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Copper-Catalyzed Synthesis of Weinreb Amides by Oxidative Amidation of Alcohols

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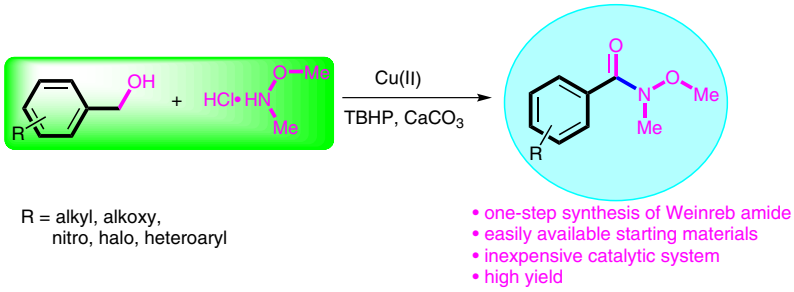

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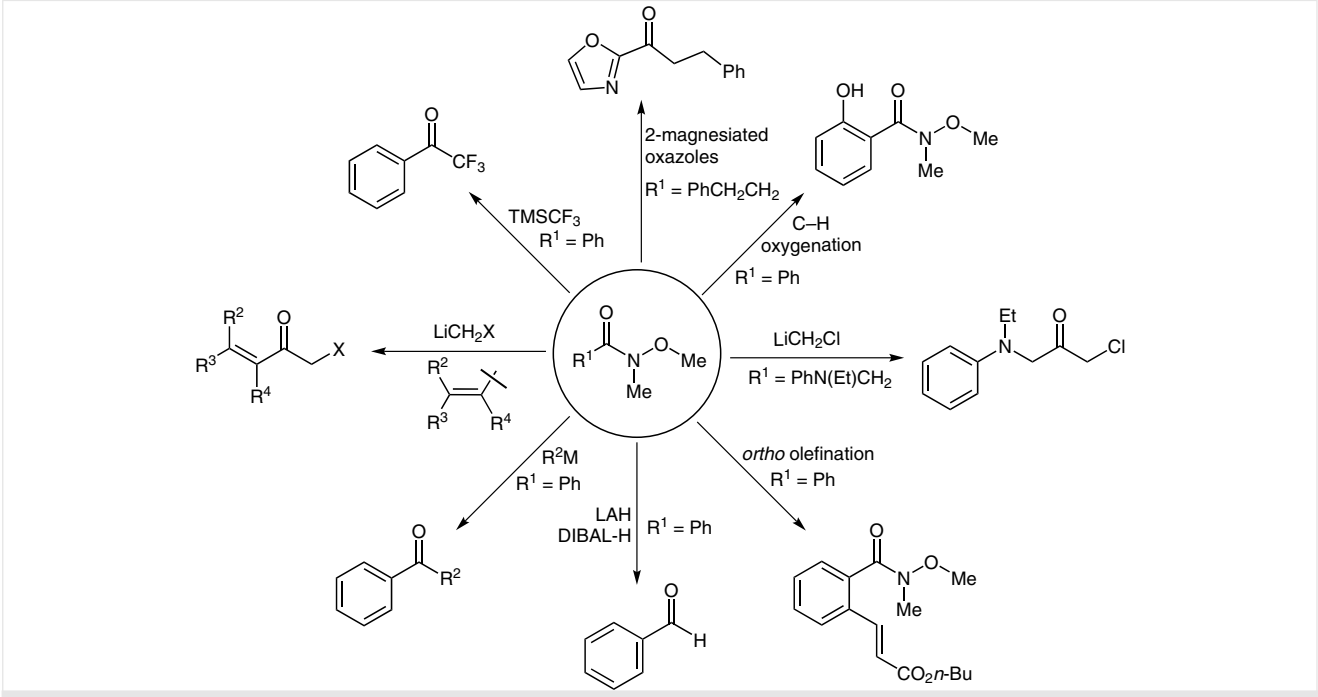
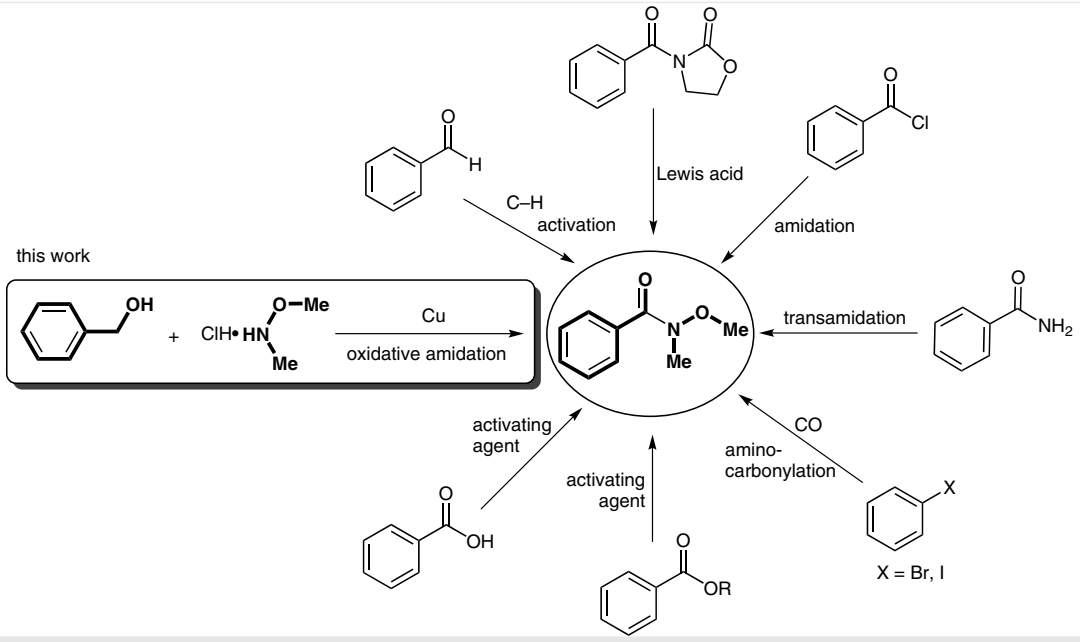
Abstract A simple and efficient protocol has been developed for the oxidative amidation of alcohols to Weinreb amides using *tert*-butyl hydroperoxide as an oxidant and an inexpensive and air stable copper catalyst. The present protocol is advantageous as it uses commercially affordable alcohols as starting materials. The developed protocol also tolerates various substituted alcohols as starting materials to provide good to excellent yields of the desired products.

Key words alcohol, amide, copper, oxidation, cross-coupling

Weinreb amides are well established acylating agents in organic chemistry.[1] They are important due to their reactivity with organometallic reagents through stable metal-chelated intermediates. In addition, Weinreb amides can also be easily transformed into a variety of compounds containing functional groups like aldehydes or ketones,[2] ynones,[3] 2-acyloxazoles and β-lactams,[4] trifluoromethyl ketones,[5] functionalized α-arylamino-α′-chloro ketones, and α,β-unsaturated α′-halo ketones.[6] Weinreb amides have been widely used in the total synthesis of natural products.[7]



Scheme 1 Applications of Weinreb amides



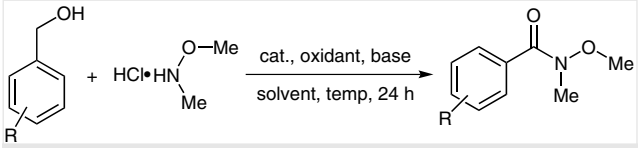
Scheme 2 Oxidative amidation of alcohol to Weinreb amide and previous reports

Ackermann and co-workers have demonstrated the utility of Weinreb amides as a directing group for *ortho*-olefination[8] and *ortho*-oxygenation[9] (Scheme 1).

Several methods with different starting materials such as acids,[10] acid chlorides,[11] aldehydes,[12] amides,[13] esters/lactams[14] or aminocarbonylation of aryl halides[15] have been reported for the synthesis of Weinreb amides (Scheme 2). However, most of these methods suffer from one or more drawbacks such as the necessity of an activator or a coupling reagent,[10] thermally unstable acid chlorides,[11] toxic carbon monoxide gas, the use of air- or moisture-sensitive phosphine ligands, stoichiometric reagents, and expensive metal catalysts.[15] Due to the growing synthetic utility of Weinreb amides,[16] the development of a simple and efficient protocol for their synthesis is highly desirable. Recently, Chen and co-workers have reported the synthesis of Weinreb amides using transition-metal-catalyzed oxidative amidation with benzaldehyde as a starting material.[12] However, a low yield of Weinreb amides and the use of only benzaldehyde as a substrate are the limitations. Thus to develop a widely applicable protocol for the oxidative synthesis of Weinreb amides using an inexpensive and easily available transition-metal catalyst under mild reaction conditions is a worthy goal.

Earlier the same group has reported iron nitrate catalyzed synthesis of simple amides from benzyl alcohols using amine hydrochloride salt.[17] However, it involves two steps. The first step is the preparation of aldehyde from alcohol followed by the conversion of the aldehyde into the amide in the next step. In addition, it also requires TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxyl and air as co-oxidants along with TBHP (*tert*-butyl hydroperoxide) as the primary oxidant for the synthesis of simple amides.

In continuation of our ongoing research on the development of facile and efficient protocols,[18] herein, we have developed a simple and economical protocol for the synthesis of Weinreb amides via oxidative amidation of alcohols with *N*,*O*-dimethylhydroxylamine hydrochloride salt in the presence of Cu/TBHP catalytic system (Scheme 3).



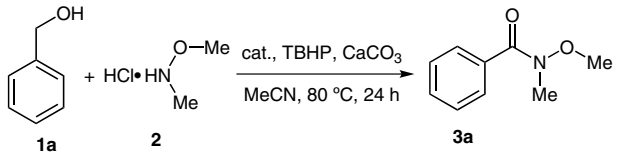
Scheme 3 Oxidative synthesis of Weinreb amides

To optimize the reaction conditions, benzyl alcohol (**1a**) and *N*,*O*-dimethylhydroxylamine hydrochloride salt (**2**) were chosen as model substrates for the oxidative amidation reaction. A series of experiments was carried out to study the effect of various reaction parameters such as catalyst loading, base, solvent, oxidant, temperature, and time, etc. on the yield of the product.

Initially, commercially available copper precursors such as $CuSO_4·5H_2O$, CuO, CuCl, CuBr, CuI, $CuCl_2·H_2O$, $CuNO_3·8H_2O$, Cu_2O, and $Cu(OAc)_2·H_2O$ using 70 wt% aqueous TBHP as oxidant were screened for the oxidative amidation reaction (Table 1, entries 1–9). Among these $Cu(OAc)_2·H_2O$ gave an excellent yield of the desired product **3a** and hence it was selected for further optimization (entry 9). Other copper

catalysts provided the amide product **3a** in a moderate to poor yields (entries 1–8). The reaction was also performed in the absence of the catalyst and it gave only a trace amount of **3a** product (entry 10).

Table 1 Screening of Copper Catalyst for the Amidation Reaction[a]



1a 2 3a

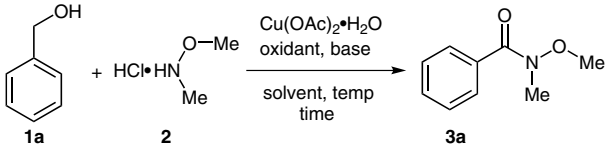
Entry	Catalyst	Base	Oxidant	Yield (%)[b]
1	$CuSO_4·5H_2O$	$CaCO_3$	TBHP	73
2	CuO	$CaCO_3$	TBHP	61
3	CuCl	$CaCO_3$	TBHP	15
4	CuBr	$CaCO_3$	TBHP	18
5	CuI	$CaCO_3$	TBHP	67
6	$CuCl_2·H_2O$	$CaCO_3$	TBHP	trace
7	$CuNO_3·8H_2O$	$CaCO_3$	TBHP	4
8	Cu_2O	$CaCO_3$	TBHP	42
9	$Cu(OAc)_2·H_2O$	$CaCO_3$	TBHP	91
10	–	$CaCO_3$	TBHP	trace

[a] Reaction conditions: **1a** (1 mmol), **2** (1.2 mmol), catalyst (6 mol%), TBHP (70 wt% in H_2O, 1.2 mmol), $CaCO_3$ (1.2 mmol), MeCN (1 mL), 80 °C.
[b] GC yields.

Next, the effect of various inorganic and organic bases was studied (Table 1, entry 9, Table 2, entries 1–4) and it was found that the base plays an important role to increase the yield of **3a**. Among these bases, $CaCO_3$ provided the desired product in 91% yield (Table 1, entry 9). It was observed that the reaction does not proceed in the absence of base (Table 2, entry 5). We further screened various oxidants such as TBHP (5.0–6.0 M in decane), TEMPO, MCPBA, (*t*-BuO)$_2$, and H_2O_2 to increase the reaction yield and it was observed that aqueous TBHP gave an excellent yield of the desired product **3a** (Table 1, entry 9, Table 2, entries 6–9). Other oxidants delivered **3a** in poor yield (Table 2, entries 6–9). The product formation was not observed in the absence of an oxidant (Table 2, entry 10). Furthermore, the effect of various solvents on the reaction outcome was studied (Table 1, entry 9, Table 2, entries 11–13) and it was found that the reaction works efficiently in acetonitrile (Table 1, entry 9). The reaction temperature study showed that a decrease in the reaction temperature decreases yield of the desired product **3a** (Table 2, entry 14). However, there was no significant effect on the reaction outcome by increasing the reaction temperature (Table 2, entry 15). The optimum temperature to obtain good yield of the desired Weinreb amide was observed to be 80 °C (Table 1, entry 9).

It was also noted that decreasing the reaction time decreased the yield of **3a** (Table 2, entry 16). Thus, 24 hours were considered as an optimum reaction time for the completion of reaction (Table 1, entry 9). The effects of catalyst, oxidant, and base loading were also studied. It was found that 6 mol% catalyst, 1.2 mmol oxidant along with 1.2 mmol base furnishes maximum yield of **3a** (Table 1, entry 9). The observations above indicate that all the three components, copper catalyst, base, and oxidant are essential for the Weinreb amide synthesis.

Table 2 Optimization of the Reaction Conditions[a]



1a 2 3a

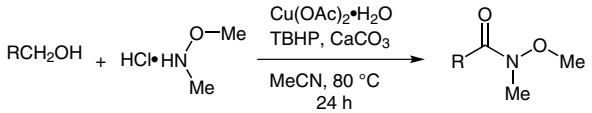
Entry	Base	Oxidant	Solvent	Yield (%)[b]
1	$NaHCO_3$	TBHP	MeCN	63
2	K_2CO_3	TBHP	MeCN	57
3	DBU	TBHP	MeCN	trace
4	DABCO	TBHP	MeCN	trace
5	–	TBHP	MeCN	0
6	$CaCO_3$	TEMPO	MeCN	trace
7	$CaCO_3$	MCPBA	MeCN	5
8	$CaCO_3$	(*t*-BuO)$_2$	MeCN	25
9	$CaCO_3$	H_2O_2	MeCN	0
10	$CaCO_3$	–	MeCN	0
11	$CaCO_3$	TBHP	1,4-dioxane	37
12	$CaCO_3$	TBHP	toluene	63
13	$CaCO_3$	TBHP	*t*-BuOH	57
14	$CaCO_3$	TBHP	MeCN	55[c]
15	$CaCO_3$	TBHP	MeCN	87[d]
16	$CaCO_3$	TBHP	MeCN	65[e]

[a] Reaction conditions: **1a** (1 mmol), **2** (1.2 mmol), $Cu(OAc)_2·H_2O$ (6 mol%), oxidant (1.2 mmol), base (1.2 mmol), solvent (1 mL), 80 °C.
[b] GC yields.
[c] At 60 °C.
[d] At 90 °C.
[e] Time: 18 h.

Thus, the optimized reaction conditions are: **1a** (1 mmol), **2** (1.2 mmol), $Cu(OAc)_2·H_2O$ (6 mol%), TBHP (1.2 mmol), $CaCO_3$ (1.2 mmol), and acetonitrile (1 mL) at 80 °C for 24 hours.

The scope of the developed protocol was further investigated for various alcohols containing different functional groups at *ortho*-, *meta*-, and *para*-positions (Table 3). The reaction of **1a** with **2** furnished 89% yield of **3a** (Table 3, entry 1).

Table 3 Synthesis of Weinreb Amides by Oxidative Amidation of Alcohols[a]



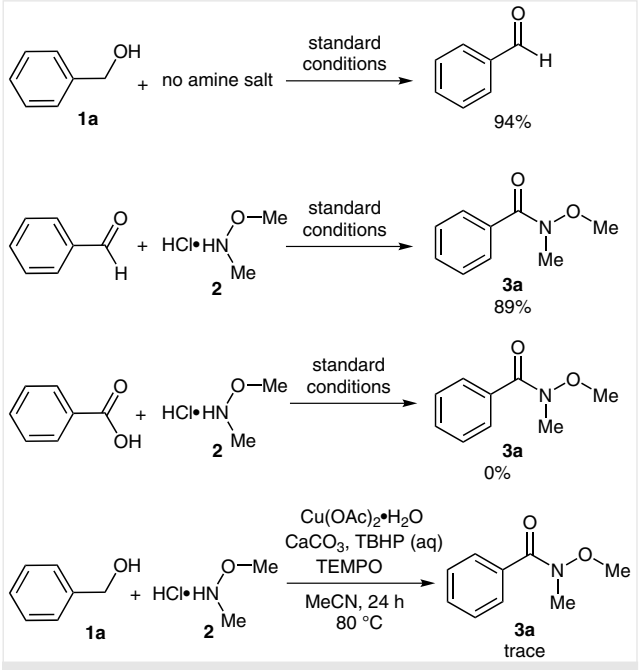
1a–p **2** **3a–p**

Entry	Substrate	R	Product	Yield (%)[b]
1	**1a**	Ph	**3a**	89
2	**1b**	4-MeC_6H_4	**3b**	87
3	**1c**	3-MeC_6H_4	**3c**	85
4	**1d**	4-MeOC_6H_4	**3d**	90
5	**1e**	2-MeOC_6H_4	**3e**	77
6	**1f**	2-naphthyl	**3f**	83
7	**1g**	2-ClC_6H_4	**3g**	84
8	**1h**	3-ClC_6H_4	**3h**	90
9	**1i**	4-ClC_6H_4	**3i**	81
10	**1j**	3-F_3COC_6H_4	**3j**	85
11	**1k**	4-O_2NC_6H_4	**3k**	70[c]
12	**1l**	3,5-$(O_2N)_2C_6H_4$	**3l**	0
13	**1m**	2-thienyl	**3m**	90
14	**1n**	Bn	**3n**	40
15	**1o**	2-MeO$C_6H_4CH_2$	**3o**	42
16	**1p**	Me	**3p**	0

[a] Reaction conditions: **1a** (1 mmol), **2** (1.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (6 mol%), TBHP (1.2 mmol), $CaCO_3$ (1.2 mmol), MeCN (1 mL), 80 °C, 24 h.
[b] Yield of isolated product.
[c] Time: 30 h.

It was observed that benzyl alcohols possessing electron-donating substituents such as methyl and methoxy groups efficiently undergo amidation reaction with *N*,*O*-dimethylhydroxylamine to afford the corresponding Weinreb amides **3b**–**e** in excellent yields (Table 3, entries 2–5). Therefore, it can be concluded that the position of the substituents on the phenyl ring of benzyl alcohol marginally affects the reaction yield. Product **3d** was obtained in higher yields as compared to **3e** because of steric hindrance of methoxy group in **3e** (entries 4 and 5). Naphthalen-2-ylmethanol (**1f**) also reacted efficiently with **2** to provide the desired product **3f** with 83% yield (entry 6). It was observed that the chloro-substituted benzyl alcohol easily undergoes oxidative amidation reaction and results into the corresponding products in good to excellent yields (entries 7–9). In *ortho*-, *meta*-, and *para*-chloro-substituted benzyl alcohol, *meta*-substituted substrates gave higher yields. It was found that [3-trifluoromethoxy)phenyl]methanol (**1j**) also offers good yield of the desired product **3j** (entry 10). 4-Nitrobenzyl alcohol (**1k**) with a strong electron-withdrawing group was also well tolerated and provided the desired product **3k** in good yield (entry 11). However *meta*-dinitro-substituted benzyl alcohol **1l** did not result into the desired Weinreb amide **3l** even on extending the reaction time up to 30 hours (entry 12). The heteroaromatic alcohol furan-3-ylmethanol (**1m**) also easily underwent the oxidative amidation reaction and provided excellent yield of the desired product **3m** (entry 13). In addition, the aliphatic alcohols **1n** and **1o** also showed moderate conversion and gave acceptable yields of the respective products **3n** and **3o** (entries 14 and 15). It was further noted that the reaction of ethanol (**1p**) with **2** failed to provide desired amidation product **3p** (entry 16).

To understand the reaction pathway control experiments were carried out. A literature study[10,12,19] points out that some groups have reported the synthesis of Weinreb amides from benzaldehyde or benzoic acid with *N*,*O*-dimethylhydroxylamine hydrochloride salt. Hence the reaction of benzaldehyde and benzoic acid with *N*,*O*-dimethylhydroxylamine hydrochloride salt was performed separately to confirm the reaction intermediates. However, only benzaldehyde furnished an excellent yield of the desired product **3a** (89%); whereas benzoic acid failed to provide **3a** (Scheme 4). Furthermore, the reaction of **1a** was performed in the absence of amine hydrochloride salt and it was observed that benzaldehyde was formed upto 94% (Scheme 4). However, the reaction of **1a** with **2** in the presence of radical scavenger such as TEMPO gave only trace amount of desired product **3a** (Scheme 4). Thus, the control experiments indicate that the reaction most probably proceeds through a radical pathway.



Scheme 4 Control experiments

Based on the outcome of the control experiments (Scheme 4) and literature survey,[11b,17] a plausible reaction mechanism is proposed, which proceeds through an amino alcohol intermediate as shown in Scheme 5. Initially, benzyl alcohol (**1a**) gets converted into benzyl radical **A** in the presence of TBHP as the oxidant. Subsequently, Cu(II) abstracts the electron from **A** and converts it into the onium ion **B**. After this, *N*,*O*-dimethylhydroxylamine couples with **B** to give the hemiaminal intermediate **C**. Next, the *tert*-butylperoxy radical reacts with **C** and form the amino alcohol radical **D**. The electron of amino alcohol radical is abstracted by Cu(II) to afford the onium ion **E**. The catalytic cycle closes with deprotonation of **E** resulting in the final product **3a**.

In summary, we have developed an efficient protocol for the synthesis of Weinreb amide by oxidative amidation of alcohol with *tert*-butyl hydroperoxide using an inexpensive and easily available copper catalyst. This protocol is applicable to a wide range of alcohols possessing electron-donating and electron-withdrawing groups as well as heteroaromatic alcohol substrates for the synthesis of Weinreb amides and it gave good to excellent yields. Mild reaction conditions, economical starting materials, and an inexpensive catalytic system are additional advantages of the present system.

All reactions were carried out in oven-dried glassware. All derivatives of alcohol, *N*,*O*-dimethylhydroxylamine hydrochloride, aq 70% TBHP, $Cu(OAc)_2$, and MeCN were purchased from Aldrich, Alfa Aesar, Spectrochem, and Thomas Baker. Analytical TLC was performed with 60 F254 silica gel plates (0.25 mm thickness). Column chromatography was performed with silica gel (100–200 mesh). NMR spectra were recorded on Bruker (^{1}H NMR at 300 MHz, ^{13}C NMR at 75 MHz) and Agilent Technologies (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz) spectrometers. The chemical shifts are reported in ppm relative to TMS as an internal standard and the coupling constant in Hz. GC yields were obtained with a PerkinElmer Clarus 400 instrument with an ELITE-1 column. Mass spectrometry was performed with a Shimadzu instrument in electrospray ionization (ESI) mode.

Oxidative Synthesis of Weinreb Amides 3 from Benzyl Alcohols 1 and *N*,*O*-Dimethylhydroxylamine Hydrochloride Salt (2); General Procedure

An oven-dried 15 mL glass vial with a magnetic stirrer bar was charged with $Cu(OAc)_2{\cdot}H_2O$ (12 mg, 6 mol%), *N*,*O*-dimethylhydroxylamine hydrochloride (**2**; 117 mg, 1.2 mmol), the respective benzyl alcohol **1** (1 mmol), aq 70% TBHP (0.17 mL, 1.2 mmol), $CaCO_3$ (120 mg, 1.2 mmol) in MeCN (1 mL). The glass vial was flushed with N_2 three times and the contents were stirred at r.t. for 1 h. Then the reaction mixture was stirred for 24 h at 80 °C. After completion of the reaction, the mixture was cooled to r.t. All volatiles were removed under vacuum. The product was extracted with EtOAc (20 mL) and the organic layer was washed with sat. aq $NaHCO_3$ (20 mL), dried (Na_2SO_4), and the solvent removed under vacuum. The Weinreb amide product **3** was purified by column chromatography (silica gel, 100–200 mesh) using a gradient of petroleum ether (bp 60–80 °C) and EtOAc. All the amides were identified by GC-MS, ^{1}H, and ^{13}C NMR spectroscopic analysis.

***N*-Methoxy-*N*-methylbenzamide (3a)**[20a]

[CAS Reg. No. 6919-61-5]

Yield: 146 mg (89%); colorless oil.

IR (film): 2922, 1638, 1236, 1090 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67–7.65 (d, *J* = 10 Hz, 2 H), 7.45–7.38 (m, 3 H), 3.55 (s, 3 H), 3.35 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 134.0, 130.5, 128.1, 127.9, 61.0, 33.7.

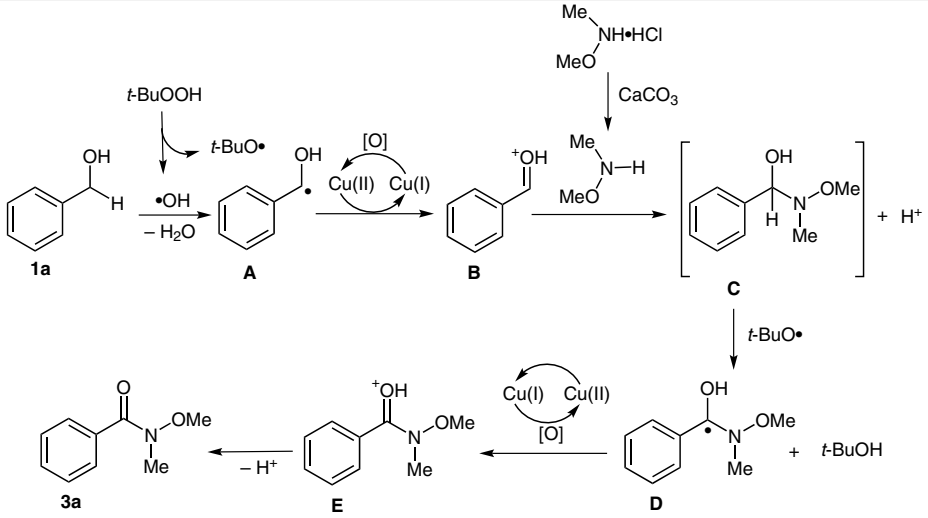
GC-MS: *m*/*z* (%) = 165 (3, [M$^+$]), 105 (100), 91 (0.5), 77 (59), 51 (20), 40 (3).

***N*-Methoxy-*N*,4-dimethylbenzamide (3b)**[10e]

[CAS Reg. No. 122334-36-5]

Yield: 155 mg (87%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.58 (m, 2 H), 7.20–7.19 (m, 2 H), 3.55 (s, 3 H), 3.34 (s, 3 H).



Scheme 5 Plausible reaction mechanism for the oxidative amidation of benzyl alcohol to Weinreb amide

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 140.8, 131.1, 128.6, 128.3, 60.9, 33.8, 21.4.

_N_-Methoxy-_N_,3-dimethylbenzamide (3c)[20b]

[CAS Reg. No. 135754-82-4]

Yield: 152 mg (85%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.43 (m, 2 H), 7.29–7.26 (m, 2 H), 3.56 (s, 3 H), 3.34 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 137.7, 134.1, 131.2, 128.6, 127.8, 125.0, 60.9, 33.9, 21.3.

_N_,4-Dimethoxy-_N_-methylbenzamide (3d)[10e]

[CAS Reg. No. 52898-49-4]

Yield: 175 mg (90%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73–7.71 (m, 2 H), 6.90–6.88 (m, 2 H), 3.83 (s, 1 H), 3.55 (s, 1 H), 3.34 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3, 161.5, 130.5, 125.9, 113.2, 60.8, 55.2, 33.8.

_N_,2-Dimethoxy-_N_-methylbenzamide (3e)[15a]

[CAS Reg. No. 130250-62-3]

Yield: 150 mg (77%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 1 H), 7.22–7.21 (m, 1 H), 6.93–6.88 (m, 2 H), 3.79 (s, 3 H), 3.51–3.34 (m, 3 H), 3.26 (br s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 155.7, 130.5, 127.6, 125.3, 120.4, 61.0, 55.7, 32.6.

_N_-Methoxy-_N_-methyl-2-naphthamide (3f)[15d]

[CAS Reg. No.113443-62-2]

Yield: 178 mg (83%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 7.91–7.89 (m, 3 H), 7.85–7.50 (m, 3 H), 3.56 (s, 3 H), 3.41 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 134.2, 132.4, 131.3, 128.8, 128.6, 127.6, 127.5, 127.3, 126.5, 125.0, 61.1, 33.8.

2-Chloro-_N_-methoxy-_N_-methylbenzamide (3g)[20b]

[CAS Reg. No. 289686-74-4]

Yield: 167 mg (84%); colorless oil.

IR (film): 2921, 1655, 1236, 1089 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.39 (m, 1 H), 7.33–7.28 (m, 3 H), 3.46 (s, 3 H), 3.38 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5, 135.2, 130.6, 130.1, 129.2, 127.6, 126.4, 61.3, 32.2.

GC-MS: _m_/_z_ (%) = 199 (2, [M$^+$]), 168 (1), 139 (100), 111 (28), 85 (2), 75 (20), 50 (9).

3-Chloro-_N_-methoxy-_N_-methylbenzamide (3h)[20b]

[CAS Reg. No. 145959-21-3]

Yield: 179 mg (90%); colorless oil.

IR (film): 2923, 1644, 1236, 1090 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (s, 1 H), 7.56 (d, _J_ = 5 Hz, 1 H), 7.42 (d, _J_ = 10 Hz, 1 H), 7.41–7.32 (m, 1 H), 3.54 (s, 3 H), 3.34 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 135.6, 133.9, 130.6, 129.3, 128.3, 126.3, 61.1, 33.5.

GC-MS: _m_/_z_ (%) = 199 (5, [M$^+$]), 168 (1), 139 (100), 111 (43), 85 (3), 75 (23), 50 (9).

4-Chloro-_N_-methoxy-_N_-methylbenzamide (3i)[20b]

[CAS Reg. No. 122334-37-6]

Yield: 161 mg (81%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, _J_ = 10 Hz, 2 H), 7.37 (d, _J_ = 10 Hz, 2 H), 3.53 (s, 3 H), 3.35 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 136.7, 132.2, 129.8, 128.2, 61.0, 33.5.

_N_-Methoxy-_N_-methyl-3-(trifluoromethoxy)benzamide (3j)[20c]

[CAS Reg. No. 1203575-93-2]

Yield: 219 mg (85%); yellow oil.

IR (film): 2922, 1644, 1236, 1090 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, _J_ = 8 Hz, 1 H), 7.57 (s, 1 H), 7.44 (m, 1 H), 7.30 (m, 1 H), 3.54 (s, 1 H), 3.36 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0, 148.6, 135.7, 129.5, 129.4, 126.7, 123.0, 121.0, 61.1, 33.4.

GC-MS: _m_/_z_ (%) = 249 (4, [M$^+$]), 218 (1), 189 (100), 161 (27), 95 (38), 75 (7), 64 (8), 40 (3).

_N_-Methoxy-_N_-methyl-4-nitrobenzamide (3k)[20d,e]

[CAS Reg. No. 52898-51-8]

Yield: 147 mg (70%); yellow solid; mp 73–74 °C.

IR (KBr): 3116, 2925, 2852, 1524, 975 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27–8.25 (m, 2 H), 7.84–7.83 (m, 2 H), 3.52 (s, 3 H), 3.39 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.7, 148.8, 140.0, 129.2, 123.2, 61.4, 33.1.

GC-MS: _m_/_z_ (%) = 210 (4, [M$^+$]), 179 (2), 150 (100), 120 (17), 104 (40), 92 (23), 76 (31), 50 (16).

_N_-Methoxy-_N_-methylfuran-3-carboxamide (3m)[20e]

[CAS Reg. No. 148900-66-7]

Yield: 139 mg (90%); yellow-red liquid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (s, 1 H), 7.40 (s, 1 H), 6.85 (m, 1 H), 3.70 (s, 3 H), 3.32 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1, 146.4, 142.6, 119.6, 111.2, 61.0, 32.7.

_N_-Methoxy-_N_-methyl-2-phenylacetamide (3n)[5]

[CAS Reg. No. 95092-10-7]

Yield: 71 mg (40%); yellow oil.

IR (film): 2922, 1724, 1656, 1382, 1091 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 5 H), 3.79 (s, 2 H), 3.60 (s, 3 H), 3.20 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.4, 134.9, 129.3, 128.4, 126.7, 61.2, 39.4, 32.2.

GC-MS: _m_/_z_ (%) = 179 (5, [M$^+$]), 148 (3), 118 (38.2), 91 (100), 65 (18).

_N_-Methoxy-2-(4-methoxyphenyl)-_N_-methylacetamide (3o)[20f]

[CAS Reg. No. 148900-66-7]

Yield: 87 mg (42%); yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21–7.19 (m, 2 H), 6.86–6.84 (m, 2 H), 3.78 (s, 3 H), 3.70 (s, 2 H), 3.61 (s, 3 H), 3.18 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.6, 158.4, 130.2, 130.2, 126.9, 113.9, 61.2, 55.2, 38.4, 32.2.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379583.

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