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A Direct and Mild Conversion of Tertiary Aryl Amides to Methyl Esters Using Trimethyloxonium Tetrafluoroborate: A Very Useful Complement to Directed Metalation Reactions

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Abstract—The scope and generality of a direct process for the conversion of tertiary amides directly to methyl esters has been investigated. The process involves a two-step, one pot procedure in which a tertiary amide is first treated with trimethyloxonium tetrafluoroborate to generate an imidate intermediate which is then hydrolyzed, generally by the addition of saturated aqueous sodium bicarbonate solution. Although this process fails for aliphatic amides, very good yields are realized for a variety of amides derived from aromatic carboxylic acids. Steric hindrance at the *N*-alkyl group is well tolerated; thus *N*,*N*-dimethyl, -diethyl, and -diisopropyl amides can all be utilized successfully.

Introduction

Polyfunctional aromatic moieties are found in a variety of important synthetic and naturally occurring products. Because of their importance and widespread occurrence, a number of methods have been developed to introduce functionality onto an aromatic nucleus. Of these, directed *ortho* lithiation reactions have proven to be one of the most effective and generally useful methods for the regioselective synthesis of 1,2-disubstituted aromatic compounds.[1] The success of these reactions is dependent upon the directing ability of the substituent on the aromatic ring, and it has been shown that tertiary amides serve well in this capacity.[2] On the other hand, the very robust nature of these amides can complicate further elaboration.

In studies toward the total synthesis of (+)-narciclasine,[3] it became necessary to perform two such directed *ortho* lithiations as shown below to prepare the pentasubstituted aromatic moiety found in this structure. It was found that directed metalation reactions using the *N*,*N*-dimethyl amide **1** served admirably for the sequential introduction of oxygen and iodide substituents; however, further progress required the conversion of the tertiary amide **3** to the methyl ester **6** (Scheme 1).

Commonly used procedures for converting tertiary amides to other functional groups usually involve harsh conditions due to the very low reactivity of these amides in nucleophilic additions. These include vigorous acid or base hydrolysis,[4] reduction to give an aldehyde,[5] reduction to give an amine,[6] and reduction to give an alcohol.[7] The difficulty of these transformations is a significant limitation in the use of directed metalation reactions. One recent approach to this problem uses *N*-acyl hydrazides as amide-like directing groups that are more easily converted to the free acid or ester.[8]

It was envisioned that the tertiary amide **3** could be reduced to the aldehyde **5** and subsequently oxidized directly to the methyl ester **6** using Corey–Gilman–Ganem conditions.[9] However, it was found that reduction with Red-Al failed. The use of $LiH_2Al(OEt)_2$ resulted in low yields of the aldehyde accompanied by a product arising from reduction of the aryl iodide. Attempts to oxidize the resulting aldehyde as planned also failed with this substrate.

In an effort to find an alternative method for converting the tertiary amide to the corresponding ester,[10] we were led to examine a procedure that involved treating amide **3** with trimethyloxonium tetrafluoroborate, followed by mild basic hydrolysis to give the desired methyl ester **7** as shown in Scheme 2. This proved to be a reliable and high yielding transformation, which was easily amenable to scale-up. Herein we report the results of a study in which we explore the generality of this method.

Previous Synthetic Work

In 1967, Hanessian reported the successful *N*-deacetylation of secondary amides in acetamido deoxy sugars using

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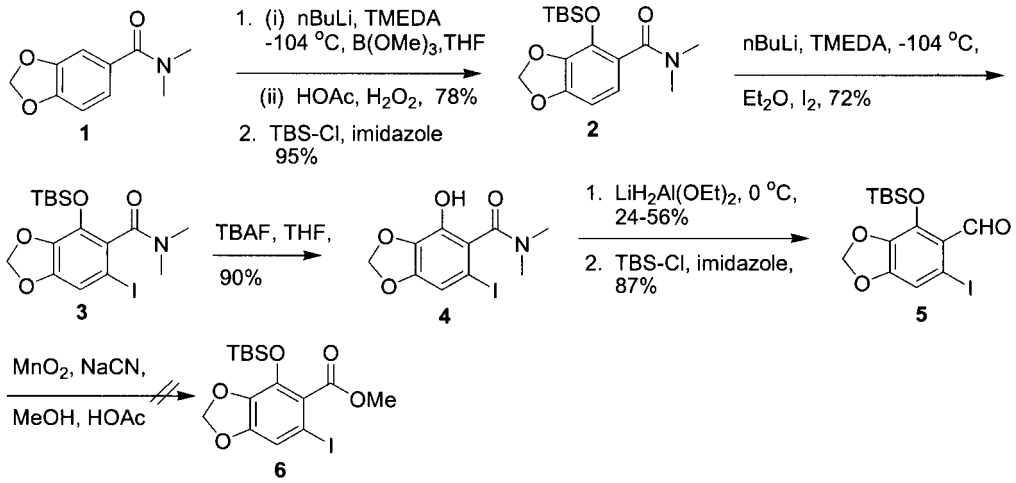


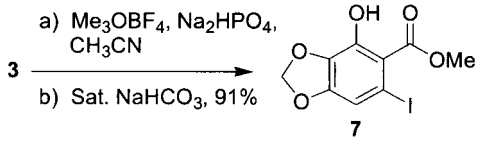
Scheme 1. Synthetic studies directed towards (+)-narciclasine.

triethyloxonium tetrafluoroborate.[11] It was shown that treating *N*-acylated sugars with the alkyloxonium salt, followed by hydrolysis resulted in the free amine and ethyl acetate. Other reports of *N*-deacetylation using this approach soon followed.[12]

The use of alkyloxonium tetrafluoroborate salts has also been investigated in the ring opening of lactams to give amino esters.[13] Thus, Smith and Menezes reported that treatment of lactams with triethyloxonium tetrafluoroborate and subsequent hydrolysis in neutral water gave amino esters.[13b] More recently, McClure and Kiessling showed that both trimethyl- and triethyloxonium tetrafluoroborate salts worked well in the conversion of a variety of primary and secondary amides to the corresponding methyl and ethyl esters. However, tertiary amides were not examined as substrates in either of these reports.[14]

Surprisingly, only a few isolated examples can be found using tertiary amides, despite the potential utility of this transformation as a very useful adjunct to directed metalation reactions. In 1968, Borch reported a two step reduction of both secondary and tertiary amides to give amines.[15] By treating an amide in dichloromethane with triethyloxonium tetrafluoroborate, the imidate ester was formed. After removal of the solvent and subsequent reduction of the residue with $NaBH_4$ in ethanol, the amine was produced. Interestingly, Borch observed that while imidate esters of secondary amides could be isolated by washing the dichloromethane solution with cold sodium carbonate solution, imidate esters of tertiary amides underwent hydrolysis to give ethyl esters.

Later, while studying cycloaddition reactions of acetylenic iminium compounds, Baum and Viehe reported the hydrolysis of an imidate ester to the ethyl ester for characterization purposes.[16] More recently, enroute to a total synthesis of (*s*)-zearalenone, Hegedus and coworkers were able to effectively convert a tertiary aryl amide to the corresponding methyl ester using this approach.[17]



Scheme 2. Direct conversion of an aryl amide to the methyl ester.

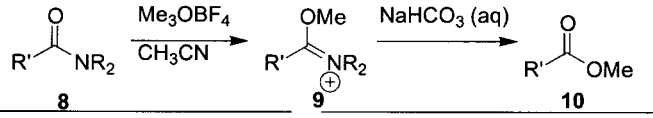
Despite the existence of these three isolated examples, no study has been reported wherein the general utility of converting tertiary amides to esters using alkyloxonium salts is explored. Indeed, in a recent report on the conversion of amides to esters using an intermediate triflate, the authors seem to suggest that this reaction does not work.[10c] We record herein the results of an extensive study of this process, which we have found to provide a powerful complement to directed metalation reactions of aromatic amides.

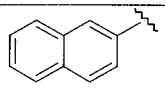
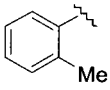
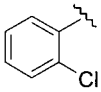
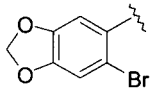
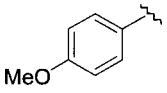
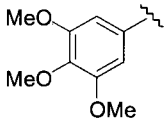
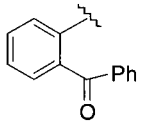
Results and Discussion

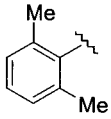
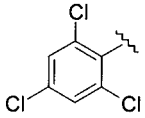
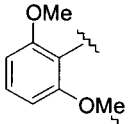
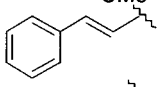
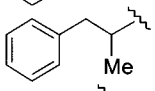
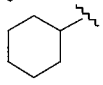
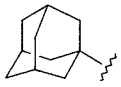
The results obtained with a variety of amides are summarized in Table 1. Since we were primarily interested in this reaction process in the context of directed metalations, our initial efforts focused on amides derived from aromatic carboxylic acids. The ease with which the imidate ester formed from the corresponding *N*,*N*-dimethyl- and *N*,*N*-diethylamides varied little from substrate to substrate. With these aryl substrates, formation of the imidate ester intermediate **9** was usually complete after six hours under the conditions utilized. However additional trimethyloxonium tetrafluoroborate was required to completely consume the amides derived from *p*-methoxybenzoic acid or from 2,4,6-trichlorobenzoic acid (entries 9, 10, 16 and 17).

Hydrolysis of the imidate esters gave mixed results. Although hydrolysis with saturated $NaHCO_3$ generally afforded the methyl ester, we were disappointed by the complete failure to produce methyl esters using the aromatic amides shown in entries 14–19. It can be seen that all of these cases correspond to aryl substrates with *o*-*o*′ substitution. The imidate esters formed from the amides in these cases hydrolyzed to give mainly recovered starting material.

Table 1. Results for the direct conversion of tertiary amides to methyl esters



Entry	R'	Amide	Product (% yield)[a]
1		**8a** R=Me	**10a** (92)
2		**8b** R=Et	(86)
3		**8c** R=*i*-Pr	(90)
4		**8d** R=Me	**10b** (94)
5		**8e** R=Et	(87)
6		**8f** R=Me	**10c** (95)
7		**8g** R=Et	(98)
8		**8h** R=Et	**10d** (88)[b]
9		**8i** R=Me	**10e** (78)[c]
10		**8j** R=Et	(85)[c]
11		**8k** R=Me	**10f** (87)
12		**8l** R=Et	(95)
13		**8m** R=*i*-Pr	**10g** (84)

Entry	R'	Amide	Product (% yield)[a]
14		**8n** R=Me	**10h** (0)[d]
15		**8o** R=Et	(0)[d]
16		**8p** R=Me	**10i** (0)[d]
17		**8q** R=Et	(0)[d]
18		**8r** R=Me	**10j** (0)[e]
19		**8s** R=Et	(0)[e]
20		**8t** R=Me	**10k** (77)[c]
21		**8u** R=Et	(72)[c]
22		**8v** R=Me	**10l** (0)[d]
23		**8w** R=Et	(0)[d]
24		**8x** R=Et	**10m** (0)[d]
25		**8y** R=Me	**10n** (0)[d]

[a] Values represent isolated yields.
[b] Only starting material was recovered.
[c] Na_2HPO_4 was used instead of $NaHCO_3$.
[d] Imidate ester formed, but major product resulted from *N*-dealkylation. Recovered only small amounts of starting material.
[e] pH=10 phosphate buffer was used instead of $NaHCO_3$.

It seems likely that this apparent hydrolysis actually occurs by nucleophilic *O*-dealkylation due to severe steric hindrance for nucleophilic addition to the iminium carbon of the intermediate imidate in these cases (Fig. 1). In an attempt to retard reaction via this pathway, we investigated the use of triethyloxonium tertrafluoroborate in two cases, using substrates **8q** and **8x**. In neither case was a preparatively useful result obtained, although a small amount of ethyl ester was detectable in the crude reaction product in the case of **8q**. The imidate esters formed from the amides derived from bromopiperonylic acid, and *p*-methoxybenzoic acid (entries 8–10) also suffered incomplete hydrolysis using $NaHCO_3$. Complete hydrolysis of these imidate esters could be accomplished using a pH=10 phosphate buffer or a saturated solution of Na_2HPO_4, however.

It is interesting to note that compounds with substitution in both positions *ortho* to the amide group failed to produce methyl esters using this method. This contradicts the earlier observation that compound **3** was efficiently converted to the methyl ester **7** despite the presence of substituents in both *ortho* positions. To better understand this apparent contradiction, the reaction was carried out using both the free hydroxyl substrate **4** and the *O*-methyl protected derivative **11** corresponding to substrate **3** as shown in Scheme 3. While compound **4** with an unprotected hydroxyl substituent worked well, the methoxy substituted compound **11** gave only starting material as well as unhydrolyzed imidate ester after several days. Since the TBS protected compound **3** actually affords the free phenol as product, it seems clear that the sequence of events in this case is initial

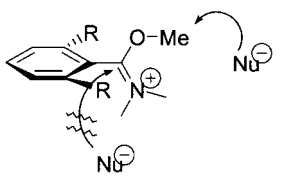
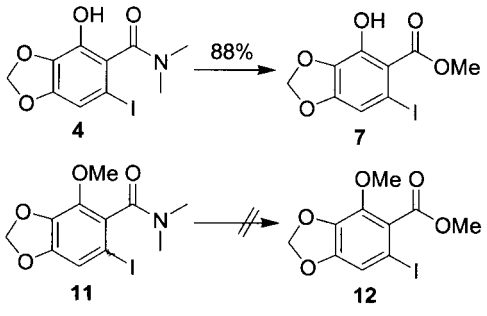
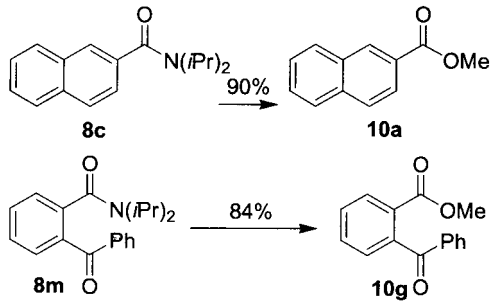


Figure 1. Pathways for imidate hydrolysis.



Scheme 3. Result for *ortho–ortho'* disubstituted aryl amides.



Scheme 4. Result for sterically demanding aryl amides.

cleavage of the TBS ether, followed by imidate hydrolysis. It is not clear in these cases whether the free hydroxyl actually serves to assist imidate hydrolysis or simply presents a sterically less demanding substituent than those in the protected substrates.

The apparent lack of sensitivity to the steric environment present at the nitrogen center prompted an examination of the use of *N*,*N*-diisopropyl aryl amides. As shown in Scheme 4 the direct conversion of *N*,*N*-diisopropyl aryl amides to methyl esters using these conditions worked well despite the extreme steric demand of the *N*-alkyl substituents.

Given the success realized with a variety of aryl amides, attention was then turned to an examination of simple aliphatic amide derivatives. The α-β unsaturated dimethyl- and diethyl amides derived from cinammic acid could be successfully converted to methyl esters in good yield using this approach provided that the hydrolysis was carried out using pH=10 phosphate buffer. Also, in this case, the starting amides were never completely converted to the imidate, even when additional Meerwein's reagent was used. However, *saturated* aliphatic amides (entries 22–25) could not be converted to methyl esters via this protocol. With these substrates, hydrolysis of the intermediate imidates occurred to give back the starting amide, rather than the desired methyl ester. This happened both with a non-enolizable substrate (adamantyl), as well as with the diethyl amide derived from cyclohexane carboxylic acid, and the dimethyl and diethyl amides derived from 2-methyl-3-phenylpropionic acid. Although a variety of conditions were examined for these hydrolyses in addition to those described previously (including the use of pH=4, 7, or 10 buffer solutions) no success was realized in these cases. The pH dependence of this reaction type has been extensively examined particularly as it relates to the mechanisms of amide hydrolysis and ester aminolysis; in general, these mechanisms are quite complex.[18]

This result stands in sharp contrast to those obtained by Charette with aliphatic amides and his triflate procedure, where good yields were obtained.[10c] An inspection of the available data suggests that Charette's procedure is far superior to the one investigated herein for aliphatic amides, but that the Meerwein method may give better yields with aromatic amides. Thus it appears that these two procedures may be complementary with respect to the scope of substrates that can be employed.

Summary and Conclusions

A mild conversion of a variety of tertiary amides to methyl esters using trimethyloxonium tetrafluoroborate has been documented. While most aryl amides were effectively converted to methyl esters using the conditions described, imidate esters of aliphatic amides and aryl amides with *ortho–ortho′* substitution hydrolyzed to give back the amide. The sole exception to this generalization was the case of aryl amides with *ortho–ortho′* substitution where one of the groups was hydroxyl, or a group which cleaves under the reaction conditions to a free hydroxyl, such as TBS. Since aryl triflates (derived from such phenols) can be elaborated in a number of useful ways, this observation has clear impact on synthetic planning en route to densely functionalized aromatic compounds using a directed metalation strategy. The steric nature of the *N*-alkyl groups has no appreciable affect on the success of the conversion. Thus, *N*,*N*-dimethyl, *N*,*N*-diethyl, and *N*,*N*-diisopropyl aryl amides were all cleanly converted to methyl esters using this mild procedure.

Experimental

All amides used are readily available from well-established chemical transformations.[19] Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, U.K., 1966). All other reagents were purchased and used without further purification. Yields were calculated for material judged homogenous by thin-layer chromatography and NMR. Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} plates eluting with the solvents indicated, visualizing by a 254 nm UV lamp, and stained with an ethanolic solution of 12-molybdophosphoric acid or *p*-anisaldehyde. Flash column chromatography was performed with Davisil 62 silica gel, slurry packed with 5% EtOAc/hexanes or $CHCl_3$ in glass columns, and flushed with hexanes or $CHCl_3$ respectively. Chromatography was also carried out using a Chromatotron, using glass plates coated with silica gel (P.F. 254 60) of 2 and 4 mm thickness (RPLC). Nuclear magnetic resonance spectra were acquired at 300 MHz for ^1H, and 75 MHz for ^{13}C. Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 77.0 ppm. The abbreviations s, d, t, apt t, q, br s, dd, tt, Abq, and m stand for the resonance multiplicity singlet, doublet, triplet, apparent triplet, quartet, broad singlet, doublet of doublets, triplet of triplets, AB quartet, and multiplet, respectively. Melting points were obtained on an Electro thermal melting point apparatus and are uncorrected. Analytical C and H combustion analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Glassware for all reactions was oven dried at 105°C and cooled in a dessicator prior to use.

Representative procedure for the direct conversion of tertiary aryl amides to esters

Preparation of methyl naphthalene-2-carboxylate (10a). To a stirring solution of *N*,*N*-dimethyl-2-naphthylcarboxamide (100 mg, 0.50 mmol) in 2.5 mL of CH_3CN at rt, was

added Na_2HPO_4 (107 mg, 0.75 mmol), followed by $(CH_3)_3OBF_4$ (223 mg, 1.5 mmol). After consumption of the amide was complete, as indicated by TLC analysis (ca. 18 h), a saturated solution of $NaHCO_3$ (10 mL) was slowly added, followed by solid $NaHCO_3$ (100 mg). The resulting mixture was stirred for 18 h then extracted with EtOAc (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered through a pad of Celite (4 mm), and concentrated under reduced pressure. Purification of this material was accomplished by RPLC using a 2 mm plate, eluting with 50% ethyl acetate/hexanes, collecting 8 mL fractions. The product containing fractions (6–7) were combined and concentrated to give **10a** (86 mg, 92% yield) as a colorless crystalline solid. Ester **10a** was also obtained in 86 and 90% yields from the corresponding *N*,*N*-diethyl and *N*,*N*-diisopropyl amides, respectively: mp 79–81°C (lit.[20] mp 78–79°C); R_f 0.56 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 8.06 (d, J=8.4 Hz, 1H), 7.95 (d, J=7.2 Hz, 1H), 7.89 (d, J=9.0 Hz, 2H), 7.54–7.60 (m, 2H), 3.98 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 167.2, 135.5, 132.4, 131.0, 129.3, 128.2, 128.1, 127.7, 127.3, 126.6, 125.2, 52.2; IR ($CHCl_3$) 1715 cm^{-1}.

Methyl (2*E*)-3-phenylprop-2-enoate (10k).[21] Obtained as a colorless crystalline solid in 77 and 72% yields from the corresponding *N*,*N*-dimethyl and *N*,*N*-diethyl amides, respectively: mp 31–31.5°C; R_f 0.65 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J=15.9 Hz, 1H), 7.53–7.51 (m, 2H), 7.39–7.37 (m, 3H), 6.44 (d, J=16.2, 1H), 3.81 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 167.4, 144.8, 134.3, 130.2, 128.8, 128.0, 117.7, 51.6; IR ($CHCl_3$) 1711 cm^{-1}.

Analytical data for methyl 2-methylbenzoate (10b).[22] Obtained as a light yellow oil in 94 and 87% yield from the corresponding *N*,*N*-dimethyl and *N*,*N*-diethyl amides, respectively: R_f 0.59 (40% Et_2O/pentane); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.91 (d, J=8.4 Hz, 1H), 7.39 (t, J=7.2 Hz, 1H), 7.26–7.21 (m, 2H), 3.89 (s, 3H), 2.60 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 168.0, 140.1, 131.9, 131.6, 130.5, 129.5, 125.6, 51.7, 21.7; IR (neat) 1724 cm^{-1}.

Analytical data for methyl 2-chlorobenzoate (10c).[23] Obtained as a light yellow oil in 95 and 98% yield from the corresponding *N*,*N*-dimethyl and *N*,*N*-diethyl amides, respectively: R_f 0.58 (40% Et_2O/pentane); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.82 (d, J=6.9 Hz, 1H), 7.45–7.31 (m, 3H), 3.94 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 166.1, 133.6, 132.5, 131.3, 131.0, 130.0, 126.5, 52.3; IR ($CHCl_3$) 1730 cm^{-1}.

Analytical data for methyl 6-bromo-2*H*-benzo[3,4-*d*]1,3-dioxolene-5-carboxylate (10d). Obtained as a colorless crystalline solid in 88% yield from the corresponding *N*,*N*-diethyl amide: mp 81–82°C (lit.[24] mp 84–85°C); R_f 0.67 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.32 (s, 1H), 7.09 (s, 1H), 6.05 (s, 2H), 3.89 (s, 3H); 75 MHz ^{13}C NMR ($CDC1_3$) δ 165.7, 150.9, 147.1, 124.4, 114.9, 114.3, 111.0, 102.5, 52.3; IR ($CHCl_3$) 1727 cm^{-1}.

Analytical data for methyl 4-methoxybenzoate (10e).[25] Obtained as a light yellow oil in 78 and 85% yield from the corresponding *N*,*N*-dimethyl and *N*,*N*-diethyl amides, respectively: R_f 0.50 (25% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J=9.0 Hz, 2H), 6.92 (d, J=9.0 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 166.8, 163.3, 131.5, 122.5, 113.5, 55.4, 51.8; IR ($CHC1_3$) 1712, 1606 cm^{-1}.

Analytical data for methyl 3,4,5-trimethoxybenzoate (10f). Obtained as a colorless crystalline solid in 87 and 95% yield from the corresponding *N*,*N*-dimethyl and *N*,*N*-diethyl amides, respectively: mp 79–81°C (lit.[26] mp 82–83°C); R_f 0.56 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.31 (s, 2H), 3.91 (s, 9H), 3.91 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 166.6, 152.9, 142.1, 125.1, 106.7, 60.8, 56.1, 52.2; IR ($CHCl_3$) 1715, 1592 cm^{-1}.

Analytical data for methyl 2-benzoylbenzoate (10g).[27] Obtained as a light yellow oil in 84% yield from the corresponding *N*,*N*-diisopropyl amide: R_f 0.45 (25% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 8.04–8.07 (m, 1H), 7.77–7.40 (m, 8H), 3.61 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 197.1, 166.4, 141.6, 137.1, 133.1, 132.4, 130.1, 129.6, 129.2, 129.1, 128.5, 127.7, 52.2; IR ($CHCl_3$) 1723, 1671 cm^{-1}.

Analytical data for methyl 4-hydroxy-6-iodo-2*H*-benzo-[3,4-*d*]1,3-dioxolene-5-carboxylate (7).[3] Obtained as a light yellow solid in 88% yield from the corresponding *N*,*N*-dimethyl amide: mp 155–157°C; R_f 0.18 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 11.00 (s, 1H), 7.20 (s, 1H), 6.08 (s, 2H), 3.97 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 168.7, 152.6, 146.7, 135.6, 115.4, 112.4, 102.9, 84.6, 51.9; IR (KBr) 1666 cm^{-1}.

Representative procedure for the syntheses of tertiary amides from the corresponding acid chloride

Preparation of *N*,*N*-dimethyl(2,4,6-trichlorophenyl)carboxamide (8p). To a stirring suspension of dimethyl amine hydrochloride salt (0.67 mg, 8.2 mmol) and pyridine (1.5 mL, 19.0 mmol) in 15 mL of CH_2Cl_2 at 0°C was added 2,4,6-trichlorobenzoyl chloride (1.0 g, 4.1 mmol) dropwise via syringe. The resulting solution was stirred 18 h at rt, then 15 mL of CH_2Cl_2 was added, and the solution was washed, alternating between saturated solutions of $CuSO_4$ (2×25 mL) and brine (2×25 mL). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification of this material was accomplished by gravity chromatography, eluting with 200 mL of each of 20, 40 and 60% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to give **8p** (1.0 g, quantitative) as a colorless crystalline solid: mp 65°C; R_f 0.48 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 2H), 3.16 (s, 3H), 2.87 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 164.5, 135.2, 134.1, 132.2, 128.0, 37.2, 34.4; IR (KBr) 1640 cm^{-1}.

Analytical data for *N*,*N*-diethyl(2,4,6-trichlorophenyl)-carboxamide (8q). Obtained as a light yellow oil: R_f 0.58 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.35 (s, 2H), 3.61 (q, J=7.2 Hz, 2H), 3.15 (q, J=7.2 Hz, 2H), 1.28 (t, J=7.2 Hz, 3H), 1.14 (t, J=7.2 Hz, 3H); 75 MHz

^{13}C NMR ($CDCl_3$) δ 163.7, 135.0, 134.4, 132.4, 128.1, 42.7, 39.0, 13.7, 12.3; IR ($CHCl_3$) 1637 cm^{-1}.

Analytical data for (2,6-dimethoxyphenyl)-*N*,*N*-dimethylcarboxamide (8r). Obtained as a colorless crystalline solid: mp 105–107°C (lit.[28] mp 105–107°C); R_f 0.13 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.26 (apt t, J=8.4 Hz, 1H), 6.56 (d, J=8.4 Hz, 2H), 3.81 (s, 6H), 3.13 (s, 3H), 2.83 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$, -20°C) δ 167.1, 156.5, 130.1, 115.0, 103.9, 55.8, 37.6, 34.4, 22.1; IR (KBr) 1636 cm^{-1}.

Analytical data for (2,6-dimethoxyphenyl)-*N*,*N*-diethylcarboxamide (8s). Obtained as a colorless crystalline solid: mp 70–71°C; R_f 0.13 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.24 (apt t, J=8.4 Hz, 1H), 6.55 (d, J=8.4 Hz, 2H), 3.79 (s, 6H), 3.59 (q, J=7.2 Hz, 2H), 3.13 (q, J=7.2 Hz, 2H), 1.24 (t, J=7.2 Hz, 3H), 1.01 (t, J=7.2 Hz, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 166.2, 156.5, 129.8, 115.6, 103.9, 55.7, 42.5, 38.6, 13.6, 12.8; IR (KBr) 1632 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found C, 65.94; H, 8.06; N, 5.87.

Analytical data for *N*,*N*-bis(methylethyl)[2-phenylcarbonyl)phenyl]carboxamide (8m).[29] Obtained as a colorless crystalline solid: mp 92–94°C; R_f 0.25 (25% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J=7.5 Hz, 2H), 7.58–7.32 (m, 7H), 3.87–3.82 (m, 1H), 3.48–3.43 (m, 1H), 1.44 (d, J=6.6 Hz, 6H), 1.20 (d, J=6.6 Hz, 6H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 196.7, 169.5, 139.8, 137.3, 136.7, 132.8, 130.7, 130.3, 129.9, 128.2, 127.5, 126.1, 51.3, 45.7, 20.4, 20.2; IR (KBr) 1661, 1628 cm^{-1}.

Analytical data for adamantanyl-*N*,*N*-dimethylcarboxamide (8y). Obtained as a colorless crystalline solid: mp 73–74°C; R_f 0.35 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.07 (br s, 6H), 2.02 (br s, 9H), 1.72 (br s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 176.8, 41.8, 38.6, 38.4, 36.5, 28.4; IR (KBr) 1613 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found C, 75.37; H, 10.13; N, 6.69.

Representative procedure for the syntheses of tertiary amides from the corresponding carboxylic acid

Preparation of *N*,*N*-dimethyl-2-naphthylcarboxamide (8a). To a stirring suspension of 2-naphthoic acid (600 mg, 3.48 mmol) in 25 mL of CH_2Cl_2 was added the minimum amount of DMF (5.00 mL) to dissolve the acid. Oxalyl chloride (460 μL, 5.25 mmol) was added dropwise at rt. The solution was heated at reflux for 2 h, then cooled to rt and transferred to a suspension of dimethyl amine hydrochloride salt (570 mg, 7.00 mmol), and pyridine (1.13 mL, 14.0 mmol) in 10 mL of CH_2Cl_2. After 20 h of stirring, the solution was washed with 2% HCl (3×25 mL), dried over $MgSO_4$, filtered through a pad of Celite (4 mm), and concentrated under reduced pressure. Purification of this material was accomplished by RPLC using a 4 mm plate, eluting with 40% Et_2O/pentane, collecting 8 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to give **8a** (572 mg, 82% yield) as a colorless crystalline solid: mp 83–84°C (lit.[30] mp 87–88°C); R_f 0.12 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.92–7.84 (m, 4H), 7.54–7.50 (m, 3H), 3.16 (br s, 3H), 3.03 (br s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 171.6, 133.6, 133.5, 132.6, 128.3, 128.1, 127.7, 126.9, 126.8, 126.5, 124.4, 39.6, 35.4; IR (KBr) 1619 cm^{-1}. Anal. Calcd for $C_9H_8Cl_3NO$: C, 42.81; H, 3.19; N, 5.55. Found C, 42.74; H, 3.18; N, 5.44.

Analytical data for *N*,*N*-diethyl-2-naphthylcarboxamide (8b). Obtained as a colorless crystalline solid: mp 35–37°C; R_f 0.33 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.88–7.84 (m, 4H), 7.53–7.45 (m, 3H), 3.59 (br s, 2H), 3.30 (br s, 2H), 1.28 (br s, 3H), 1.13 (br s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 171.2, 134.6, 133.3, 132.7, 128.2, 128.1, 127.7, 126.7, 126.5, 125.7, 123.9, 43.3, 39.3, 14.2, 12.9; IR (KBr) 1617 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found C, 79.04; H, 7.50; N, 6.06.

Analytical data for (2*E*)-*N*,*N*-dimethyl-3-phenylprop-2-enamide (8t). Obtained as a colorless crystalline solid: mp 93–95°C (lit.[31] mp 96–98°C); R_f 0.12 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J=15.6 Hz, 1H), 7.55–7.52 (m, 2H), 7.38–7.36 (m, 3H), 6.90 (d, J=15.6 Hz, 1H), 3.18 (s, 3H), 3.08 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 166.7, 142.3, 135.3, 129.5, 128.8, 127.8, 117.4, 37.4, 35.9; IR (KBr) 1652 cm^{-1}.

Analytical data for (2*E*)-*N*,*N*-diethyl-3-phenylprop-2-enamide (8u). Obtained as a colorless crystalline solid: mp 65–66°C (lit.[32] mp 67°C); R_f 0.25 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J=15.4 Hz, 1H), 7.55–7.51 (m, 2H), 7.40–7.34 (m, 3H), 6.83 (d, J=15.4 Hz, 1H), 3.49 (br d, 4H), 1.26–1.20 (m, 6H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 165.6, 142.2, 135.4, 129.4, 128.7, 127.7, 117.7, 42.2, 41.0, 15.0, 13.2; IR (KBr) 1648 cm^{-1}.

Analytical data for *N*,*N*-dimethyl(2-methylphenyl)carboxamide (8d).[33] Obtained as a light yellow oil: R_f 0.07 (40% Et_2O/pentane); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.29–7.17 (m, 4H), 3.13 (s, 3H), 2.83 (s, 3H), 2.29 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 171.4, 136.6, 133.8, 130.2, 128.6, 125.8, 125.6, 38.2, 34.4; IR (neat) 1641 cm^{-1}.

Analytical data for *N*,*N*-diethyl(2-methylphenyl)carboxamide (8e).[2] Obtained as a light yellow oil: R_f 0.42 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.28–7.14 (m, 4H), 3.74 (br s, 1H), 3.37 (br s, 1H), 3.13 (q, J=7.2 Hz, 2H), 2.29 (s, 3H), 1.26 (t, J=7.2 Hz, 3H), 1.03 (t, J=7.2 Hz, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 170.8, 137.0, 133.8, 130.2, 128.5, 125.7, 125.4, 42.6, 38.6, 18.7, 13.9, 12.8; IR (neat) 1634 cm^{-1}.

Analytical data for (2-chlorophenyl)-*N*,*N*-dimethylcarboxamide (8f).[34] Obtained as a light yellow oil: R_f 0.09 (40% Et_2O/pentane); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.41–7.26 (m, 4H), 3.14 (s, 3H), 2.86 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 168.2, 136.1, 130.0, 129.9, 129.3, 127.5, 127.0, 37.9, 34.4; IR (neat) 1639 cm^{-1}.

Analytical data for (2-chlorophenyl)-*N*,*N*-diethylcarboxamide (8g).[2] Obtained as a light yellow oil: R_f 0.39 (50%

EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.41–7.26 (m, 4H), 3.83–3.76 (m, 1H), 3.41–3.18 (m, 1H), 3.19–3.12 (m, 2H), 1.27 (t, J=7.5 Hz, 3H), 1.06 (t, J=6.9 Hz, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 167.7, 136.6, 130.2, 129.7, 129.5, 127.4, 126.9, 42.6, 38.9, 13.9, 12.6; IR (neat) 1638 cm^{-1}.

Analytical data for *N*,*N*-diethyl(4-methoxyphenyl)carboxamide (8j).[35] Obtained as a light yellow oil: R_f 0.34 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J=9.0 Hz, 2H), 6.90 (d, J=9.0 Hz, 2H), 3.83 (s, 3H), 3.42 (br s, 4H), 1.18 (br s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$, -20°C) δ 171.1, 159.8, 128.9, 127.9, 113.3, 55.1, 43.2, 39.0, 14.1, 12.7; IR (neat) 1631 cm^{-1}.

Analytical data for *N*,*N*-diethyl(3,4,5-trimethoxyphenyl)carboxamide (8l). Obtained as a light yellow oil: R_f 0.16 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.60 (s, 2H), 3.87 (s, 6H), 3.86 (s, 3H), 3.51 (br s, 2H), 3.32 (br s, 2H), 1.21 (br s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$, -20°C) δ 170.9, 153.8, 137.6, 132.6, 102.6, 60.9, 56.0, 43.2, 39.1, 14.3, 12.8; IR ($CHCl_3$) 1618 cm^{-1}. Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found C, 62.82; H, 8.00; N, 5.34.

Analytical data for (2,6-dimethylphenyl)-*N*,*N*-dimethylcarboxamide (8n). Obtained as a colorless crystalline solid: mp 59–60°C (lit.[36] mp 62–63°C); R_f 0.18 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.14 (dd, J=6.9, J=8.4 Hz, 1H), 7.02 (d, J=7.2 Hz, 2H), 3.15 (s, 3H), 2.79 (s, 3H), 2.23 (s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 171.2, 136.5, 133.3, 128.1, 127.3, 37.3, 34.0, 18.8; IR (KBr) 1633 cm^{-1}.

Analytical data for (2,6-dimethylphenyl)-*N*,*N*-diethylcarboxamide (8o).[37] Obtained as a colorless crystalline solid: mp 31–33°C; R_f 0.38 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.13 (dd, J=6.9, J=8.4 Hz, 2H), 7.01 (d, J=7.2 Hz, 2H), 3.61 (q, J=7.2 Hz, 2H), 3.11 (q, J=7.2 Hz, 2H), 2.25 (s, 6H), 1.28 (t, J=7.2 Hz, 3H), 1.03 (t, J=7.2 Hz, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 170.3, 136.8, 133.4, 128.0, 127.4, 42.2, 38.1, 19.0, 13.8, 12.7; IR (KBr) 1625 cm^{-1}.

Analytical data for 2-methyl-*N*,*N*-dimethyl-3-phenylpropanamide (8v).[38] Obtained as a light yellow oil: R_f 0.33 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.29–7.16 (m, 5H), 3.02–2.94 (m, 2H), 2.88 (s, 3H), 2.79 (s, 3H), 2.68–2.60 (m, 1H), 1.14 (d, J=6.6 Hz, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 175.8, 140.1, 128.9, 128.2, 126.1, 40.4, 37.8, 36.9, 35.5, 17.4; IR (neat) 1644 cm^{-1}.

Analytical data for 2-methyl-*N*,*N*-diethyl-3-phenylpropanamide (8w). Obtained as a light yellow oil: R_f 0.15 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.27–7.15 (m, 5H), 3.47–3.36 (m, 1H), 3.25–3.12 (m, 1H), 3.09–3.00 (m, 3H), 2.92–2.82 (m, 1H), 2.67–2.60 (m, 1H), 1.16 (d, J=6.6 Hz, 3H), 1.02 (t, J=7.2 Hz, 3H), 0.96 (t, J=7.2 Hz, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 175.1, 140.2, 129.0, 128.2, 126.0, 41.2, 40.7, 40.4, 38.1, 18.2, 14.5, 12.9; IR (neat) 1638 cm^{-1}.

Representative procedure for the syntheses of tertiary amides from the corresponding aldehyde via Gilman oxidation[19a]

Preparation of *N*,*N*-dimethyl(3,4,5-trimethoxyphenyl)-carboxamide (8k). To a stirring solution of NaCN (625 mg, 12.7 mmol) in 27 mL of *i*-PrOH was added a 2.0 M solution of dimethyl amine in $CHCl_3$ (12.7 mL, 25.5 mmol), 3,4,5-trimethoxy benzaldehyde (500 mg, 2.55 mmol), and MnO_2 (4.40 g, 51.0 mmol). After stirring for 20 h at rt, the solution was filtered through a pad of Celite (8 mm) and concentrated under reduced pressure to give **8k** (600 mg, 98% yield) as a light yellow oil: R_f 0.10 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.64 (s, 2H), 3.87 (s, 6H), 3.86 (s, 3H), 3.10 (br s, 3H), 3.02 (br s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$, −20°C) δ 171.2, 152.9, 138.0, 131.6, 103.4, 60.8, 55.9, 39.6, 35.2; IR (neat) 1626 cm^{-1}.

Analytical data for (6-bromo(2*H*-benzo[3,4-*d*]1,3-dioxolen-5-yl))-*N*,*N*-diethylcarbamide (8h). Obtained as a colorless crystalline solid: mp 74–76°C; R_f 0.39 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.99 (s, 1H), 6.71(s, 1H), 6.00 (d, J=6.0 Hz, 2H), 3.85–3.74 (m, 1H), 3.35–3.24 (m, 1H), 3.18 (q, J=7.2 Hz, 2H), 1.25 (t, J=7.2 Hz, 3H), 1.08 (t, J=7.2 Hz, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 168.0, 148.5, 147.4, 131.7, 112.8, 110.1, 107.4, 101.0, 42.7, 38.9, 13.9, 12.4; IR (KBr) 1626 cm^{-1}. Anal. Calcd for $C_{12}H_{14}BrNO_3$: C, 48.02; H, 4.70; N, 4.67. Found C, 48.03; H, 4.63; N, 4.61.

Analytical data for *N*,*N*-dimethyl(4-methoxyphenyl)carboxamide (8i).[39] Obtained as a light yellow oil: R_f 0.13 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.41 (d, J=9.0 Hz, 2H), 6.90 (d, J=8.7 Hz, 2H), 3.83 (s, 3H), 3.06 (br s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$, −20°C) δ 171.3, 160.2, 129.0, 127.8, 113.2, 55.2, 39.7, 35.4; IR (neat) 1633 cm^{-1}.

Representative procedure for the syntheses of tertiary amides from the corresponding aldehyde via radical oxidation[19b]

Preparation of cyclohexyl-*N*,*N*-diethylcarboxamide (8x).[40] To a stirring solution of cyclohexanecarboxaldehyde (2.00 g, 1.80 mmol) in 50 mL of CCl_4 at rt was added AIBN (50.0 mg, 0.300 mmol), and NBS (4.13 g, 23.2 mmol). The flask was then equipped with a reflux condenser, placed in a pre-heated oil bath at 95°C, and stirred for 12 min. The reaction was then cooled to 0°C, and diethyl amine (2.80 mL, 27.0 mmol) was added dropwise via syringe. The solution was stirred for 10 min at rt, then filtered to remove solid material, washing with 20 mL of CCl_4. The filtrate was washed with water (2×50 mL), the layers were separated, dried over $MgSO_4$, and concentrated under reduced pressure. This material was purified by RPLC using a 4 mm plate, eluting with 40% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to give **8x** (1.96 g, 60% yield) as a light yellow oil: R_f 0.45 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.36 (q, J=7.0 Hz, 2H), 3.33(q, J=7.2 Hz, 2H), 2.40 (tt, J=3.5, J=11.4 Hz, 1H), 1.82–1.78 (m, 2H), 1.72–1.67 (m, 2H),

1.62–1.49 (m, 2H), 1.30–1.23 (m, 4H), 1.18 (t, J=7.2 Hz, 3H), 1.09 (t, J=7.2 Hz, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 175.5, 41.6, 40.8, 29.6, 25.9, 25.8, 15.0, 13.1; IR (neat) 1647 cm^{-1}.

Analytical data for *N*,*N*-bis(methylethyl)-2-naphthylcarboxamide (8c). Obtained as a colorless crystalline solid: mp 146–148°C (lit.[41] mp 150–152°C); R_f 0.63 (50% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.87–7.80 (m, 4H), 7.52–7.49 (m, 2H), 7.43–7.26 (m, 1H); 3.75 (br s, 1H), 3.64 (br s, 1H), 1.50 (br s, 6H), 1.23 (br s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$, −20°C) δ 170.9, 136.0, 132.8, 132.7, 128.2, 128.1, 127.7, 126.5, 124.7, 123.2, 51.0, 45.8, 20.7, 20.5; IR (KBr) 1620 cm^{-1}.

Representative procedure for the syntheses of tertiary amides from the corresponding methyl ester[19c]

Preparation of (6-iodo-4-methoxy(2*H*-benzo[3,4-*d*]1,3-dioxolen-5-yl))-*N*,*N*-dimethylcarboxamide (11). To a stirring suspension of dimethyl amine hydrochloride salt (206 mg, 2.6 mmol) in 20 mL of benzene at 0°C was added a 2.0 M solution of trimethyl aluminum in hexanes (1.3 mL, 2.6 mmol) dropwise. The resulting mixture was stirred for 2 h at rt, then transferred to a stirring solution of methyl 6-iodo-4-methoxy-2*H*-benzo[3,4-*d*]1,3-dioxolene-5-carboxylate (425 mg, 1.3 mmol) in 15 mL of benzene. This mixture was heated at reflux for 72 h, then cooled to rt and quenched by addition of 5% HCl solution. The layers were separated and the aqueous layer was extracted with EtOAc (2×25 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by flash chromatography, eluting with 100 mL of each of 25, 50, 75 and 100% EtOAc/hexanes, collecting 8 mL fractions. The product containing fractions were combined and concentrated under reduced pressure to give **11** (93 mg, 21% yield) as a light yellow crystalline solid: R_f 0.18 (50% EtOAc/hexanes); mp 130–132°C; 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.95 (s, 1H), 5.96 (Abq, $\Delta\nu$=5.6 Hz, J=1.2 Hz, 2H), 3.98 (s, 3H), 3.12 (s, 3H), 2.86 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 168.3,150.2, 140.2, 137.0, 129.0, 113.0, 101.6, 81.6, 60.2, 37.8, 34.7; IR (KBr) 1610 cm^{-1}.

Analytical data for (4-hydroxy-6-iodo(2*H*-benzo[3,4-*d*]1,3-dioxolen-5-yl))-*N*,*N*-dimethylcarboxamide (4). Obtained as a colorless crystalline solid: mp 217–219°C (lit.[3] mp 218–220°C) R_f 0.33 (100% EtOAc/hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.55 (br s, 1H), 6.73 (s, 1H), 5.92 (d, J=19.7 Hz, 2H), 3.14 (s, 3H), 2.91 (s, 3H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 170.5, 149.8, 138.0, 137.1, 126.6, 110.8, 102.3, 80.6, 38.3, 35.0; IR (KBr) 1604 cm^{-1}.

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