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Copper-Catalyzed Aerobic Oxidative Amidation of Benzyl Alcohols

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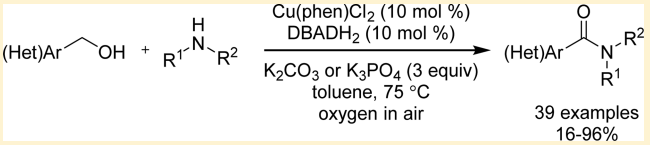
Supporting Information

ABSTRACT: A Cu-catalyzed synthesis of amides from alcohols and secondary amines using the oxygen in air as the terminal oxidant has been developed. The methodology is operationally simple requiring no high pressure equipment or handling of pure oxygen. The commercially available, nonprecious metal catalyst, $Cu(phen)Cl_2$, in conjunction with di-*tert*-butyl hydrazine dicarboxylate and an inorganic base provides a variety of benzamides in moderate to excellent yields. The pK_a of amine conjugate acid and electronics of alcohol were shown to impact the selection of base for optimal reactivity. A mechanism consistent with the observed reactivity trends, KIE, and Hammett study is proposed.



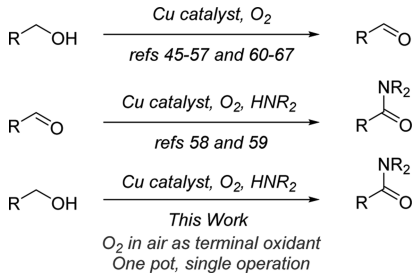
INTRODUCTION

Amides are an important structural motif found in diverse natural products, pharmaceuticals, and agrochemicals.[1,2] Due to their abundance in synthetically targeted molecules, a wide variety of methodologies have been developed to form amides.[3−7] Although effective, many of the commonly used methods are not atom economical because of the need to use stoichiometric coupling reagents to activate the carboxylic acid prior to reaction with the amine.[8,9] Moreover, the stoichiometric byproducts from these coupling reagents can be carcinogenic,[10] cytotoxic,[11] and challenging to remove requiring multiple aqueous extractions or recrystallizations.[9] In light of these limitations, the ACS Green Chemistry Institute Pharmaceutical Roundtable has identified "*amide formation avoiding poor atom economy reagents*" as a key area of research.[12]

In recent years, the catalytic amidation of alcohols has emerged as an atom- and step-economical alternative that circumvents the need for preactivation of carboxylic acids. While direct amidations of alcohols have been developed with second- and third-row transition metals (e.g., Ru,[13−21] Rh,[22−24] Re,[25] and Au[26,27]), far fewer methods have been reported with cheaper, more abundant nonprecious metals.[28−34] Given the cost,[35] toxicity,[36] and long-term supply issues[37] associated with precious metal catalysts,[38−40] the identification of efficient and reliable nonprecious metal alternatives is especially important with regards to sustainability. In addition, direct amidation of alcohols necessarily rely on oxidative pathways, and the majority of methods catalyzed by nonprecious metals utilize *tert*-butylhydroperoxide as the terminal oxidant, while oxygen is the ideal oxidant from a green chemistry perspective.[41−43] From a safety perspective, the use of pure oxygen with organic solvents can represent an untenable risk. This risk can be partially mitigated by using lower concentrations of oxygen.[41] While air is obviously the convenient oxygen gas blend available, its use still presents risk in the presence of flammable vapor.[41,44]

Copper-catalyzed aerobic oxidations of alcohols to aldehydes are well-known and have been the subject of numerous mechanistic studies.[45−57] Only a few reports of the corresponding oxidation of aldehydes to amides have been reported.[58,59] We postulated this concept could be extended to a one-pot, double-oxidation of an alcohol to amide that proceeds through a hemiaminal intermediate (Scheme 1).[34]

Scheme 1. Proposed Oxidative Amidation of Alcohols



One of the challenges in developing this method is to identify reaction conditions that limit formation of related byproducts (i.e., esters and carboxylic acids) and also tolerate the potentially oxidizable amine functionality. In this regard, reports by Markó and co-workers in which alcohols were effectively converted to aldehydes by a copper species in concert with di-*tert*-butyl azodicarboxylate (DBAD) were of particular interest to us.[60−67]

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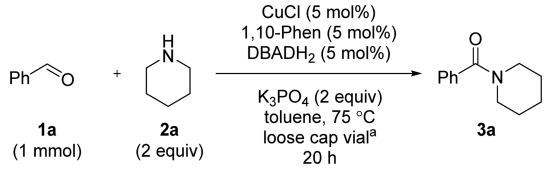
RESULTS AND DISCUSSION

To establish proof-of-concept and demonstrate that a hemiaminal could be oxidized to the amide, we evaluated the reaction of benzaldehyde (**1a**) and piperidine (**2a**) in the presence of CuCl, 1,10-phenanthroline (phen), di-*tert*-butyl hydrazine dicarboxylate ($DBADH_2$), and K_3PO_4 in toluene under air. Gratifyingly, after 20 h at 75 °C, 76% yield of benzamide **3a** was observed (Table 1, entry 1). The particle size

Table 1. Initial Optimization of Oxidative Amidation from Benzaldehyde Using Oxygen in Air as the Terminal Oxidant



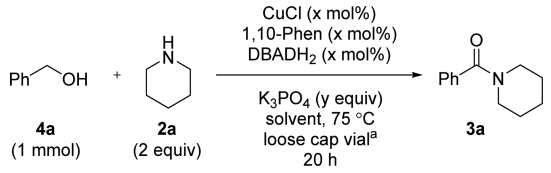
entry	change from conditions in scheme	yield (**3a**)[b]
1	none	76
2	10% CuCl, phen, and $DBADH_2$	79
3[c]	Pelleted K_3PO_4 instead of milled K_3PO_4	9
4[c]	K_2CO_3 instead of K_3PO_4	60
5[c]	Cs_2CO_3 instead of K_3PO_4	62
6	CuI instead of CuCl	54
7	Cu_2O instead of CuCl	5
8	$CuCl_2$ instead of CuCl	70
9	4,7-dimethoxy-1,10-phen instead of phen	77
10	4,7-diphenyl-1,10-phen instead of phen	73
11	2,9-dimethy-4,7-diphenyl-1,10-phen instead of phen	18
12	4,4′-di-*tert*-butyl-2,2′-bipy instead of phen	7
13[c]	No $DBADH_2$	50
14	1.5 equiv piperidine	70
15	1.5 equiv K_3PO_4	64
16	No CuCl	3
17	No 1,10-phenanthroline	18

[a]Loose cap vial refers to tightening cap 1/4 turn when 1 turn is required for full closure. [b]Assay yield (% wt/wt) determined by HPLC against a standard of **3a**. [c]10 mol % CuCl, phen and $DBADH_2$ (when present) were used.

of K_3PO_4 had a significant impact on reaction conversion; replacing milled K_3PO_4 (29 μm) with pelleted K_3PO_4 led to a drastic decrease in yield of **3a** (entry 1 vs 3). Other inorganic bases proved less efficient than K_3PO_4 (entries 4 and 5). Alternative Cu(I) sources did not perform as well as CuCl. A Cu(II) source, $CuCl_2$, provided only slightly lower yield of **3a** (entries 6−8[68]). Varying the electronics of the phen ligands (entries 9 and 10[68]) provided similar results except when the binding site was sterically encumbered (entry 11). 4,4′-Di-*tert*-butyl-2,2′-bipyridine was not as effective a ligand as phen (entry 12). A control experiment performed without $DBADH_2$ afforded 50% yield of **3a** (entry 13); the observation of an operative DBAD-free oxidation pathway is consistent with recent findings reported by Stahl and co-workers.[53] Performing the reaction with less than 2 equiv of **2a** or K_3PO_4 resulted in lower yields of **3a** (entries 14 and 15). Only trace amounts of **3a** were observed in the absence of CuCl (entry 16). Ligandless CuCl formed **3a** in 18% yield (entry 17), indicating a Cu/phen species is critical to the oxidative amidation. Screening of additional azenes was also conducted but none of those investigated provided better results than $DBADH_2$.[68]

Having identified effective conditions for an oxidative amidation of benzaldehyde and piperidine that avoided the use of high pressure equipment or pure oxygen (Table 1, entry 1), we turned our attention to the ultimate goal of starting directly from alcohols (Table 2). The conditions optimized for

Table 2. Optimization of Oxidative Amidation from Alcohol Oxidation State



entry	catalyst loading (mol %)[b]	K_3PO_4 (equiv)	solvent	yield (**3a**)[c]
1	5	2	Toluene	38
2	10	2	Toluene	67
3	5	3	Toluene	51
4	5	4	Toluene	48
5	10	3	Toluene	75
6[d]	10	3	Toluene	76
7[d]	10	3	1,4-dioxane	4
8[d]	10	3	DMF	66
9[d]	10	3	2-Me-THF	74
10[d]	10	3	DME	74

[a]Loose cap vial refers to tightening cap 1/4 turn when 1 turn is required for full closure. [b]Catalyst loading refers to loading of CuCl, 1,10-phenanthroline, and $DBADH_2$ unless otherwise stated. [c]Assay yield (% wt/wt) determined by HPLC with a product standard. [d]$Cu(phen)Cl_2$ and $DBADH_2$.

amidation of benzaldehyde gave complete conversion of benzyl alcohol to benzaldehyde, but significantly lower yield of **3a** (Table 2, entry 1). Increasing the catalyst loading from 5 to 10 mol % provided a significant improvement in yield of **3a** (entry 2). Given the need for 2 equiv of K_3PO_4 in the amide formation from benzaldehyde, it was postulated that additional base was required now that two sequential oxidations were occurring. The use of 3 equiv K_3PO_4 at 5 mol % catalyst loading also provided an improved yield (entry 3), but a further increase to four equivalents provided no additional improvement (entry 4). The highest yield of **3a** was achieved by using 10 mol % catalyst and 3 equiv K_3PO_4 (entry 5), providing similar yield to that observed for aldehyde to amide oxidation (Table 1, entry 1).

On the basis of the similar performance of $CuCl_2$ and CuCl in earlier optimization (Table 1), the commercially available $(phen)CuCl_2$ complex was subjected to the optimized conditions; the preformed complex furnished **3a** in 76% yield, comparable to the in situ generated catalyst (Table 2, entries 5 and 6). Among the other solvents evaluated (Table 2, entries 7−10), 2-methyltetrahydrofuran (2-MeTHF) and 1,2-dimethoxyethane (DME) were identified as viable alternatives. However, toluene was chosen for examination of the substrate scope due to its more favorable safety profile (vs DME) and higher boiling point (vs 2-MeTHF).[69−71]

Using the optimized conditions for the oxidative amidation of benzyl alcohol, the scope of substituted benzylic alcohols was explored (Table 3). A variety of *ortho*-, *meta*-, and *para*-substituted benzyl alcohols with diverse electronic character were well-tolerated, providing the corresponding amides (**3b**−**3o**) in synthetically useful yields. In general, the remaining mass balance can be accounted for in unreacted aldehyde, although

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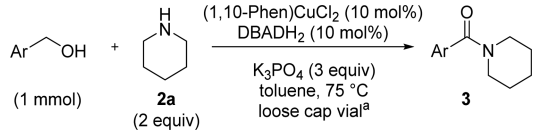
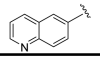
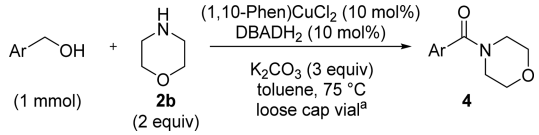
Table 3. Alcohol Substrate Scope with Piperidine



entry	Ar	Amide	ArCHO Conv. (%)[b]	Yield[c]
1	Ph	**3a**	96	83[d]
2	2-Cl-C_6H_4	**3b**	91	76
3a	2-NO_2-C_6H_4	**3c**	71	43
3b[e]			84	50
4a	3-CF_3-C_6H_4	**3d**	42	ND[f]
4b[e]			67	57
5	3-Br-C_6H_4	**3e**	76	55
6	3-Me-C_6H_4	**3f**	94	81
7	3-NMe_2-C_6H_4	**3g**	72[g]	66
8	4-CO_2Me-C_6H_4	**3h**	93	51
9	4-Cl-C_6H_4	**3i**	96	76[h]
10	4-F-C_6H_4	**3j**	95	76
11	4-OMe-C_6H_4	**3k**	76	55[i]
12	2-Naphthyl	**3l**	97	83
13	1-Naphthyl	**3m**	81	81
14		**3n**	50	45
15a		**3o**	24	ND[f]
15b[e]			70	54

[a]Loose cap vial refers to tightening cap 1/4 turn when 1 turn is required for full closure. [b]The reaction progress was monitored by HPLC. Conversion refers to the ratio: [amide/(**aldehyde** + amide)] based on peak area percent; In most cases, < 1% alcohol remained as determined by HPLC analysis. [c]Isolated yield following purification by column chromatography, unless otherwise noted. [d]8% PhCOOH extracted from crude precipitate. [e]K_2CO_3 as base. [f]Not determined due to lower conversion observed by HPLC versus K_2CO_3 as base. [g]9% alcohol and 19% aldehyde remained. [h]13% 4-Cl-C_6H_4COOH extracted from crude precipitate. [i]3% 4-MeO-C_6H_4COOH extracted from crude precipitate.

Table 4. Alcohol Substrate Scope with Morpholine



entry	Ar	Amide	ArCHO Conv. (%)[b]	Yield[c]
1	3-CF_3-C_6H_4	**4a**	95	84
2[d]	3-NMe_2-C_6H_4	**4b**	88	88
3a	4-Cl-C_6H_4	**4c**	97	92
3b[d]			40	ND[e]
4a[d]	4-OMe-C_6H_4	**4d**	96	84
4b			80	65
5	4-SMe-C_6H_4	**4e**	96	91
6a		**4f**	53	53
6b[d]			87	81
7		**4g**	94	91[f]
8		**4h**	73	65
9		**4i**	89	82[f]
10		**4j**	88	83[f]
11		**4k**	86	83

[a]Loose cap vial refers to tightening cap 1/4 turn when 1 turn is required for full closure. [b]The reaction progress was monitored by HPLC. Conversion refers to the ratio: [amide/(**aldehyde** + amide)] based on peak area percent; In most cases, < 1% alcohol remained as determined by HPLC analysis. [c]Isolated yield unless otherwise noted. [d]K_3PO_4 as base. [e]Not determined due to lower conversion observed by HPLC versus K_2CO_3 as base. [f]Yield determined by quantitative NMR; amide was not separated from phen by column chromatography.

the corresponding carboxylic acids were observed in some cases. Representative amounts of carboxylic acid formed (3–13%) are provided for entries 1, 9, and 11 in which carboxylic acid was extracted from the crude reaction precipitate. In the case of 3-bromobenzyl alcohol (Table 3, entry 5) 20% (by HPLC) of *N*-arylation at the bromide of 3-bromobenzaldehyde was observed, resulting in lower yield of **3h**. Furthermore, a methyl ester was susceptible to hydrolysis under the current conditions resulting in formation of 4-formylbenzoic acid as a major side product (Table 3, entry 8).

Interestingly, several electron-deficient benzyl alcohols in Table 3 gave low conversion to amide despite achieving full oxidation of alcohol to aldehyde (entries 3a, 4a, and 15a). Because electron-poor aldehydes should form hemiaminals more readily, the lower yield of amide suggests the amide formation is not directly analogous to the corresponding aldehyde formation. Because the base used is expected to impact hemiaminal formation, we re-examined bases, and found in contrast to our initial optimization, that switching to a weaker base such as K_2CO_3, resulted in improved conversion and greater yield of amides **3c**, **3d**, and **3o**.

The results showing the amidation with electron-poor alcohols was more efficient using K_2CO_3, a weaker base, led us to investigate how the basicity of the amine would impact this transformation. The coupling of morpholine (**2b**)[72] with a variety of benzylic alcohols was investigated (Table 4) and in the majority of cases, K_2CO_3 provided superior yields. Again, exceptions were observed when the alcohols were more electron-rich (entry 4a vs 4b and 6a vs 6b), in which case switching to K_3PO_4 offered better reactivity. Collectively, these results suggest an assessment to correlate the electronic nature of alcohol substrate and amine pK_a is required.

Having noted the reactivity differences between morpholine and piperidine, we varied the amine nucleophiles to elucidate the criteria for base selection. A variety of cyclic and acyclic amines with pK_a's of the conjugate acid ranging from 6.5 to 11[73] were subjected to the amidation conditions (Table 5). Amines more acidic than morpholine (pK_a = 8.97) gave excellent yields of the corresponding benzamide products **5a**–**5d** when K_2CO_3 was used (entries 1–4). As the amine pK_a was increased, > 90% conversion of aldehyde to amide was observed in most cases (entries 6a, 7a, and 9a) until the pK_a approached 10.2 when the stronger base, K_3PO_4, became more effective (entry 10b). By contrast, amines with pK_a lower than 10.2 performed more poorly with K_3PO_4 (Table 5, entry 7b vs 7a and Table 4, entry 3b vs 3a). Synthetically useful amide yields were obtained with pyrrolidine and azepane (entries 12 and 15, respectively). Acyclic amines gave poor to modest yields depending on amine pK_a (Table 5, entries 9 and 14). A hindered amine, (*S*)-2-methylpiperidine, provided only 16% yield of **5k** with no racemization. A few primary amines have been investigated under the current conditions and despite achieving full oxidation of alcohol to aldehyde, little to no amide products were formed, likely due to facile imine formation.[68]

The data for oxidative amidation of 4-chlorobenzyl alcohol (Table 5) provides guidance for selecting an inorganic base for a given secondary amine. When the conjugate ammonium pK_a is <10.2, K_2CO_3 is likely to give the highest yields. By contrast, K_3PO_4 is optimal for amines with ammonium pK_a ≥ 10.2. The

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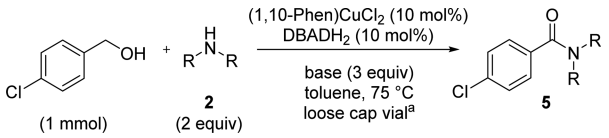
Table 5. Scope of Amines and Reactivity Trends with 4-Chlorobenzyl Alcohol Based on Predicted Amine pK_a



entry	Amine	Predicted pK_a[b]	base	Amide	ArCHO Conv. (%)[c]	Yield[d]
1		6.48	K_2CO_3	**5a**	97	85
2		8.20	K_2CO_3	**5b**	99	91
3		8.41	K_2CO_3	**5c**	95	95[e]
4		8.45	K_2CO_3	**5d**	96	92
5		8.97	K_2CO_3	**4c**	97	92[f]
6		9.12	K_2CO_3	**5e**	96	96
7a		9.62	K_2CO_3	**5f**	96	93
7b			K_3PO_4		96[g]	76
8a		9.77	K_2CO_3	**5g**	49	32
8b			K_3PO_4		69	59
9a		9.78	K_2CO_3	**5h**	90	90
9b			K_3PO_4		92	83
10a		10.20	K_2CO_3	**5i**	72	64
10b			K_3PO_4		97	82
11		10.45	K_3PO_4	**3i**	96	76
12		10.50	K_3PO_4	**5j**	78	65
13		10.63	K_3PO_4	**5k**	46	16[e]
14		11.03	K_3PO_4	**5l**	65	32
15		11.24	K_3PO_4	**5m**	85	51

[a]Loose cap vial refers to tightening cap 1/4 turn when 1 turn is required for full closure. [b]Predicted amine conjugate acid pK_a from Scifinder; calculated using Advanced Chemistry Development (ACD/Laboratories) Software V11.02. [c]The reaction progress was monitored by HPLC. Conversion refers to the ratio: [amide/(**aldehyde** + amide)] based on peak area percent; In most cases, < 1% alcohol remained as determined by HPLC analysis. [d]Isolated yield unless otherwise noted. [e]Amide obtained in 99.6% ee. [f]Reaction performed on 35 mmol scale provided identical yield. [g]13% carboxylic acid was observed.

pK_a range over which base selection changes will likely also depend on electronics of the alcohol substrate.

The mechanism proposed by Stahl and co-workers for alcohol oxidation to aldehyde with the Cu/DBADH$_2$/O_2 system involves two interdependent catalytic cycles, one of which does not require DBAD.[53] Furthermore, one cycle relies on redox between Cu(I) and Cu(II) while Cu(II) undergoes no formal oxidation state change in the other. In the presence of piperidine, benzyl alcohol undergoes rapid oxidation to benzaldehyde prior to the formation of amide **3a**,[68] suggesting two distinct oxidation steps, alcohol to aldehyde followed by aldehyde to amide, which allows for the independent study of each step. Given the significant levels of amide formation from benzaldehyde observed in the *absence* of DBADH$_2$ (Table 1, entry 13) we postulate a bimodal mechanism for the amidation similar to the alcohol oxidation (Figure 1). The first part of the catalytic cycle (Figure 1, left) begins with coordination of benzaldehyde to copper providing complex **I** which can react with **2a** to form **II**. Deprotonation forms Cu-bound hemiaminal **III** which upon reaction with DBAD liberates benzamide **3a**, DBADH$_2$ and reforms complex **I**. The resulting DBADH$_2$ is reoxidized in conjunction with two molecules of Cu(I) (**V** to **VI**); these oxidations account for the net consumption of one molecule of oxygen, a four electron oxidant. The second part of the catalytic cycle (Figure 1, right) begins with complex **VI** coordinating to **1a** forming intermediate **VII** which reacts with **2a** to form intermediate **III** and water. Following oxidation, **III** liberates benzamide **3a** and two molecules of Cu(I) complex **V**. A variety of results including control experiments with DBAD(H$_2$), kinetic isotope effect, and a Hammett study were found to be consistent with the proposed mechanism.

Oxygen serves as the terminal oxidant evidenced by trace formation of **3a** under N_2 atmosphere (<5 ppm of O_2, Table 6, entry 1). Also, nearly identical conversions were obtained when the amidation was conducted with catalytic DBADH$_2$ (Table 1, entry 1) or its oxidized equivalent di-*tert*-butyl azodicarboxylate, DBAD (Table 6, entry 2) under aerobic conditions, suggesting an active redox interconversion between the two. The omission of DBAD or DBADH$_2$ results in lower conversion to **3a** (Table 1, entry 13). Under a N_2 atmosphere (<5 ppm of O_2), 32% of benzamide **3a** was formed with one equivalent of DBAD present (Table 6, entry 3), while stoichiometric DBADH$_2$

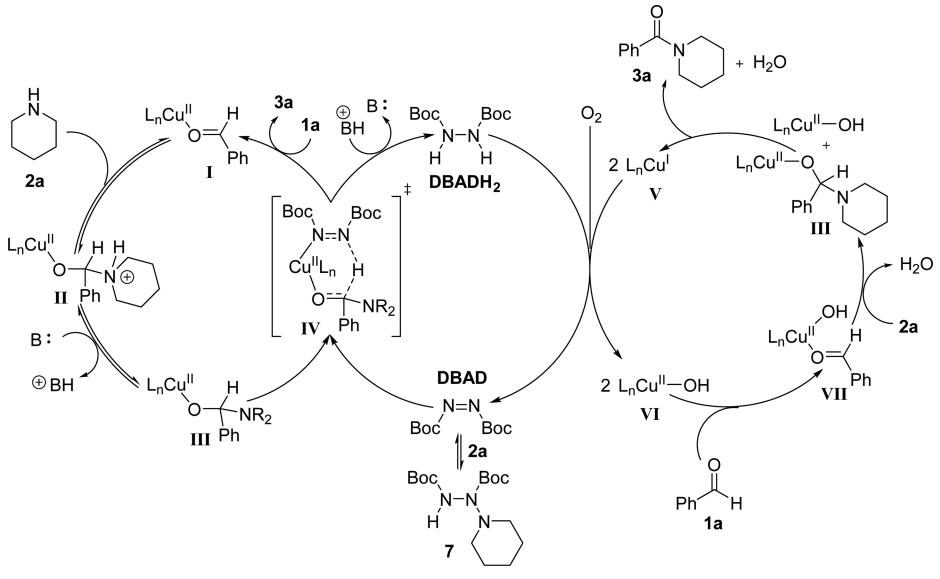


Figure 1. Proposed mechanism for oxidative amidation of benzaldehyde with piperidine.

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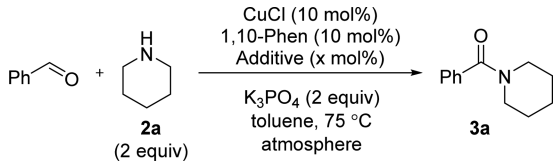
Table 6. Control Experiments with $DBADH_2$/DBAD



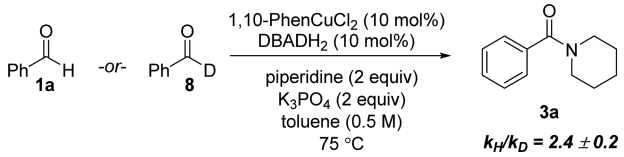
entry	atmosphere	additive (equiv)	yield (%)[a]
1	N_2	$DBADH_2$ (0.1)	3
2	air	DBAD (0.1)	75
3	N_2	DBAD (1)	32
4	N_2	$DBADH_2$ (1)	1
5	air	7 (0.1)	80

[a]Assay yield (% wt/wt) as determined by HPLC against a standard of **3a**.

provided only trace conversion to product (entry 4) confirming that DBAD does participate in the oxidation of the hemiaminal to amide. The stoichiometric DBAD experiment was complicated due to a background reaction with **2a** to form triazane **7** (Figure 1). The formation of **7** is reversible[68] and the substitution of **7** for DBAD(H_2) resulted in similar yield of **3a** (Table 6, entry 5).

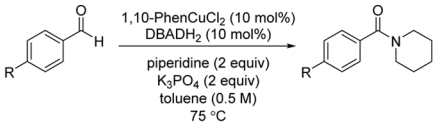
The observation of a kinetic isotope effect (KIE) can provide useful information about the bonds being broken or formed during the rate-determining step (RDS) of a reaction.[74,75] An experiment was performed to determine if a KIE could be observed with the aldehyde C−H(D) (Scheme 2). By considering initial reaction rates, a k_H/k_D of 2.4 ± 0.2 was found. This primary isotope effect is consistent with benzylic C−H bond cleavage in the RDS of amide formation.

Scheme 2. KIE Experiment for Cu/$DBADH_2$ Oxidative Amidation



Having established the hemiaminal oxidation as the RDS, a Hammett study was performed to further probe the nature of this step. Initial rates were measured for the reaction between piperidine and a variety of benzaldehydes and it was found that electron-deficient aldehydes reacted more rapidly.[76] From the resulting Hammett plot (Figure 2), the ρ value was +2.6, suggesting significant development of anionic character at the benzylic position during the formal "oxidation" step. The ρ value is consistent with a deprotonation rather than hydrogen atom or hydride abstraction, which might be expected for a Cu-catalyzed benzylic oxidation based on recent work by Stahl[50] and Riisager,[77] respectively. A RDS involving deprotonation is consistent with the observation that with more basic amines, which will reduce the acidity of the Cu-hemiaminal intermediate **III**, a stronger base like K_3PO_4 is necessary to achieve good yields of amides. Furthermore, more electron-deficient benzaldehydes will furnish a more acidic Cu-bound hemiaminal **III**, allowing the use of a weaker base (K_2CO_3) for deprotonation in the formal "oxidation" step.

In conclusion, a copper-catalyzed oxidative amidation has been developed for the direct conversion of benzylic alcohols to



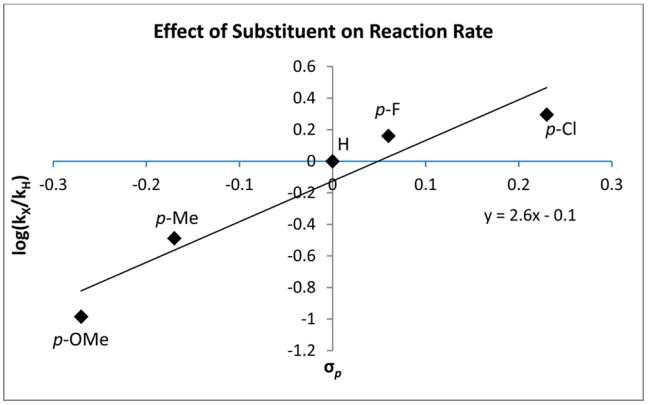


Figure 2. Hammett plot for reaction of piperidine with electronically varied benzaldehydes.

the corresponding tertiary benzamides with a variety of secondary amines. The new methodology utilizes a readily available nonprecious metal catalyst and oxygen in air as the terminal oxidant. The pK_a of amine conjugate acid and electronics of alcohol were shown to impact the selection of base for optimal reactivity. A primary KIE was observed for the oxidative amidation, which is consistent with benzylic C−H bond cleavage in the rate-determining step. Furthermore, a Hammett study revealed the buildup of anionic character at the benzylic position, pointing to a deprotonation in the formal oxidation step. A catalytic cycle consistent with observed reactivity trends and mechanistic experiments has been proposed.

EXPERIMENTAL SECTION

General Information. Reagents were used as obtained from the vendor without further purification. HPLC grade toluene, milled K_3PO_4 (29 μm) and K_2CO_3 (44 μm) were used unless otherwise stated. Analytical thin layer chromatography (TLC) was performed utilizing precoated silica gel 60 F_{254} plates containing a fluorescent indicator. Flash chromatography was performed using an automated fraction collector at 254 and 280 nm with prepacked silica gel columns and EtOAc/heptane mixtures. Loose cap vial refers to tightening cap 1/4 turn when 1 turn is required for full closure.

Routine NMR experiments were recorded at room temperature (unless otherwise stated) at 400, 600, or 700 MHz for ^{1}H NMR and 100, 150, or 175 MHz for ^{13}C NMR. Chemical shifts are reported in parts-per-million (ppm) relative to residual solvent signal of $CHCl_3$ (δ 7.26 ppm for ^{1}H and δ 77.1 ppm for ^{13}C) and scalar coupling constants are reported in hertz (Hz). High-pressure liquid chromatography (HPLC) analyses were performed with a detector at 210 nm using CH_3CN/H_2O mixtures as the mobile phase. Liquid chromatography mass spectrometry (LCMS) was performed at 210 nm using a quadrapole APCI mass detector. Accurate mass measurements were acquired using a Q-TOF mass analyzer. Melting points were obtained using a benchtop melting point apparatus equipped with digital thermometer.

Unless otherwise stated, all reactions were performed on 1 mmol scale.

General Procedure A (GP-A). To a 1 dram vial equipped with cross stir bar was added dichloro(1,10-phenanthroline)copper(II) (31 mg, 0.1 mmol, 10 mol %), K_3PO_4 (637 mg, 3 equiv, 3.0 mmol), di-*tert*-butyl hydrazine 1,3-dicarboxylate (23 mg, 0.1 mmol, 10 mol %), toluene (2.0 mL, 0.5 M), alcohol (1.0 mmol, 1 equiv), and amine (2.0

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mmol, 2 equiv). The cap was loosely placed on the vial, and the mixture was heated to 75 °C with stirring at 1000 rpm. After stirring for the indicated time, the reaction was cooled to room temperature, diluted with ethyl acetate (2 mL) and filtered through a polyethylene fritted funnel. The precipitate was washed with ethyl acetate (10 mL). The combined filtrate was concentrated on a rotary evaporator and purified by flash chromatography on silica gel with the indicated solvent system.

General Procedure B (GP-B). To a 1 dram vial equipped with cross stir bar was added dichloro(1,10-phenanthroline)copper(II) (31 mg, 0.1 mmol, 10 mol %), K_2CO_3 (415 mg, 3 equiv, 3.0 mmol), di-*tert*-butyl hydrazine 1,3-dicarboxylate (23 mg, 0.1 mmol, 10 mol %), toluene (2.0 mL, 0.5 M), alcohol (1.0 mmol, 1 equiv), and amine (2.0 mmol, 2 equiv). The cap was loosely placed on the vial, and the mixture was heated to 75 °C with stirring at 1000 rpm. After stirring for the indicated time, the reaction was cooled to room temperature, diluted with ethyl acetate (2 mL) and filtered through a polyethylene fritted funnel. The precipitate was washed with ethyl acetate (10 mL). The combined filtrate was concentrated on a rotary evaporator and purified by flash chromatography on silica gel with the indicated solvent system.

Phenyl(piperidin-1-yl)methanone ***3a***. Following GP-A, **3a** (156 mg, 0.83 mmol, 83% yield) was prepared in 20 h and isolated as a colorless oil by flash chromatography on silica gel (4 g column, 10% EtOAc for 4 CV, then 10−60% EtOAc over 11 CV). Analytical data for **3a** was consistent with that previously reported.[59] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.31 (m, 4H), 3.89 (s, 2H), 3.52 (s, 2H), 1.96−1.56 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 136.6, 129.4, 128.5, 126.9, 48.8, 43.2, 26.6, 25.7, 24.7; LCMS (APCI) Calculated for [M + H]+ $C_{12}H_{16}NO$: 190.12, found 190.20.

2-Chlorophenyl(piperidin-1-yl)methanone ***3b***. Following GP-A, **3b** (170 mg, 0.76 mmol, 76% yield) was prepared in 21 h and isolated as a colorless oil by flash chromatography on silica gel (4 g column, 20% EtOAc for 4 CV, then 20−40% EtOAc over 12 CV). Analytical data for **3b** was consistent with that previously reported.[78] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−6.84 (m, 4H), 3.98−3.50 (m, 2H), 3.39−3.00 (m, 2H), 1.75−1.53 (m, 5H), 1.50−1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 136.5, 130.4, 129.9, 129.6, 127.6, 127.1, 47.9, 42.6, 26.4, 25.6, 24.5; LCMS (APCI) Calculated for [M + H]+ $C_{12}H_{14}ClNO$: 224.08, found 224.10.

2-Nitrophenyl(piperidin-1-yl)methanone ***3c***. Following GP-B, **3c** (117.5 mg, 0.50 mmol, 50% yield) was prepared in 20 h and isolated as a pale orange oil by flash chromatography on silica gel (4 g column, 20% EtOAc for 4 CV, then 20−40% EtOAc over 12 CV). Analytical data for **3c** was consistent with that previously reported.[79] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 8.4, 1.2 Hz, 1H), 7.69 (td, J = 7.5, 1.2 Hz, 1H), 7.55 (ddd, J = 8.3, 7.5, 1.5 Hz, 1H), 7.38 (dd, J = 7.6, 1.5 Hz, 1H), 3.84−3.67 (m, 2H), 3.16 (t, J = 5.6 Hz, 2H), 1.83−1.30 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 145.2, 134.5, 133.4, 129.6, 128.0, 124.7, 48.0, 42.7, 25.8, 25.2, 24.5; LCMS (APCI) Calculated for [M + H]+ $C_{12}H_{15}N_2O_3$: 235.11, found 235.10.

3-Trifluoromethylphenyl(piperidin-1-yl)methanone ***3d***. Following GP-B, **3d** (146 mg, 0.57 mmol, 57% yield) was prepared in 24 h and isolated as a pale yellow oil by flash chromatography on silica gel (4 g column, 10% EtOAc for 10 CV, then 10−80% EtOAc over 10 CV). Analytical data for **3d** was consistent with that previously reported.[80] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.56 (m, 2H), 7.56−7.43 (m, 2H), 3.65 (s, 2H), 3.25 (s, 2H), 1.85−1.18 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 137.3, 130.9 (q, J = 32.5 Hz), 130.1, 129.0, 126.1 (d, J = 16 Hz), 123.8 (d, J = 16 Hz), 123.7 (q, J = 272.6 Hz), 48.7, 43.2, 26.4, 25.5, 24.4; LCMS (APCI) Calculated for [M + H]+ $C_{13}H_{15}F_3NO$: 258.11, found 258.30.

3-Bromophenyl(piperidin-1-yl)methanone ***3e***. Following GP-A, **3e** (148 mg, 0.55 mmol, 55% yield) was prepared in 21 h and isolated as white solid by flash chromatography on silica gel (4 g column, 20% EtOAc for 11 CV, then 20−60% EtOAc over 7 CV). Analytical data for **3e** was consistent with that previously reported.[81] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.42 (m, 2H), 7.35−7.11 (m, 2H), 3.73−3.62 (m, 2H), 3.30 (s, 2H), 1.83−1.34 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 138.5, 132.4, 130.1, 129.9, 125.3, 122.6, 48.7, 43.2, 26.5, 25.6, 24.5; LCMS (APCI) Calculated for [M + H]+ $C_{12}H_{15}BrNO$: 268.03, found 268.05.

3-Methylphenyl(piperidin-1-yl)methanone ***3f***. Following GP-A, **3f** (165 mg, 0.81 mmol, 81% yield) was prepared in 21 h and isolated as a colorless oil by flash chromatography on silica gel (4 g column, 20% EtOAc for 4 CV, then 20−40% EtOAc over 15 CV). Analytical data for **3f** was consistent with that previously reported.[59] ^{1}H NMR (400 MHz, $CDCl_3$): 7.20 (m, 1H), 7.16−7.06 (m, 3H), 3.64 (s, 2H), 3.27 (s, 2H), 2.30 (s, 3H), 1.66−1.40 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 138.1, 136.4, 129.9, 128.1, 127.3, 123.5, 48.6, 42.9, 26.4, 25.5, 24.5, 21.3; LCMS (APCI) Calculated for [M + H]+ $C_{13}H_{18}NO$: 204.14, found 204.10.

3-(Dimethylamino)phenyl(piperidin-1-yl)methanone ***3g***. Following GP-A, **3g** (154 mg, 0.66 mmol, 66% yield) was prepared in 24 h and isolated as viscous, pale yellow oil by flash chromatography on silica gel (4 g column, 20% EtOAc for 10 CV, then 20−80% EtOAc over 20 CV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (td, J = 7.4, 1.4 Hz, 1H), 6.70 (dd, J = 7.3, 1.1 Hz, 2H), 6.65 (dd, J = 7.4, 1.2 Hz, 1H), 3.67 (s, 2H), 3.32 (s, 2H), 2.92 (s, 6H), 1.71−1.40 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 150.5, 137.3, 129.0, 114.4, 113.2, 110.6, 48.7, 43.0, 40.5, 26.6, 25.7, 24.6; TLC (40% EtOAc/heptanes) R_f 0.14; HRMS (ESI-Q-TOF) m/z [M + H]$^+$ Calculated for $C_{14}H_{21}N_2O$ 233.1648, found 233.1649.

Methyl 4-(piperidine-1-carbonyl)benzoate ***3h***. Following GP-A, **3h** (125 mg, 0.51 mmol, 51% yield) was prepared in 8 h and isolated as a pale yellow oil by flash chromatography on silica gel (4 g column, 10% EtOAc for 8 CV, then 20−60% EtOAc over 28 CV). Analytical data for **3h** was consistent with that previously reported.[59] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.00 (m, 2H), 7.45−7.38 (m, 2H), 3.89 (s, 3H), 3.68 (s, 2H), 3.25 (s, 2H), 1.56 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 166.4, 140.9, 130.9, 129.8, 126.8, 52.3, 48.7, 43.1, 26.5, 25.6, 24.5; LCMS (APCI) Calculated for [M + H]+ $C_{14}H_{18}NO_3$: 248.13, found 248.15.

3-Chlorophenyl(piperidin-1-yl)methanone ***3i***. Following GP-A, **3i** (171 mg, 0.76 mmol, 76% yield) was prepared in 18 h and isolated as a white solid by flash chromatography on silica gel (4 g column, 20% EtOAc for 8 CV, then 20−80% EtOAc over 20 CV). Analytical data for **3i** was consistent with that previously reported.[78] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 4H), 3.66 (s, 2H), 3.30 (s, 2H), 1.97−1.33 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 135.4, 134.9, 128.7, 128.4, 48.8, 43.3, 26.6, 25.7, 24.6; LCMS (APCI) Calculated for [M + H]+ $C_{12}H_{15}ClNO$: 224.08, found 224.10.

4-Fluorophenyl(piperidin-1-yl)methanone ***3j***. Following GP-A, **3j** (171 mg, 0.76 mmol, 76% yield) was prepared 20 h and isolated as a colorless oil by flash chromatography on silica gel (4 g column, 20% EtOAc for 8 CV, then 20−80% EtOAc over 20 CV). Analytical data for **3j** was consistent with that previously reported.[59] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.32 (m, 2H), 7.09−6.98 (m, 2H), 3.64 (s, 2H), 3.31 (s, 2H), 1.73−1.40 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 163.2 (d, J = 249.1 Hz), 132.5, 129.1 (d, J = 8.4 Hz), 115.4 (d, J = 21.8 Hz), 48.8, 43.3, 26.5, 25.7, 24.6; LCMS (APCI) Calculated for [M + H]+ $C_{12}H_{15}FNO$: 208.11, found 208.10.

4-Methoxyphenyl(piperidin-1-yl)methanone ***3k***. Following GP-A, **3k** (120 mg, 0.55 mmol, 55% yield) was prepared in 27 h and isolated as a pale yellow solid by flash chromatography on silica gel (4 g column, 20% EtOAc for 8 CV, then 20−80% EtOAc over 20 CV). Analytical data for **3k** was consistent with that previously reported.[59] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J = 8.8, 1.1 Hz, 1H), 6.86 (dd, J = 8.8, 1.1 Hz, 1H), 3.78 (s, 3H), 3.54 (m, 4H), 1.73−1.41 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 160.5, 128.8, 128.6, 113.6, 55.3, 48.9, 43.5, 26.1, 24.7; LCMS (APCI) Calculated for [M + H]+ $C_{13}H_{18}NO_2$: 220.13, found 220.30.

Naphthalen-2-yl(piperidin-1-yl)methanone ***3l***. Following GP-A, **3l** (198 mg, 0.83 mmol, 83% yield) was prepared in 21 h and isolated as a white solid by flash chromatography on silica gel (4 g column, 20% EtOAc for 4 CV, then 20−35% EtOAc over 13 CV). Analytical data for **3l** was consistent with that previously reported.[59] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.77 (m, 4H), 7.54−7.43 (m, 3H), 3.74 (s, 2H), 3.37 (s, 2H), 1.87−1.30 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ133.9, 133.5, 132.8, 128.4, 128.2, 127.8, 127.8, 126.9, 126.6, 126.5,

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124.3, 48.8, 43.2, 26.5, 25.7, 24.6; LCMS (APCI) Calculated for [M + H]+ $C_{16}H_{18}NO$: 240.14, found 240.30.

Naphthalen-1-yl(piperidin-1-yl)methanone ***3m***. Following GP-A, **3m** (197 mg, 0.82 mmol, 82% yield) was prepared in 18 h and isolated as a white solid by flash chromatography on silica gel (4 g column, 5% EtOAc for 15 CV, then 5−70% EtOAc over 20 CV). Analytical data for **3m** was consistent with that previously reported.[82] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.79 (m, 3H), 7.54−7.42 (m, 3H), 7.38 (m, 1H), 3.86 (m, 2H), 3.11 (m, 2H), 1.81−1.58 (m, 4H), 1.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 134.9, 133.5, 129.6, 128.8, 128.3, 126.8, 126.3, 125.2, 124.9, 123.4, 48.3, 42.6, 26.7, 25.8, 24.5; LCMS (APCI) Calculated for [M + H]+ $C_{16}H_{18}NO$: 240.14, found 240.20.

(2-(Allyloxy)phenyl)(piperidin-1-yl)methanone ***3n***. Following GP-A, **3n** (110 mg, 0.45 mmol, 45% yield) was prepared in 19 h and isolated as a colorless oil by flash chromatography on silica gel (4 g column, 5% EtOAc for 6 CV, then 5−80% EtOAc over 15 CV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.23 (m, 1H), 7.21 (dd, J = 7.4, 1.7 Hz, 1H), 6.95 (td, J = 7.5, 1.0 Hz, 1H), 6.86 (dd, J = 8.4, 0.9 Hz, 1H), 6.08−5.91 (m, 1H), 5.36 (dq, J = 17.2, 1.7 Hz, 1H), 5.23 (dq, J = 10.6, 1.4 Hz, 1H), 4.54 (ddt, J = 5.5, 3.1, 1.6 Hz, 2H), 3.81−3.61 (m, 2H), 3.17 (qdt, J = 10.7, 6.7, 3.8 Hz, 2H), 1.71−1.35 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 154.3, 133.1, 130.0, 127.9, 127.0, 121.2, 117.2, 112.3, 69.0, 48.0, 42.6, 26.4, 25.7, 24.7; TLC (40% EtOAc/heptanes) R_f 0.23; HRMS (ESI-Q-TOF) m/z [M + H]$^+$ Calculated for $C_{15}H_{20}NO_2$ 246.1489, found 246.1491.

Piperidin-1-yl(quinolin-6-yl)methanone ***3o***. Following GP-A, **3o** (129 mg, 0.54 mmol, 54% yield) was prepared in 19 h and isolated as a pale yellow oil by flash chromatography on silica gel (4 g column, 20% EtOAc for 15 CV, then 20−50% EtOAc over 3 CV, hold 50% EtOAc for 15 CV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (dd, J = 4.2, 1.7 Hz, 1H), 8.16 (ddd, J = 8.4, 1.9, 0.9 Hz, 1H), 8.13−8.07 (m, 1H), 7.90−7.83 (m, 1H), 7.69 (dd, J = 8.7, 1.9 Hz, 1H), 7.42 (dd, J = 8.3, 4.3 Hz, 1H), 3.74 (s, 2H), 3.36 (s, 2H), 1.75−1.44 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 151.4, 148.4, 136.5, 134.8, 129.9, 127.9, 126.6, 121.8, 48.9, 43.4, 26.7, 25.7, 24.6; TLC (90% EtOAc/heptanes) R_f 0.14; HRMS (ESI-Q-TOF) m/z [M + H]$^+$ Calculated for $C_{15}H_{17}N_2O$ 241.1335, found 241.1335.

Morpholino(3-(trifluoromethyl)phenyl)methanone ***4a***. Following GP-B, **4a** (218 mg, 0.84 mmol, 84% yield) was prepared in 22 h and isolated as a white solid by flash chromatography on silica gel (4 g column, 10% EtOAc for 10 CV, then 10−80% EtOAc over 10 CV). Analytical data for **4a** was consistent with that previously reported.[80] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.58−7.48 (m, 2H), 3.96−3.15 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 136.2, 131.2 (q, J = 32.9 Hz), 130.4, 129.2, 126.6 (d, J = 3.7 Hz), 124.2 (d, J = 4.0 Hz), 123.7 (q, J = 272.6 Hz), 66.8, 48.2, 42.7; LCMS (APCI) Calculated for [M + H]+ $C_{12}H_{13}F_3NO_2$: 260.09, found 260.10.

(3-(Dimethylamino)phenyl)(morpholino)methanone ***4b***. Following GP-A, **4b** (206 mg, 0.88 mmol, 88% yield) was prepared in 24 h and isolated as a viscous, pale yellow oil by flash chromatography on silica gel (4 g column, 20% EtOAc for 10 CV, then 10−80% EtOAc over 20 CV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.20 (m, 1H), 6.83−6.61 (m, 3H), 3.96−3.30 (m, 8H), 2.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ169.7, 150.2, 136.4, 128.9, 114.1, 114.0, 113.1, 110.3, 66.1, 47.6, 41.9, 39.1; TLC (40% EtOAc/heptanes) R_f 0.09; HRMS (ESI-Q-TOF) m/z [M + H]$^+$ Calculated for $C_{13}H_{19}N_2O_2$ 235.1441, found 235.1443.

(4-Chlorophenyl)(morpholino)methanone ***4c***. Following GP-B, **4c** (208 mg, 0.92 mmol, 92% yield) was prepared in 21 h and isolated as a white solid by flash chromatography on silica gel (4 g column, 20% EtOAc for 12 CV, then 20−80% EtOAc over 23 CV). Analytical data for **4c** was consistent with that previously reported.[83] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.27 (m, 4H), 3.89−3.15 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 136.0, 133.7, 128.9, 128.7, 66.8, 48.2, 42.7; LCMS (APCI) Calculated for [M + H]+ $C_{11}H_{13}ClNO_2$: 226.06, found 226.20.

(4-Methoxyphenyl)(morpholino)methanone ***4d***. Following GP-A, **4d** (187 mg, 0.84 mmol, 84% yield) was prepared in 18 h and isolated as a colorless oil by flash chromatography on silica gel (4 g column, 20% EtOAc for 12 CV, then 20−80% EtOAc over 23 CV). Analytical data for **4d** was consistent with that previously reported.[83] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.31 (m, 2H), 6.90−6.84 (m, 2H), 3.78 (s, 3H), 3.66−3.58 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 160.9, 129.2, 127.3, 113.8, 66.9, 55.3, 48.1, 43.4; LCMS (APCI) Calculated for [M + H]+ $C_{12}H_{16}NO_3$: 222.11, found 222.20.

(4-(Methylthio)phenyl)(morpholino)methanone ***4e***. Following GP-B, **4e** (215 mg, 0.91 mmol, 91% yield) was prepared in 24 h and isolated as a white solid by flash chromatography on silica gel (4 g column, 20% EtOAc for 12 CV, then 20−80% EtOAc over 15 CV, hold at 80% EtOAc for 10 CV). Analytical data for **4e** was consistent with that previously reported.[84] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.34 (m, 2H), 7.30−7.25 (m, 2H), 3.90−3.45 (m, 8H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 141.4, 131.5, 127.8, 125.8, 66.9, 48.1, 42.7, 15.3; LCMS (APCI) Calculated for [M + H]+ $C_{12}H_{16}NO_2S$: 238.09, found 238.10.

(2-(Allyloxy)phenyl)(morpholino)methanone ***4f***. Following GP-A, **4f** (200 mg, 0.81 mmol, 81% yield) was prepared in 18 h and isolated as a colorless oil by flash chromatography on silica gel (4 g column, 5% EtOAc for 7 CV, then 5−80% EtOAc over 13 CV, hold at 80% EtOAc for 10 CV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dddd, J = 8.4, 7.4, 1.8, 0.9 Hz, 1H), 7.30−7.23 (m, 1H), 7.00 (tt, J = 7.5, 1.0 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.02 (ddtd, J = 16.7, 10.4, 5.1, 0.9 Hz, 1H), 5.45−5.23 (m, 2H), 4.57 (m, 2H), 3.90−3.71 (m, 4H), 3.70−3.52 (m, 2H), 3.40−3.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 154.3, 132.8, 130.6, 128.4, 125.8, 121.4, 117.8, 112.3, 69.2, 67.0, 66.9, 47.3, 42.2; TLC (40% EtOAc/heptanes) R_f 0.14; HRMS (ESI-Q-TOF) m/z [M + H]$^+$ Calculated for $C_{14}H_{18}NO_3$ 248.1281, found 248.1280.

Morpholino(quinolin-6-yl)methanone ***4g***. Following GP-B, **4g** was prepared in 18 h and purified by flash chromatography on silica gel (4 g column, 60% EtOAc for 12 CV, then 60−100% EtOAc over 18 CV, hold 100% EtOAc for 10 CV). The material isolated from the column (230 mg) was analyzed by Q-NMR and shown to contain 4 wt % 1,10-phenanthroine. Yield of **4g** (220 mg, 0.91 mmol, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (dd, J = 4.2, 1.8 Hz, 1H), 8.18−8.09 (m, 2H), 7.88 (d, J = 2.0 Hz, 1H), 7.68 (dd, J = 8.6, 1.9 Hz, 1H), 7.42 (dd, J = 8.3, 4.2 Hz, 1H), 4.06−3.25 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 151.7, 148.4, 136.5, 133.5, 130.1, 127.8, 127.8, 127.1, 122.0, 121.9, 66.9, 48.3, 42.7; TLC (85% EtOAc, 14% heptanes, 1% Et_3N) R_f 0.12; HRMS (ESI-Q-TOF) m/z [M + H]$^+$ Calculated for $C_{14}H_{15}N_2O_2$ 243.1128, found 243.1133.

Morpholino(pyridin-2-yl)methanone ***4h***. Following GP-B, **4h** (124 mg, 0.65 mmol, 65% yield) was prepared in 24 h and purified by flash chromatography on silica gel (4 g column, heptanes contained 5% Et_3N, 30% EtOAc for 10 CV, then 30−50% EtOAc over 16 CV). Analytical data for **4h** was consistent with that previously reported.[85] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.73 (td, J = 7.7, 1.7 Hz, 1H), 7.59 (dt, J = 7.8, 1.1 Hz, 1H), 7.27 (ddd, J = 7.6, 4.9, 1.3 Hz, 1H), 3.82−3.65 (m, 4H), 3.64−3.52 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 153.6, 148.2, 137.1, 124.6, 124.1, 67.0, 66.7, 47.7, 42.7; LCMS (APCI) Calculated for [M + H]+ $C_{10}H_{13}N_2O_2$: 193.10, found 193.10.

Morpholino(pyridin-3-yl)methanone ***4i***. Following GP-B, **4i** was prepared in 18 h and purified by flash chromatography on silica gel (4 g column, heptanes contained 5% Et_3N, 20% EtOAc for 5 CV, then 20−80% EtOAc over 15 CV, hold 80% EtOAc for 20 CV). The material isolated from the column (168 mg) was analyzed by Q-NMR and shown to contain 6 wt % 1,10-phenanthroline. Yield of **4i** (158 mg, 0.82 mmol, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69−8.64 (m, 2H), 7.76 (dt, J = 7.8, 2.0 Hz, 1H), 7.37 (ddd, J = 7.9, 4.9, 1.0 Hz, 1H), 4.11−3.11 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 151.0, 148.0, 135.1, 131.2, 123.6, 66.8, 48.2, 42.7; TLC (85% EtOAc, 14% heptanes, 1% Et_3N) R_f 0.11; HRMS (ESI-Q-TOF) m/z [M + H]$^+$ Calculated for $C_{10}H_{13}N_2O_2$: 193.0972, found 193.0971.

Morpholino(pyridin-4-yl)methanone ***4j***. Following GP-B, **4j** was prepared in 24 h and purified by flash chromatography on silica gel (4 g column, heptanes contained 5% Et_3N, 30% EtOAc for 10 CV, then 30−90% EtOAc over 15 CV, hold 90% EtOAc for 10 CV). The material isolated from the column (167 mg) was analyzed by Q-NMR

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and shown to contain 5 wt % 1,10-phenanthroline. Yield of **4j** (159 mg, 0.83 mmol, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74−8.66 (m, 2H), 7.32−7.22 (m, 2H), 3.79 (br s, 4H), 3.62 (s, 2H), 3.37 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 150.3, 142.9, 121.2, 66.7, 47.8, 42.3; TLC (85% EtOAc, 14% heptanes, 1% Et_3N) R_f 0.10; HRMS (ESI-Q-TOF) m/z $[M + H]^+$ Calculated for $C_{10}H_{13}N_2O_2$: 193.0972, found 193.0970.

Morpholino(thiophen-2-yl)methanone ***4k***. Following GP-B, **4k** (215 mg, 0.91 mmol, 91% yield) was prepared in 24 h and isolated as a pale yellow oil by flash chromatography on silica gel (4 g column, 20% EtOAc for 12 CV, then 20−80% EtOAc over 15 CV, hold at 80% EtOAc for 10 CV). Analytical data for **4k** was consistent with that previously reported.[83] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, J = 3.0, 1.3 Hz, 1H), 7.31 (dd, J = 5.0, 2.9 Hz, 1H), 7.14 (dd, J = 5.0, 1.3 Hz, 1H), 3.86−3.30 (s, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 135.9, 127.0, 126.7, 126.2, 66.9, 47.8, 42.9; LCMS (APCI) Calculated for $[M + H]$+ $C_9H_{12}NO_2S$: 198.06, found 198.10.

(4-Chlorophenyl)(1,1-dioxidothiomorpholino)methanone ***5a***. Following GP-B, **5a** (233 mg, 0.85 mmol, 85% yield) was prepared in 20 h and isolated as a white solid by flash chromatography on silica gel (4 g column, 20% EtOAc for 10 CV, then 20−80% EtOAc over 20 CV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 4.08 (s, 4H), 3.06 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 137.0, 132.4, 129.3, 128.6, 52.0, 45.9, 41.2; mp 163−165 °C; TLC (40% EtOAc/heptanes) R_f 0.13; LCMS (APCI) Calculated for $[M + H]$+ $C_{11}H_{13}ClNO_3S$: 274.03, found 274.10. We were unable to obtain an accurate mass measurement for compound **5a** because it did not ionize with ESI. Elemental Analysis (average of 4 runs): Calculated for $C_{11}H_{12}ClNO_3S$: C, 48.27; H, 4.42; N, 5.12. Found: C, 48.53; H, 4.40; N, 5.00.

(4-Chlorophenyl)(4,4-difluoropiperidin-1-yl)methanone ***5b***. Following GP-B, **5b** (237 mg, 0.91 mmol, 91% yield) was prepared in 21 h and isolated as a white solid by flash chromatography on silica gel (4 g column, 5% EtOAc for 10 CV, then 10−50% EtOAc over 20 CV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.30 (m, 4H), 3.90−3.41 (m, 4H), 2.14−1.84 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 136.2, 133.6, 129.0, 128.5, 121.4 (t, J = 242.3 Hz), 44.4, 39.3, 34.1; mp 69−71 °C; TLC (40% EtOAc/heptanes) R_f 0.43; HRMS (ESI-Q-TOF) m/z $[M + H]^+$ Calculated for $C_{12}H_{13}ClF_2NO$ 260.0648, found 260.0641.

tert-Butyl (R)-4-(4-chlorobenzoyl)-2-isopropylpiperazine-1-carboxylate ***5c***. Following GP-B, **5c** (349 mg, 0.95 mmol, 95% yield) was prepared in 18 h and isolated as a viscous, colorless oil by flash chromatography on silica gel (4 g column, 5% EtOAc for 15 CV, then 5−40% EtOAc over 20 CV). Chiral purity (99.6%ee) was measured by HPLC with a ChiralPak IC 250 × 4.6 mm column (80:20 hexanes:ethanol, 25 min, 1.0 mL/min, 210 nm). ^{1}H NMR (600 MHz, DMSO-d_6, 90 °C) δ 7.49 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 4.14 (br s, 1H), 3.90−3.83 (m, 2H), 3.76−3.60 (m, 1H), 3.12−2.96 (m, 2H), 2.90 (ddd, J = 13.4, 12.1, 3.6 Hz, 1H), 1.95 (dq, J = 10.3, 6.6 Hz, 1H), 1.43 (s, 9H), 0.82 (d, J = 6.8 Hz, 6H). ^{13}C NMR (150 MHz, DMSO-d_6, 90 °C) δ 168.2, 153.6, 134.2, 133.8, 128.3, 127.9, 78.6, 56.6, 38.2, 27.6, 25.3, 19.2, 17.9; TLC (40% EtOAc/heptanes) R_f 0.36; HRMS (ESI-Q-TOF) m/z $[M + H]^+ - [C_5H_8O_2]$ Calculated for $C_{14}H_{20}ClN_2O$ 267.1259, found 267.1255. HRMS (ESI-Q-TOF) m/z $[M + H]^+ - [C_4H_8]$ Calculated for $C_{15}H_{20}ClN_2O_3$ 311.1157, found 311.1153.

tert-Butyl 4-(4-chlorobenzoyl)piperazine-1-carboxylate ***5d***. Following GP-B, **5d** (298 mg, 0.92 mmol, 92% yield) was prepared in 19 h and isolated as a white solid by flash chromatography on silica gel (4 g column, 10% EtOAc for 10 CV, then 10−80% EtOAc over 20 CV). Analytical data for **5d** was consistent with that previously reported.[86] ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.33 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 3.65 (br s, 2H), 3.48−3.26 (m, 4H), 1.40 (s, 9H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.4, 154.4, 135.9, 133.8, 128.8, 128.6, 80.3, 47.5, 43.8, 43.4, 42.1, 28.3; LCMS (APCI, acidic mobile phase): Calculated for $[M + 2H - {}^tBu]$+ $C_{12}H_{14}ClN_2O_3$: 269.07, Found 269.25; Calculated for $[M + 2H - Boc]$+ $C_{11}H_{14}ClN_2O$: 225.08, found 225.20.

(4-Chlorophenyl)(2,2,6,6-tetramethylmorpholino)methanone ***5e***. Following GP-B, **5e** (271 mg, 0.96 mmol, 96% yield) was prepared in 18 h and isolated as a viscous, colorless oil by flash chromatography on silica gel (4 g column, 10% EtOAc for 10 CV, then 10−50% EtOAc over 20 CV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.30 (m, 4H), 3.54 (br s, 2H), 3.18 (br s, 2H), 1.37−0.98 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 135.8, 134.2, 128.9, 128.7, 71.5, 56.4, 51.1, 28.2; mp 74−75 °C; TLC (40% EtOAc/heptanes) R_f 0.40; HRMS (ESI-Q-TOF) m/z $[M + H]^+$ Calculated for $C_{15}H_{21}ClNO_2$ 282.1255, found 282.1251.

(4-Chlorophenyl)(4-(trifluoromethyl)piperidin-1-yl)methanone ***5f***. Following GP-B, **5f** (271 mg, 0.93 mmol, 93% yield) was prepared in 20 h and isolated as a white solid by flash chromatography on silica gel (4 g column, 10% EtOAc for 10 CV, then 10−80% EtOAc over 20 CV). ^{1}H NMR (600 MHz, 120 °C, DMSO-d_6) δ 7.48 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 4.08 (d, J = 13.3 Hz, 2H), 3.03−2.98 (m, 2H), 2.63−2.54 (m, 1H), 1.88 (dd, J = 12.6, 3.2 Hz, 2H), 1.51−1.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 136.0, 134.0, 128.9, 128.5, 126.9 (q, J = 278.2 Hz), 46.5, 41.3 40.6 (q, J = 27.7 Hz), 24.8; mp 103−105 °C; TLC (40% EtOAc/heptanes) R_f 0.33; HRMS (ESI-Q-TOF) m/z $[M + H]^+$ Calculated for $C_{13}H_{14}ClF_3NO$ 292.0711, found 292.0705.

N-Benzyl-4-chloro-N-ethylbenzamide ***5g***. Following GP-A, **5g** (161 mg, 0.59 mmol, 59% yield) was prepared in 24 h and isolated as a pale yellow oil by flash chromatography on silica gel (4 g column, 5% EtOAc for 10 CV, then 5−30% EtOAc over 20 CV). ^{1}H NMR (600 MHz, DMSO-d_6, 90 °C) δ 7.49−7.40 (m, 4H), 7.35 (t, J = 7.6 Hz, 2H), 7.32−7.24 (m, 3H), 4.61 (s, 2H), 3.30 (q, J = 7.1 Hz, 2H), 1.06 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d_6, 90 °C) δ 169.1, 137.1, 135.3, 133.5, 127.9, 127.9, 127.7, 126.8, 126.5, 125.7, 48.5, 41.1, 12.4; HRMS (ESI-Q-TOF) m/z $[M + H]^+$ Calculated for $C_{16}H_{17}ClNO$ 274.0993, found 274.0991.

tert-Butyl 1-(4-chlorobenzoyl)piperidine-4-carboxylate ***5h***. Following GP-B, **5h** (291 mg, 0.90 mmol, 90% yield) was prepared in 18 h and isolated as viscous, colorless oil by flash chromatography on silica gel (4 g column, 5% EtOAc for 10 CV, then 5−40% EtOAc over 25 CV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.30 (m, 4H), 4.46 (br s, 1H), 3.69 (br s, 1H), 3.03 (br s, 2H), 2.47 (tt, J = 10.6, 4.1 Hz, 1H), 2.02−1.55 (m, 4H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 169.4, 135.7, 134.5, 128.8, 128.7, 128.5, 80.8, 47.1, 41.9, 28.1; TLC (40% EtOAc/heptanes) R_f 0.33; HRMS (ESI-Q-TOF) m/z $[M + H]^+$ Calculated for $C_{17}H_{23}ClNO_3$ 324.1361, found 324.1358.

(4-Chlorophenyl)(4-phenylpiperidin-1-yl)methanone ***5i***. Following GP-A, **5i** (247 mg, 0.82 mmol, 92% yield) was prepared in 20 h and isolated as a white solid by flash chromatography on silica gel (4 g column, 10% EtOAc for 10 CV, then 10−80% EtOAc over 20 CV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.38 (m, 4H), 7.36−7.28 (m, 2H), 7.28−7.18 (m, 3H), 4.86 (br s, 1H), 3.85 (br s, 1H), 3.13 (br s, 1H), 2.99−2.67 (m, 2H), 2.11−1.57 (m, 4H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.3, 145.0, 135.6, 134.6, 128.8, 128.6, 128.5, 126.7, 126.6, 48.4, 43.0, 42.8, 42.7, 33.9, 32.9, 32.8; mp 75−77 °C; TLC (40% EtOAc/heptanes) R_f 0.38; HRMS (ESI-Q-TOF) m/z $[M + H]^+$ Calculated for $C_{18}H_{19}ClNO$ 300.1150, found 300.1144.

(4-Chlorophenyl)(pyrrolidin-1-yl)methanone ***5j***. Following GP-A, **5j** (137 mg, 0.65 mmol, 65% yield) was prepared in 24 h and isolated as a pale yellow oil by flash chromatography on silica gel (4 g column, 20% EtOAc for 10 CV, then 20−80% EtOAc over 20 CV). Analytical data for **5j** was consistent with that previously reported.[80] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.42 (m, 2H), 7.40−7.32 (m, 2H), 3.71−3.55 (m, 2H), 3.49−3.29 (m, 2H), 2.02−1.79 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 135.8, 135.6, 128.7, 128.5, 49.6, 46.3, 26.4, 24.4; LCMS (APCI) Calculated for $[M + H]$+ $C_{11}H_{13}ClNO$: 210.07, found 210.20.

(S)-(4-Chlorophenyl)(2-methylpiperidin-1-yl)methanone ***5k***. Following GP-A, **5k** (38 mg, 0.16 mmol, 16% yield) was prepared in 29 h and isolated as a pale yellow oil by flash chromatography on silica gel (4 g column, 10% EtOAc for 15 CV, then 10−0% EtOAc over 25 CV). Chiral purity (99.6%ee) was measured by HPLC with a Regis Whelk O (S,S) IC 250 × 4.6 mm column (80:15 hexanes:ethanol, 25 min, 1.0 mL/min, 210 nm). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.28 (m,

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4H), 2.99 (s, 1H), 1.77−1.62 (m, 4H), 1.60−1.35 (m, 4H), 1.24 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 135.5, 135.3, 128.8, 128.1, 30.4, 26.1, 19.0, 16.3; TLC (40% EtOAc/heptanes) R_f 0.38; HRMS (ESI-Q-TOF) m/z [M + H]$^+$ Calculated for $C_{13}H_{17}ClNO$ 238.0993, found 238.0989.

N,N-Dibutyl-4-chlorobenzamide ***5l***. Following GP-A, **5l** (86 mg, 0.32 mmol, 32% yield) was prepared in 48 h and isolated as a pale yellow oil by flash chromatography on silica gel (4 g column, 5% EtOAc for 10 CV, then 5−10% EtOAc over 5 CV). Analytical data for **5l** was consistent with that previously reported.[87] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.34 (m, 2H), 7.32−7.26 (m, 2H), 3.46 (br s, 2H), 3.16 (br s, 2H), 1.62 (br s, 2H), 1.53−1.33 (m, 4H), 1.20−1.07 (m, 2H), 1.03−0.88 (m, 3H), 0.87−0.73 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 135.8, 135.0, 128.6, 128.0, 48.8, 44.6, 30.8, 29.6, 20.3, 19.8, 13.9, 13.7; LCMS (APCI) Calculated for [M + H]+ $C_{15}H_{23}ClNO$: 268.15, found 268.10.

Azepan-1-yl(4-chlorophenyl)methanone ***5m***. Following GP-A, **5m** (120 mg, 0.51 mmol, 51% yield) was prepared in 20 h and isolated as a white solid by flash chromatography on silica gel (4 g column, 10% EtOAc for 10 CV, then 10−80% EtOAc over 20 CV). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.28 (m, 4H), 3.73−3.60 (m, 2H), 3.47−3.23 (m, 2H), 1.88−1.77 (m, 2H), 1.68−1.52 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 135.8, 135.1, 128.7, 128.1, 49.8, 46.5, 29.6, 27.8, 27.3, 26.5; mp 53−55 °C; TLC (40% EtOAc/heptanes) R_f 0.30; HRMS (ESI-Q-TOF) m/z [M + H]$^+$ Calculated for $C_{13}H_{17}ClNO$ 238.0993, found 238.0994.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01686.

Additional optimization experiments, characterization data including copies of ^{1}H and ^{13}C NMR (PDF)

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Notes

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