# Polyethylene glycol as a recyclable reaction medium for gold-catalysed direct oxidative amide synthesis from aldehydes and amines

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Polyethylene glycol (PEG) was used as the recyclable reaction medium for gold-catalysed oxidative amidation of aldehydes with amines by using *tert*-butyl hydroperoxide (TBHP, 70% aqueous) as the oxidant. The reaction proceeded efficiently to provide the corresponding products in moderate to good yields under mild conditions. Both the catalysts and solvent can be easily recovered and reused by simple extraction without significant loss of activity.

Keywords: gold catalysis, oxidative amidation, polyethylene glycol medium, recycling

Amides are ubiquitous and very important structural motifs present in a wide range of materials and in pharmaceuticals and biologically active compounds.<sup>1-4</sup> Traditional approaches for the synthesis of amides mainly involve amidation reactions between carboxylic acids or activated carboxylic acid derivatives such as acid anhydrides and acid halides with amines.<sup>5.6</sup> However, the toxicity of the reagents and the harsh reaction conditions are major drawbacks that still need to be addressed.

Recently, direct amidation of alcohols or aldehydes with amines has attracted considerable attention due to the high atom economy and easy availability of substrates.<sup>7-17</sup> In 2006, the Li group<sup>18</sup> reported a CuI/AgIO<sub>3</sub>/T-HYDRO mediated oxidative coupling reaction between aldehydes and amine hydrochlorides (Scheme 1a). The Leow group<sup>19</sup> and the Wong group<sup>20</sup> disclosed a photo-induced aerobic oxidative amidation of aromatic aldehydes with amines by using phenazinium salt and rose bengal as the catalyst, respectively (Scheme 1b). Recently, Wang *et al.*<sup>21</sup> developed a catalyst-free amidation of aldehydes with amines in aqueous media by employing trichloroisocyanuric acid (TCCA) as additive (Scheme 1c). On the other hand, Barbas et al.<sup>22,23</sup> developed the oxidative amidation of alcohols with amines and azides using gold as catalyst (Scheme 1d). Although these methods afforded satisfactory results, recovery and reuse of the catalysts could not be achieved. Thus, the high cost of both catalysts and ligands as well as organic solvents limited their practical use in industry. In recent years, PEG (polyethylene glycol) has been applied as a novel solvent for organic reactions due to its non-toxicity and its cheap, stable and environmentally friendly properties.<sup>24-27</sup> More importantly, PEG can be used for catalyst recycling in a broad range of organic reactions including polymerisation and biotransformation.<sup>28-33</sup> We now report a Ph<sub>3</sub>PAuCl/TBHP mediated oxidative coupling reaction between aldehydes and amines in PEG-400 (Scheme 1e). The catalysts immobilised in PEG-400 medium can be easily recycled without significant loss of activity.

## **Results and discussion**

Initially, benzaldehyde **1a** and aniline **2a** were employed as the starting materials to optimise the reaction conditions. A variety



Scheme 1 Different pathways for oxidative amidation.

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<sup>a</sup>Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), catalyst (2 mol%), oxidant (1.1 equiv.), solvent (1 mL), 50°C.

<sup>b</sup>lsolated yield.

° No reaction.

<sup>d</sup>1 mol% of catalyst.

°4 mol% of catalyst.

<sup>f</sup>2.0 equiv. of oxidant

<sup>9</sup>2 mL of solvent.

<sup>h</sup>0.5 mL of solvent. <sup>i</sup>Room temperature.

<sup>J</sup> 80 °C.

of reaction conditions including catalyst, oxidant, solvent as well as temperature were explored (Table 1). Results showed that, the reaction proceeded smoothly in the presence of 2 mol% of Ph<sub>3</sub>PAuCl and 1.1 equiv. of TBHP in PEG-400 at 50 °C for 8 h. The desired product **3a** was furnished in 78% yield (Table 1, entry 11). Catalysts such as Pd(OAc), AgOTf, Cu(OAc), and CuI resulted in either the failure of the reaction or much lower yields (Table 1, entries 1-4). The oxidants also showed an important influence on this transformation. No desired product was observed when K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, PhI(OAc)<sub>2</sub> and O<sub>2</sub> were used (Table 1, entries 6-8). A reaction using DDQ and H<sub>2</sub>O<sub>2</sub> gave rather low yields of product (Table 1, entries 9 and 10). Compared with CH<sub>2</sub>CN, DMF, THF, MeOH and 1,4-dioxane, the use of PEG-400 as solvent resulted in higher yields (Table 1, entries 11-15). Further optimisation showed that no higher yield was obtained when the amount of catalyst or oxidant was increased (Table 1, entries 16 and 17). Reaction concentration was further evaluated. The result clearly showed that 1 mol L<sup>-1</sup> of aldehyde was the optimum (Table 1, entry 18). Finally, the survey on the reaction temperature showed that 50 °C was the optimum (Table 1, entry 19).

With these optimised conditions in hand, the scope of the reaction was explored (Table 2). Generally, all of the investigated aldehydes coupled with amines smoothly to provide the desired products in moderate to good yields (44–86%). For substituted aromatic aldehydes, both electron-withdrawing and electron-

Table 2 Reaction scope for aldehyes and amines<sup>a</sup>

Table 2 Reaction scope for aldenyes and animes					
C 	) + L		Ph <sub>3</sub> PAu	CI, TBHF	
R <sup>1</sup> /	`H '	1211-13	PEG-400		R <sup>1</sup> N <sup>-</sup> K <sup>-</sup>
1		2			3
Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield/% <sup>b</sup>	M.p./°C <sup>lit.</sup>
1	Ph	Ph	3a	78	160–162 (162–163) <sup>22</sup>
2	$4-\text{CIC}_6\text{H}_4$	Ph	3b	82	200-204 (200-201)22
3	$2-\text{CIC}_6\text{H}_4$	Ph	3c	66	113–114 (114–115) <sup>22</sup>
4	$4-BrC_{6}H_{4}$	Ph	3d	75	198-200 (202-204)22
5	$4-\text{MeC}_6H_4$	Ph	3e	83	146–147 (143–144) <sup>22</sup>
6	4-0MeC <sub>6</sub> H <sub>4</sub>	Ph	3f	72	170–173 (173–174) <sup>22</sup>
7	4-N0 <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ph	3g	80	214-216 (215-216)22
8	2-furyl	Ph	3h	56	124–125 (126–127) <sup>22</sup>
9	1-naphthyl	Ph	3i	61	165–167 (164–165) <sup>22</sup>
10	1-butyl	Ph	3j	51	60-61 (59-61) <sup>22</sup>
11	Ph	$4-CIC_{6}H_{4}$	3k	78	202-204 (199-200)22
12	Ph	$4 - \text{MeC}_6 H_4$	31	86	155–156 (157–158) <sup>22</sup>
13	Ph	4-0MeC <sub>6</sub> H <sub>4</sub>	3m	75	160-162 (161-162) <sup>22</sup>
14	Ph	4-N0 <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	3n	53	198–200 (197–198) <sup>22</sup>
15	Ph	piperidine	30	77	80-82 (82-84)23
16	Ph	benzyl	3p	68	104-106 (104-105)22
17	Ph	1-butyl	3q	46	Yellow oil <sup>22</sup>

 $^{\rm a}$  Reaction conditions: 1 (1 mmol), 2 (1 mmol), Ph\_3PAuCl (2 mol%), TBHP (1.1 equiv.), PEG-400 (1 mL), 50 °C.

<sup>b</sup> Isolated yield.



Fig. 1 Recycling experiment (Reaction conditions: 1 (1 mmol), 2 (1 mmol), Ph<sub>2</sub>PAuCl (2 mol%), TBHP (1.1 equiv.), PEG-400 (1 mL), 50 °C.)

donating groups gave satisfactory results (Table 2, entries 2–7). Other aromatic or heterocyclic aldehydes, such as 2-furaldehyde and1-naphthaldehyde, were found to be compatible with this system affording products 3h and 3i in moderate yields (Table 2, entries 8 and 9). For alkyl aldehydes such as propionaldehyde, relatively lower yields were obtained (Table 2, entry 10). The steric hindrance also had some influence on the reaction. For example, 4-chloroaniline provided the product 3b in 82%, and 3c was obtained in 66% yield when 2-chloroaniline was used (Table 2, entries 2 and 3). Moreover, the electronic properties of the substituent on aromatic amines had a significant influence on this reaction. Amines bearing electron-withdrawing groups such as nitro gave the desired products in relatively lower yields (Table 2, entry 14). Both heterocyclic and alkyl amines were found to be compatible with the reaction conditions to afford the desired products in 77–46% yields (Table 2, entries 15–17).

Having established the efficiency of this catalytic system, the recovery and reuse of the catalysts were then studied. When the reaction was completed, the mixture was extracted with methyl *tert*-butyl ether (MTBE). The PEG phase was then washed with MTBE and reused directly for the next run. The catalyst system could be reused four times without significant loss of activity (Fig. 1).

In summary, a gold-catalysed direct amidation of aldehydes with amines using PEG-400 as the solvent has been developed. A wide range of aldehydes and amines survived the reaction conditions to give the corresponding products in moderate to good yields. Both the catalyst and solvent could be readily recycled by simple extraction with MTBE four times with slight decrease in its activity.

## Experimental

PEG-400 was purchased from the petrochemical plant of Jiangsu Haian. All other chemicals (AR grade) were commercially available and used without further purification. Analytical TLC was performed on glass plates precoated with silica gel impregnated with a fluorescent indicator (254 nm). The plates were visualised by exposure to UV light. <sup>1</sup>H NMR spectra were recorded on a Bruker DRX500 (500 MHz) spectrometer. All the products are known compounds and were identified by comparison of their physical and spectra data with those reported in the literature.

#### General procedure

A suspension of the amine (1 mmol), aldehyde (1 mmol), TBHP (1.1 equiv.) and Ph<sub>3</sub>PAuCl (2% mol) in 1 mL PEG-400 was stirred at 50°C overnight. After the reaction, the mixtures were extracted by MTBE (3 mL x 2). The organic layer was separated and concentrated under reduced pressure to give the crude products, which were further purified by column chromatography with *n*-hexane/EtOAc (v:v = 2:1) as eluent to afford the pure product. The PEG-400 phase containing the catalyst was directly reused for the next run under identical conditions.

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#### References

- 1 J.M. Humphrey and A.R. Chamberlin, Chem. Rev., 1997, 97, 2243.
- 2 V.R. Pattabiraman and J.W. Bode, *Nature*, 2011, **480**, 471.

- 3 X. Fang, H. Li, R. Jackstell and M. Beller, J. Am. Chem. Soc., 2014, 136, 16039.
- 4 S.D. Roughley and A.M. Jordan, J. Med. Chem., 2011, 54, 3451.
- 5 R.C. Larock, Comprehensive organic transformation. VCH, New York, 1999.
- 6 E. Valeur and M. Bradley, Chem. Soc. Rev., 2009, 38, 606.
- 7 K. Ekoue-Kovi and C. Wolf, Org. Lett., 2007, 9, 3429.
- 8 S. Seo and T.J. Marks, Org. Lett., 2008, 10, 317.
- 9 M. Zhu, K. Fujita and R. Yamaguchi, J. Org. Chem., 2012, 77, 9102.
- 10 R. Tank, U. Pathak, M. Vimal, S. Bhattacharyya and L.K. Pandey, Green Chem., 2011, 13, 3350.
- 11 X. Liu and K.F. Jensen, Green Chem., 2012, 14, 1471.
- 12 V. Prasad, R.R. Kale, B.B. Mishra, D. Kumar and V.K. Tiwari, Org. Lett., 2012, 14, 2936.
- 13 C. L. Allen, S. Davulcu and J.M.J. Williams, Org. Lett., 2010, 12, 5096.
- 14 S. Kumari, A. Shekhar, H.P. Mungse, O.P. Khatri and D.D. Pathak, *RSC Adv.*, 2014, 4, 41690.
- 15 R. Cadoni, A. Porcheddu, G. Giacomelli and L.D Luca, Org. Lett., 2012, 14, 5014.
- 16 M. Zhang and X.F. Wu, Tetrahedron Lett., 2013, 54, 1059.
- 17 O.S. Patel, D. Anand, R.K. Maurya and P.P. Yadav, Green Chem., 2015, 17, 3728.
- 18 W.J. Woo and C.J. Li, J. Am. Chem. Soc., 2006, 128, 13064.
- 19 D. Leow, Org. Lett., 2014, 16, 5812.
- 20 F.K.C. Leung, J.F. Cui, T.W. Hui, K.K.Y. Kung and M.k. Wong, Asian J. Org. Chem., 2015, 4, 533.
- 21 H. Yang, W. Hu, S. Deng, T. Wu, H. Cen, Y. Chen, D. Zhang and B. Wang, New J. Chem., 2015, 39, 5912.
- 22 Y. Wang, D. Zhu, L. Tang, S. Wang and Z. Wang, Angew. Chem. Int. Ed., 2011, 50, 8917.
- 23 X. Guo, L. Tang, Y. Yang, Z. Zha and Z. Wang, Green Chem., 2014, 16, 2443.
- 24 C.K.Z. Andrade and L.M. Alves, Curr. Org. Chem., 2005, 9, 195.
- 25 J. Chen, S.K. Spear, J.G. Huddleston and R.D. Rogers, *Green Chem.*, 2005, 7, 64.
- 26 C. Xu, Z.Q. Wang, W.J. Fu, X.H. Lou, Y.F. Li, F.F. Cen, H.J. Ma and B.M. Ji, Organometallics, 2009, 28; 1909.
- 27 H. Zhao, T. Zhang, T. Yan and M. Cai, J. Org. Chem., 2015, 80, 8849.
- 28 D.J. Heldebrant and P.G. Jessop, J. Am. Chem. Soc., 2003, 125, 5600.
- 29 L.A. Blanchard, D. Hancu, E.J. Beckman and J.F. Brennecke, *Nature*, 1999, 399, 28.
- 30 Z.S. Hou, N. Theyssen, A. Brinkmann and W. Leitner, *Angew. Chem. Int.* Ed., 2005, 44, 1346.
- 31 J.H. Li, Q.M. Zhu, Y. Liang and D. Yang, J. Org. Chem., 2005, 70, 5347.
- 32 J.H. Li, W.J. Liu and Y.X. Xie, J. Org. Chem., 2005, 70, 5409.
- 33 T.M. Razler, Y. Hsiao, F. Qian, R. Fu, R.K. Khan and W. Doubleday, J. Org. Chem., 2009, 74. 1381.