View Article Online View Journal

# Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Yu, C. Zhang, X. Yang and W. Su, *Org. Biomol. Chem.*, 2019, DOI: 10.1039/C9OB00622B.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the **author guidelines**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the ethical guidelines, outlined in our <u>author and reviewer resource centre</u>, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.



rsc.li/obc

### **Journal Name**



## Decarboxylative acylation of *N*-free indoles enabled by catalytic amount of copper catalysis and liquid-assisted grinding

Current works:

Received 00th January 20xx, Accepted 00th January 20xx

Jingbo Yu,\* Chao Zhang, Xinjie Yang, Weike Su\*

DOI: 10.1039/x0xx00000x

www.rsc.org/

Published on 06 April 2019. Downloaded by University of Victoria on 4/7/2019 11:23:34 AM

A facile decarboxylative acylation of *N*-free indoles with  $\alpha$ ketonates *via* liquid-assisted grinding was reported. The reaction requires only a catalytic amount of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O in combination with O<sub>2</sub> as the terminal oxidant to give various 3-acylindoles in high efficiency. Additionally, this new methodology was applicable to a gram-scale synthesis.

Transition-metal decarboxylative C-H cross coupling offers an atom- and step-economical alternative for C–C bond formation.<sup>1</sup> This strategy has attracted considerable interest in the past decade due to the merit integration of inexpensive, accessible and environmentally benign properties of carboxylic acids with circumvented prefunctionalized coupling partner.<sup>2</sup> Extensive studies have been accomplished in this area since the first Pd catalyzed decarboxylative C-H arylation was reported by Crabtree et al.<sup>3</sup> Among the investigated carboxylic acids,  $\alpha$ -keto acids<sup>4</sup> were also used as decarboxylative coupling partners for direct acylation, which provided a new approach to ketones. Representative examples are Ge's works<sup>5</sup> of Pd-catalyzed decarboxylative acylations of 2-phenylpyridines, acetanilides, potassium aryltrifluoroborates and benzoic acids with  $\alpha$ -keto acid derivatives; and Kim's reports<sup>b</sup> of Pd-catalyzed decarboxylative acylation of omethyl ketoximes, phenylacetamides and o-phenyl carbamates with  $\alpha$ -keto acids. Besides, azoxybenzenes, azobenzenes, tetrahydroquinolines and N-nitrosoanilines were also amenable substrates to be acylated by  $\alpha\text{-keto}$  acids.  $^7$  However, albeit heteroaromatics ketones are ubiquitous among biologically active natural products and pharmaceutical compounds,<sup>8</sup> transition-metalcatalyzed decarboxylative acylation on aromatic heterocyclic compounds is still less explored (Scheme 1). In 2013, Zhu<sup>9</sup> and Wang<sup>10</sup> et al. independently reported expedient access to 2- and 3acylindoles via Pd(II)/Ag and stoichiometric Cu catalyzed decarboxylative acylation of N-substituted indoles. N-free indoles could also be involved in the Cu catalyzed decarboxylative acylation by using excessive silver salt as oxidant.<sup>11</sup> Later, decarboxylative 2-



metal-catalyzed decarboxylative acylation

acylation of azoles with  $\alpha$ -keto acids was achieved under novel Ni/Ag and Co/Ag catalysis by Ge's<sup>12</sup> and Lu's group<sup>13</sup>, respectively. Very recently, a direct acylation for 2*H*-indazoles using Ag-catalyzed decarboxylative cross-coupling of  $\alpha$ -keto acids was developed by Oh's group.<sup>14</sup> Besides the conventional reaction way, visible light photoredox catalysis was also explored for C3-acylation of indoles.<sup>15</sup> Despite undisputable advances, the deficiency of these methods can be shared given the required expensive catalyst, stoichiometric metal oxidant and some harsh reaction conditions. Therefore, developing a modern strategy enabling facile decarboxylative C-H

National Engineering Research Center for Process Development of Active Pharmaceutical Ingredients, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology. Hangzhou 310014, PR China. E-mail: yjb@zjut.edu.cn, Pharmlab@zjut.edu.cn

<sup>&</sup>lt;sup>+</sup> Electronic Supplementary Information (ESI) available: mechanical parameters screening, characterization and <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F NMR spectra of the synthesized compounds. See DOI: 10.1039/x0xx00000x

Journal Name

#### COMMUNICATION

acylation by catalytic amounts of low-cost metal is highly desired.

Mechanosynthesis by ball milling has been developed into a valuable technique to conduct organic reactions, of which the boundaries have been pushed into an elaborated set of synthetic transformations,<sup>16</sup> particularly metal catalyzed cross-couplings.<sup>17</sup> In recent years, since the finding that adding a small amount of liquid can modify mechanochemical reaction environment, the methodology termed liquid assisted grinding (LAG)<sup>18</sup> leads to a breakthrough reactivity compared to conventional solution-based reactions, rather than a solvent-less alternative synthetic method.<sup>19</sup> On the basis of our previous research program on LAG accelerated cross-couplings<sup>20</sup> as well as our focuses on the construction of indole derivatives<sup>20b, 21</sup>, we wish to report herein a novel and mild decarboxylative acylation of *N*-free indoles *via* liquid assisted grinding in the presence of catalytic amounts of Cu(II) and O<sub>2</sub>.

Initial investigation began with the decarboxylative coupling of indole (**1a**) and potassium 2-oxo-2-phenylacetate<sup>22</sup> (**2a**) as model reaction (Table 1). We were delighted to find that co-grinding of carboxylate and indole in the presence of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (20 mol%) or Cu(OAc)<sub>2</sub> (20 mol%), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (1.0 equiv.), MeCN (LAGs,  $\eta$  = 0.11) and NaCl (grinding auxiliary, 2.0 g) provided the desired

**Table 1**. Optimization of the reaction conditions<sup>a</sup>

Published on 06 April 2019. Downloaded by University of Victoria on 4/7/2019 11:23:34 AM

	TN + Ph	OK Cu(OAc) <sub>2</sub> OK oxidan grinding & LA	H <sub>2</sub> O (20 mol%) t, LAGs ( <i>η</i> ) g auxiliary (g) <b>G</b> , 750 rpm	Ph N H 3aa
Entry	Oxidant (eq)	LAGs (µL/mg)	Auxiliary (g)	<b>3aa</b> Yield <sup>b</sup> (%)
1	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (1)	MeCN (0.11)	NaCl (2)	66, 64 <sup>c</sup>
2	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (1)	_	NaCl (2)	12
3	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (1)	MeCN (0.11)	_	18
4	$K_2S_2O_8$ (1)	DMSO (0.11)	NaCl (2)	64
5	$K_2S_2O_8$ (1)	EtOH (0.11)	NaCl (2)	49
6	$K_2S_2O_8$ (1)	Dioxane (0.11)	NaCl (2)	47
7	$K_2S_2O_8$ (1)	EtOAc (0.11)	NaCl (2)	35
8	$K_2S_2O_8$ (1)	Toluene (0.11)	NaCl (2)	28
9	$K_2S_2O_8$ (1)	MeCN (0.11)	NaBr (2)	60
10	$K_2S_2O_8$ (1)	MeCN (0.11)	$Na_2SO_4$ (2)	57
11	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (1)	MeCN (0.11)	KCI (2)	35
12	$K_2S_2O_8$ (1)	MeCN (0.11)	Silica gel (2)	40
13	(NH <sub>4</sub> ) <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (1)	MeCN (0.11)	NaCl (2)	62
14	DDQ (1)	MeCN (0.11)	NaCl (2)	0
15	BQ (1)	MeCN (0.11)	NaCl (2)	trace
16	d	MeCN (0.11)	NaCl (2)	35
17	O2 (1 atm)	MeCN (0.11)	NaCl (2)	62, 61 <sup>°</sup> , 57 <sup>f</sup>
18	O <sub>2</sub> (1 atm)	MeCN (0.14)	NaCl (2)	50
19	O <sub>2</sub> (1 atm)	MeCN (0.08)	NaCl (2)	47
20	O <sub>2</sub> (1 atm)	MeCN (0.11)	NaCl (3.5)	62
21	O <sub>2</sub> (1 atm)	MeCN (0.11)	NaCl (3)	67
22	O <sub>2</sub> (1 atm)	MeCN (0.11)	NaCl (2.5)	65

<sup>*a*</sup> Unless otherwise noted, all reactions were carried out with **1a** (1.0 mmol), **2a** (2.0 mmol), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (20 mol%), oxidant, LAGs [ $\eta$  = V (liquid;  $\mu$ L)/m (reagents; mg)] and grinding auxiliary at 750 rpm in planet mill [8(15 min + 1 min break)], using 32 stainless-steel balls ( $d_{MB}$  = 6 mm,  $\Phi_{MB}$  = 0.08) in a 45 mL stainless steel vial. <sup>*b*</sup> isolated yields. <sup>*c*</sup> Cu(OAc)<sub>2</sub> (20 mol%) was used. <sup>*d*</sup> the reaction was performed under air. <sup>*e*</sup> Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (15 mol%) was used. <sup>*f*</sup> Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (10 mol%) was used.

#### acylated indole product (3aa) in 66% (or 64%) yield, in which Cu(OAc)<sub>2</sub>·H<sub>2</sub>O seemed to be a better choice 1(entry CP)? BCOntrol experiments highlighted the crucial roles of the assisted liquid (LAGs) and grinding auxiliary in this transformation (entries 2-3, < 20%). Strong fluctuation of yields was found within the screened LAGs. High polarity aprotic solvent like MeCN and DMSO were more effective than less-polar dioxane, EtOAc and toluene, which probably due to their facile coordination with Cu catalyst that helped promote the reaction (entries 1 and 4 vs entries 6-7). It was interesting to find that polar protic alcohol could also increase the product yield mildly (entry 5). Subsequently, various grinding auxiliary were examined since the solid additives were always vital for the reactivity in mechanosynthesis that feature one or more liquid component.<sup>16i</sup> Clearly, sodium salts, particularly the nonadsorptive NaCl, gave better results than others (entries 1, 9-12), while silica gel commonly used as grinding auxiliary in our previous works<sup>20b, 21, 23</sup> afforded poor yield (entry 12). A preliminary evaluation of oxidants revealed persulfate was a promising oxidant. However, 35% of acylate indole could be afforded when the reaction proceeded in the absence of an additional oxidant (entry 16). Thus, a positive effect was anticipated when the reaction performed under an atmosphere of dioxygen<sup>24</sup> instead of air. This assumption was confirmed, and the utilization of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (20 mol%), O<sub>2</sub> (1 atm), MeCN ( $\eta$ = 0.11) and NaCl (2 g) provided 62% yield of 3aa (entry 17). Delightedly, the catalyst loading could be reduced to 15 mol% without significant decrease in product yield (entry 17). Changing the n value of MeCN to 0.14 or 0.08 proved to be detrimental to the product yield, result in 50% and 47% of 3aa, respectively (entries 18 and 19), whereas raising the amount of NaCl to 3 g improved the product yield to 67% (entry 21).

To the best of our knowledge, the mechanical parameters in mechanosynthesis usually play an important role in reaction control, and the combined evaluation of the reaction parameters may result in a highly efficient synthesis.<sup>23e, 25</sup> As expected, after delicate adjustment of the synergistic effects of the rotation speed ( $v_{rot}$ ), the milling-ball filling degree ( $\Phi_{MB}$ ) and the milling-ball size ( $d_{MB}$ ), we were pleased to obtain **3aa** in the best yield of 76% (see Figure S1 in supporting information). In summary, the optimal conditions for the decarboxylative coupling of **1a** and **2a** showed unexpectedly good reactivity, provided that the use of Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (20 mol%), MeCN ( $\eta = 0.11$ ) and NaCl (3 g) at 750 rpm in planet mill for [8(15 min + 1 min break)] under O<sub>2</sub> atmosphere.

Encouraged by the above results, we then turned our focus on exploring the generality of this direct acylation reaction. Various substituted indoles were first reacted with potassium 2-oxo-2-phenylacetate (**2a**) under the optimized conditions and the results are listed in Table 2. Both electron-poor and electron-rich groups on 5-7 positions of indoles were compatible with the decarboxylative coupling conditions (**3da-3oa**). Indoles with OMe and OBn on their 4-positions showed unexpectedly good reactivity provided that the amount of catalyst and the rotation speed were increased (**3ba**, **3ca**). It is worth noting that strong electron-withdrawing NO<sub>2</sub> group was also tolerable when the milling time was extended, giving the desired product (**3ia**) in 70% yield. Furthermore, 5,6-dichlor-1*H*-

**Table 3.** Scope of  $\alpha$ -ketonates<sup>*a*</sup>

#### Journal Name

#### Table 2. Scope of indoles<sup>a</sup>



<sup>*a*</sup> Unless otherwise noted, all reactions were carried out with **1** (1.0 mmol), **2a** (2.0 mmol), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (20 mol%), MeCN ( $\eta = 0.11$ ) and NaCl (3 g) under O<sub>2</sub> atmosphere at 750 rpm in planet mill [8(15 min + 1 min break)], using 225 stainless-steel grinding balls ( $d_{MB} = 4 \text{ mm}$ ,  $\Phi_{MB} = 0.16$ ) in a 45 mL stainless steel vial. <sup>*b*</sup> Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (30 mol%), 800 rpm [8(15 min + 1 min break)]. <sup>*c*</sup> 800 rpm [11(15 min + 1 min break)].

indole, 2-methyl-1*H*-indole, and 2,5-dimethyl-1*H*-methylindole could also be involved in the decarboxylative acylation reactions, affording good yields of the desired products (86% for **3pa**, 68% for **3qa** and 89% for **3ra**).

As shown in Table 3, the present Cu-catalyzed acylation method also showed good tolerance toward various  $\alpha$ -ketoates 2 with indole (1a). No significant electronic effects and substitution patterns of the acyl substitute group of  $\alpha$ -ketoates were found except *p*-OMe and 2-Me (3ab-3aj). Unsurprisingly, heteroaromatic and aliphatic  $\alpha$ -ketoates gave the anticipated product 3ak-3am in synthetically acceptable yields. It should be noted that a series of  $\alpha$ ketoates possessing both electron-sufficient and electron-deficient groups on different (*ortho, meta* or *para*) positions of the phenyl ring reacted smoothly with 5- and 6-substituted indoles to provide the corresponding cross-coupling products (3gb, 3hd, 3de, 3rg and 3mi) in moderate to good yields. In addition, the protocol's mild oxidation aptitude enables the rapid and concise construction of the potential anticancer drug SCB01A (BPR0L075, phase II trial), which is generally achieved by Friedel-crafts reaction.<sup>26</sup>



<sup>*a*</sup> Unless otherwise noted, all reactions were carried out with **1** (1.0 mmol), **2** (2.0 mmol), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (20 mol%), MeCN ( $\eta = 0.11$ ) and NaCl (3 g) under O<sub>2</sub> atmosphere at 750 rpm in planet mill [8(15 min + 1 min break)], using 225 stainless-steel grinding balls ( $d_{MB} = 4$  mm,  $\Phi_{MB} = 0.16$ ) in a 45 mL stainless steel vial. <sup>*b*</sup> 800 rpm [8(15 min + 1 min break)].



The remarkable advantage of the decarboxylative acylation for *N*-free indoles was demonstrated by the gram-scale-reaction with a relative low catalyst loading and afforded good yield (Scheme 2).

To gain insight into the reaction mechanism, some control experiments were performed as depicted in Scheme 3. It was found that the addition of BHT had no obvious influence on the yield of this reaction<sup>27</sup>, suggesting that a radical mechanism can be excluded in the decarboxylative coupling reaction. Comparison experiments between CuO (1 eq) and CuO/HOAc (1/1 eq) catalyzed

Published on 06 April 2019. Downloaded by University of Victoria on 4/7/2019 11:23:34 AM.

liew Article Online

#### COMMUNICATION



Scheme 3. Control experiment

Published on 06 April 2019. Downloaded by University of Victoria on 4/7/2019 11:23:34 AM

reactions revealed that  $Cu(OAc)_2$  was the actual catalyst that could be formed *in situ* from the reaction of CuO and HOAc. Exhilarating, 20 mol% freshly prepared copper powder instead of  $Cu(OAc)_2$  could also promote the reaction in the presence of HOAc as additive and  $O_2$  as terminal oxidant to give **3aa** in 45% yield, which implied a  $Cu^0-Cu^{II}O-Cu^{II}(OAc)_2$  oxidative pathway.

On the basis of our results and previous reports<sup>10-11, 28</sup>, a plausible catalytic cycle is proposed (Scheme 2). Initially,  $\alpha$ -ketonate reacts with Cu(OAc)<sub>2</sub>·H<sub>2</sub>O to form Cu<sup>II</sup> carboxylate I, which can undergo decarboxylation to generate acyl Cu<sup>II</sup> species II. Then, a nucleophilic attack by indole occurs from its C3-position forming the intermediate III, which is followed by a rearomatization to give intermediate IV. The reductive elimination of IV provides the C3-acylation product and a Cu<sup>0</sup>, which is reoxidized by O<sub>2</sub> to afford Cu<sup>II</sup>O. Cu(OAc)<sub>2</sub> was finally regenerated with the aid of HOAc to finish the catalytic cycle.



Scheme 4. Proposed catalytic cycle

In summary, we have developed a mechanochemically (LAG) induced 3-acylindoles synthesis by copper-catalysed decarboxylative acylation in a ball mill. In this protocol, only a catalytic amount of  $Cu(OAc)_2 \cdot H_2O$  is needed by employing  $O_2$  as terminal oxidant. The reaction tolerates a wide range of functional groups and gives 3-acylindoles in high yields. Moreover, a practical gram-scale reaction and a facile synthesis of potential anticancer drug **SCB01A** (BPR0L075, phase II trial) render the methodology very efficacious.

#### **Conflicts of interest**

There are no conflicts to declare.

#### Acknowledgement

DOI: 10.1039/C9OB006228 The authors thank the Zhejiang Province Science and Technology Plan Project (No. LGF18B060004) and National Natural Science Foundation of China (No. 21406201) for financial support.

#### Notes and references

- (a) Y. Wei, P. Hu, M. Zhang and W. Su, *Chem. Rev.*, 2017, **117**, 8864; (b) X. Shi, X. Chen, M. Wang, X. Zhang and X. Fan, *J. Org. Chem.*, 2018, **83**, 6524; (c) Y. Yu, X. Chen, Q. Wu, D. Liu, L. Hu, L. Yu, Z. Tan, Q. Gui and G. Zhu, *J. Org. Chem.*, 2018, **83**, 8556; (d) S. Mkrtchyan and V. O. Iaroshenko, *Eur. J. Org. Chem.*, 2018, 6867.
- 2 (a) N. Rodríguez and L. J. Goossen, *Chem. Soc. Rev.*, 2011, 40, 5030; (b) J. D. Weaver, A. Recio III, A. J. Grenning and J. A. Tunge, *Chem. Rev.*, 2011, 111, 1846; (c) R. Shang and L. Liu, *Sci. China Chem.*, 2011, 54, 1670; (d) W. I. Dzik, P. P. Lange and L. J. Gooßen, *Chem. Sci.* 2012, 3, 2671; (e) J. Cornella and I. Larrosa, *Synthesis*, 2012, 44, 653.
- 3 A. Voutchkova, A. Coplin, N. E. Leadbeater and R. H. Crabtree, *Chem. Commun.*, 2008, 6312.
- 4 (a) L. J. Gooßen, F. Rudolphi, C. Oppel and N. Rodríguez, Angew. Chem. Int. Ed., 2008, 47, 3043; (b) L.-N. Guo, H. Wang and X.-H. Duan, Org. Biomol. Chem., 2016, 14, 7380.
- 5 (a) M. Li and H. Ge, Org. Lett., 2010, 12, 3464; (b) P. Fang, M. Li and H. Ge, J. Am. Chem. Soc., 2010, 132, 11898; (c) M. Li, C. Wang and H. Ge, Org. Lett., 2011, 13, 2062; (d) J. Miao and H. Ge, Org. Lett., 2013, 15, 2930.
- 6 (a) M. Kim, J. Park, S. Sharma, A. Kim, E. Park, J. H. Kwak, Y. H. Jung and I. S. Kim, *Chem. Commun.*, 2013, **49**, 925; (b) J. Park, M. Kim, S. Sharma, E. Park, A. Kim, S. H. Lee, J. H. Kwak, Y. H. Jung and I. S. Kim, *Chem. Commun.*, 2013, **49**, 1654; (c) S. Sharma, A. Kim, E. Park, J. Park, M. Kim, J. H. Kwak, S. H. Lee, Y. H. Jung and I. S. Kim, *Adv. Synth. Catal.*, 2013, **355**, 667.
- 7 (a) H. Li, P. Li, Q. Zhao and L. Wang, *Chem. Commun.* 2013, 49, 9170; (b) H. Li, P. Li, H. Tan and Lei Wang, *Chem.-Eur. J.*, 2013, 19, 14432; (c) L. Han, Y. Wang, H. Song, H. Han, L. Wang, W. Chu and Z. Sun, *RSC Adv.*, 2016, 6, 20637; (d) J.-P. Yao and G.-W. Wang, *Tetrahedron Lett.*, 2016, 57, 1687.
- 8 For a few selected references, see: (a) I. Nicolaou and V. J. Demopoulos, J. Med. Chem., 2003, 46, 417; (b) J. Zhang, H. I. Pettersson, C. Huitema, C. Niu, J.Yin M. N. G. James, L. D. Eltis and J. C. Vederas, J. Med. Chem., 2007, 50, 1850; (c) M. J. Myllymäki, S. M. Saario, A. O. Kataja, J. A. Castillo-Melendez, T. Nevalainen, R. O. Juvonen, T. Järvinen and A. M. P. Koskinen, J. Med. Chem., 2007, 50, 4236; (d) K. Steert, M. Berg, J. C. Mottram, G. D. Westrop, G. H. Coombs, P. Cos, L. Maes, J. Joossens, P. V. Veken, A. Haemers and K. Augustyns, ChemMedChem, 2010, 5, 1734; (e) J. Chen, C.-M. Li, J. Wang, S. Ahn, Z. Wang, Y. Lu, J. T. Dalton, D. D. Miller and W. Li, Bioorg. Med. Chem., 2011, 19, 4782; (f) M. Rusch, S. Zahov, I. R. Vetter, M. Lehr and C. Hedberg, Bioorg. Med. Chem., 2012, 20, 1100; (g) M. Kim, J. Jeon, J. Song, K. H. Suh, Y. H. Kim, K. H. Min and K.-O. Lee, Bioorg. Med. Chem. Lett., 2013, 23, 3140; (h) S. R. Chowdhury, R. Maini, L. M. Dedkova and S. M. Hecht, Bioorg. Med. Chem. Lett., 2015, 25, 4715; (i) M. P. Tantak, V. Gupta, K. Nikhil, V. Arun, R. P. Singh, P. N. Jha, K. Shah and D. Kumar, Bioorg. Med. Chem. Lett., 2016, 26, 3167.
- 9 C. Pan, H. Jin, X. Liu, Y. Cheng and C. Zhu, Chem. Commun., 2013, 49, 2933.
- L. Yu, P. Li and L. Wang, *Chem. Commun.*, 2013, **49**, 2368.
   C. Wang, S. Wang, H. Li, J. Yan, H. Chi, X. Chen and Z. Zhang, *Org. Biomol. Chem.*, 2014, **12**, 1721.
- 12 K. Yang, C. Zhang, P. Wang, Y. Zhang and H. Ge, *Chem.-Eur. J.*, 2014, **20**, 7241.

This journal is © The Royal Society of Chemistry 20xx

Page 4 of 5

Journal Name

View Article Online

<sup>4 |</sup> J. Name., 2012, 00, 1-3

#### COMMUNICATION

- Journal Name
- K. Yang, X. Chen, Y. Wang, W. Li, A. A. Kadi, H.-K. Fun, H. Sun, Y. Zhang, G. Li and H. Lu, *J. Org. Chem.*, 2015, **80**, 11065.
- 14 G. Bogonda, H. Y. Kim and K. Oh, Org. Lett., 2018, 20, 2711.
- 15 (a) L. Gu, C. Jin, J. Liu, H. Zhang, M. Yuan and G. Li, *Green Chem.*, 2016, **18**, 1201; (b) Q. Shi, P. Li, X. Zhu and L. Wang, *Green Chem.*, 2016, **18**, 4916.
- 16 For selected reviews on mechanosynthesis, see: (a) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. C. Waddell, *Chem. Soc. Rev.*, 2012, 41, 413; (b) G.-W. Wang, *Chem. Soc. Rev.*, 2013, 42, 7668; (c) S. L. James and T. Friščić, *Chem. Soc. Rev.*, 2013, 42, 7494; (d) D. Tan, L. Loots and T. Friščić, *Chem. Commun.*, 2016, 52, 7760; (e) T. K. Achar, A. Bose and P. Mal, *Beilstein J. Org. Chem.*, 2017, 13, 1907; (f) J.-L. Do and T. Friščić, *ACS Cent. Sci.*, 2017, 3, 13; (g) J. G. Hernández and C. Bolm, *J. Org. Chem.*, 2017, 82, 4007; (h) D. Tan and T. Friščić, *Eur. J. Org. Chem.*, 2018, 18; (i) J. L. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, 9, 3080.
- 17 For mechanochemical metal catalyzed cross-couplings see:
  (a) J. G. Hernández, T. Friščić, *Tetrahedron Lett.*, 2015, 56, 4253;
  (b) J. G. Hernández *Chem. Eur. J.*, 2017, 23, 17157;
  (c) W. Shi, J. Yu, Z. Jiang, Q. Shao and W. Su, *Beilstein J. Org. Chem.*, 2017, 13, 1661;
  (d) J. Yu, Z. Hong, X. Yang, Y. Jiang, Z. Jiang and W. Su, *Beilstein J. Org. Chem.*, 2018, 14, 786;
  (e) Q.-L. Shao, Z.-J. Jiang and W.-K. Su, *Tetrahedron Lett.*, 2018, 59, 2277.
- 18 (a) T. Friščić, S. L. Childs, S. A. A. Rizvi and W. Jones, *CrystEngComm*, 2009, **11**, 418; (b) G. A. Bowmaker, *Chem. Commun.*, 2013, **49**, 334.
- 19 (a) W. C. Shearouse and J. Mack, *Green Chem.*, 2012, 14, 2771; (b) J.-L. Do, C. Mottillo, D. Tan, V. štrukil and T. Friščić, *J. Am. Chem. Soc.*, 2015, 137, 2476; (c) M. Tireli, M. J. Kulcsár, N. Cindro, D. Gracin, N. Biliškov, M. Borovina, M. Ćurić, I. Halasz and K. Užarević, *Chem. Commun.*, 2015, 51, 8058; (d) L. Chen, M. Regan and J. Mack, *ACS Catal.*, 2016, 6, 868; (e) S.-J. Lou, Y.-J. Mao, D.-Q. Xu, J.-Q. He, Q. Chen and Z.-Y. Xu, *ACS Catal.*, 2016, 6, 3890.
- 20 (a) Z.-J. Jiang, Z.-H. Li, J.-B. Yu and W.-K. Su, J. Org. Chem., 2016, 81, 10049; (b) K.-Y. Jia, J.-B. Yu, Z.-J. Jiang and W.-K. Su, J. Org. Chem., 2016, 81, 6049.
- 21 J.-B. Yu, Y. Zhang, Z.-J. Jiang and W.-K. Su, J. Org. Chem., 2016, 81, 11514.
- 22 Phenylglyoxylic acid and sodium 2-oxo-2-phenylacetate were also evaluated in this reaction, but gave lower product yields (33% and 56%, respectively). This result was in accord with that of Stoltz's study, see C. K. Haley, C. D. Gilmore, B. M. Stoltz, *Tetrahedron*, 2013, **6**, 5732. No direct relation was found between the cations of the salts (grinding auxiliary) and the reactivity of  $\alpha$ -ketoates.
- 23 (a) W. Su, J. Yu, Z. Li and Z. Jiang, J. Org. Chem., 2011, 76, 9144; (b) J. Yu, Z. Li, K. Jia, Z. Jiang, M. Liu and W. Su, Tetrahedron Lett., 2013, 54, 2006; (c) J. Yu, Z. Jiang and W. Su, Cross Dehydrogenative Coupling Reactions by Ball Milling. In Ball Milling Towards Green Synthesis: Applications, Projects, Challenges; RSC Green Chemistry Series 31, A. Stolle and B. C. Ranu, Eds., Royal Society of Chemistry: Cambridge, U.K., 2015, 96–113; (d) J. Yu, Z. Wang, Y. Zhang and W. Su, Tetrahedron, 2015, 71, 6116; (e) J.-B. Yu, G. Peng, Z.-J. Jiang, Z.-K. Hong and W.-K. Su, Eur. J. Org. Chem., 2016, 5340.
- 24 Recent works of using the gaseous O<sub>2</sub> present inside the milling container to conduct oxidative steps by ball milling, see (a) G. N. Hermann, C. L. Jung and C, Bolm, Green Chem., 2017, **19**, 2520; (b) A. Beillard, T.-X. M &ro, X. Bantreil, J. Martinez and F. Lamaty, Chem. Sci., 2017, **8**, 1086; (c) R. Eckert, M. Felderhoff and F. Schüth, Angew. Chem. Int. Ed.,

2017, 56, 2445; (d) G. N. Hermann, P. Becker and C. Bolm, Angew. Chem. Int. Ed., 2015, 54, 7414<sub>DOI: 10.1039/C9OB00622B</sub>

- 25 (a) T. Szuppa, A. Stolle, B. Ondruschka and W. Hopfe, *ChemSusChem*, 2010, **3**, 1181; (b) G. C. Paveglio, K. Longhi, D. N. Moreira, T. S. München, A. Z. Tier, I. M. Gindri, C. R. Bender, C. P. Frizzo, N. Zanatta, H. G. Bonacorso and M. A. P. Martins, *ACS Sustainable Chem. Eng.*, 2014, **2**, 1895; (c) R. Schmidt, C. F. Burmeister, M. Baláž, A. Kwade and A. Stolle, *Org. Process Res. Dev.*, 2015, **19**, 427.
- 26 (a) J.-P. Liou, Y.-L. Chang, F.-M. Kuo, C.-W. Chang, H.-Y. Tseng, C.-C. Wang, Y.-N. Yang, J.-Y. Chang, S.-J. Lee and H.-P. Hsieh, J. Med. Chem., 2004, 47, 4247; (b) S. K. Guchhait, M. Kashyap and H. Kamble, J. Org. Chem., 2011, 76, 4753.
- 27 When 1 eq TEMPO was added to the reaction, indole 1a was mostly converted into unseparated polymers, see: W.-B. Qin, Q. Chang, Y.-H. Bao, N. Wang, Z.-W. Chen and L.-X. Liu, Org. Biomol. Chem., 2012, 10, 8814.
- 28 (a) R. J. Phipps, N. P. Grimster and M. J. Gaunt, J. Am. Chem. Soc., 2008, **130**, 8172; (b) K. Takamatsu, K. Hirano and M. Miura, Angew. Chem. Int. Ed., 2017, **56**, 5353.