Advanced Synthesis & Catalysis

Accepted Article

Title: Double Carbonylation Using Glyoxal (HCOCOH): A Practical Copper-Promoted Synthesis of Isatins from Primary and Secondary Anilines

Authors: Suzie Hui Chin Kuan, Wei Sun, Lu Wang, Chungu Xia, Meng Guan Tay, and Chao Liu

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700583

Link to VoR: http://dx.doi.org/10.1002/adsc.201700583

10.1002/adsc.201700583

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Double Carbonylation Using Glyoxal (HCOCOH): A Practical Copper-Promoted Synthesis of Isatins from Primary and Secondary Anilines

Suzie Hui Chin Kuan,[a,b,†] Wei Sun,[a,†] Lu Wang,[a] Chungu Xia,[a] Meng Guan Tay,[b] and Chao Liu,[a,*]

[a] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Suzhou Research Institute of LICP, Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences, Lanzhou 730000, P. R. China. E-mail: chaoliu@licp.cas.cn.

[b] Department of Chemistry, Faculty of Resource Science and Technology, Universiti Malaysia Sarawak, 94300 Kota Samarahan, Sarawak, Malaysia.

[†] These authors contributed equally to this work

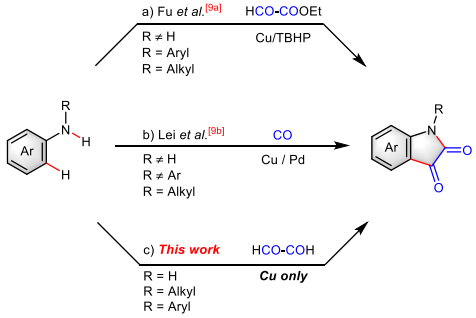
Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. A novel double carbonylation process has been demonstrated with easily available HCOCOH (glyoxal) as the double carbonylation reagent. Simple $CuCl_2 \cdot 2H_2O$ (copper(II) chloride dihydrate) was used as the oxidant for this transformation. Under optimized reaction conditions, various primary and secondary anilines were double-carbonylated to afford their corresponding isatins (26 examples, up to 80% yields).

Keywords: Double Carbonylation; Glyoxal; Isatin Synthesis; Anilines

Transition-metal-catalysed carbonylation is the fundamental transformation for introducing carbonyls into various organic molecules.[1] CO (carbon monoxide) was majorly utilized as the carbonyl source.[2] In recent years, due to its toxicity and uneasy handling, increasing attention has been focused on developing other chemical feedstocks, such as HCHO (formaldehyde), CO_2 (carbon dioxide), formic acid and its derivatives, as the COgens to replace CO gas as the carbonylative reagents.[3] Up to date, most of the efforts were focused on the mono-carbonylation processes. While the double carbonylation with introducing two adjacent carbonyls into organic molecules has been less explored and CO gas was the majorly applied carbonyl source.[4] Organic compounds with two adjacent carbonyls are usually important molecules. However, using CO as the double carbonylation source usually has the challenge on controlling the selectivity between mono- and di- carbonylation, which restrict the development of di-carbonylation with CO. Therefore, it is highly desirable to find new, cheap, widely available and easy-handling di-carbonylation sources. Inspired by the mono-carbonylation with HCHO,[5] we assumed that whether HCOCOH could be used as the di-carbonyl source to achieve di-carbonylation compounds, because of that glyoxal is a widely available basic chemical feedstock in industry. Moreover, it is much easier to handle than CO gas. However, scarce examples have been reported by utilizing glyoxal as the di-carbonylation reagent in synthetic community.[6] Herein, we demonstrated the first copper promoted practical synthesis of isatins from primary and secondary anilines by using glyoxal as the double-carbonyl source (Scheme 1, approach c).



Scheme 1. Synthesis of isatins from anilines derivatives.

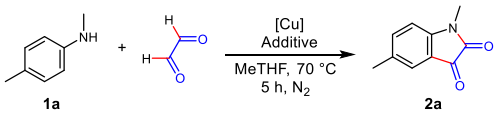
Isatin and its derivatives widely exist in nature products and many of them are bioactive compounds and pharmaceuticals.[7] Therefore, it has drawn much attention to develop novel and practical methods for the synthesis of isatins. Although many synthetic methods have been reported for their synthesis, most of the methods suffers from substrate pre-functionalization and inaccessible starting

10.1002/adsc.201700583

materials.[8] An ideal approach would be the direct double carbonylation of simple aniline derivatives. Very early synthesis involves oxalyl chloride or diethyl ketomalonate as the di-carbonylation reagent. Recently, Fu et al. has used ethyl glyoxalate as the double carbonyl source and Lei et al. has used carbon monoxide as carbonyl source for the double carbonylation of anilines (Scheme 1, approaches a and b).[9] While both approaches were limited to secondary anilines. Here, a double carbonylation of both primary and secondary anilines by utilizing glyoxal aqueous solution as the double carbonylation reagent was demonstrated with Cu(II) as the oxidant (Scheme 1, approach c).

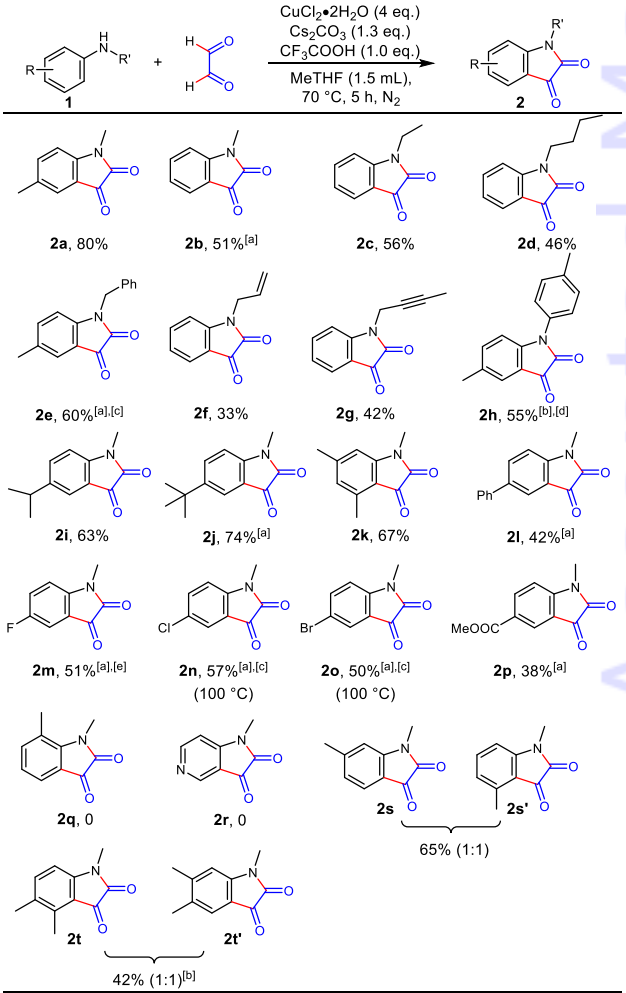
We started our research by applying *N*-methyl-4-methylaniline (**1a**) and glyoxal in a model reaction to test different reaction conditions. From the chemical equation, it can be seen that oxidant is required for this oxidative cross-coupling. After considerable efforts, the transformation was achieved by using the following optimal conditions: 2 equivalents of glyoxal, 4 equivalents of $CuCl_2{\cdot}2H_2O$ as the oxidant, Cs_2CO_3 (1.3 equiv) and CF_3COOH (1.0 equiv) as the additives in MeTHF (2-methyltetrahydrofuran) at 70 °C to react for 5 hours under N_2 atmosphere (Table 1, Entry 1), in which 80% of **2a** was isolated. Variation from the standard conditions is listed in Table 1.[10] In the absence of CF_3COOH, the yield of **2a** decreased to 59% (Table 1, Entry 2). The yield of **2a** decreased dramatically in the absence of Cs_2CO_3 (Table 1, Entry 2), indicating the importance of base in this transformation. In the absence of both CF_3COOH and Cs_2CO_3, only 20% of **2a** was obtained (Table 1, Entry 3). The reaction between Cs_2CO_3 and CF_3COOH will generate CF_3COOCs, therefore, CF_3COOCs was used instead of Cs_2CO_3/CF_3COOH. As a result, 64% of **2a** was obtained (Table 1, Entry 5). When the reaction was performed with CF_3COOCs in the presence of CF_3COOH, 78% of **2a** was obtained (Table 1, Entry 6), showing that an acidic condition is also suitable for this transformation. A combination of CF_3COOCs and Cs_2CO_3 resulted in a lower yield of **2a** (50%) (Table 1, Entry 7), which is similar to that of using single Cs_2CO_3 as the additive in Entry 2. Overall, along with the reaction proceeded, the system will be more acidic due to the formation of HCl. Cs_2CO_3 may be used to keep the reaction not to be too acidic. In the absence of the oxidant $CuCl_2{\cdot}2H_2O$, no **2a** was observed (Table 1, Entry 8). When the reaction was performed under O_2 atmosphere, a relatively lower yield of **2a** was obtained (Table 1, Entry 9). We also tried to lower the amount of $CuCl_2{\cdot}2H_2O$ to be 1.0, 2.0 or 3.0 equivalents. However, decreased yields were observed (see Table S1 in the Supporting Information). Therefore, 4.0 equivalents of $CuCl_2{\cdot}2H_2O$ was necessary in this transformation. Attempt to utilize catalytic amount of $CuCl_2{\cdot}2H_2O$ with O_2, *tert*-butyl hydroperoxide or $Na_2S_2O_8$ as the terminal oxidant failed to deliver any desired **2a** (Table 1, Entry 10).

Table 1. Reaction Parameters of Conversion Aniline to Isatin.[a]



Entry	[Cu]	Additive	Yield[%][b]
1	$CuCl_2{\cdot}2H_2O$	Cs_2CO_3/TFA	89(80)[f]
2	$CuCl_2{\cdot}2H_2O$	Cs_2CO_3	59
3	$CuCl_2{\cdot}2H_2O$	TFA	25
4	$CuCl_2{\cdot}2H_2O$	-	20
5	$CuCl_2{\cdot}2H_2O$	CF_3COOCs	64
6	$CuCl_2{\cdot}2H_2O$	CF_3COOCs/TFA	78
7[c]	$CuCl_2{\cdot}2H_2O$	CF_3COOCs/Cs_2CO_3	50
8	-	Cs_2CO_3/TFA	0
9[d]	$CuCl_2{\cdot}2H_2O$	Cs_2CO_3/TFA	65
10[e]	$CuCl_2{\cdot}2H_2O$	Cs_2CO_3/TFA	0/0/0

Reaction conditions: [a] **1a** (0.5 mmol), Glyoxal (1.0 mmol, glyoxal solution 30% w/w in water), $CuCl_2{\cdot}2H_2O$ (2.0 mmol), Cs_2CO_3 (0.65 mmol), CF_3COOCs (1.0 mmol), CF_3COOH (0.5 mmol), MeTHF (1.5 mL), 70 °C, 5 hours. [b] The yield was determined by GC analysis using naphthalene as an internal standard. [c] 0.5 mmol Cs_2CO_3. [d] Under oxygen atmosphere. [e] 10 mol% of [Cu] with O_2 or $Na_2S_2O_8$ or TBHP as the terminal oxidant. [f] Isolated yield.

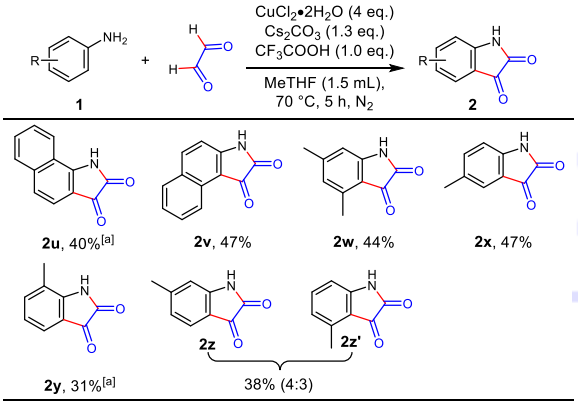


Scheme 2. Substrate scope of secondary anilines. Reaction conditions: **1** (0.5 mmol), Glyoxal (1.0 mmol),

$CuCl_2 \cdot 2H_2O$ (2.0 mmol), Cs_2CO_3 (0.65 mmol), CF_3COOH (0.5 mmol), MeTHF (1.5 mL), 70 °C, 5 h. Isolated yields. [a] CF_3COOCs (1.0 mmol) instead of Cs_2CO_3 (0.65 mmol) and CF_3COOH (0.5 mmol). [b] CF_3COOCs (1.0 mmol) instead of Cs_2CO_3. [c] 24h. [d] 40 h. [e] 8 h.

With the optimized condition in hand, a series of secondary anilines were first tested as the substrates in this transformation (Scheme 2). *N*-alkyl anilines such as *N*-Me, *N*-Et and *N*-^{n}Bu afforded their corresponding isatins **2b-2d** in moderate yields. *N*-Benzyl aniline solely generated the isatin product **2e** without any observation of the reaction on benzyl group. *N*-allyl group and *N*-propargyl were also tolerated, afforded the desired products **2f** and **2g** in moderate yields. Diaryl amines are usually less reactive than alkylanilines. In this transformation, with di-*p*-tolylamine as the substrate, the desired isatin **2h** could be obtained in a 55% yield when prolonging the reaction time to 40 hours. *p*-^{i}Pr, *p*-^{t}Bu, 3,5-dimethyl and *p*-Ph substituted *N*-Me anilines all proceeded well to give their desired isatins in good yields (**2i**, **2j**, **2k, 2l**). It was worth to note that carbon halogen bonds such as C-F, C-Cl and C-Br were well tolerated, which allows further functionalization to achieve complex molecule synthesis. In the case of C-Cl and C-Br substrates, the reaction temperature was raised up to 100 °C and the reaction time was prolonged to 24 hours (**2n**, **2o**). Furthermore, those halogen-containing isatins are usually precursors of highly active anticancer therapeutic agents and antioxidant agents.[11] Electron-withdrawing group substituted anilines have not been used in those carbonylation with CO or ethyl glyoxalate strategies. However, the electron-withdrawing *p*-COOMe group was tolerated and the corresponding isatin **2p** was obtained in a 38% isolated yield. An *o*-Me substituted *N*-methylaniline afforded no desired **2q**, indicating that this transformation may not be compatible with *ortho*-substituted secondary anilines. We have also tested heteroaromatic aniline such as methyl 4-aminopyridine, while no desired isatin **2r** was observed. When *meta*-substituted *N*-Me anilines were applied as the substrates, the two different reactive sites on the phenyl ring resulted in two isomers with a 1:1 ratio (**2s**/**2s'**, **2t**/**2t'**).

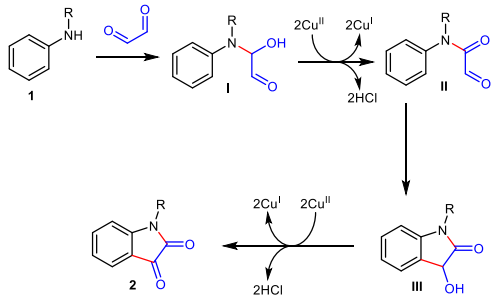
The Sandmeyer procedure, the Stolle procedure and the Martinet procedure are the classical methods for the conversion of primary anilines to their corresponding isatins. The recently developed Fu procedure and Lei procedure only limited to secondary anilines. Therefore, we want to know that whether this reaction condition is suitable for converting primary anilines to their corresponding isatins. To our delight, a series of primary anilines were successfully converted to their desired isatins in moderate yields (**2u-2z**). 1-Naphthylamine and 2-naphthylamine afforded their corresponding isatins **2u** and **2v** in 40% and 47% yields, respectively. Usually, the 1-position of naphthalene cycle has higher reactivity towards electrophilic substitution. The last cyclization step of Sandmeyer isatin synthesis is generally believed to occur via an electrophilic substation on the phenyl ring. Meanwhile, 2-naphthylamine has been demonstrated to selectively occur on its 1-position in Sandmeyer isatin synthesis.[12] The result of **2v** supports that the formation of isatin in this transformation may occur via an electrophilic substitution process. 3,5-Dimethylaniline and *p*-toluidine were also successfully double-carbonylated to give their isatins in moderate yields (**2x-2y**). *o*-Toluidine gave a 31% yield of its corresponding isatin **2y**. When *meta*-substituted primary anilines were applied as the substrates, the two different reactive sites on the phenyl ring resulted in two isomers with a 4:3 ratio (**2z**/**2z'**).



Scheme 3. Double carbonylation of primary anilines with glyoxal. Reaction conditions: **1** (0.5 mmol), Glyoxal (1.0 mmol), $CuCl_2 \cdot 2H_2O$ (2.0 mmol), Cs_2CO_3 (0.65 mmol), CF_3COOH (0.5 mmol), MeTHF (1.5 mL), 70 °C, 5 hours. Isolated yields. [a] CF_3COOCs (1.0 mmol) instead of Cs_2CO_3 (0.65 mmol) and CF_3COOH (0.5 mmol).

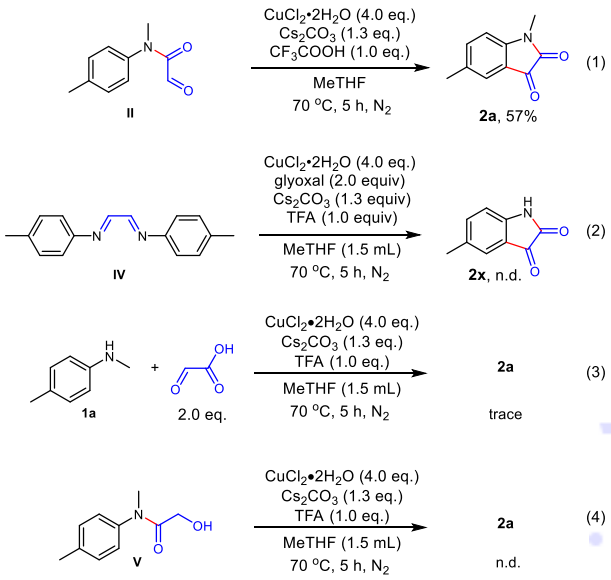
Mechanistically, mixing amine with aldehyde initially forms a *gem*-aminoalcohol which can be easily oxidized by [Cu^{II}] species.[13] Moreover, in the reaction mixture, yellow deposition was observed at the end of the reaction and no copper mirror was observed, indicating that the resulting Cu species was most likely to be Cu(I). From the reaction equation, transferring one molecular aniline to its corresponding isatin requires four electrons. Thus, 4 equivalents of [Cu^{II}] is required for the transformation to proceed. Based on those information, a tentative reaction pathway is proposed in Scheme 4. Initially, aniline **1** reacts with glyoxal to generate intermediate **I**. The oxidation of **I** by [Cu^{II}] affords intermediate **II**. Then, an intramolecular

Friedel-Crafts alkylation of **II** generates **III**.[8a, 8k] In this case, Cu(II) acts as a Lewis acid to promote this transformation in the beginning of the reaction. Then, the oxidation of **III** with [Cu^{II}] as the oxidant affords the final product **2**. As demonstrated above, the reaction mixture will be more and more acidic due to the formation of HCl. Cs_2CO_3 may be used to keep the mixture to be a buffer solution.

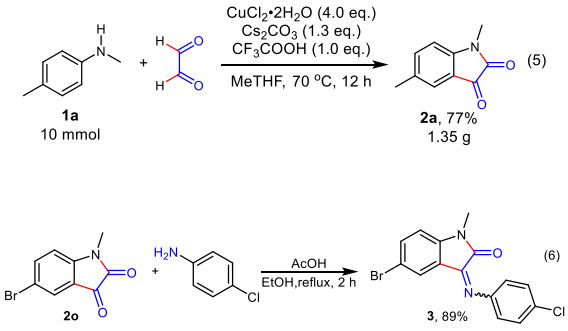


Scheme 4. Proposed mechanism

Intermediate **II** was synthesized according to literature report [14] and it was subjected to the reaction condition to support this reaction mechanism. As a result, 57% of **2a** was obtained under the standard condition (eq. 1), indicating the possible involvement of intermediate **II** in this double carbonylation process. Actually, other possible mechanisms have also been considered during the investigation of this transformation. For example, Di-imine (**IV**) is usually easy to be formed when mixing aniline with glyoxal. Therefore, it was prepared to subject to the reaction condition, yet no desired product was detected (eq. 2), indicating that di-imine is not the intermediate in this transformation. In another aspect, glyoxal is easy to be oxidized to 2-oxoacetic acid. Then, it was subjected to react with aniline **1a** to test whether the reaction proceeded via the generation of 2-oxoacetic acid under the standard conditions, as a result, only trace amount of **2a** was detected (eq. 3), indicating the less possibility of involving 2-oxoacetic acid as an intermediate. Furthermore, a Cannizzaro type reaction [15] of intermediate **I** may generate compound **V**. To test the feasibility of this compound as an intermediate in this transformation, **V** was synthesized [16] and was subjected to the standard conditions (eq. 4). As a result, no desired **2a** was observed and only **V** was recovered. Thus, it illuminated that the reaction did not proceed via the generation of **V**. Finally, the reaction pathway proposed in Scheme 4 is most likely the mechanism for this double carbonylation of anilines with glyoxal.



To further demonstrate the practicality of this transformation, a gram-scale transformation of **1a** was carried out (eq. 5). As a result, 1.35 g of **2a** was obtained (77% isolated yield), indicating the easy scale up of this transformation. Furthermore, a simple condensation of **2o** with 4-chloroaniline generates a compound **3** which has been shown to have better anticonvulsant activity than the standard drugs phenytoin, carbamazepine and valproic acid (eq. 6).[17]



In conclusions, we have demonstrated a novel double carbonylation reagent glyoxal for the direct double carbonylation of primary and secondary anilines, in which various isatins were generated. Simple $CuCl_2 \cdot 2H_2O$ was used as the oxidant for this transformation.

Experimental Section

In a 25 mL Schlenk tube, cesium carbonate (211.8 mg, 0.65 mmol) and $CuCl_2 \cdot 2H_2O$ (341.0 mg, 2.0 mmol) were added and charged with N_2 three times. Then, anhydrous MeTHF (1.5 mL) was added followed by trifluoroacetic acid (57.0 mg, 0.5 mmol), aniline **1** (0.5 mmol) and

glyoxal solution 30% w/w in water (153 μL, 1.0 mmol). The mixture was allowed to stir at 70 °C for 5 hours. After completion of the reaction (monitored by TLC), water was added, and the mixture was extracted with ethyl acetate. The organic layer was separated and combined, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (EtOAc/petroleum ether) to give the pure product.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21673261, 21603245, and 21633013). We also gratefully thank the State Key Laboratory for Oxo Synthesis and Selective Oxidation (OSSO), Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences for generous financial support. Support from CAS Interdisciplinary Innovation Team and Young Elite Scientist Sponsorship Program by CAST were also acknowledged. MGT and SHCK thank to Malaysian Toray Science Foundation (MTSF) for research financial support under grant number of GL(F07)/MTSF/2014(14).

References

[1] a) H. M. Colquhoun, D. J. Thompson, M. V. Twigg, *Carbonylation : direct synthesis of carbonyl compounds*, Plenum Press, New York, **1991**; b) M. Beller, *Catalytic carbonylation reactions*, Springer, Berlin ; New York, **2006**; c) L. Kollár, *Modern carbonylation methods*, Wiley-VCH, Weinheim, **2008**.

[2] a) Q. Liu, H. Zhang, A. Lei, *Angew. Chem., Int. Ed.* **2011**, *50*, 10788-10799; b) X.-F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986-5009; c) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1-35.

[3] a) J. Cao, Z.-J. Zheng, Z. Xu, L.-W. Xu, *Coord. Chem. Rev.* **2017**, *336*, 43-53; b) S. D. Friis, A. T. Lindhardt, T. Skrydstrup, *Acc. Chem. Res.* **2016**, *49*, 594-605.

[4] a) Y.-S. Lin, A. Yamamoto, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, John Wiley & Sons, Inc., **2003**, pp. 2399-2423; b) H. des Abbayes, J.-Y. Salaun, *Dalton Trans.* **2003**, 1041-1052.

[5] a) K. Fuji, T. Morimoto, K. Tsutsumi, K. Kakiuchi, *Angew. Chem., Int. Ed.* **2003**, *42*, 2409-2411; b) Q. Liu, K. Yuan, P.-B. Arockiam, R. Franke, H. Doucet, R. Jackstell, M. Beller, *Angew. Chem., Int. Ed.* **2015**, *54*, 4493-4497.

[6] a) S. Gobec, U. Urleb, *Sci. Synth.* **2004**, *16*, 845-911; b) D.-L. Yang, J.-R. Li, H.-Y. Lu, P. Zhang, D.-X. Shi, *J. Chem. Res.* **2014**, *38*, 625-626.

[7] G. S. Singh, Z. Y. Desta, *Chem. Rev.* **2012**, *112*, 6104-6155.

[8] a) Y. Zheng, J. Li, X. Yu, S. Lv, L. Hai, Y. Wu, *Tetrahedron Lett.* **2016**, *57*, 39-42; b) Y. Wang, W. Li, X. Cheng, Z. Zhan, X. Ma, L. Guo, H. Jin, Y. Wu, *Tetrahedron* **2016**, *72*, 3193-3197; c) S. R. Laursen, M. T. Jensen, A. T. Lindhardt, M. F. Jacobsen, T. Skrydstrup, *Eur. J. Org. Chem.* **2016**, *2016*, 1881-1885; d) G. Satish, A. Polu, T. Ramar, A. Ilangovan, *J. Org. Chem.* **2015**, *80*, 5167-5175; e) P. Sai Prathima, R. Bikshapathi, V. J. Rao, *Tetrahedron Lett.* **2015**, *56*, 6385-6388; f) J. Li, Y. Zheng, X. Yu, S. Lv, Q. Wang, L. Hai, Y. Wu, *RSC Adv.* **2015**, *5*, 103280-103283; g) Y. Zi, Z. J. Cai, S. Y. Wang, S. J. Ji, *Org. Lett.* **2014**, *16*, 3094-3097; h) M. Raghavender Reddy, N. Nageswara Rao, K. Ramakrishna, H. M. Meshram, *Tetrahedron Lett.* **2014**, *55*, 4758-4762; i) A. Ilangovan, G. Satish, *J. Org. Chem.* **2014**, *79*, 4984-4991; j) J. Huang, T. Mao, Q. Zhu, *Eur. J. Org. Chem.* **2014**, *2014*, 2878-2882; k) Q. Gui, F. Dai, J. Liu, P. Chen, Z. Yang, X. Chen, Z. Tan, *Org. Biomol. Chem.* **2014**, *12*, 3349-3353; l) J. Sun, B. Liu, B. Xu, *RSC Adv.* **2013**, *3*, 5824; m) A. Ilangovan, G. Satish, *Org. Lett.* **2013**, *15*, 5726-5729; n) B. X. Tang, R. J. Song, C. Y. Wu, Y. Liu, M. B. Zhou, W. T. Wei, G. B. Deng, D. L. Yin, J. H. Li, *J. Am. Chem. Soc.* **2010**, *132*, 8900-8902.

[9] a) T. Liu, H. Yang, Y. Jiang, H. Fu, *Adv. Synth. Catal.* **2013**, *355*, 1169-1176; b) W. Li, Z. Duan, X. Zhang, H. Zhang, M. Wang, R. Jiang, H. Zeng, C. Liu, A. Lei, *Angew. Chem., Int. Ed.* **2015**, *54*, 1893-1896.

[10] Detailed condition screening was listed in the supporting information.

[11] P. Pakravan, S. Kashanian, M. M. Khodaei, F. J. Harding, *Pharmacol. Rep.* **2013**, *65*, 313-335.

[12] A. S. Karpenko, M. O. Shibinskaya, N. M. Zholobak, Z. M. Olevinskaya, S. A. Lyakhov, L. A. Litvinova, M. Y. Spivak, S. A. Andronati, *Pharm. Chem. J.* **2006**, *40*, 595-602.

[13] H. Yi, G. Zhang, J. Xin, Y. Deng, J. T. Miller, A. J. Kropf, E. E. Bunel, X. Qi, Y. Lan, J.-F. Lee, A. Lei, *Chem. Commun.* **2016**, *52*, 6914-6917.

[14] M. Miller, J. C. Vogel, W. Tsang, A. Merrit, D. J. Procter, *Org. Biomol. Chem.* **2009**, *7*, 589-597.

[15] P. Wang, W.-J. Tao, X.-L. Sun, S. Liao, Y. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 16849-16852.

[16] Z.-S. Li, W.-X. Wang, J.-D. Yang, Y.-W. Wu, W. Zhang, *Org. Lett.* **2013**, *15*, 3820-3823.

[17] M. Verma, S. N. Pandeya, K. N. Singh, J. P. Stables, *Acta Pharm.* **2004**, *54*, 49-56.

10.1002/adsc.201700583

COMMUNICATION

Double Carbonylation Using Glyoxal (HCOCOH): A Practical Copper-Promoted Synthesis of Isatins from Primary and Secondary Anilines

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Suzie Hui Chin Kuan,[a,b,†] Wei Sun,[a,†] Lu Wang,[a] Chungu Xia,[a] Meng Guan Tay,[b] and Chao Liu,[*a]