF (2.5 mL)–H₂O (0.15 mL) was performed at 70 °C under air. ^{*b*} Isolated yield. ^{*c*} The reaction was performed under nitrogen. ^{*d*} There is no water. FeCl₃ was used due to crystallizing water in Cu(ClO₄)₂·6H₂O. ^{*e*} The reaction was carried out under pure oxygen (1 atm). ^{*f*} 2.0 equiv. MnO₂ was employed as a co-oxidant.

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respectively (compare entry 2 with 3, 4 or 5, Table 1). When $Cu(ClO_4)_2 \cdot 6H_2O$ was employed as an optimal SET reagent, organocatalysts 1–3 and various pyrrolidine salts 4b–e were probed in the reaction, which led to 7a in the lower yields of 0–25% and 21–30% respectively (entry 6 and 7, Table 1; for details see ESI†). Experiments demonstrated that if there was

Table 2 The cascade carbo-carbonylation reaction of arylalkenes 5 with ketones or aldehydes 6 catalyzed by 4a and $Cu(n)^7$

R ¹		$+ \int_{\mathbb{R}^3}^{0} \mathbb{R}^2$	4a (30 Cu(ClO ₄) ₂ .6 MnO ₂ (2 DMF/H ₂ O, /	mol%) 0 R H ₂ O (50 mol%) 0 . <u>0 equiv)</u> Air, 70°C R ¹	\mathbf{H}^{3}
5 5a: R ¹	a-f =H; 5	6a-f d: R ¹ =Cl;	6a : R ² , R ³ =	7a-I (CH ₂) ₄ ; 6d : R ² = H, R ³ = CH ₂	k .;
5b : R [*] 5c : R [*]	¹ =CH ₃ ; 5 ¹ =OCH ₃ ; 5	ie: R ¹ =Br; 5f: R ¹ =NO _{2.}	6b: R ² , R ³ = 6c: R ² = CH	$(CH_2)_3$; 6e : R ² = H, R ³ = (CH_3)_3, R ³ = H; 6f : R ² = H, R ³ = CH_3	₃) ₂ CH; (CH ₂) _{5.}
Entry	Aryl-al- kene	· Ketone of aldehyde	r Time/ h	γ-Diketone or γ-carbo- nyl aldehyde 7	Yield ^a (%)
1	5a	6a	48	o o − 7a	61
2	5b	6a	48	° ⊂ 7b	58
3	5c	6a	48	Meo 7c	64
4	5d	6a	48	CI O Td	62
5	5e	6a	48	Br 7e	71
6	5f	6a	48	02N 07f	40
7	5a	6b	50	₩	43
8 ^{<i>b</i>}	5a	6с	72	₩ Th	55
9 ^{<i>b</i>}	5a	6d	16	<u>т</u> 7і	50
10 ^b	5a	6e	24	о т т т т т	62
11 ^b	5a	6f	24		56

^{*a*} Isolated yield. ^{*b*} The temperature was decreased to 55 $^{\circ}$ C due to the low b.p. of acetone or high activities of aldehydes.

an absence of any one of 4a, SET reagent, air or H₂O, no 7a was obtained (entry 8-11, Table 1). These results suggested that organocatalyst, SET reagent, O₂ and protons were necessary in the reaction. When THF, DCE, 1,4-dioxane or acetonitrile was employed instead of DMF, the reaction hardly occurred (see ESI[†]). If the reaction was performed at room temperature or 90 °C, only a small amount of 7a was obtained. It is interesting to note that although the reaction could not occur without oxygen, only a low yield (10%) of 7a was obtained when the reaction was performed under pure oxygen (1 atm) (entry 12, Table 1).⁶ Besides, some other cheap co-oxidants were examined in order to decrease the amount of $Cu(ClO_4)_2 \cdot 6H_2O$. It was found that using KClO₃, Na₂S₂O₈, or MnO₂ as the co-oxidant of Cu(ClO₄)₂·6H₂O (50 mol%) resulted in the increased yields of 43%, 50% and 61%, respectively (entry 13, Table 1 and ESI⁺). Experiments also indicated that further decreasing the amount of $Cu(ClO_4)_2$. 6H₂O was not beneficial to the reaction (see ESI[†]).

From the screening of various organocatalysts, solvents, SET reagents and co-oxidants, the optimized reaction should be catalyzed by 30 mol% pyrrolidine salt 4a and 50 mol% $Cu(ClO_4)_2$ 6H₂O with 2.0 equiv. of MnO₂ in DMF-H₂O at 70 °C under air. Under the optimal reaction conditions, a variety of substituted styrenes 5a-f and different ketones or aldehydes 6a-f were examined in the carbo-carbonylation reaction. The experimental results showed that except for strongly electron-deficient arylalkene 5f, both electron-rich and electron-deficient arvlalkenes 5a-e underwent the reaction smoothly with cyclohexanone to give the desired γ -diketones 7a-e in satisfactory yields (entry 1-5, Table 2). On the other hand, different ketones 6a-c and aldehydes 6d-f could also perform the reaction readily to furnish the desired γ -diketones **7a-h** or γ -carbonyl aldehydes **7i-k** in the yields of 40–71%. The plausible mechanism for the direct carbo-carbonylation reaction of styrene is depicted in Scheme 2. Pyrrolidine as an organocatalyst initially reacts with cyclohexanone to form enamine 8, followed by the oxidation with SET reagent to generate a eletrophilic three- π -electron radical cationic enamine 9. Then the cationic enamine 9 undergoes the electrophilic addition with styrene to form the radical cationic imine 10. The α -carbon radical and imine cation in 10 is respectively reacted with oxygen⁸ and hydrolyzed to give intermediate 11,



Scheme 2 Plausible mechanism.

which is oxidized further under the catalysis of copper,⁹ affording γ -diketone **7a** ultimately.

In conclusion, we have developed a novel carbo-carbonylation reaction of unactivated arylalkenes by cascade SOMO catalysis and oxidation. Both ketones and aldehydes react directly with the arylalkenes without any prefunctionalization under the catalysis of pyrrolidine and Cu(ClO₄)₂·6H₂O in the presence of MnO₂ and air, affording a novel approach to γ -diketones and γ -carbonyl aldehydes. Further studies about the cascade carbo-carbonylation reaction are currently underway.

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