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A sustainable byproduct catalyzed domino strategy: facile synthesis of α -formyloxy and acetoxy ketones *via* iodination/nucleophilic substitution/ hydrolyzation/oxidation sequences[†]

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The sustainable byproduct catalyzed domino strategy has been performed for the facile synthesis of α -formyloxy and acetoxy ketones *via* iodination/nucleophilic substitution/hydrolyzation/ oxidation sequences from simple and readily available aromatic ketones/unsaturated methyl ketones.

Domino reactions, in which multiple reactions are performed simultaneously and self-sequentially in a single reaction vessel, have been widely utilized for the efficient construction of complex molecules from readily available starting materials. These reactions, by virtue of their atom-economy, operational simplicity, saving reagents, energy, time and labor, have been used in many chemical transformations.¹

Maximizing synthetic efficiency and minimizing waste generation is a very important but challenging task in organic chemistry.² Nevertheless, stoichiometric byproducts are still unavoidable in many chemical transformations, such as some PPh₃-triggered reactions,³ and Grignard reactions.⁴ Therefore, developing new strategies to improve the utilization efficiency of byproducts is greatly desirable.

Recently, a sustainable synthetic strategy has been proposed for a domino process, in which the byproduct of an upstream step could be used to catalyze the downstream reaction.^{2d,5} In 2008, Alaimo *et al.* first demonstrated the graceful strategy in a domino nitroarene reduction–aldimine formation–aza-Diels–Alder reaction, which utilized the In^{III} byproducts generated in the reduction step to catalyze the downstream aza-Diels–Alder reaction.^{5a} Tian and co-workers reported the utilization of a catalytic amount of water as a hydrolyzing agent to decompose the upstream byproduct TMSCl to yield the secondary byproduct HCl that serves as an active catalyst for the following two steps.^{5b} In our recent reports, we proposed a sustainable

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integration of coupled domino processes to construct multisubstituted hydantoins. This strategy can efficiently utilize the excess or partly regenerated I_2 in upstream domino reactions to catalyze the following domino processes.^{5c}

Direct C–H bond acetoxylation and formyloxylation is a synthetically and mechanistically interesting field. In recent years, many typical synthetic methods have been established.⁶ Moreover, α -acetoxy and formyloxy ketones as important intermediates have attracted much attention.⁷ Generally α -acetoxy and formyloxy ketones can be prepared *via* various methods which include the reaction of α -bromo ketones with carboxylate ions or carboxylic acid,⁸ acetoxylation of aromatic ketones with Tl(OTf)₃ or Pb(OAc)₄,⁹ iodobenzene and *m*-CMPA catalyzed acetoxylation¹⁰ and PhI(OAc)₂ catalyzed acetoxylation.¹¹ However, developing a green and practical methodology is still needed for the preparation of α -acetoxy and formyloxy ketones from simple and readily available starting materials free of highly toxic reagents (Tl³⁺ or Pb⁴⁺) or noble metals.

In our previous studies, 5c,12 we have proposed novel self-sorting and focusing domino strategies for the efficient construction of C=C bonds from simple and readily available aromatic ketones in the presence of I₂ and CuO, wherein α -iodo ketones were generated *in situ*. Meanwhile, CuI was generated as a byproduct. To demonstrate the power of sustainable byproduct catalyzed domino strategy, we wonder whether it would be possible for simple methyl ketones to form α -iodo ketone intermediates, which were further catalyzed by the byproduct CuI to afford α -acetoxy and formyloxy ketones in the presence of DMF or DMA (*N*,*N*-dimethylacetamide).

To initiate our study, we first optimized the procedure for the preparation of α -formyloxy acetophenone from phenacyl iodine **1a**. As DMF is a good formyloxying agent,^{9a} we first conducted the reaction of phenacyl iodine (**1a**) in 3 mL DMF and 1 equiv. of CuI at 90 °C for 2 h. Fortunately, the α -formyloxy acetophenone **2a** was obtained in 85% yield. In the absence of CuI, a lower yield was obtained (50%). Following these results, other catalysts, such as CuO, Cu(OAc)₂, CuCl, CuBr₂, and PdCl₂, were tested for this reaction in the presence of DMF (Table 1, entries 2–6), but only CuCl and PdCl₂ could afford a trace amount of the desired product. Moreover, CuO, Cu(OAc)₂, and CuBr₂ can afford the desired product in 75%,

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 Table 1 Optimization of the reaction conditions^a

MeO	0 ↓ 0 Me N Me 1a Sol.	Catalyst H ₂ O MeO	о 0 1 0 4 2а
Entry	Catalyst/equiv.	$Temp/^{\circ}C$	Yield ^b (%)
1	CuI (1.0)	90	85
2	c	90	50
2	CuO (1.0)	90	75
3	$Cu(OAc)_{2}$ (1.0)	90	66
4	CuCl (1.0)	90	< 5
5	$CuBr_{2}(1.0)$	90	40
6	$PdCl_2(1.0)$	90	< 5
7	CuI (1.0)	110	95
8	CuI (1.0)	130	93
9	CuI (0.5)	110	96
10	CuI (0.3)	110	94
11	CuI (0.1)	110	88
^{<i>a</i>} Reaction ^{<i>b</i>} Isolated	conditions: 1a (1.0 m yields. ^c No catalyst.	mol), in 3 mL DM	IF in open air.

66% and 40% yields, respectively. It was obvious that CuI was the most efficient catalyst. The reaction temperature was also tested. Elevation of the reaction temperature to 110 °C can increase the reaction yield (up to 95%). Further elevation of temperature to 130 °C obviously could not enhance the reaction yield. A slightly lower yield was obtained when the dose of CuI was decreased to 30% mmol. However, a significant drop of yield was observed when the dose of CuI was decreased to 10% mmol. Thus, the optimal reaction conditions were obtained; that is, phenacyl iodine (1a) was heated at 110 °C for 2-4 h with 30 mol% of CuI as catalyst in DMF (Table 1, entry 10). With these optimal conditions in hand, we wondered whether it would be possible to prepare the α -formyloxy acetophenone via a sustainable byproduct catalyzed strategy on the basis of aromatic ketone, I2 and CuO. After many screening experiments, we found that the reaction of aromatic ketone **1b** (1.0 mmol) with I_2 (1.0 mmol), and CuO (1.0 mmol) in DMF (3 mL) at 110 °C could provide the desired product in 96% yield.

The efficient formation of the desired product prompted us to study the reaction scope further. A series of aromatic ketones 1b-x were examined under the optimal conditions. While the benzene rings bore electron-donating groups (e.g., 4-Me, 4-OMe, 2,4-OMe₂), the corresponding products 2a, **2c-d** were obtained in good yields (89–92%, entries 1, 3 and 4, Table 2). And when the benzene rings were substituted with electron-withdrawing groups (e.g., 4-Cl, 4-Br, 3-NO₂, 4-Ph), the corresponding products 2e-g were obtained in moderate to good yields (70-86%, entries 5-7, Table 2). It should be noted that an electron-donating substituent on the benzene ring caused a considerable increase in the yield. To our great satisfaction, the sensitive hydroxy group (OH) was not affected under these reaction conditions, and the expected product 2h was obtained in 50% yield. Moreover, 2-naphthyl methyl ketone (1i) also gave a satisfying result. Encouraged by the results obtained with aryl methyl ketones, we turned our attention to the heteroaryl ketones. The heterocycles, including furan (1j), thiophene (1k), benzofuryl (1l), and 3-indolyl (1m), did not affect the overall efficiency, and the corresponding products 2j,

 Table 2
 Reaction scope of aromatic ketones 1 and DMF^a

Table 2 Reaction scope of aromatic rectores T and Divit				
R R 1	O Me + N H Me I₂, CuO, H₂O H Me 110 °C, 1-6 h sol.	R	✓ ⁰ ↓ ^H 2	
Entry	R	2	Yield ^b (%)	
1	$4\text{-MeOC}_{6}\text{H}_{4}$ (1a)	2a	92	
2	Ph (1b)	2b	96	
3	$4 - MeC_6H_4$ (1c)	2c	90	
4	$2,4-OMe_2C_6H_3$ (1d)	2d	89	
5	$4-NO_2C_6H_4$ (1e)	2e	70	
6	$4-BrC_{6}H_{4}$ (1f)	2f	86	
7	$3,4-Cl_2C_6H_3$ (1g)	2g	82	
8	$4-OHC_6H_4$ (1h)	2h	50	
9	2-Naphthyl (1i)	2i	65	
10	2-Furyl (1j)	2j	80	
11	2-Thienyl (1k)	2k	75	
12	2-Benzofuryl (11)	21	72	
13	3-Indolyl (1m)	2m	82	
14	$4 - PhC_6H_4$ (1n)	2n	72	
15	(E)-C ₆ H ₅ -CH=CH-(10)	20	75	
16	(E)-4-MeC ₆ H ₄ -CH=CH- (1p)	2p	72	
17	(E)-4-OMeC ₆ H ₄ -CH=CH-(1q)	2q	80	
18	(E)-3,4-OMe ₂ C ₆ H ₄ -CH=CH-(1r)	2r	68	
19	(E)-3-OMe-4-	2s	80	
	$C_6H_5OCH_2-C_6H_4-CH=CH-(1s)$			
20	(E)-4-NMe ₂ C ₆ H ₄ -CH=CH-(1t)	2t	50	
21	(E)-4-BrC ₆ H ₄ -CH=CH-(1u)	2u	55	
22	(E)-4-NO ₂ C ₆ H ₄ -CH=CH-(1v)	2v	65	
23	(E)-3-NO ₂ C ₆ H ₄ -CH=CH-(1w)	2w	60	
24	$(E)-4-OHC_6H_4-CH=CH-(1\mathbf{x})$	2x	58	

^{*a*} Reaction conditions: **1** (1.0 mmol), I_2 (1.0 mmol), CuO (1.0 mmol) in DMF (3 mL) at 110 °C for 1–6 h. ^{*b*} Isolated yields.

2k, **2l**, and **2m** were obtained in 80%, 75%, 72% and 82% yields, respectively. To further expand the scope of the ketones, unsaturated methyl ketones such as **10–1x** were also investigated.¹³ To our delight, unsaturated methyl ketones could also react with I₂ and CuO in DMF to give the corresponding product in 50–80% yields.

When the same reaction protocol used in α -formyloxylation of ketones was conducted in DMA instead of DMF, the α -acetoxy ketones were obtained in moderate to good yields (52–80%) (Table 3). Significantly, heterocycles containing aromatic ketones, including furan (**1f**) and thiophene (**1g**), were tolerated in the transformation. What's more, unsaturated methyl ketones could also undergo α -acetoxylation with satisfying yields (57–70%) using the same reaction protocol.

All these target molecules were characterized by the NMR, HRMS and IR spectra. Furthermore, the target compounds **2e** and **3d** were further determined by X-ray single diffraction analysis (see ESI[†]).

To gain insight into the mechanism, the isotope labeling experiment and control experiment were performed (Scheme 1). In eqn (1) and (2), air and moisture had shown little effect on the reaction efficiency. However, lower yields were obtained in either an O₂ or Ar atmosphere with anhydrous DMF, which indicated that the water was necessary for this transformation (eqn (3) and (4)). Further investigation in the presence of H_2O^{18} (0.15 mL) indicates that water participated in the reaction (eqn (5), determined by MS (ESI), see ESI[†]). Table 3 Reaction scope of aromatic ketones 1 and DMA^a



Entry	R	3	Yield ^b (%)
1	Ph (1a)	3a	80
2	$4 - MeC_6H_4$ (1b)	3b	74
3	$4-\text{MeOC}_6\text{H}_4$ (1c)	3c	78
4	$4 - NO_2C_6H_4$ (1d)	3d	52
5	$4-\operatorname{BrC}_{6}H_{4}(1e)$	3e	68
6	2-Furyl (1f)	3f	80
7	2-Thienyl (1g)	3g	75
8	2-Naphthyl (1h)	3ĥ	58
9	(E) - C_6H_5 - CH = CH - (10)	30	70
10	(E)-3,4-OMe ₂ C ₆ H ₄ -CH=CH-(1r)	3r	62
11	(E)-3-OMe-4-	3s	65
	$C_6H_5OCH_2-C_6H_4-CH=CH-(1s)$		
12	(E)-4-NO ₂ C ₆ H ₄ -CH=CH-(1v)	3v	65
13	(E)-3-NO ₂ C ₆ H ₄ -CH=CH-(1w)	3w	57

^{*a*} Reaction conditions: **1** (1.0 mmol), I_2 (1.0 mmol), CuO (1.0 mmol) in DMA (3 mL) at 110 °C for 1–6 h. ^{*b*} Isolated yields.



Scheme 1 The isotope labeling experiment and control experiment. Unless otherwise noted, reactions conditions were I_2 (1.0 mmol), CuO (1.0 mmol), DMF (3 mL), 110 °C for 2 h.

On the basis of the above results, a plausible mechanism of the present reaction could be described as follows using acetophenone (**1b**) as an example (Scheme 2). Initially, the acetophenone **1b** is converted to **B** in the media of I₂ and CuO. Subsequently, DMF as a nucleophilic agent reacts with intermediate **B** in the presence of CuI, which forms as a byproduct from the upstream iodination process, to afford intermediate **C**. Finally, intermediate **C** undergoes hydrolyzation/oxidation reaction to furnish the desired product in the presence of a catalytic amount of water.^{9a,14} More importantly, both I₂ and DMF play dual roles in this process. Molecule I₂ could not only react with acetophenone (**1a**) to afford intermediate **B**, but also promotes the transformation of CuO into the secondary catalyst CuI. DMF acts as both the solvent and nucleophilic reagent.

In summary, we have developed a sustainable byproduct catalyzed domino method for the facile synthesis of α -formyloxy and acetoxy ketones from simple and readily available aromatic



Scheme 2 The plausible mechanism of the present reaction.

ketones and unsaturated methyl ketones. This transformation contains three noteworthy characteristics: (1) both I_2 and DMF play dual roles in the whole transformation, (2) byproduct CuI generated in the upstream reaction was utilized as the secondary catalyst, (3) a broad scope of substrates were tolerated.

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