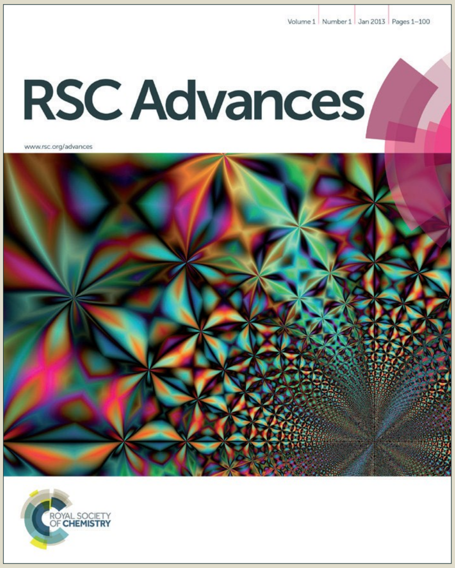
RSC Advances

This article can be cited before page numbers have been issued, to do this please use: C. Liu, Z. Fang, Z. Yang, Q. Li, S. Guo and K. Guo, *RSC Adv.*, 2016, DOI: 10.1039/C5RA27653E.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C5RA27653E

Journal Name

ARTICLE

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

A two-step continuous synthesis of α-ketoamides and α-amino ketones from 2^o benzylic alcohols using hydrogen peroxide as an economical and benign oxidant

Chengkou Liu,[a] Zheng Fang,[a] Zhao Yang,[b] Qingwen Li,[a] Shiyu Guo,[a] and Kai Guo[a,c,]*

A practical two-step synthesis of α-ketoamides and α-amino ketones via direct oxidative coupling between 2^o benzylic alcohols and amines was developed. Hydrogen peroxide, an econimic and envirmental friendly oxidant, was used. And, metal catalyst was unnecessary. Moreover, the continuous-flow technique was employed to increase the functional group tolerance, efficiency and safety.

Introduction

The α-ketoamide functionalities are common among numerous natural products and pharmaceutically active compounds because of their attractive biological and pharmacological properties.[1-14] So, the synthesis of these structural elements has been attracting pursuit of many chemists. Over the past few decades, many traditional synthesis strategies have been developed.[15-34] The amidation of a-ketoacids and a-keto acyl halides is one of the most widely used and has been extensively studied.[26, 32-34] However, harsh reaction conditions and the use of hazardous reagents limited their application. In 2012, a series of publications of one-pot preparation of a-ketoamides by direct coupling of α-carbonyls with functionalized amines[35-45] have inspired a new wave of research.

In the recent past, many chemists have done tremendous amount of work about one-pot preparation of a-ketoamides. The one-pot synthesis of a-ketoamides from different starting materials, such as acetophenone,[35-39] ethylenzene,[46] styrene,[47, 48] phenylacetylene,[49] 1-arylethanol,[45] phenylglyoxal,[40, 50-52] phenylacetaldehyde[53] and 2-hydroxy-1-phenyl-ethanon,[43] was developed successfully as shown in figure 1. Among these starting materials, acetophenone and ethylenzene were more economical and easy available. However, greater scope in terms of coupling partners was highly significant to the organic synthesis. After summarizing the literatures, we found that molecular oxygen (O_2) and tert-butyl hydroperoxide (TBHP) were used as the terminal oxidant mostly. Molecular oxygen is an ideal oxidant. Nevertheless, the metal catalyst (CuI, CuBr) was necessary when molecular oxygen was served as the terminal oxidant, which was not environmental friendly and increased the possibility of metal residual. As for TBHP, it was a little costly compared with some other oxidants, such as hydrogen peroxide (H_2O_2) or sodium hypochlorite (NaClO). So, it was meaningful to build a synthesis methodology of one-pot preparation of a-ketoamides using economical oxidant without any metal catalyst.

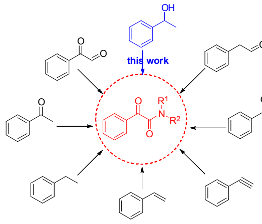


Figure 1 Methods of Synthesis of α-Ketoamide.

Results and discussion

We reported an oxidant of benzylic alcohols into the corresponding carbonyl compounds under $H_2O_2/Br^-/H^+$ in 2015.[54] Bromine (Br_2), the important intermediate, was generated. Similarly, we believed that iodine (I_2) could be obtained under $H_2O_2/I^-/H^+$, which could promote the oxidation of 1-arylethanols and oxidative coupling of methyl ketones and amines to α-ketoamide. A while ago, a practical synthesis method of directly oxidative synthesis of α-ketoamides and α C-H amination of ketones from methyl ketones and amines under $H_2O_2/I^-/H^+$ was developed successfully by our group. The investigation of one-pot synthesis of a-ketoamides from 1-arylethanols and functionally amines is immediately started in our laboratory.

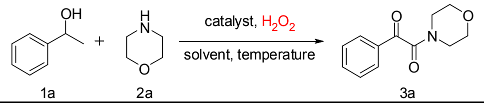
---

[a] College of Biotechnology and Pharmaceutical Engineering Nanjing Tech University 30 Puzhu South Road, Nanjing, 211816, China
[b] College of Engineering China Pharmaceutical University, 24 Tongjiaxiang, NanJing, 210003, China
[c] State Key Laboratory of Materials-Oriented Chemical Engineering Nanjing Tech University 30 Puzhu South Road, Nanjing, 211816, China
E-mail: guok@njtech.edu.cn; Tel.: +862558139935; fax: +862558139926

Electronic Supplementary Information (ESI) was available. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C5RA27653E

Table 1 screening of reaction conditions



Entry	Catalyst	Solvent	Temp (℃)	Yield[f] (%)
1[a]	KI	DMF	70	trace
2[b]	KI	DMF	70	<10
3[c]	KI	DMF	70	95
4[d]	KI	DMF	70	trace
5[e]	KI	DMF	70	95
6[e]	NH_4I	DMF	70	94
7[e]	TBAI	DMF	70	96
8[e]	I_2	DMF	70	96
9[e]	NaBr	DMF	70	<10
10[e]	KBr	DMF	70	<10
11[e]	NaCl	DMF	70	NO
12[e]	KI	ACN	70	92
13[e]	KI	DCE	70	62
14[e]	KI	Dioxane	70	95
15[e]	KI	DMF	60	94
16[e]	KI	DMF	50	80
17[e]	KI	DMF	40	45

[a, b, c, d, e] The experimental details were listed in supporting information, DMF: N,N-dimethylformamide, ACN: acetonitrile, DCE: 1,2-dichloroethane, TBAI: tetrabutylammonium iodide. [f] Isolated yield.

Initially, optimization studies were based on the model substrates of DL-1-phenethylalcohol (1a) and 1-oxa-4-azacyclohexane (2a) to examine the feasibility of the oxidation system of $H_2O_2/I^-/H^+$ as shown in Table 1. Firstly, the mixing way of the reactants was screened. The reaction was carried out using a 25 mL round bottom flask charged with DL-1-phenethylalcohol (1 mmol), 1-oxa-4-azacyclohexane (3 mmol), potassium iodide (0.2 mmol), sulfuric acid (0.2 mmol), hydrogen peroxide (6 mmol), DMF (3 mL) and a magnetic stir bar. The reaction mixture was stirred at 70℃. Unfortunately, only trace amount of 1a had been transformed into the corresponding ketone and α-ketoamide 3a after 24h (table 1, entry 1). Next, the hydrogen peroxide (a solution of H_2O_2 (6 mmol) in DMF (1.5 mL)) was added to the reaction mixture by springe with the help of a springe pump within 12h instead of adding the oxidant (H_2O_2) in a whole. It was a pity that only a little (<10%) desired product was obtained (table 1, entry 2). Afterwards, a two-step loading way was tested. A solution of DL-1-phenethylalcohol (1 mmol), potassium iodide (0.2 mmol), sulfuric acid (0.2 mmol) and hydrogen peroxide (2 mmol) in DMF (1.5 mL) was stirred at 70℃. After 12h, 1-oxa-4-azacyclohexane (3 mmol) was added in a whole. Then, the hydrogen peroxide (a solution of H_2O_2 (4 mmol) in DMF (1.5 mL)) was syringed addition within 2h. Inspiringly, excellent yield of desired oxidative coupling product 3a was isolated (table 1, entry 3). Considering the functional group tolerance and reaction time consumed, continuous-flow technique was employed, which was possessed of high surface-to-volume ratio, efficient mass transfer and heat transfer and high selectivity. Firstly, one-step synthesis of a-ketoamides from the oxidation of alcohol and direct coupling of α-carbonyl with functionalized amine was tested (figure 1). However, the desired product was detected with a very low conversion (table 1, entry 4). Afterwards, a two-step of synthesis methodology was performed shown in figure 2. To our delight, an almost quantitative conversion was obtained (table 1, entry 5). It seemed that the high efficiency of H_2O_2 in this oxidation coupling was inconsistent with many literatures, which could be explained by a phenomenon observed. After H_2O_2 was added into the reaction mixture only one time, the mixture was brownish red and much colourless gas was produced. The colour of the mixture changed into white quickly and no more gas observed, which indicated that H_2O_2 was decomposed. So, a high conversion and yield was obtained when H_2O_2 was added slowly with the help of spring pump within a certain time. A series of reactions were carried out to examine the different catalysts, including KI, NH_4I, TBAI, I_2, NaBr, KBr and NaCl. According to the results shown in table 1, this reaction could be promoted to give the expected products in good yields by all iodine salts (table 1, entries 3, 5-8). When bromine salts were involved, the yields dropped to minute quantity (table 1, entries 9, 10). And, NaCl failed to promote this reaction (table 1, entry 11). Subsequently, various solvents were examined. To our delight, excellent isolated yield (>90%) of 3a was obtained when the reaction was performed in DMF, ACN or dioxane (table 1, entries 5, 12, 14). However, DCE was less effective (table 1, entry 13). When the reaction temperature was decreased from 70℃ to 40℃, an obvious decrease in yield was observed (table 1, entries 5, 15-17). Among different temperature examined, 60℃ turned out to be the proper choice. Finally, the optimizations of the amount of potassium iodide, sulfuric acid and hydrogen peroxide were carried out. To our delight, the full conversions and good yields were obtained even though the amount of potassium iodide and sulfuric acid were dropped to 5 mol% (table SI, S2, ESI). Moreover, less than 5.6 equiv. of hydrogen peroxide led to the incompletion of the reaction (table S3, ESI).

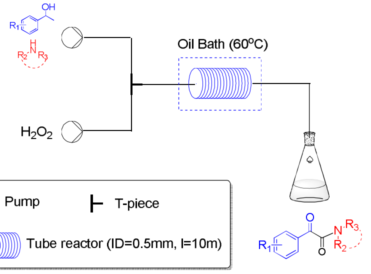


Figure 2 A two-step continuous flow synthesis of α-ketoamide

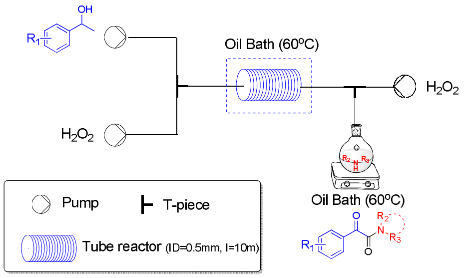
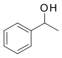
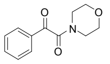
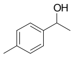
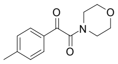
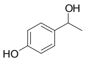
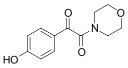
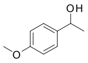
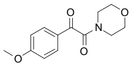
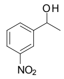
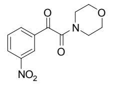
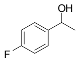
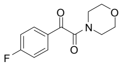
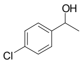
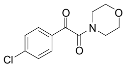
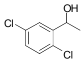
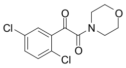
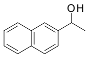
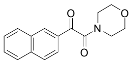
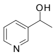
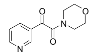
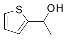
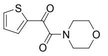


Figure 3 A two-step continuous flow synthesis of α-ketoamide

Table 2 scope of 1-arylethanols for the two-step synthesis of α-ketoamides[a]

Entry	1-Arylethanol	Product	Yield (%)[b]
1			90(88)[c]
2			89
3			NO
4			50
5			90
6			92
7			91
8			88
9			90
10			91
11			87

[a]Store solution A: 0.667 M of alcohol in the DMF, flow rate 0.327 mL/min; store solution B: 1.333 M of hydrogen peroxide, 5 mol % sulphuric acid (98%) and 5 mol % potassium iodide in DMF and H_2O (29:1), flow rate 0.327 mL/min, 60℃, 3 min. 1-oxa-4-azacyclohexane (3 mmol, 0.2614 g), hydrogen peroxide (30% aq, 3.6 mmol, 0.4081 g in DMF (1.5 mL), which was syringed within 2h), 3 mL reaction mixture before, T (60℃). [b]Isolated yields. [c]Isolated yields in gram scale.

In the course of the investigation into the scope of different substituents, a series of substituted aryl methyl ketones and amines were explored (table 2, 3). Fortunately, the direct coupling of 1-oxa-4-azacyclohexane with aryl ketones containing electron-withdrawing or electron-donating groups proceeded successfully to afford the desired products with moderate to excellent yields (table 2, 1, 2, 4-9). However, an obvious lower yield (50%) was obtained when 1-(4-methoxyphenyl)ethanol containing an instable substituent group was involved (table 2, entry 4). Remarkably, 4-(1-hydroxyethyl)phenol failed to afford the corresponding α-ketoamide, which was similar to the previous literatures (table 2, entry 3). And, a little iodine byproduct in the aryl ring was detected, which consumed the catalyst and restrained the process of coupling. As for 3-nitroacetophenone, a strong electron-deficient aromatic ketone, there was not any obvious defect observed (table 2, entry 5). It was noted that the hetero aryl methyl ketones could be transformed into the corresponding products in good yields (table 2, entry 10-11).

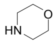
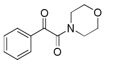
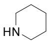
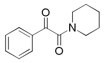
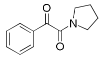
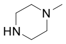
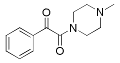
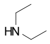
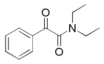
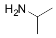
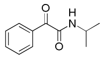
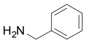
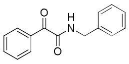
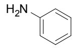
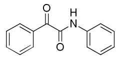
Different amines were tested under the optimized conditions. The secondary amines could be transformed to afford the corresponding products with moderate to good yields (table 3, entries 1-5). Furthermore, cyclic secondary amines showed higher activity compared with acyclic secondary amines. As for primary amines, the weak nucleophiles, only trace amount of products were detected, which was similar to many conventional method.

After the establishment of the one-pot preparation of α-ketoamides, we believed that a cross dehydrogenative coupling (CDC) reaction between aryl propanols and functional amines could undergo successfully under the established reaction conditions before.

1-phenyl-1-propanol and 1-oxa-4-azacyclohexane were chosen to test our conjecture as shown in scheme 1.

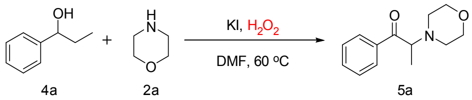
To our delight, 5a, the desired product was generated smoothly with good yield (91%). Moreover, only a slight decrease of isolated yield in gram scale was observed with no further optimization (table 4, entry 1). These structural elements of α-amino ketones are present in many drugs[55-57] and photoinitiators.[58] Moreover, they could be used as precursors to synthetize β-aminoalcohols[59] and some heterocyclic compounds.[60] Now, only a few literatures were reported to one-pot synthetize α-amino ketones from direct α-C–H amination of ketones. For example, MacMillan[61] reported a $O_2/CuBr_2$-promoted direct coupling of α-carbonyls with functionalized amines. Meanwhile, Guo[62] developed a oxidation system of $NH_4I/NaCO_3•1.5H_2O_2$ and prabhu[35] reported a NIS/TBHP system to do the similar work. There has been no report on the synthesis α-amino ketones using H_2O_2 as the oxidant. As far as we know, this is the first report of synthesis α-amino ketones from aryl propanols. Later, the amount of H_2O_2 was screened. 3.5 equiv. of H_2O_2 was proper, which was shown in table S4 (ESI). Next, the scope of aryl propanols and amines was investigated (table 4).

Table 3 scope of amines for the two-step synthesis of α-ketoamides[a]

Entry	Amines	Product	Yield (%)[b]
1			90
2			89(84)[c]
3			86
4			89
5			73
6			NO
7			NO
8			NO

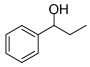
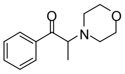
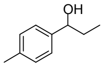
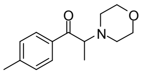
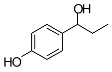
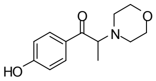
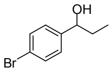
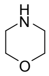
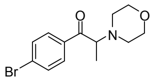
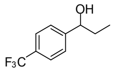
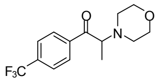
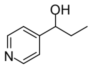
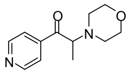
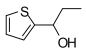
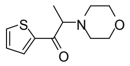
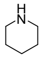
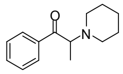
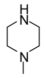
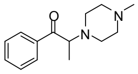
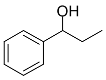
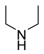
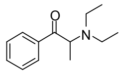
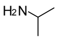
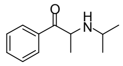
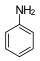
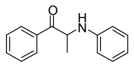
[a]Store solution A: 0.667 M of DL-1-phenethylalcohol in the DMF, flow rate 0.327 mL/min; store solution B: 1.333 M of hydrogen peroxide, 5 mol % sulphuric acid (98%) and 5 mol % potassium iodide in DMF and H_2O (29:1), flow rate 0.327 mL/min, 60℃, 3 min. Amine (3 mmol), hydrogen peroxide (30% aq, 3.6 mmol, 0.4081 g in DMF (1.5 mL), which was syringed within 2h), 3 mL reaction mixture before, T (60℃). [b]Isolated yields. [c]Isolated yields in gram scale.

View Article Online
DOI: 10.1039/C5RA27653E



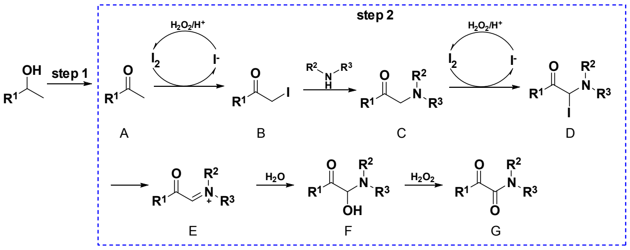
Scheme 1 direct coupling between 1-phenyl-1-propanol and 1-oxa-4-azacyclohexane

Table 4 scope of aryl propanols and amines for the two-step synthesis of α-amino ketones

Entry	Aryl propanols	Amines	Product	Yield (%)[b]
1				91(86)[c]
2				88
3				NO
4				87
5				88
6				85
7				84
8				89
9				90
10				41
11				NO
12				NO

[a] Store solution A: 0.667 M of alcohol in the DMF, flow rate 0.327 mL/min; store solution B: 1.333 M of hydrogen peroxide, 5 mol % sulphuric acid (98%) and 5 mol % potassium iodide in DMF and H_2O (29:1), flow rate 0.327 mL/min, 60℃, 3 min. Amine (3 mmol), hydrogen peroxide (30% aq, 1.5 mmol, 0.1700 g in DMF (1.5 mL), which was syringed within 2h), 3 mL reaction mixture before, T (60℃). [b] Isolated yields. [c] Isolated yields in gram scale.

The reaction between 1-oxa-4-azacyclohexane and aryl propanols containing electron-withdrawing and electron-donating groups could be underwent smoothly to generate the desired products with good yields (table 4, entries 1, 2, 4, 5). Specially, there was no obvious decrease of yield observed when 4-(1-hydroxypropyl)benzotrifluoride, a strong electron-deficient aryl propanol, was involved (table 4, entry 5). However, 4-(1-hydroxypropyl)phenol failed to afford the desired product, which was similar to many previous methods reported (table 4, entry 3). Inspiringly, hetero aromatic propanols reacted with 1-oxa-4-azacyclohexane to yield the correspond products with satisfactory yields (table 4, entries 6, 7). As for the amines, both cyclic and acyclic secondary amines could be transformed to the α-amino ketones in moderate to good yields (table 4, entries 1, 8-10). Interestingly, cyclic secondary amines showed higher reactivity than acyclic secondary amines. Unfortunately, almost no products were obtained when primary amines were employed (table 4, entries 11, 12). The optimization of coupling with primary amines is ongoing in our laboratory.



Scheme 2 possible reaction pathway

As for reaction mechanism, we believed that in was similar to Wan's report (TBHP/I_2),[38] which was shown in scheme 2. Detailed discussion was summarized in ESI. A control experiment was performed to validate this mechanism. When the temperature was decreased to 30℃, the intermediate C could be obtained with 32% isolated yield. Moreover, intermediate E could be detected with the help of high resolution mass spectrometry. These supported this mechanism strongly.

Conclusions

In conclusion, a two-step method to construct the C-N to synthetize the α-ketoamide and α-amine ketones from benzylic alcohols and amines was established successfully. The continuous-flow technique was employed in the oxidation of benzylic alcohols, which increased the efficiency and expansion the scope of substituents with benefits of high surface to volume ratio and efficient mass transfer and heat transfer. H_2O_2, an economic and environmental oxidant, was used in this process. This oxidation coupling was economical and practical with metal free catalyst and a wide scope of aryl alcohols. And, further investigations into expansion the scope of amines is ongoing in our laboratory.

Acknowledgements

The research has been supported by National Key Basic Research Program of China (973 Program) 2012CB721104; the National High Technology Research and Development Program of China (863 Program) 2014AA022101; the National Natural Science Foundation of China (Grant No.U1463201 and 81302632).

Notes and references

View Article Online
DOI: 10.1039/C5RA27653E

1 A. Ovat, Z. Z. Li, C. Y. Hampton, S. A. Asress, F. M. Fernandez, J. D. Glass and J. C. Powers, J. Med. Chem., 2010, **53**, 6326.
2 S. Alvarez, R. Alvarez, H. Khanwalkar, P. Germain, G. Lemaire, F. Rodriguez-Barrios, H. Gronemeyer and A. R. de Lera, Bioorg. Med. Chem., 2009, **17**, 4345.
3 J. Qian, D. Cuerrier, P. L. Davies, Z. Li, J. C. Powers and R. L. Campbell, J. Med. Chem., 2008, **51**, 5264.
4 Y. H. Chen, Y. H. Zhang, H. J. Zhang, D. Z. Liu, M. Gu, J. Y. Li, F. Wu, X. Z. Zhu, J. Li and F. Nan, J. Med. Chem., 2006, **49**, 1613.
5 M. M. Sheha, N. M. Mahfouz, H. Y. Hassan, A. F. Youssef, T. Mimoto and Y. Kiso, Eur. J. Med. Chem., 2000, **35**, 887.
6 S. Chatterjee, D. Dunn, M. Tao, G. Wells, Z. Q. Gu, R. Bihovsky, M. A. Ator, R. Siman and J. P. Mallamo, Biooge. Med. Chem Lett., 1999, **9**, 2371.
7 Z. Z. Li, A. C. OrtegaVilain, G. S. Patil, D. L. Chu, J. E. Foreman, D. D. Eveleth and J. C. Powers, J. Med. Chem., 1996, **39**, 4089.
8 B. E. Maryanoff, M. N. Greco, H. C. Zhang, P. Andradegordon, J. A. Kauffman, K. C. Nicolaou, A. J. Liu and P. H. Brungs, J. Am. Chem. Soc., 1995, **117**, 5427.
9 D. H. Slee, K. L. Laslo, J. H. Elder, I. R. Ollmann, A. Gustchina, J. Kervinen, A. Zdanov, A. Wlodawer and C. H. Wong, J. Am. Chem. Soc., 1995, **117**, 11867.
10 B. E. Maryanoff, M. N. Greco, H. C. Zhang, P. Andradegordon, J. A. Kauffman, K. C. Nicolaou, A. J. Liu and P. H. Brungs, J. Am. Chem. Soc., 1995, **117**, 1225.
11 B. Munoz, C. Z. Giam and C. H. Wong, Bioorg. Med. Chem., 1994, **2**, 1085.
12 M. Hagihara and S. L. Schreiber, J. Am. Chem. Soc., 1992, **114**, 6570.
13 T. D. Ocain and D. H. Rich, J. Med. Chem., 1992, **35**, 451.
14 H. Tanaka, A. Kuroda, H. Marusawa, H. Hatanaka, T. Kino, T. Goto, M. Hashimoto and T. Taga, J. Am. Chem. Soc., 1987, **109**, 5031.
15 C. Zhang and N. Jiao, J. Am. Chem. Soc., 2010, **132**, 28.
16 M. Bouma, G. Masson and J. Zhu, J. Org. Chem., 2010, **75**, 2748.
17 P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp and T. Skrydstrup, J. Am. Chem. Soc., 2011, **133**, 6061.
18 S. D. Friis, R. H. Taaning, A. T. Lindhardt and T. Skrydstrup, J. Am. Chem. Soc., 2011, **133**, 18114.
19 J. Liu, R. Zhang, S. Wang, W. Sun and C. Xia, Org. Lett., 2009, **11**, 1321.
20 J.-M. Grassot, G. Masson and J. Zhu, Angew. Chem., Int. Ed., 2008, **47**, 947.
21 L. El Kaim, R. Gamez-Montano, L. Grimaud and T. Ibarra-Rivera, Chem. Commun., 2008, **44**, 1350.
22 E. R. Murphy, J. R. Martinelli, N. Zaborenko, S. L. Buchwald and K. F. Jensen, Angew. Chem., Int. Ed., 2007, **46**, 1734.
23 Z. F. Al-Rashid, W. L. Johnson, R. P. Hsung, Y. Wei, P.-Y. Yao, R. Liu and K. Zhao, J. Org. Chem., 2008, **73**, 8780.
24 M. Iizuka and Y. Kondo, Chem. Commun., 2006, **41**, 1739.
25 B. Song, S. Wang, C. Sun, H. Deng and B. Xu, Tetrahedron Lett., 2007, **48**, 8982.
26 R. P. Singh and J. M. Shreeve, J. Org. Chem., 2003, **68**, 6063.
27 Z. Yang, Z. X. Zhang, N. A. Meanwell, J. F. Kadow and T. Wang, Org. Lett., 2002, **4**, 1103.
28 Y. Uozumi, T. Arii and T. Watanabe, J. Org. Chem., 2001, **66**, 5272.
29 G. M. Dubowchik, V. M. Vrudhula, B. Dasgupta, J. Ditta, T. Chen, S. Sheriff, K. Sipman, M. Witmer, J. Tredup, D. M. Vyas, T. A. Verdoorn, S. Bollini and A. Vinitsky, Org. Lett., 2001, **3**, 3987.
30 J. L. Zhu, H. Wong, Z. X. Zhang, Z. W. Yin, J. F. Kadow, N. A. Meanwell and T. Wang, Tetrahedron Lett., 2005, **46**, 3587.
31 H. H. Wasserman and W. B. Ho, J. Org. Chem., 1994, **59**, 4364.
32 F. Ozawa, H. Soyama, H. Yanagihara, I. Aoyama, H. Takino, K. Izawa, T. Yamamoto and A. Yamamoto, J. Am. Chem. Soc., 1985, **107**, 3235.
33 A. Papanikos, J. Rademann and M. Meldal, J. Am. Chem. Soc., 2001, **123**, 2176.
34 M. Nakamura, J. Inoue and T. Yamada, Biooge. Med. Chem Lett., 2000, **10**, 2807.
35 M. Lamani and K. R. Prabhu, Chem-Eur. J., 2012, **18**, 14638.
36 F.-T. Du and J.-X. Ji, Chem. Sci., 2012, **3**, 460.
37 X. Zhang and L. Wang, Green Chem., 2012, **14**, 2141.
38 W. Wei, Y. Shao, H. Hu, F. Zhang, C. Zhang, Y. Xu and X. Wan, J. Org. Chem., 2012, **77**, 7157.
39 J. Zhang, Y. Wei, S. Lin, F. Liang and P. Liu, Org. Biomol. Chem., 2012, **10**, 9237.
40 C. Zhang, X. Zong, L. Zhang and N. Jiao, Org. Lett., 2012, **14**, 3280.
41 J. Zhang, Y. Liu, S. Chiba and T. P. Loh, Chem. Commun., 2013, **49**, 11439.
42 Z. Zhang, J. Su, Z. Zha and Z. Wang, Chem. Commun., 2013, **49**, 8982.
43 S. S. Kotha, S. Chandrasekar, S. Sahu and G. Sekar, Eur. J. Org. Chem., 2014, **183**, 7451.
44 Y. Shao, Z. Wu, C. Miao and L. Liu, J. Organomet. Chem., 2014, **767**, 60.
45 G. Sekar, N. Sharma, S. Kotha and N. Lahiri, Synthesis, 2015, **47**, 726.
46 B. Du, B. Jin and P. Sun, Org. Biomol. Chem., 2014, **12**, 4586.
47 R. Deshidi, S. Devari and B. A. Shah, Eur. J. Org. Chem., 2015, **184**, 1428.
48 S. Dutta, S. S. Kotha and G. Sekar, RSC Adv., 2015, **5**, 47265.
49 R. Deshidi, M. Kumar, S. Devari and B. A. Shah, Chem. Commun., 2014, **50**, 9533.
50 N. Mupparapu, S. Khan, S. Battula, M. Kushwaha, A. P. Gupta, Q. N. Ahmed and R. A. Vishwakarma, Org. Lett., 2014, **16**, 1152.
51 N. Mupparapu, N. Battini, S. Battula, S. Khan, R. A. Vishwakarma and Q. N. Ahmed, Chem-Eur. J., 2015, **21**, 2954.
52 S. Shi, T. Wang, V. Weingand, M. Rudolph and A. S. Hashmi, Angew. Chem., Int. Ed., 2014, **53**, 1148.
53 C. Zhang, Z. Xu, L. Zhang and N. Jiao, Angew. Chem., Int. Ed., 2011, **50**, 11088.
54 C. Liu, Z. Fang, Z. Yang, Q. Li, S. Guo, K. Zhang, P. Ouyang and K. Guo, Tetrahedron Lett., 2015, **56**, 5973.
55 C. Bouteiller, J. Becerril-Ortega, P. Marchand, O. Nicole, L. Barre, A. Buisson and C. Perrio, Org. Biomol. Chem., 2010, **8**, 1111.
56 F. I. Carroll, B. E. Blough, P. Abraham, A. C. Mills, J. A. Holleman, S. A. Wolckenhauer, A. M. Decker, A. Landavazo, K. T. McElroy, H. A. Navarro, M. B. Gatch and M. J. Forster, J. Med. Chem., 2009, **52**, 6768.
57 M. C. Myers, J. Wang, J. A. Iera, J. K. Bang, T. Hara, S. Saito, G. P. Zambetti and D. H. Appella, J. Am. Chem. Soc., 2005, **127**, 6152.
58 W. R. Bergmark and D. G. Whitten, J. Am. Chem. Soc., 1990, **112**, 4042.
59 M. R. Paleo, M. I. Calaza and F. J. Sardina, J. Org. Chem., 1997, **62**, 6862.
60 S. Belot, S. Sulzer-Mosse, S. Kehrli and A. Alexakis, Chem. Commun., 2008, **44**, 4694.
61 R. W. Evans, J. R. Zbieg, S. Zhu, W. Li and D. W. MacMillan, J Am Chem Soc, 2013, **135**, 16074.
62 Q. Jiang, B. Xu, A. Zhao, J. Jia, T. Liu and C. Guo, J. Org. Chem., 2014, **79**, 8750.

View Article Online
DOI: 10.1039/C5RA27653E

A practical two-step flow synthesis of α-ketoamides and α-amino ketones via direct oxidative coupling between 2° benzylic alcohols and amines was developed.