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Copper-Catalyzed One-Pot Synthesis of α-Ketoamides from 1-Arylethanols

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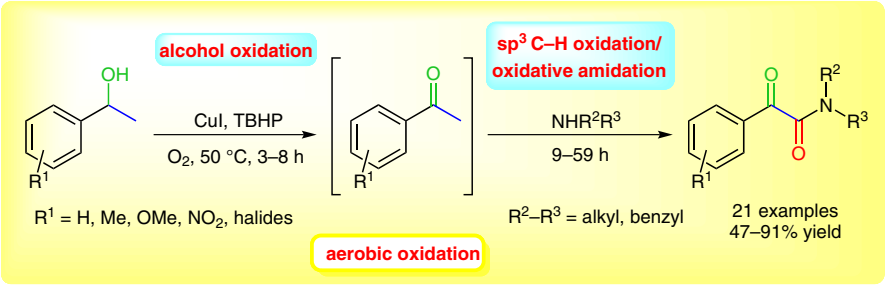

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Abstract A copper-catalyzed one-pot strategy for the synthesis of α-ketoamides from 1-arylethanols is described. This triple oxidation of 1-arylethanols involves alcohol oxidation, sp^3 C–H oxidation, and oxidative amidation with amines. The protocol is highly efficient, delivering α-ketoamides in good to excellent yields.

Key words copper catalyst, one-pot synthesis, oxidative amidation, α-ketoamides, 1-arylethanols

α-Ketoamides are important structural motifs found in various biologically active compounds[1,2] and in key precursors for the synthesis of a wide range of organic molecules (Figure 1).[3]

Traditionally, these compounds were prepared by reacting α-keto acids or α-keto acyl halides with amines.[4] Later, α-ketoamides were synthesized by metal-catalyzed oxidation of alkynes[5] or ynamides,[6] oxidative double carbonylation reactions,[7] oxidative coupling of isocyanides and aldehydes,[8] amidation of α-oxocarboxylic acids,[9] aerobic oxidation of arylacetamides[10] and metal-catalyzed or metal-free cross-dehydrogenative coupling of α-ketoaldehydes with amines.[11] In addition, α-ketoamides have been prepared from acetophenones and amines using oxidative coupling processes,[12] including an iodine/*tert*-butyl hydroperoxide (I_2/TBHP) mediated synthetic procedure.[13] Although a great deal of research has been conducted in this field, an efficient methodology to synthesize α-ketoamides from alcohols and free amines has yet to be developed.

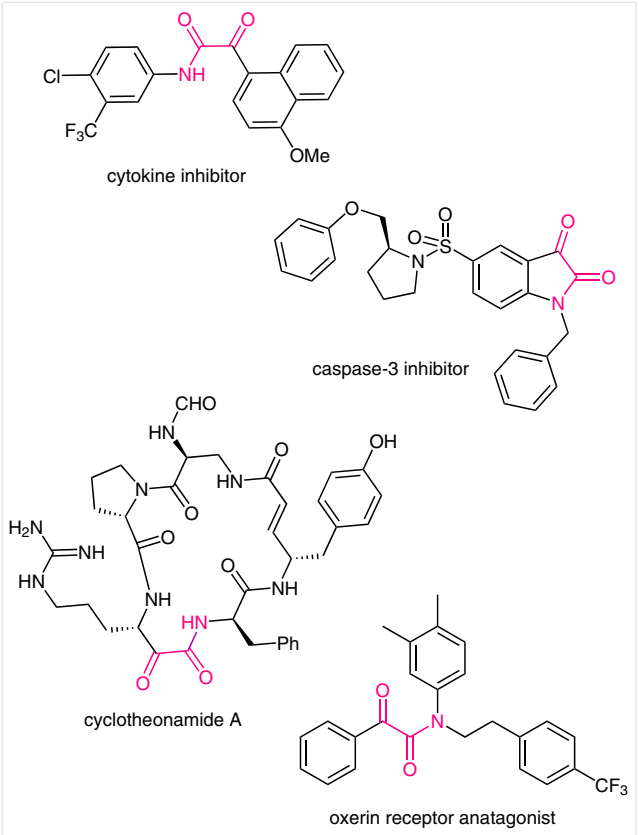
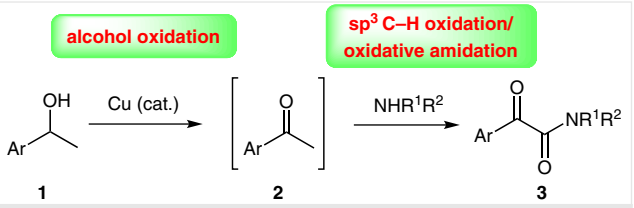


Figure 1 Representative examples of biologically active compounds containing an α-ketoamide structural motif

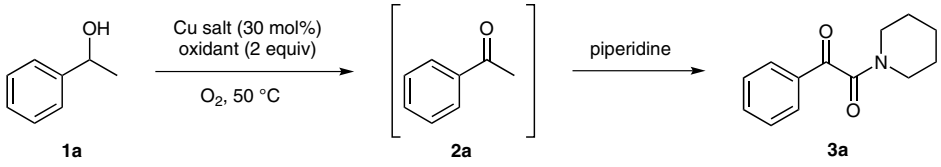
As part of our ongoing research on copper-catalyzed organic reactions,[14] herein, we report for the first time, the copper-catalyzed one-pot synthesis of α-ketoamides from 1-arylethanols and free amines under an oxygen atmosphere (Scheme 1).



Scheme 1 Copper-catalyzed one-pot synthesis of α-ketoamides

We commenced our investigations using 1-phenylethanol (**1a**) as a model substrate and the one-pot reaction was carried out using copper(I) iodide (CuI) (30 mol%) in acetonitrile under an oxygen atmosphere at 50 °C. After 12 hours, only a trace amount of 1-phenylethanol (**1a**) had been converted into the corresponding ketone **2a**. Next, piperidine was added to the reaction mixture and after eight hours, a trace amount of the desired α-ketoamide **3a** had formed. When the same reaction was carried out in the presence of *tert*-butyl hydroperoxide (5–6 M in decane) instead of oxygen, the reaction returned about 60% of ketone **2a**, however, the formation of **3a** was not observed. To our surprise, the same reaction yielded 56% of product **3a** when carried out with two equivalents of *tert*-butyl hydroperoxide under an oxygen atmosphere (Table 1, entry 1). It is important to note that the formation of **3a** was not observed in the absence of the copper salt.

Table 1 Screening of the Reaction Parameters for the One-Pot Synthesis of α-Ketoamides[a]



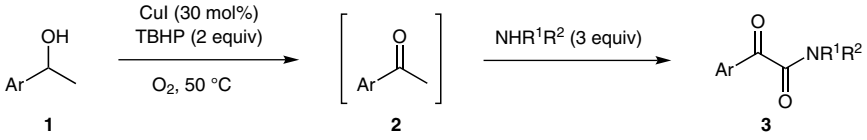
Entry	Cu salt	Oxidant	Solvent	Time (h)	Yield (%)[b]
1	CuI	TBHP	MeCN	12 (4 + 8)	56
2	CuBr	TBHP	MeCN	22 (9 + 13)	40
3	Cu_2O	TBHP	MeCN	28 (9 + 19)	–[c]
4	$CuCl_2$	TBHP	MeCN	28 (8 + 20)	–[c]
5	$Cu(OAc)_2·H_2O$	TBHP	MeCN	28 (8 + 20)	–[c]
6	CuI	TBHP	1,4-dioxane	20 (6 + 14)	38
7	CuI	TBHP	xylene	22 (6 + 16)	50
8	CuI	TBHP	toluene	30 (9 + 21)	62
9	CuI	TBHP	DMF	27 (8 + 19)	38
10	CuI	TBHP	hexanes	21 (6 + 15)	74
11	**CuI**	**TBHP**	**neat**	**20 (4 + 16)**	**90**
12	CuI	30% aq H_2O_2	neat	24 (9 + 15)	30
13	CuI	TEMPO	neat	18 (5 + 13)	33
14	CuI	DCP	neat	24 (10 + 14)	–[c]
15	CuI	DTBP	neat	25 (7 + 18)	–[c]
16	CuI	70% aq TBHP	neat	18 (6 + 12)	78
17	CuI	TBHP	neat	35 (12 + 23)	65[d]
18	CuI	TBHP	neat	28 (3 + 25)	75[e]

[a] Reaction conditions: **1a** (1 mmol), piperidine (3 mmol).
[b] Yield of isolated product.
[c] No reaction.
[d] With 1 equiv of TBHP.
[e] With 3 equiv of TBHP.

To increase the efficiency of this one-pot reaction, different copper salts were screened (Table 1, entries 1–5). The use of copper(I) iodide led to good yields for the alcohol oxidation and sp^3 C–H oxidation/oxidative amidation. Other copper salts such as copper(I) oxide (Cu_2O), copper(II) chloride ($CuCl_2$) and copper(II) acetate monohydrate [$Cu(OAc)_2{\cdot}H_2O$] were inefficient in this reaction. Although they provided considerable amounts of the ketone, the desired product **3a** was not formed. To understand the role of counterions (iodide or bromide), we used sodium iodide (NaI) (30 mol%) with copper(I) oxide, copper(II) chloride and copper(II) acetate monohydrate under the same reaction conditions and 40%, 50% and 49% yields of **3a** were isolated, respectively. These results show that the copper counterion (iodide or bromide) plays a major role in catalyzing the reaction. Next, the reaction was screened with different solvents such as 1,4-dioxane, toluene, hexanes, etc. (Table 1, entries 6–10). Hexanes proved to be the best solvent affording a 74% yield of **3a**. When the same reaction was carried out without a solvent, the yield increased considerably to 90% (Table 1, entry 11). The use of other oxidants such as 30% aqueous hydrogen peroxide (H_2O_2), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), dicumyl peroxide (DCP) and di-*tert*-butyl peroxide (DTBP) gave inferior results (Table 1, entries 12–15). Employing 70% aqueous *tert*-butyl hydroperoxide afforded a 78% yield of **3a** (Table 1, entry 16), whilst decreasing or increasing the quantity of *tert*-butyl hydroperoxide (1 or 3 equiv) led to reduced yields of the product (Table 1, entries 17 and 18).

Next, the scope of the reaction under the optimized conditions (Table 1, entry 11) was investigated using different substituted alcohols and amines, and the results are summarized in Table 2. It was found that alcohols with electron-withdrawing or electron-releasing groups on the phenyl ring were well tolerated. Substrates with strong electron-withdrawing groups such as nitro gave better results than those possessing electron-donating groups (**3b** vs **3f**). The reaction also worked well when different secondary amines were employed.[15]

Table 2 Copper-Catalyzed One-Pot Synthesis of α-Ketoamides[a,b]



1 2 3

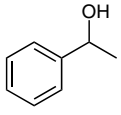
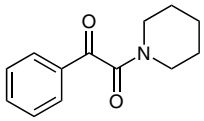
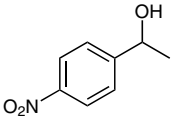
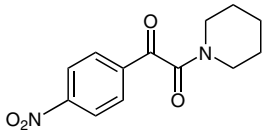
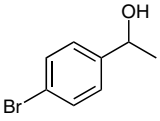
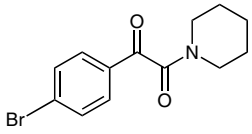
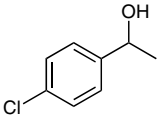
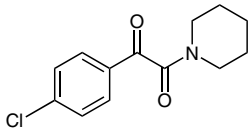
Entry	1-Arylethanol	Amine	Product	Time (h)	Yield (%)[c]
1			**3a** 	20 (4 + 16)	90
2			**3b** 	15 (4 + 11)	91
3			**3c** 	26 (6 + 20)	72
4			**3d** 	26 (6 + 20)	83

Table 2 (continued)

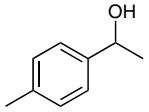
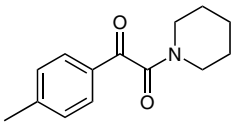
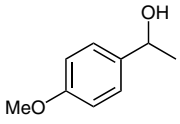
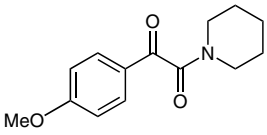
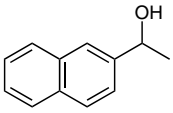
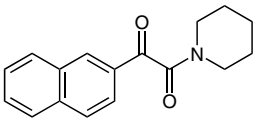
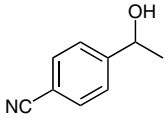
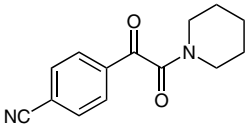
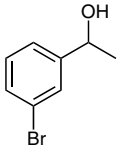
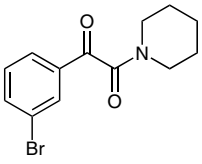
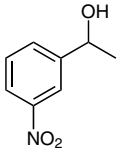
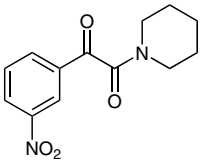
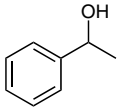
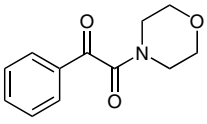
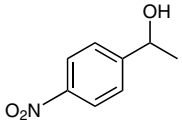
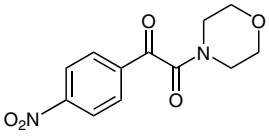
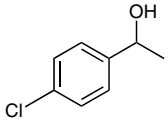
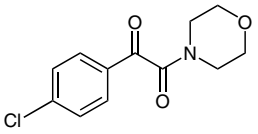
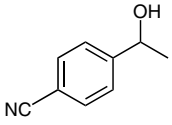
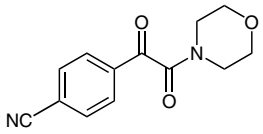
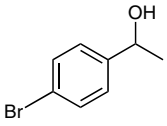
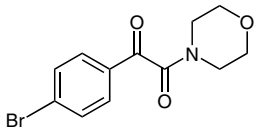
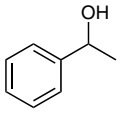
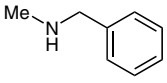
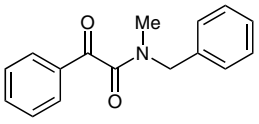
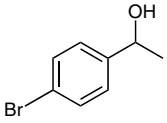
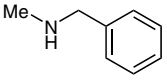
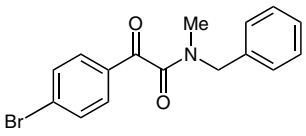
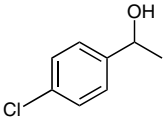
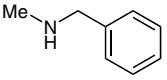
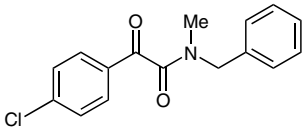
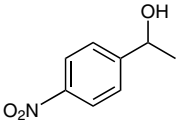
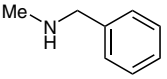
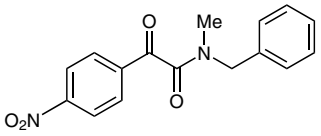
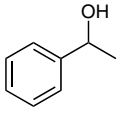
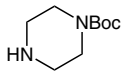
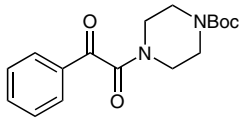
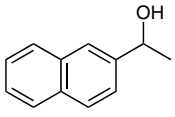
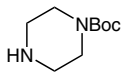
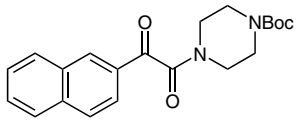
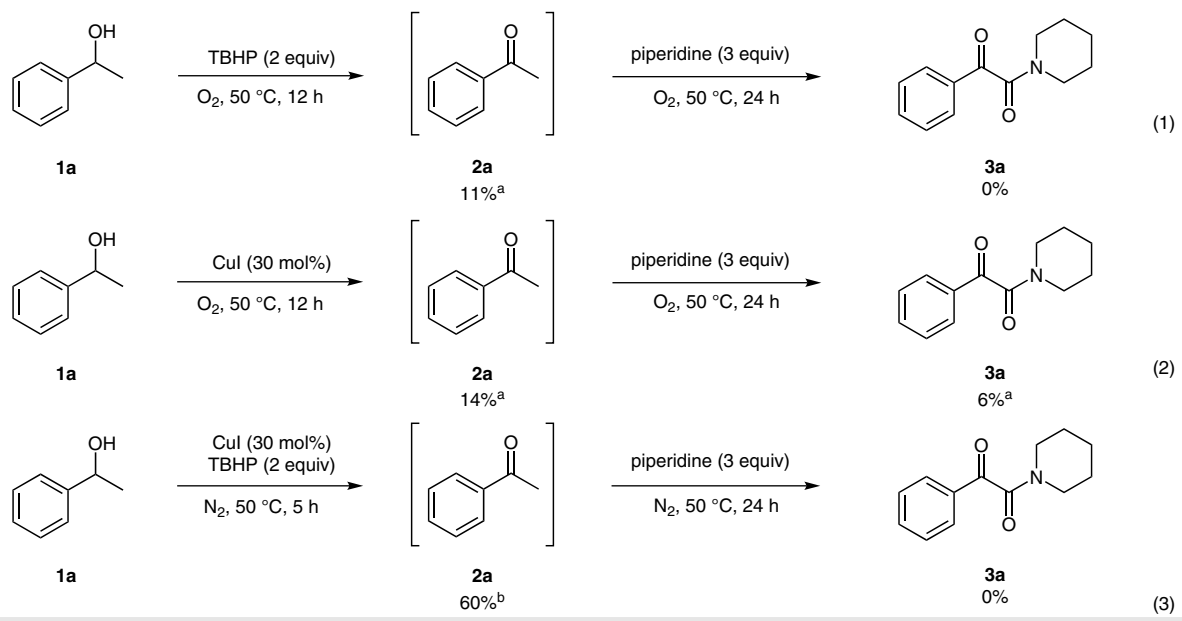
Entry	1-Arylethanol	Amine	Product	Time (h)	Yield (%)[c]
5			**3e** 	37 (8 + 29)	50
6			**3f** 	19 (4 + 15)	52[d]
7			**3g** 	20 (5 + 15)	65
8			**3h** 	31 (3 + 28)	47
9			**3i** 	21 (6 + 15)	80
10			**3j** 	14 (4 + 10)	70
11			**3k** 	24 (4 + 20)	65
12			**3l** 	16 (4 + 12)	65
13			**3m** 	25 (6 + 19)	62

Table 2 (continued)

Entry	1-Arylethanol	Amine	Product	Time (h)	Yield (%)[c]
14			**3n** 	30 (3 + 27)	55
15			**3o** 	21 (6 + 15)	62
16			**3p** 	37 (4 + 33)	80
17			**3q** 	40 (6 + 34)	65
18			**3r** 	37 (6 + 31)	70
19			**3s** 	22 (5 + 17)	61
20			**3t** 	58 (4 + 54)	56
21			**3u** 	64 (5 + 59)	55

[a] Reaction conditions: 1-arylethanol **1** (1 mmol).
[b] The corresponding amide was isolated as a side product in all the reactions, ranging from a trace amount up to 5%.
[c] Yield of isolated product.
[d] The corresponding amide (16%) was isolated.

To understand the mechanism of this one-pot reaction, several control experiments were carried out and the results are shown in Scheme 2. The one-pot reaction did not yield α-ketoamide **3a** when a copper salt was not used, but an 11% yield of the corresponding ketone **2a** was obtained (Scheme 2, eq 1). This transformation could have taken place via *tert*-butyl hydroperoxide mediated homolytic cleavage (to some extent) under heating (50 °C). This was confirmed by carrying out the same reaction at room temperature during which ketone **2a** was not detected. When the same reaction was carried out without *tert*-butyl hydroperoxide, only a 14% yield of **2a** was obtained (Scheme



Scheme 2 Control experiments. [a] ^{1}H NMR yield. [b] Isolated yield.

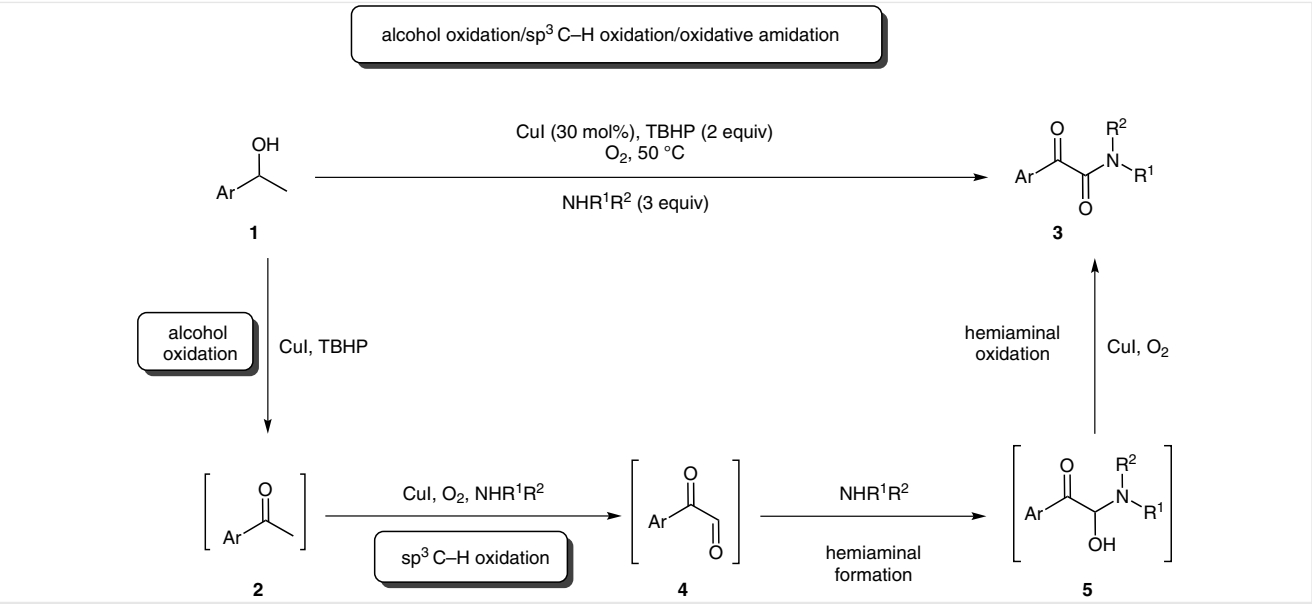
2, eq 2), and the same reaction with *tert*-butyl hydroperoxide yielded 60% of **2a**. These results indicate that the copper/*tert*-butyl hydroperoxide combination is responsible for oxidation of the alcohol. When the reaction was carried out under a nitrogen atmosphere (without O_2), product **3a** was not formed, however ketone **2a** (60%) was isolated (Scheme 2, eq 3). This confirms that the copper/oxygen system is responsible for the sp^3 C–H oxidation and oxidative amidation steps. Moreover, no product was formed when primary or tertiary amines were used, which indicated that the reaction might proceed via a pathway involving enamine intermediate **6** (see Scheme 4). This intermediate is obtained through reaction of the ketone formed after oxidation of the alcohol, with secondary amines. The results clearly show that copper is the main oxidant for the alcohol oxidation, sp^3 C–H oxidation and hemiaminal oxidation. Moreover, copper acting as a Lewis acid should favor the hemiaminal formation.

Based on the preliminary results obtained from the control experiments, a possible mechanism is shown for this one-pot reaction (Scheme 3). Initially, copper(I) is oxidized by *tert*-butyl hydroperoxide or oxygen to give copper(II). This copper(II) species will be reduced to copper(I) during the oxidation reactions, and the copper/*tert*-butyl hydroperoxide (Cu/TBHP) system should oxidize the alcohol to give arylmethyl ketone **2**. The ketone **2** then undergoes copper-catalyzed oxidation in the presence of oxygen to afford α-oxoaldehyde **4**. This α-oxoaldehyde **4** is converted into hemiaminal **5** in the presence of the amine, facilitated by the Lewis acid nature of copper. Finally, hemiaminal oxidation by copper/oxygen gives the α-ketoamide **3**.

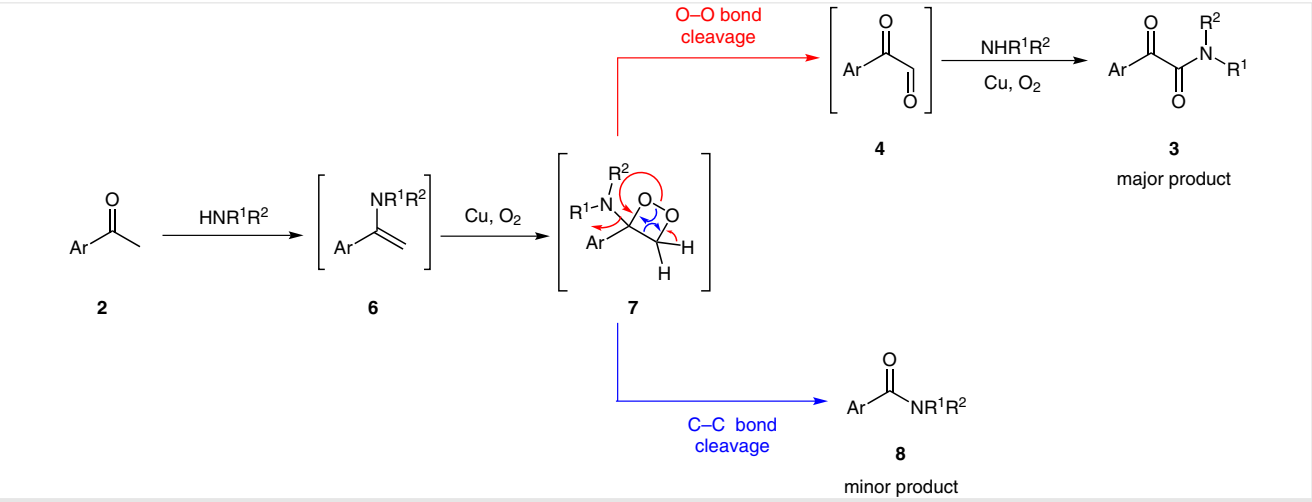
In all the reactions, trace quantities of the corresponding amides were observed (up to 5%); in the case of 1-(4-methoxyphenyl)ethanol (**1f**), the side product amide, (4-methoxyphenyl)(piperidin-1-yl)methanone, was isolated in 16% yield. This shows that the oxidative amidation step may proceed via an aminodioxetane intermediate **7** (Scheme 4).[12a] Cleavage of the O–O bond in **7** should give the α-oxoaldehyde **4** as the major product, whereas C–C bond cleavage should give amide **8** as the minor product. Since O–O bond cleavage should be easier than C–C bond cleavage, α-ketoamides are formed as the major products.

In conclusion, a novel, efficient and cost-effective copper-catalyzed one-pot synthesis of α-ketoamides has been developed using 1-arylethanols as precursors. This one-pot method yielded various α-ketoamides in good to excellent yields. Preliminary results show that the copper/*tert*-butyl hydroperoxide system is responsible for the oxidation of the alcohol and that the copper/oxygen system is responsible for oxidative amidation.

All reactions were carried out in reaction tubes under an oxygen atmosphere. Solvents were obtained from Merck, India. CuI was obtained from Alfa-Aesar. The 1-arylethanols were purchased from Alfa-Aesar and Sigma-Aldrich. 1-Phenylethanol, piperidine, morpholine, *N*-Boc-piperazine and 70% aq TBHP were obtained from Spectrochem Pvt. Ltd., Mumbai, India. *N*-Methylbenzylamine was purchased from Avra and TBHP (5–6 M in decane) was obtained from Sigma-Aldrich. Reactions were carried out using temperature-controlled IKA magnetic stirrers. Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized by UV fluorescence following elution using appropri-



Scheme 3 A plausible mechanism for the one-pot synthesis of α-ketoamides from 1-arylethanols



Scheme 4 A plausible pathway for the synthesis of α-ketoamides and amides

ate mixtures of ethyl acetate and hexanes. Silica gel (particle size: 100–200 mesh) was purchased from SRL India and Avra and was used for column chromatography with mixtures of hexanes and EtOAc as eluents. Melting points were obtained using a Toshniwal melting point apparatus. FTIR spectra were recorded on a Nicolet 6700 spectrophotometer and are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on Bruker 400 or 500 MHz spectrometers. ^1H NMR spectra are reported relative to Me_4Si (δ 0.0) or residual $CDCl_3$ (δ 7.26). ^{13}C NMR are reported relative to $CDCl_3$ (δ 77.16). High-resolution mass spectra (HRMS) were recorded on a Q-Tof Micromass spectrometer.

α-Ketoamides; Typical Procedure

The 1-arylethanol (1 mmol) was added to a mixture of CuI (30 mol%) and TBHP (5–6 M in decane, 2 equiv) in a reaction tube at r.t. under an O_2 atm (O_2 balloon). The resulting mixture was stirred at 50 °C for 3–8 h (TLC monitoring). After complete disappearance of the 1-arylethanol, the amine (3 equiv) was added at r.t. and the mixture was stirred at 50 °C until completion of the reaction. The mixture was allowed to cool to r.t. and then filtered through Celite. The filter cake was rinsed with CH_2Cl_2 and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes–EtOAc) to afford pure α-ketoamide **3**.

1-Phenyl-2-(piperidin-1-yl)ethane-1,2-dione (3a)[12e]

Yield: 195.6 mg (90%); light yellow solid; mp 90–92 °C; R_f = 0.32 (20% EtOAc in hexanes).

IR (KBr): 3064, 2857, 1675, 1638, 1536, 1446, 720 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.6 Hz, 2 H), 7.64 (t, *J* = 7.2 Hz, 1 H), 7.51 (t, *J* = 7.2 Hz, 2 H), 3.71 (br s, 2 H), 3.37–3.32 (m, 2 H), 1.70 (br s, 4 H), 1.55 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.1, 165.6, 134.8, 133.5, 129.7, 129.1, 47.2, 42.3, 26.4, 25.6, 24.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{15}NO_2Na$: 240.1002; found: 240.1005.

1-(4-Nitrophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3b)[10c]

Yield: 239 mg (91%); light yellow solid; mp 95–97 °C (Lit.[12h] 94–96; R_f = 0.33 (30% EtOAc in hexanes).

IR (KBr): 3103, 2867, 1686, 1637, 1536, 1468, 1346, 1281, 844 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.8 Hz, 2 H), 8.13 (d, *J* = 8.8 Hz, 2 H), 3.75–3.68 (m, 2 H), 3.31 (t, *J* = 5.2 Hz, 2 H), 1.76–1.68 (m, 4 H), 1.62–1.54 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.6, 164.3, 151.2, 137.9, 130.8, 124.3, 47.3, 42.7, 26.5, 25.6, 24.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}N_2O_4Na$: 285.0851; found: 285.0859.

1-(4-Bromophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3c)[13]

Yield: 213.3 mg (72%); yellow oil; R_f = 0.53 (30% EtOAc in hexanes).

IR (neat): 3021, 2853, 1680, 1644, 1581, 872, 743 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.4 Hz, 2 H), 7.65 (d, *J* = 8.0 Hz, 2 H), 3.72–3.65 (m, 2 H), 3.28 (t, *J* = 5.6 Hz, 2 H), 1.73–1.65 (m, 4 H), 1.58–1.51 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.9, 165.0, 132.5, 132.3, 131.1, 130.2, 47.2, 42.4, 26.4, 25.6.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}NO_2BrNa$: 318.0106; found: 318.0111.

1-(4-Chlorophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3d)[12h]

Yield: 209 mg (83%); yellow liquid; R_f = 0.53 (30% EtOAc in hexanes).

IR (neat): 3021, 2846, 1680, 1638, 1581, 851 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.0 Hz, 2 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 3.70 (br s, 2 H), 3.28 (br s, 2 H), 1.70 (br s, 4 H), 1.55 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7, 165.1, 141.4, 131.9, 131.1, 129.5, 47.2, 42.4, 26.4, 25.6, 24.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}NO_2ClNa$: 274.0611; found: 274.0605.

1-(Piperidin-1-yl)-2-(*p*-tolyl)ethane-1,2-dione (3e)[12b]

Yield: 115.6 mg (50%); light yellow liquid; R_f = 0.33 (20% EtOAc in hexanes).

IR (neat): 3039, 2862, 1669, 1640, 1453, 850 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 3.72–3.66 (m, 2 H), 3.27 (t, *J* = 5.6 Hz, 2 H), 2.42 (s, 3 H), 1.71–1.64 (m, 4 H), 1.57–1.48 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.8, 165.8, 146.0, 131.0, 129.8, 129.7, 47.1, 42.2, 26.3, 25.6, 24.5, 22.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO_2$: 232.1338; found: 232.1329.

1-(4-Methoxyphenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3f)[12b]

Yield: 128.6 mg (52%); yellow liquid; R_f = 0.21 (10% EtOAc in hexanes).

IR (neat): 3053, 2860, 1671, 1641, 1500, 1266, 1129, 862 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 7.2 Hz, 2 H), 6.96 (d, *J* = 7.2 Hz, 2 H), 3.87 (s, 3 H), 3.70–3.62 (m, 2 H), 3.27 (t, *J* = 4.4 Hz, 2 H), 1.70–1.63 (m, 4 H), 1.55–1.48 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.8, 165.9, 164.9, 132.1, 126.5, 114.4, 55.7, 47.2, 42.2, 26.3, 25.6, 24.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{18}NO_3$: 248.1287; found: 248.1283.

1-(Naphthalen-2-yl)-2-(piperidin-1-yl)ethane-1,2-dione (3g)[12h]

Yield: 174 mg (65%); yellow-brown solid; mp 72–74 °C; R_f = 0.33 (20% EtOAc in hexanes).

IR (KBr): 3058, 2858, 1668, 1633, 1446, 1352 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.44 (s, 1 H), 8.05–8.00 (m, 1 H), 7.99–7.92 (m, 2 H), 7.89 (d, *J* = 8.4 Hz, 1 H), 7.64 (t, *J* = 7.2 Hz, 1 H), 7.57 (t, *J* = 7.2 Hz, 1 H), 3.77 (t, *J* = 5.6 Hz, 2 H), 3.33 (t, *J* = 5.2 Hz, 2 H), 1.77–1.68 (m, 4 H), 1.60–1.51 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.2, 165.7, 136.5, 132.9, 132.6, 130.8, 130.0, 129.5, 129.2, 128.1, 127.2, 123.8, 47.3, 42.4, 26.4, 25.7, 24.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}NO_2$: 268.1338; found: 268.1326.

4-[2-Oxo-2-(piperidin-1yl)acetyl]benzonitrile (3h)[12a]

Yield: 114 mg (47%); yellow-brown solid; mp 70–72 °C; R_f = 0.45 (40% EtOAc in hexanes).

IR (KBr): 3095, 2857, 2230, 1686, 1641, 1448, 848 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.4 Hz, 2 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 3.70 (t, *J* = 5.2 Hz, 2 H), 3.29 (t, *J* = 5.2 Hz, 2 H), 1.76–1.65 (m, 4 H), 1.60–1.55 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.0, 164.3, 136.5, 132.9, 130.1, 117.8, 47.2, 42.6, 26.4, 25.6, 24.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found: 243.1141.

1-(3-Bromophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3i)[10a]

Yield: 237 mg (80%); yellow liquid; R_f = 0.56 (30% EtOAc in hexanes).

IR (neat): 3059, 2856, 1680, 1643, 1445, 869, 765 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (s, 1 H), 7.86 (d, *J* = 7.6 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 3.73–3.67 (m, 2 H), 3.28 (t, *J* = 5.6 Hz, 2 H), 1.74–1.64 (m, 4 H), 1.59–1.52 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.5, 164.8, 137.6, 135.2, 132.4, 130.7, 128.4, 123.4, 47.2, 42.4, 26.4, 25.6, 24.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}NO_2BrNa$: 318.0106; found: 318.0093.

1-(3-Nitrophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3j)

Yield: 184 mg (70%); yellow liquid; R_f = 0.30 (30% EtOAc in hexanes).

IR (neat): 3109, 2854, 1682, 1634, 1528, 1444, 1346, 771, 715 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.77 (s, 1 H), 8.48 (d, *J* = 8.4 Hz, 1 H), 8.28 (d, *J* = 7.6 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 3.73 (br s, 2 H), 3.33 (t, *J* = 4.4 Hz, 2 H), 1.72 (br s, 4 H), 1.59 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.1, 164.1, 148.8, 135.1, 134.9, 130.4, 128.8, 124.5, 47.3, 42.7, 26.5, 25.6, 24.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}N_2O_4$: 263.1032; found: 263.1029.

1-Morpholino-2-phenylethane-1,2-dione (3k)[12b]

Yield: 142.9 mg (65%); yellow liquid; R_f = 0.26 (30% EtOAc in hexanes).

IR (neat): 3077, 2854, 1671, 1641, 1574, 1107, 719 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.6 Hz, 2 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 3.79 (br s, 4 H), 3.65 (t, *J* = 4.8 Hz, 2 H), 3.38 (t, *J* = 4.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 165.6, 135.1, 133.3, 129.8, 129.2, 66.9, 66.8, 46.4, 41.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}NO_3$: 220.0973; found: 220.0975.

1-Morpholino-2-(4-nitrophenyl)ethane-1,2-dione (3l)[12g]

Yield: 172.8 mg (65%); creamy-white solid; mp 138–140 °C; R_f = 0.43 (40% EtOAc in hexanes).

IR (KBr): 3073, 2862, 1683, 1639, 1525, 1454, 1347, 1113, 833 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 8.8 Hz, 2 H), 8.16 (d, *J* = 8.8 Hz, 2 H), 3.81 (br s, 4 H), 3.70 (t, *J* = 5.2 Hz, 2 H), 3.43 (t, *J* = 5.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.8, 164.2, 151.3, 137.6, 131.0, 124.3, 66.9, 66.8, 46.5, 42.1.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{12}N_2O_5Na$: 287.0644; found: 287.0641.

1-(4-Chlorophenyl)-2-morpholinoethane-1,2-dione (3m)[9b]

Yield: 157.3 mg (62%); light brown solid; mp 111–113 °C; R_f = 0.34 (30% EtOAc in hexanes).

IR (KBr): 3011, 2850, 1675, 1630, 1111, 848 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.4 Hz, 2 H), 7.50 (d, *J* = 8.4 Hz, 2 H), 3.79 (br s, 4 H), 3.66 (t, *J* = 4.8 Hz, 2 H), 3.38 (t, *J* = 4.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.8, 165.1, 141.8, 131.6, 131.2, 129.6, 66.9, 66.8, 46.4, 41.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}NO_3Cl$: 254.0584; found: 254.0572.

4-(2-Morpholino-2-oxoacetyl)benzonitrile (3n)[13]

Yield: 134.5 mg (55%); light brown solid; mp 111–113 °C; R_f = 0.37 (40% EtOAc in hexanes).

IR (KBr): 3099, 2854, 2230, 1686, 1641, 1497, 1135, 1024, 848 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.0 Hz, 2 H), 7.82 (d, *J* = 8.4 Hz, 2 H), 3.80 (br s, 4 H), 3.72–3.63 (m, 2 H), 3.41 (t, *J* = 4.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.1, 164.2, 136.2, 133.0, 130.2, 118.1, 117.7, 66.9, 66.8, 46.5, 42.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}N_2O_3$: 245.0926; found: 245.0919.

1-(4-Bromophenyl)-2-morpholinoethane-1,2-dione (3o)[13]

Yield: 184.8 mg (62%); white solid; mp 122–124 °C; R_f = 0.34 (30% EtOAc in hexanes).

IR (KBr): 3446, 3071, 2948, 2839, 1669, 1630, 1570, 1107, 841, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 8.4 Hz, 2 H), 7.67 (d, *J* = 8.8 Hz, 2 H), 3.79 (br s, 4 H), 3.66 (t, *J* = 4.8 Hz, 2 H), 3.38 (t, *J* = 4.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.0, 165.0, 132.7, 132.1, 131.2, 130.7, 66.9, 66.8, 46.5, 41.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}NO_3Br$: 299.0048; found: 299.0043.

***N*-Benzyl-*N*-methyl-2-oxo-2-phenylacetamide (3p)**[12a]

Yield: 202.6 mg (80%); light yellow liquid; R_f = 0.28 (15% EtOAc in hexanes).

IR (neat): 3058, 2986, 2934, 1683, 1645, 1494, 1448, 731 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (47.6:52.4 mixture of *cis*/*trans* isomers) = 7.99–7.92 (m, 4 H), 7.65–7.59 (m, 2 H), 7.52–7.46 (m, 4 H), 7.40–7.27 (m, 8 H), 7.25–7.20 (m, 2 H), 4.71 (s, 2 H), 4.37 (s, 2 H), 2.97 (s, 3 H), 2.82 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.7, 167.5, 167.3, 135.9, 135.0, 134.9, 133.3, 133.2, 129.9, 129.8, 129.2, 129.1, 129.0, 128.9, 128.5, 128.47, 128.35, 128.1, 128.0, 53.7, 50.0, 34.6, 31.5.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}NO_2$: 254.1181; found: 254.1179.

***N*-Benzyl-2-(4-bromophenyl)-*N*-methyl-2-oxoacetamide (3q)**

Yield: 216 mg (65%); yellow liquid; R_f = 0.63 (20% EtOAc in hexanes).

IR (neat): 3099, 3056, 2962, 2920, 2854, 1679, 1644, 1489, 848, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (47:53 mixture of *cis*/*trans* isomers) = 7.88–7.79 (m, 4 H), 7.69–7.63 (m, 4 H), 7.42–7.28 (m, 8 H), 7.25–7.21 (m, 2 H), 4.72 (s, 2 H), 4.39 (s, 2 H), 3.00 (s, 3 H), 2.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.4, 166.9, 166.7, 135.8, 135.0, 132.6, 132.5, 132.2, 132.0, 131.3, 131.2, 130.4, 129.1, 129.0, 128.44, 124.41, 128.1, 127.9, 53.7, 50.1, 34.6, 31.8.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{14}NO_2BrNa$: 354.0106; found: 354.0103.

***N*-Benzyl-2-(4-chlorophenyl)-*N*-methyl-2-oxoacetamide (3r)**[12a]

Yield: 201.4 mg (70%); yellow liquid; R_f = 0.63 (20% EtOAc in hexanes).

IR (neat): 3060, 3036, 2931, 2864, 2807, 1682, 1644, 1489, 848 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (47.8:52.2 mixture of *cis*/*trans* isomers) = 7.93–7.84 (m, 4 H), 7.49–7.42 (m, 4 H), 7.40–7.27 (m, 8 H), 7.24–7.18 (m, 2 H), 4.70 (s, 2 H), 4.37 (s, 2 H), 2.97 (s, 3 H), 2.82 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.2, 167.0, 166.8, 141.5, 135.8, 135.0, 131.8, 131.7, 131.3, 131.2, 129.6, 129.5, 129.1, 129.0, 128.5, 128.4, 128.1, 127.9, 53.7, 50.1, 34.6, 31.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}NO_2Cl$: 288.0791; found: 288.0786.

***N*-Benzyl-*N*-methyl-2-(4-nitrophenyl)-2-oxoacetamide (3s)**[12a]

Yield: 182 mg (61%); yellow liquid; R_f = 0.53 (30% EtOAc in hexanes).

IR (neat): 3144, 3081, 2987, 2920, 2857, 1679, 1637, 1546, 1518, 1377, 831 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ (48.2:51.8 mixture of *cis*/*trans* isomers) = 8.38–8.27 (m, 4 H), 8.20–8.09 (m, 4 H), 7.43–7.27 (m, 8 H), 7.25–7.19 (m, 2 H), 4.74 (s, 2 H), 4.44 (s, 2 H), 3.05 (s, 3 H), 2.88 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.2, 166.2, 165.9, 151.2, 151.1, 137.8, 137.6, 135.5, 134.8, 131.0, 130.9, 129.1, 129.0, 128.5, 128.4, 128.3, 127.8, 124.3, 124.1, 53.7, 50.3, 34.7, 32.2.

HRMS: *m*/*z* [M + K]$^+$ calcd for $C_{16}H_{14}N_2O_4K$: 337.1085; found: 337.1081.

***tert*-Butyl 4-(2-Oxo-2-phenylacetyl)piperazine-1-carboxylate (3t)**

Yield: 178.3 mg (56%); light brown solid; mp 120–122 °C; R_f = 0.24 (20% EtOAc in hexanes).

IR (KBr): 3064, 2976, 2864, 1675, 1647, 1609, 1493, 764 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.93 (m, 2 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 2 H), 3.77–3.71 (m, 2 H), 3.59–3.52 (m, 2 H), 3.46–3.40 (m, 2 H), 3.36–3.00 (m, 2 H), 1.46 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.3, 165.8, 154.5, 135.1, 133.2, 129.8, 129.3, 80.8, 41.4, 28.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{22}N_2O_4Na$: 341.1477; found: 341.1494.

***tert*-Butyl 4-[2-(Naphthalen-2-yl)-2-oxoacetyl]piperazine-1-carboxylate (3u)**

Yield: 202.6 mg (55%); light brown solid; mp 141–143 °C; R_f = 0.45 (30% EtOAc in hexanes).

IR (KBr): 3056, 2854, 1682, 1641, 1595, 1423 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.45 (s, 1 H), 8.05–8.00 (m, 1 H), 7.99–7.93 (m, 2 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.69–7.63 (m, 1 H), 7.62–7.56 (m, 1 H), 3.83–3.78 (m, 2 H), 3.62–3.57 (m, 2 H), 3.47–3.41 (m, 2 H), 3.40–3.14 (m, 2 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.4, 165.9, 154.5, 136.5, 133.2, 132.6, 130.5, 130.1, 129.7, 129.4, 128.1, 127.4, 123.7, 80.8, 46.0, 41.5, 28.5.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{24}N_2O_4Na$: 391.1634; found: 391.1651.

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Supporting Information

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(15) When acyclic amines such as *N*,*N*-diethylamine, *N*,*N*-diallylamine, *N*,*N*-diisopropylamine and *N*,*N*-dibenzylamine were used under the same reaction conditions, all gave inseparable complex mixtures (numerous spots by TLC).