JOC Article

Highly Diastereoselective Arylation of (*S*)-Mandelic Acid Enolate: Enantioselective Synthesis of Substituted (*R*)-3-Hydroxy-3-phenyloxindoles and (*R*)-Benzylic Acids and Synthesis of Nitrobenzophenones[#]

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An easy access to substituted (*R*)-3-hydroxy-3-phenyloxindoles, (*R*)-benzylic acids, and benzophenones is described. The reaction of the lithium enolate of the (2*S*,5*S*)-*cis*-1,3-dioxolan-4-one derived from optically active (*S*)-mandelic acid and pivalaldehyde with several *o*- and *p*-halonitrobenzenes proceeds readily to give the corresponding arylation products in good yields and diastereoselectivities. The reduction of the nitro group with Zn/HCl/EtOH in the *o*-nitro arylation products with concomitant intramolecular aminolysis of the dioxolanone moiety leads directly to enantiomerically pure (*R*)-3-hydroxy-3-phenyloxindoles. On the other hand the basic hydrolysis of the dioxolanone moiety in all the arylation products (ortho and para) leads to enantiomerically pure substituted (*R*)-benzylic acids. The oxidative decarboxylation of these latter with oxygen as terminal oxidant in the presence of pivalaldehyde and the Co(III)-Me$_2$opba complex as catalyst gives substituted nitrobenzophenones.

Recently, we have reported a highly diastereoselective Michael reaction of the (*S*)-mandelic acid enolate using α,*β*-unsaturated carbonyl compounds[1] and nitroalkenes[2] as acceptors and the transformation of the corresponding adducts into highly enantioenriched 2-substituted 1,4-dicarbonyl compounds[1] and α-hydroxy-α,*β*-diaryl-*γ*-lactams,[2] respectively. In both syntheses the strategy employed to exert stereochemical control in the newly created stereogenic centers involved the use of (*S*)-mandelic acid (**1**) as the source of chiral information through its previous conversion into (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one (**2**) by reaction with pivalaldehyde (Seebach principle of self-regeneration of stereocenters).[3]

In this paper we wish to report an extension of this methodology[4] to a diastereoselective arylation of (*S*)-mandelic acid enolate with *o*- and *p*-fluoronitrobenzenes **3** and the transformation of the corresponding products **4** into enantiomerically pure substituted (*R*)-3-hydroxy-3-phenyloxindoles **5** and (*R*)-benzylic acids **6**. We will also describe the aerobic oxidative decarboxylation of benzylic acids **6** to give substituted benzophenones **7**.

Oxindoles (2-indolinones) are a class of heterocyclic compounds found in many natural products[5] and in a number of marketed drugs.[6] Their biological activities and their role as essential intermediates in the total synthesis of other indole alkaloids make these compounds attractive targets in medicinal and synthetic organic chemistry. Of particular interest are 3-hydroxyoxindoles,[7] specially 3-aryl-3-hydroxyoxindoles and their 3-fluoro derivatives (Figure 1). Very recently, chemists at Sumitomo Pharmaceuticals have reported the growth hormone secretagogue activity of the nonpeptidyl oxindole derivative SM-130686,[8] and researchers at Brystol-Myers Squibb

[#] This paper is dedicated to Professor José L. Soto on occasion of his retirement.

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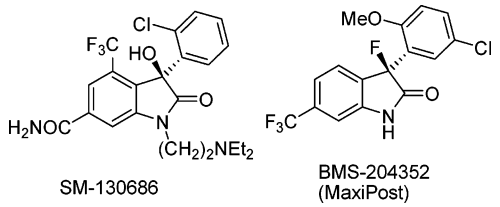

FIGURE 1. Examples of bioactive oxindoles.

laboratories have prepared and tested several 3-aryl-3-hydroxy-[9] and 3-aryl-3-fluorooxindoles which culminated in the discovery of BMS-204352 (MaxiPost), a potent opener of Maxi-K channels of application in the treatment of stroke.[10] Interest in the synthesis of 3-aryl-3-hydroxyoxindoles lies not only in its intrinsic biological activity but also in the fact that they are used as intermediates for the synthesis of the corresponding 3-fluorooxindoles.[10,11] Racemic 3-phenyl-3-hydroxyoxindoles have been prepared by cyclization of benzoylformic acid aryl amides,[12] radical oxidation of oxindoles,[13] or addition of Grignard reagents to isatin.[10] An extension of this last method has allowed the preparation of enantiomerically enriched 3-aryl-3-hydroxyoxindoles by asymmetric hydroxylation of the 3-aryloxindoles prepared by dehydroxylation of the Grignard-isatin adducts.[9] However, the preparation of the starting isatins required for these syntheses needs long synthetic sequences and/or presents regioselectivity problems.

Optically active α-hydroxy acids are structural units present in many biologically and pharmacologically important compounds.[14] In addition α-hydroxy acid derivatives are important intermediates for asymmetric synthesis.[15] Consequently a number of useful synthetic methods for α-hydroxy acids have been developed over the years, the α-alkylation of optically active natural α-hydroxy acids such as lactic or mandelic acids, or the α-alkylation of chiral glycolic acid equivalents being among the most commonly used.[14e,16] However, to the best of our knowledge, no examples of arylation of mandelic acids to benzylic acids have been reported so far. The clinical application of this kind of compounds is under study, and for example, 3-quinuclidinyl 4-halobenzylates show a high affinity for muscarinic acetyl choline receptors[17] and their radioactive halogen counterparts are useful as tomography imaging agents.[18] Nevertheless, the syntheses of optically active substituted benzylic acids are limited to organometallic additions to benzoylformate with 8-phenylmenthol as a chiral auxiliary.[19]

Finally, the presence of the benzophenone scaffold in the framework of natural and synthetic compounds with important physiological activities, such as antimalaria,[20] antiinflammatory,[21] anticancer,[22] or antibiotic,[23] continues to spur synthetic efforts regarding their preparation.[24] Most of the classical synthetic protocols for benzophenones involve Friedel−Crafts benzoylations between an aromatic substrate and an electrophilic reagent. However, these reactions, which are catalyzed by acidic catalysts (generally used in excess of molar amounts), do not proceed successfully with aromatic substrates having electron-withdrawing groups.[25] An alternative route involves the substitution on the aromatic substrate by the action of an appropriate nucleophilic species, such as a synthetic equivalent of benzoyl carbanion.[1,26]

Results and Discussion

Our synthesis of enantiomerically pure (*R*)-3-hydroxy-3-phenyloxindoles, substituted (*R*)-benzylic acids, and

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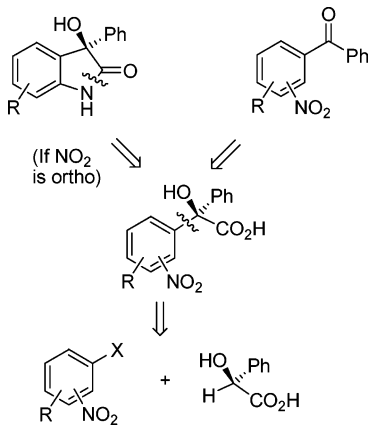
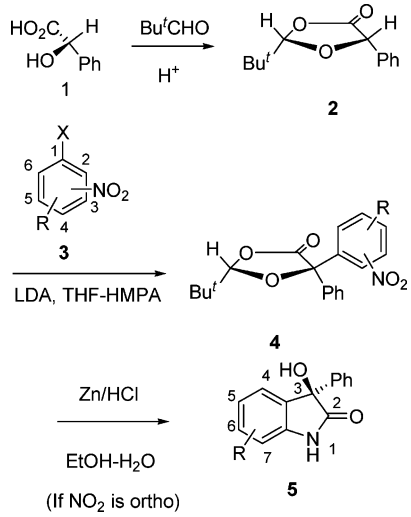
SCHEME 1



SCHEME 2



benzophenones from (*S*)-(+)-mandelic acid and *o*- and *p*-fluoronitrobenzenes is based on retrosynthetic Scheme 1.

According to this analysis, the first synthetic step should involve an aromatic nucleophilic substitution with the (*S*)-(+)-mandelic acid enolate onto a halonitrobenzene. Although the formation of the mandelic acid enolate leads to loss of chirality at the stereogenic center, it should be possible to regenerate that chiral information if (*S*)-(+)-mandelic acid (**1**) is previously transformed into (2*S*,5*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolanone (**2**) (Scheme 2), according to the principle of self-regeneration of stereocenters,[3] as shown by Seebach[16a,27] and us.[1,2]

Although the nucleophilic substitution of oxygen and nitrogen nucleophiles onto halonitrobenzenes is a standard reaction in organic synthesis, there are not many successful methods to carry out the aromatic nucleophilic substitutions with enolates, in part because the nitro group often reacts with carbanions by electron-transfer processes.[28] Among the described procedures, the nucleophilic substitution to arene−transition metal carbonyl complexes,[29] the transition metal catalyzed aromatic nucleophilic substitution of aryl halides,[30] and the aromatic substitution via nucleophilic addition to electron-deficient arenes (including vicarious[31] and ipso[28a,32]) are the most interesting ones.

TABLE 1. Reaction of (2*S*,5*S*)-*cis*-1,3-Dioxolan-4-one (2) with *p*-Halonitrobenzenes 3a

entry	**3a** (X)	solvent	additive	base	**4a** (yield, %)	**8** (yield, %)
1	Cl	THF		LDA		40 (30)[a]
2	Cl	THF	HMPA (3 equiv)	LDA	30	40
3	F	THF	HMPA (3 equiv)	LDA	85	
4	Br	THF	HMPA (3 equiv)	LDA	27	30
5	F	THF	HMPA (3 equiv)	*t*-BuLi	50	
6	F	THF		NaHMDS	*b*	
7	F	DMF		NaH	35	

[a] Recovered **2** in parentheses. [b] Enolate decomposition.

The starting materials in our synthesis were commercially available aromatic nitro compounds having a leaving group in either the ortho or para position with respect to the nitro group. The aromatic nucleophilic substitution was first tested with different *p*-halonitrobenzenes in order to optimize the reaction conditions (Scheme 2, Table 1).[33]

Compound **2** was deprotonated with a LDA solution at −78 °C in THF, and then *p*-chloronitrobenzene **3a** (X = Cl) was added to the resulting enolate solution. Under these conditions none of the expected product was obtained (Entry 1). Instead, compound **8** was obtained in 40% yield besides 30% of recovered starting material. Compound **8** is the aldol product of the 1,3-dioxolan-4-one **2** enolate and pivalaldehyde.[34] The presence of pivalaldehyde in the reaction mixture is not completely clear, but since formation of compound **8** is only observed after the addition of the nitrobenzene compound, we believe that it most likely results from a redox process between the 1,3-dioxolan-4-one enolate and the nitro group,[28] which would take place faster than the addition of the enolate to the aromatic ring (Scheme 3). As a matter of fact, the use of 3 equiv of HMPA, an additive

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SCHEME 3

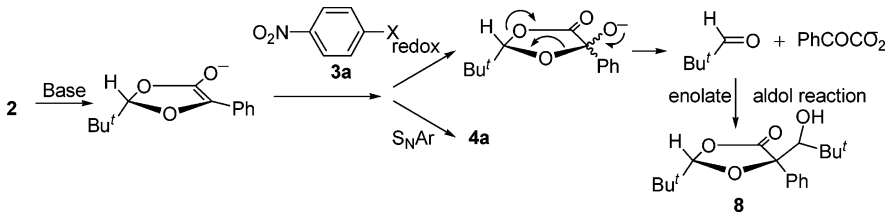

TABLE 2. Reaction of Arylation of (2*S*,5*S*)-*cis*-1,3-Dioxolan-4-one 2 with Fluoronitrobenzenes 3 (X = F)'

entry	**3** and **4**	NO_2	R	**4** (yield, %)
1	**a**	4-NO_2	H	85
2	**b**	2-NO_2	H	37
3	**c**	4-NO_2	3-Me	82
4	**d**	4-NO_2	3-OMe	75
5	**e**	4-NO_2	3-CF_3	75
6	**f**	4-NO_2	2-CH_2OMEM	80
7	**g**	4-NO_2	2-Cl	66
8	**h**	4-NO_2	2-CN	94
9	**i**	2-NO_2	5-Me	88
10	**j**	2-NO_2	5-OMe	66
11	**k**	2-NO_2	4-CF_3	80
12	***l***	2-NO_2	4-CO_2Me	77
13	**m**	2-NO_2	4-N(Me)COPh	60
14	**n**	2-NO_2	4-NO_2	90

that increases the reactivity of enolates toward nucleophilic substitution,[35] allowed us to obtain the desired product **4a** in 30% yield, although still accompanied by 40% of **8** (Entry 2). The formation of compound **8** could be prevented only when *p*-fluoronitrobenzene **3a** (X = F) was used as arylating reagent (Entry 3) while the use of *p*-bromonitrobenzene **3a** (X = Br) did not provide satisfactory results (Entry 4). The use of *tert*-butyllithium instead of LDA gave poorer results (Entry 5). Sodium bases also gave disappointing results. Thus, NaHDMS in THF (Entry 6) brought about decomposition of the enolate, even at −78 °C, while the combination NaH-DMF[28a] (Entry 7) gave low yields of the expected product. The tendency of compound **4a** to decompose upon prolonged reaction times or higher temperatures was also observed. Accordingly, a short reaction time (5−10 min) and quenching at −78 °C was established as the best experimental protocol. Other electron-deficient fluorobenzenes such as *p*-cyano- and *p*-trifluoromethylfluorobenzene were also tested as arylating reagents. However, none of these electron-withdrawing groups was able to induce nucleophilic substitution with the enolate of **2** under the optimized conditions (LDA, THF−HMPA).

The nucleophilic aromatic substitution reaction with the enolate of **2** was carried out with a number of fluoronitrobenzenes **3** (X = F) under similar conditions (Table 2). In the case of *o*-fluoronitrobenzene **3b** (Entry 2) the reaction proceeded but only with modest yield. The presence of an additional group on the aromatic ring was also studied. In the case of substituted *p*-fluoronitrobenzenes the reaction worked well if the additional group was in the meta position with respect to the fluorine atom, regardless of its electronic nature. Thus, fair to good yields of the corresponding compounds **4** were obtained with 3-methyl-4-nitrofluorobenzene **3c** (Entry 3), 3-methoxy-4-nitrofluorobenzene **3d** (Entry 4), and 3-trifluoromethyl-4-nitrofluorobenzene **3e** (Entry 5). The reaction was also carried out with *p*-fluoronitrobenzenes substituted in the ortho position with respect to the fluorine atom in order to determine possible steric effects (Entries 6−8). Again, the reaction proceeded readily in all cases, including the bulky MEM-protected benzyl alcohol group (Entry 6), without much influence of the electron-donating (Entries 6 and 7) or electron-withdrawing (Entry 8) features of the additional substituent.

Despite the low yield obtained with *o*-fluoronitrobenzene we decided to examine the reaction with substituted *o*-fluoronitrobenzenes **3i**−**n** and we were very pleased to observe that in these cases the reaction proceeded with fair to good yields to give the expected nucleophilic aromatic substitution products **4i**−**n** (Table 2, Entries 9−14). The reaction proceeded well regardless of the location of the additional substituent, although the presence of strong electron-donating groups on the aromatic ring slightly decreased the yield of the reaction (Entries 10 and 13).

In all cases, the reaction was stereoselective either with *o*- or *p*-fluoronitrobenzene compounds and only one stereoisomer out of the two possible was obtained. The stereochemical structures of compounds **4** were elucidated by NOE experiments. These experiments showed in all of the cases the cis relationship between the *tert*-butyl group and the phenyl group from the original (*S*)-(+)-mandelic acid. The absolute configuration of the newly formed quaternary carbon atom was then assigned to be *R*, upon the consideration that the absolute configuration of the dioxolanone C-2 carbon atom bearing the *tert*-butyl group in **2** is *S* and remains unaltered from **2** to **4**. These results indicate that compounds **4** are obtained from the exclusive approach of the fluoronitrobenzene reagent anti to the *tert*-butyl group, in good agreement with the results reported by Seebach[3,16a,27] and us[1,2] in related reactions.

The second step in the synthetic sequence to oxindoles involved the reduction of the aromatic nitro group in the *o*-nitro arylation products **4b**,**i**−**m** (Scheme 2). This reaction was carried out with Zn/HCl/EtOH. The reduction of the nitro group to amine took place with concomitant intramolecular aminolysis of the dioxolanone ring to afford the corresponding (*R*)-3-hydroxy-3-phenyloxindoles **5** with high yields (Table 3). The resulting (*R*)-3-hydroxy-3-phenyloxindoles **5b**,**i**−**m** were enantiomerically pure (ee>99%) as was proven by ^{1}H NMR experiments with the chiral lanthanide shift reagent Eu(hfc)$_3$ under conditions previously optimized for racemic mixtures prepared from (±)-mandelic acid dioxolanone, indicating no sign of epimerization at C-3 during the

(35) *Handbook of Reagents for Organic Synthesis. Acidic and Basic Reagents*; Reich, J. H., Rigby, J. H., Eds.; John Wiley and Sons: Chichester, UK, 1999; pp 160−166.

TABLE 3. Synthesis of (*R*)-3-Hydroxy-3-phenyloxindoles 5 from *o*-Arylation Products 4

entry	**4** and **5**	**5** (R)[a]	**5** (yield, %)
1	**b**	H	79
2	**i**	5-Me	99
3	**j**	5-OMe	95
4	**k**	6-CF_3	89
5	***l***	6-CO_2Me	72
6	**m**	6-N(Me)COPh	98

[a] For numbering of oxindole compounds **5** see Scheme 2.

SCHEME 4

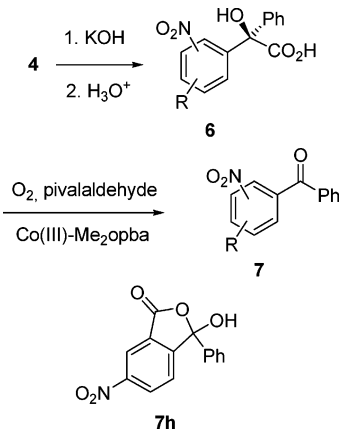

TABLE 4. Reaction of Hydrolysis of the 1,3-Dioxolan-4-one Moiety 4 and Oxidative Decarboxylation of Benzylic Acids 6

entry	**4**, **6**, and **7**	**6** (yield, %)	**7** (yield, %)
1	**a**	94	82
2	**b**	78	90
3	**c**	87	87
4	**d**	93	80
5	**e**	64	95
6	**f**	80	65
7	**g**	81	91
8	**h**		77[a]
9	**i**	79	90
10	**j**	73	88
11	**k**	84	84
12	**m**	70	56
13	**n**		63[a]

[a] Product obtained during hydrolysis of compound **4**.

acidic reductive treatment of the *o*-nitro arylation products **4b**,**i**−**m**.

The second step in the synthetic sequence to substituted (*R*)-benzylic acids was the cleavage of the 1,3-dioxolan-4-one moiety in compounds **4**, which was achieved upon basic hydrolysis with ethanolic KOH and reprotonation to give the corresponding hydroxy acids **6**, with good yields (Scheme 4, Table 4). The resulting (*R*)-benzylic acids **6a**−**g**,**i**−**k**,**m** were enantiomerically pure (ee >99%) as was proven by ^{1}H NMR experiments with the chiral lanthanide shift reagent Eu(hfc)$_3$. In the cases of the arylation products **4h** and **4n**, which bear two strongly electron-withdrawing groups, benzophenones **7h** and **7n** were directly obtained from the reaction mixture. In both cases, the presence of the two strongly electron-withdrawing groups facilitates decarboxylation of the α-hydroxy acids **6h** and **6n** because of the mesomeric stabilization by these groups at ortho and para positions

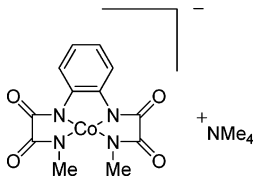

FIGURE 2. Structure of the Co(III)-Me_2opba complex.

of the resulting hydroxybenzyl carbanion, which is then oxidized by oxygen to ketone **7n** and **7h** under the hydrolysis conditions.[32b,36] In the case of **7h**, this compound is obtained as the hydroxy phthalide tautomer[37] after concomitant hydrolysis of the cyano group.

Finally, the oxidative decarboxylation of the rest of the benzylic acids **6** to benzophenones **7** (Scheme 4) was carried out by using a catalytic system developed in our laboratory that employs oxygen as terminal oxidant in the presence of pivalaldehyde and a catalytic amount of a Co(III)-Me_2opba complex (Figure 2).[26] Under these conditions, nitrobenzophenones **7** were obtained with good yields from benzylic acids **6** (Table 4).

In summary, concise, regio- and enantioselective syntheses of (*R*)-3-hydroxy-3-phenyloxindoles and substituted (*R*)-benzylic acids starting from (*S*)-mandelic acid are presented. The syntheses are advantageous over other available syntheses since they are shorter, avoid problems of regioselectivity in the functionalization of the aromatic ring, and do not require the use of expensive chiral reagents nor difficult racemic resolution. Enantiomerically enriched substituted mandelic acids are readily available via asymmetric Friedel−Crafts reactions with glyoxylates,[38] which will allow extending the scope of this methodology to the preparation of 3-aryl-3-hydroxyoxindoles and benzylic acids substituted in both aromatic rings. Finally a new method for the synthesis of nitrobenzophenones is presented. The overall sequence involves mandelic acid as an "Umpoled" equivalent of the benzoyl carbanion, and it is an alternative to the electrophilic Friedel−Crafts benzoylation of electron-deficient nitrobenzenes

Experimental Section

General Procedure for the Arylation of (2*S*,5*S*)-*cis*-2-*tert*-Butyl-5-phenyl-1,3-dioxolan-4-one (2) with Fluoronitrobenzenes 3. A solution of (*S*,*S*)-*cis*-2-*tert*-butyl-5-phenyl-1,3-dioxolan-4-one[16a] **2** (220 mg, 1 mmol) in 1.5 mL of dry THF was added to a −78 °C precooled solution prepared from 0.625 mL of a 2 M commercial solution of LDA in heptane−THF−ethylbenzene (1.25 mmol), 0.56 mL of HMPA (3 mmol), and 4 mL of THF. After 30 min, a solution of fluoronitrobenzene **3** (1.25 mmol) in 0.5 mL of THF was added dropwise, and 10 min later, the reaction was quenched with the addition of 2−3 drops of water and silica gel. Once the mixture reached room temperature, the solvent was evaporated under reduced pressure and the resulting powder chromatographed on silica gel to give compounds **4**.

(2*S*,5*R*)-2-*tert*-Butyl-5-(4-nitrophenyl)-5-phenyl-1,3-dioxolan-4-one (4a): 85% yield; pale yellow powder; mp 100−102 °C (hexane−diethyl ether); $[\alpha]^{25}_D$ +44.1 (*c* 2.60, $CHCl_3$);

(36) Bull, D. J.; Fray, M. J.; Mackenny, M. C.; Malloy, K. A. *Synlett* **1996**, 647−648.

(37) Fabian, W. M. F.; Bowden, K. *Eur. J. Org. Chem.* **2001**, *2*, 303−309.

(38) Gathergood, N.; Zhuang, W.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517−12522.

^{1}H NMR ($CDCl_3$) δ 1.00 (9H, s), 5.13 (1H, s), 7.27 (3H, m), 7.36 (2H, m), 7.72 (2H, d, J = 9.0 Hz), 8.17 (2H, d, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 23.6 (CH_3), 34.0 (C), 83.7 (C), 108.3 (CH), 124.1 (CH), 126.3 (CH), 127.5 (CH), 128.7 (CH), 129.0 (CH), 137.8 (C), 143.8 (C), 148.2 (C), 171.1 (C). HRMS (EI) m/z 297.1374 ($M^+ - CO_2$, 100) ($C_{18}H_{19}NO_3$ requires 297.1365), 280 (30), 228 (48), 211 (58), 165 (58).

(2*S*,5*R*)-2-*tert*-Butyl-5-(2-nitrophenyl)-5-phenyl-1,3-dioxolan-4-one (4b): 37% yield; oil; $[\alpha]^{25}_D$ +402.2 (*c* 1.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s), 5.06 (1H, s), 7.25−7.50 (5H, m), 7.55−7.64 (3H, m), 7.91 (1H, d, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 23.5 (CH_3), 34.3 (C), 83.7 (C), 108.5 (CH), 124.3 (CH), 126.1 (CH), 127.8 (C), 128.4 (CH), 128.8 (CH), 129.3 (CH), 130.2 (CH), 131.1 (CH), 137.2 (C), 149.4 (C), 170.6 (C); HRMS (EI) m/z 341.1279 (M^+, 0.1) ($C_{19}H_{19}NO_5$ requires 341.1263), 284 (7), 256 (49), 211 (66), 194 (46), 167 (100).

(2*S*,5*R*)-2-*tert*-Butyl-5-(3-methyl-4-nitrophenyl)-5-phenyl-1,3-dioxolan-4-one (4c): 82% yield; oil; $[\alpha]^{25}_D$ +111.4 (*c* 1.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.06 (9H, s), 2.60 (3H, s), 5.18 (1H, s), 7.33−7.44 (5H, m), 7.54 (1H, s), 7.57 (1H, d, J = 8.0 Hz), 7.98 (1H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6 (CH_3), 23.5 (CH_3), 34.5 (C), 83.6 (C), 108.1 (CH), 125.0 (CH), 125.2 (CH), 126.3 (CH), 128.6 (CH), 128.9 (CH), 130.6 (CH), 134.3 (C), 137.8 (C), 141.8 (C), 149.3 (C), 171.2 (C); HRMS (EI) m/z 311.1532 ($M^+ - CO_2$, 100) ($C_{19}H_{21}NO_3$ requires 311.1521), 294 (26), 242 (58), 225 (85), 178 (37), 164 (19), 152 (15).

(2*S*,5*R*)-2-*tert*-Butyl-5-(3-methoxy-4-nitrophenyl)-5-phenyl-1,3-dioxolan-4-one (4d): 75% yield; oil; $[\alpha]^{25}_D$ +109.1 (*c* 1.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.07 (9H, s), 3.92 (3H, s), 5.18 (1H, s), 7.24−7.42 (7H, m), 7.86 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 23.5 (CH_3), 34.5 (C), 56.6 (CH), 83.8 (C), 108.2 (CH), 111.6 (CH), 118.1 (CH), 126.1 (CH), 126.5 (CH), 128.7 CH), 129.1 (CH), 137.7 (C), 139.7 (C), 143.0 (C), 153.1 (C), 171.3 (C); HRMS (EI) m/z 371.1373 (M^+, 10) ($C_{20}H_{21}NO_6$ requires 371.1369), 327 (100), 258 (59), 165 (35), 105 (47).

(2*S*,5*R*)-2-*tert*-Butyl-5-(4-nitro-3-trifluoromethylphenyl)-5-phenyl-1,3-dioxolan-4-one (4e): 75% yield; oil; $[\alpha]^{25}_D$ +76.2 (*c* 1.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 1.06 (9H, s), 5.22 (1H, s), 7.34−7.45 (5H, m), 7.90 (1H, d, J = 8.2 Hz), 7.98 (1H, dd, J = 8.2, 1.8 Hz), 8.04 (1H, d, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 23.5 (CH_3), 34.7 (C), 83.0 (C), 108.6 (CH), 121.6 (C, q, J_{C-F} = 272.1 Hz), 124.4 (C, q, J_{C-F} = 34.4 Hz), 125.7 (CH, q, J_{C-F} = 5.0 Hz), 125.6 (CH), 126.1 (CH), 129.0 (CH), 129.3 (CH), 131.0 (CH), 137.0 (C), 142.7 (C), 148.0 (C, q, J_{C-F} = 3.5 Hz), 171.0 (C); HRMS (EI) m/z 365.1245 ($M^+ - CO_2$, 41) ($C_{19}H_{18}F_3NO_3$ requires 365.1239), 314 (36), 269 (45), 254 (100).

(2*S*,5*R*)-2-*tert*-Butyl-5-(2-methoxyethoxymethoxymethyl-4-nitrophenyl)-5-phenyl-1,3-dioxolan-4-one (4f): 80% yield; oil; $[\alpha]^{25}_D$ +168.1 (*c* 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.08 (9H, s), 3.31 (3H, s), 3.36−3.39 (2H, m), 3.47−3.55 (2H, m), 4.35 (1H, d, J = 14.7 Hz), 4.58 (1H, d, J = 6.6 Hz), 4.64 (1H, d, J = 14.7 Hz), 4.66 (1H, d, J = 6.6 Hz), 5.00 (1H, s), 7.33 (5H, m), 7.81 (1H, d, J = 8.7 Hz), 8.17 (1H, dd, J = 8.7, 2.4 Hz), 8.57 (1H, d, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 23.6 (CH_3), 34.3 (C), 58.9 (C), 65.5 (CH_2), 66.9 (CH_2), 71.5 (CH_2), 76.4 (CH_2), 85.8 (C), 95.3 (CH_2), 107.7 (CH), 121.7 (CH), 124.2 (CH), 126.2 (CH), 128.5 (CH), 128.7 (CH), 129.2 (CH), 136.2 (C), 138.7 (C), 141.4 (C), 148.7 (C), 170.7 (C); HRMS (EI) m/z 353.1247 ($M^+ - C_4H_{10}O_3$, 5) ($C_{20}H_{19}NO_5$ requires 353.1263), 284 (16), 267 (96), 240 (100), 165 (62), 105 (15), 89 (99).

(2*S*,5*R*)-2-*tert*-Butyl-5-(2-chloro-4-nitrophenyl)-5-phenyl-1,3-dioxolan-4-one (4g): 66% yield; oil; $[\alpha]^{25}_D$ +247.0 (*c* 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 1.10 (9H, s), 5.10 (1H, s), 7.37 (5H, m), 7.81 (1H, d, J = 8.5 Hz), 8.17 (1H, dd, J = 8.5, 2.4 Hz), 8.28 (1H, d, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$) δ 23.7 (CH_3), 34.5 (C), 85.1 (C), 108.4 (CH), 121.2 (C), 126.2 (CH), 127.5 (CH), 128.5 (CH), 128.9 (CH), 130.4 (CH), 135.9 (C), 136.3 (C), 140.2 (C), 148.2 (C), 170.4 (C); HRMS (EI) m/z 331.0958 ($M^+ - CO_2$, 100) ($C_{18}H_{18}NO_3Cl$ requires 331.0975), 333 (32), 275 (19), 262 (55), 245 (54), 164 (23).

(2*S*,5*R*)-2-*tert*-Butyl-5-(2-cyano-4-nitrophenyl)-5-phenyl-1,3-dioxolan-4-one (4h): 94% yield; pale yellow crystals; mp 136−137 °C (hexane−diethyl ether); $[\alpha]^{25}_D$ +178.5 (*c* 4.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.11 (9H, s), 5.24 (1H, s), 7.46 (5H, m), 8.10 (1H, d, J = 8.7 Hz), 8.45 (1H, dd, J = 8.7, 2.3 Hz), 8.58 (1H, d, J = 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 23.4 (CH_3), 34.6 (C), 83.2 (C), 108.7 (CH), 113.0 (C), 115.0 (C), 126.1 (CH), 127.0 (CH), 128.7 (CH), 129.3 (CH), 130.8 (CH), 135.5 (C), 146.5 (C), 147.6 (C), 169.5 (C); HRMS (EI) m/z 322.1330 ($M^+ - CO_2$, 37) ($C_{19}H_{18}N_2O_3$ requires 322.1317), 253 (100), 190 (41), 70 (64).

(2*S*,5*R*)-2-*tert*-Butyl-5-(5-methyl-2-nitrophenyl)-5-phenyl-1,3-dioxolan-4-one (4i): 88% yield; slightly pale yellow crystals; mp 104−105 °C (hexane−diethyl ether); $[\alpha]^{25}_D$ +526.9 (*c* 0.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.03 (9H, s), 2.46 (3H, s), 5.05 (1H, s), 7.20−7.50 (7H, m), 7.69 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.5 (CH_3), 23.5 (CH_3), 34.3 (C), 83.9 (C), 108.4 (CH), 124.4 (CH), 126.2 (CH), 127.7 (C), 128.3 (CH), 128.8 (CH), 129.6 (CH), 130.6 (CH), 137.3 (C), 142.1 (C), 147.4 (C), 170.8 (C); HRMS (EI) m/z 355.1403 (M^+, 3) ($C_{20}H_{21}NO_5$ requires 355.1420), 331 (7), 270 (42), 225 (50), 208 (45), 180 (100).

(2*S*,5*R*)-2-*tert*-Butyl-5-(5-methoxy-2-nitrophenyl)-5-phenyl-1,3-dioxolan-4-one (4j): 66% yield; pale yellow crystals; mp 99−101 °C (hexane−diethyl ether); $[\alpha]^{25}_D$ +584.5 (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.02 (9H, s), 3.87 (3H, s), 5.03 (1H, s), 6.95 (1H, dd, J = 9.0, 2.7 Hz), 7.40−7.50 (6H, m), 7.57 (1H, d, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 23.5 (CH_3), 34.5 (C), 56.0 (CH_3), 84.0 (C), 108.6 (CH), 114.4 (CH), 114.8 (CH), 126.1 (CH), 126.7 (CH), 128.3 (CH), 128.8 (CH), 131.0 (C), 137.3 (C), 142.9 (C), 161.2 (C), 170.8 (C); HRMS (EI) m/z 371.1386 (M^+, 0.3) ($C_{20}H_{21}NO_6$ requires 371.1369), 314 (2), 286 (23), 224 (33), 182 (100).

(2*S*,5*R*)-2-*tert*-Butyl-5-(2-nitro-4-trifluoromethylphenyl)-5-phenyl-1,3-dioxolan-4-one (4k): 80% yield; pale yellow crystals; mp 110−111 °C (hexane−diethyl ether); $[\alpha]^{25}_D$ +356.4 (*c* 0.88, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.01 (9H, s), 5.08 (1H, s), 7.35−7.50 (5H, m), 7.77 (1H, d, J = 1.5 Hz), 7.84 (1H, dd, J = 8.3, 1.5 Hz), 8.09 (1H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 23.4 (CH_3), 34.4 (C), 83.3 (C), 109.0 (CH), 121.6 (CH, q, J_{C-F} = 3.4 Hz), 122.4 (CH, q, J_{C-F} = 271.3 Hz), 126.0 (CH), 127.8 (CH, q, J_{C-F} = 3.4 Hz), 128.6 (CH), 129.2 (CH), 130.4 (CH), 132.2 (C), 132.8 (C, q, J_{C-F} = 34.8 Hz), 136.5 (C), 149.4 (C), 170.1 (C); HRMS (EI) m/z 331.0681 ($M^+ - C_6H_6$, 100) ($C_{14}H_{12}NO_5F_3$ requires 331.0668), 262 (63), 245 (63).

(2*S*,5*R*)-2-*tert*-Butyl-5-(4-methoxycarbonyl-2-nitrophenyl)-5-phenyl-1,3-dioxolan-4-one (4l): 77% yield; slightly pale yellow crystals; mp 114−116 °C (hexane−diethyl ether); $[\alpha]^{25}_D$ +281.2 (*c* 0.09, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.01 (9H, s), 3.95 (3H, s), 5.06 (1H, s), 7.30−7.50 (5H, m), 8.00 (1H, d, J = 8.3 Hz), 8.15 (1H, d, J = 1.7 Hz), 8.23 (1H, dd, J = 8.3, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 23.4 (CH_3), 34.4 (C), 52.8 (CH_3), 83.5 (C), 108.8 (CH), 125.3 (CH), 126.0 (CH), 128.5 (CH), 129.0 (CH), 129.7 (CH), 131.7 (CH), 132.3 (C), 132.4 (C), 136.7 (C), 149.4 (C), 164.2 (C), 170.2 (C); HRMS (EI) m/z 368.1129 ($M^+ - MeO$, 10) ($C_{20}H_{18}NO_6$ requires 368.1134), 314 (60), 269 (100).

(2*S*,5*R*)-2-*tert*-Butyl-5-[4-(*N*-benzoyl-*N*-methylamino)-2-nitrophenyl]-5-phenyl-1,3-dioxolan-4-one (4m): 60% yield; pale yellow-orange powder; mp 140−142 °C (hexanes−EtOAc); $[\alpha]^{25}_D$ +326.3 (*c* 0.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.94 (9H, s), 3.44 (3H, s), 4.93 (1H, s), 7.14−7.35 (12H, m), 7.65 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 23.4 (CH_3), 34.3 (C), 38.0 (CH_3), 83.4 (C), 108.7 (CH), 121.5 (CH), 125.0 (CH), 126.1 (CH), 128.3 (CH), 128.38 (CH), 128.4 (CH), 128.43 (CH), 129.0 (CH), 130.6 (CH), 134.8 (C), 137.0 (C), 146.2 (C), 149.6 (C), 170.4 (C), 170.6 (C); HRMS (EI) m/z 474.1769 (M^+, 10) ($C_{27}H_{26}N_2O_6$ requires 474.1791), 389 (3), 344 (5), 222 (2), 105 (100).

(2*S*,5*R*)-2-*tert*-Butyl-5-(2,4-dinitrophenyl)-5-phenyl-1,3-dioxolan-4-one (4n): 90% yield; yellow crystals; mp 144−145 °C (hexane−diethyl ether); $[\alpha]^{25}_D$ +355.4 (*c* 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$) 1.02 (9H, s), 5.11 (1H, s), 7.42 (5H, m), 8.19 (1H, d, J = 8.7 Hz), 8.37 (1H, d, J = 2.2 Hz), 8.67 (1H, dd, J = 8.7, 2.2 Hz); ^{13}C NMR ($CDCl_3$) δ 23.4 (CH_3), 34.5 (C), 83.1 (C), 109.3 (CH), 119.7 (CH), 125.4 (CH), 126.0 (CH), 128.8 (CH), 129.4 (CH), 130.9 (CH), 135.0 (C), 136.2 (C), 148.1 (C), 149.3 (C), 169.8 (C); HRMS (EI) m/z 329.0414 ($M^+ - C_4H_9$, 6.1) ($C_{15}H_{19}$

N_2O_7 requires 329.0410), 301 (73), 273 (13), 256 (100), 239 (62), 210 (16), 195 (24).

General Procedure for the reduction of *o*-Nitro Arylation Compounds 4 to Oxindoles 5. Zn dust (256 mg, 2.56 mmol) and concentrated HCl (0.28 mL) were added to a solution of compound **4** (0.35 mmol) in 3.3 mL of EtOH−H_2O (4:1). The mixture was heated at reflux temperature until complete transformation of compound **4** into oxindole **5**, as shown by TLC. In some cases, additional amounts of Zn and HCl were required. The mixture was cooled, filtered, diluted with EtOAc, and washed with water, and the aqueous layer was re-extracted with EtOAc. The combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to afford oxindoles **5**.

(*R*)-3-Hydroxy-3-phenyl-2-oxindole (5b): 79% yield; white crystals; mp 230−233 °C dec (EtOAc); $[\alpha]^{25}_D$ −12.3 (*c* 0.91, CH_3OH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.68 (1H, s), 6.95 (1H, d, J = 7.5 Hz), 7.02 (1H, t, J = 7.5 Hz), 7.15 (1H, d, J = 7.5 Hz), 7.45−7.25 (6H, m), 10.46 (1H, s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.25 (1H, br s), 6.95 (1H, br d, J = 7.8 Hz), 7.09 (1H, td, J = 7.6, 0.8 Hz), 7.29−7.40 (5H, m), 7.43−7.46 (2H, m), 7.63 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 77.6 (C), 110.2 (CH), 122.4 (CH), 125.1 (CH), 125.7 (CH), 127.7 (CH), 128.5 (CH), 129.6 (CH), 134.1 (C), 141.9 (C), 142.3 (C), 142.3 (C), 178.8 (C); HRMS (EI) *m*/*z* 225.0801 (M^+, 44) ($C_{14}H_{11}NO_2$ requires 225.0790), 197 (60), 196 (100), 120 (17), 77 (14).

(*R*)-3-Hydroxy-5-methyl-3-phenyl-2-oxindole (5i): 99% yield; white crystals; mp 175−178 °C dec (MeOH); $[\alpha]^{25}_D$ −51.3 (*c* 1.21, CH_3OH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.21 (3H, s), 6.57 (1H, s), 6.79 (1H, d, J = 7.9 Hz), 6.90 (1H, br s), 7.05 (1H, br d, J = 7.9 Hz), 7.25−7.35 (5H, m), 10.29 (1H, s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.30 (3H, s), 3.25 (1H, br s), 6.84 (1H, d, J = 8.0 Hz), 7.09 (1H, br s), 7.10 (1H, br d, J = 8.0 Hz), 7.30−7.40 (3H, m), 7.43−7.47 (2H, m), 7.69 (1H, br s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.1 (CH_3), 77.9 (C), 110.0 (CH), 125.7 (CH), 125.8 (CH), 127.8 (CH), 128.5 (CH), 129.8 (CH), 131.3 (C), 134.3 (C), 139.9 (C), 142.1 (C), 179.0 (C); HRMS (EI) *m*/*z* 239.0948 (M^+, 58) ($C_{15}H_{13}NO_2$ requires 239.0946), 211 (65), 210 (100), 134 (14) 105 (11), 77 (15).

(*R*)-3-Hydroxy-5-methoxy-3-phenyl-2-oxindole (5j): 95% yield; white crystals; mp 173−175 °C dec (EtOAc); $[\alpha]^{25}_D$ −75.3 (*c* 1.14, CH_3OH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.66 (3H, s), 6.63 (1H, br s), 6.70 (1H, br s), 6.83 (2H, br s), 7.25−7.35 (5H, m), 10.22 (1H, s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.25 (1H, br s), 3.76 (3H, s), 6.67 (1H, dd, J = 8.6, 2.2 Hz), 6.86 (1H, br s), 6.88 (1H, t, J = 1.5 Hz), 7.33−7.39 (3H, m), 7.43−7.45 (2H, m), 7.56 (1H, br s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 55.9 (CH_3), 78.2 (C), 110.8 (CH), 111.8 (CH), 114.4 (CH), 125.9 (CH), 127.9 (CH), 128.5 (CH), 135.4 (C), 135.5 (C), 142.0 (C), 155.6 (C), 178.8 (C); HRMS (EI) *m*/*z* 255.0917 (M^+, 100) ($C_{15}H_{13}NO_3$ requires 255.0895), 227 (69), 226 (51), 212 (29), 194 (10), 105 (10), 77 (14).

(*R*)-3-Hydroxy-3-phenyl-6-trifluoromethyl-2-oxindole (5k): 89% yield; white crystals; mp 206−208 °C dec (EtOAc); $[\alpha]^{25}_D$ +11.4 (*c* 0.70, CH_3OH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.85 (1H, s), 7.12 (1H, s), 7.25−7.35 (7H, m), 10.70 (1H, br s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.40 (1H, br s), 7.20 (1H, br s), 7.35−7.45 (7H, m), 7.77 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 77.3 (C), 106.5 (CH, q, J_{C-F} = 4.0 Hz), 119.5 (CH, q, J_{C-F} = 4.0 Hz), 124.3 (C, q, J_{C-F} = 271.8 Hz), 125.6 (CH), 125.9 (CH), 128.1 (CH), 128.6 (CH), 130.0 (C, q, J_{C-F} = 31.6 Hz), 138.4 (C), 140.8 (C), 143.2 (C), 178.5 (C); HRMS (EI) *m*/*z* 293.0668 (M^+, 37) ($C_{15}H_{10}F_3NO_2$ requires 293.0664), 274 (6), 265 (54), 264 (100), 188 (15), 105 (13), 77 (13).

(*R*)-3-Hydroxy-6-methoxycarbonyl-3-phenyl-2-oxindole (5l): 72% yield; white crystals; mp 223−225 °C dec (EtOAc); $[\alpha]^{25}_D$ +24.5 (*c* 0.95, CH_3OH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.86 (3H, s), 6.83 (1H, s), 7.27−7.35 (5H, m), 7.25 (1H, d, J = 7.7 Hz), 7.43 (1H, d, J = 1.5 Hz), 7.62 (1H, dd, J = 7.7, 1.5 Hz), 10.64 (1H, s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.40 (1H, br s), 3.94 (3H, s), 7.30−7.40 (4H, m), 7.42−7.45 (2H, m), 7.62 (1H, br d, J = 1.4 Hz), 7.80 (1H, dd, J = 7.8, 1.4 Hz), 7.80 (1H, br s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 52.7 (CH_3), 77.6 (C), 114.7 (CH), 124.0 (CH), 125.4 (CH), 125.8 (CH), 128.1 (CH), 128.7 (CH), 130.9 (C), 139.3 (C), 141.1 (C), 142.8 (C), 166.3 (C), 178.6 (C); HRMS (EI) *m*/*z* 283.0841 (M^+, 53) ($C_{16}H_{13}NO_4$ requires 283.0845), 255 (77), 154 (100), 252 (9), 178 (16), 105 (11), 77 (11).

(*R*)-3-Hydroxy-6-(*N*-benzoyl-*N*-methylamino)-3-phenyl-2-oxindole (5m): 98% yield; white crystals; mp 225−227 °C dec (EtOAc); $[\alpha]^{25}_D$ +7.1 (*c* 0.92, CH_3OH); ^{1}H NMR (DMSO-d_6) δ 3.36 (3H, s), 6.62 (1H, s), 6.68 (1H, d, J = 1.7 Hz), 6.73 (1H, dd, J = 7.9, 1.7 Hz), 6.95 (1H, d, J = 7.9 Hz), 7.10−7.40 (10H, m), 10.37 (1H, s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.49 (3H, s), 6.67 (1H, d, J = 1.9 Hz), 6.81 (1H, dd, J = 8.0, 1.9 Hz), 7.16 (1H, d, J = 8.0 Hz), 7.20−7.40 (11 H, m), 7.88 (1H, br s); ^{13}C NMR (DMSO-d_6) δ 38.3 (CH_3), 77.3 (C), 109.1 (CH), 121.2 (CH), 125.6 (CH), 125.7 (CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 129.9 (CH), 132.0 (C), 136.6 (C), 141.6 (C), 142.8 (C), 145.7 (C), 169.7 (C), 178.6 (C); HRMS (EI) *m*/*z* 358.1325 (M^+, 53) ($C_{22}H_{18}N_2O_3$ requires 358.1317), 330 (18), 329 (6), 118 (13), 105 (100), 77 (37).

General Procedure for the Hydrolysis of the 1,3-Dioxolan-4-one Moiety. Compound **4** (0.5 mmol) was treated with 5% ethanolic KOH (1.1 mL, 1 mmol) at room temperature until complete reaction of the starting material (TLC). The solution was poured into ice and acidified with 1 M HCl until pH ∼2. The aqueous mixture was extracted with EtOAc, and the organic layers were washed with brine, dried, filtered, and concentrated under reduced pressure to give compound **6**.

(*R*)-4-Nitrobenzylic acid (6a): 94% yield; oil; $[\alpha]^{25}_D$ −45.6 (*c* 0.84, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.10 (2H, br s), 7.37 (5H, br s), 7.66 (2H, d, J = 8.5 Hz), 8.14 (2H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 80.7 (C), 123.2 (CH), 126.9 (CH), 128.6 (CH), 128.7 (CH), 129.0 (CH), 140.6 (C), 147.7 (C), 147.8 (C), 176.9 (C); HRMS (EI) *m*/*z* 227.0566 ($M^+ - CO_2H_2$, 25) ($C_{13}H_9NO_3$ requires 227.0582), 197 (12), 150 (7), 105 (100).

(*R*)-2-Nitrobenzylic acid (6b): 78% yield; yellow powder; mp 147−151 °C (EtOAc); $[\alpha]^{25}_D$ −278 (*c* 0.28, MeOH); ^{1}H NMR ($CDCl_3$) δ 6.94 (1H, d, J = 7.6 Hz), 7.40−7.46 (5H, m), 7.59−7.61 (2H, m), 7.84 (1H, dd, J = 7.6, 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 79.9 (C), 125.0 (CH), 126.9 (CH), 128.7 (CH), 129.3 (CH), 130.5 (CH), 131.7 (CH), 132.5 (CH), 136.1 (C), 138.7 (C), 149.0 (C), 176.0 (C); HRMS (EI) *m*/*z* 228.0650 ($M^+ - CO_2H$, 65) ($C_{13}H_{10}NO_3$ requires 228.0661), 167 (79), 152 (81), 105 (64), 77 (100).

(*R*)-3-Methyl-4-nitrobenzylic acid (6c): 87% yield; pale yellow powder; mp 118−124 °C (EtOAc); $[\alpha]^{25}_D$ −43.2 (*c* 0.81, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.54 (3H, s), 7.34−7.39 (5H, m), 7.43 (1H, dd, J = 8.6, 1.6 Hz), 7.49 (1H, br s), 7.89 (1H, d, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 20.5 (CH_3), 80.7 (C), 124.4 (CH), 126.1 (CH), 127.0 (CH), 128.7 (CH), 128.9 (CH), 131.7 (CH), 133.5 (C), 140.6 (C), 145.8 (C), 148.9 (C), 176.6 (C); HRMS (EI) *m*/*z* 242.0827 ($M^+ - CO_2H$, 95) ($C_{14}H_{12}NO_3$ requires 242.0817), 224 (46), 164 (37), 150 (15), 105 (100), 77 (48).

(*R*)-3-Methoxy-4-nitrobenzylic acid (6d): 93% yield; oil; $[\alpha]^{25}_D$ −44.1 (*c* 0.55, MeOH); ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s), 7.13 (1H, dd, J = 6.5, 1.2 Hz), 7.32−7.41 (6H, m), 7.75 (1H, d, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 56.5 (CH_3), 80.6 (C), 112.8 (CH), 119.6 (CH), 125.3 (CH), 127.0 (CH), 128.6 (CH), 128.9 (CH), 139.0 (C), 140.7 (C), 147.5 (C), 152.7 (C), 176.5 (C); HRMS (EI) *m*/*z* 258.0761 ($M^+ - CO_2H$, 46) ($C_{14}H_{12}NO_4$ requires 258.0766), 257 (36), 241 (26), 227 (21), 180 (16), 150 (16), 105 (100), 77 (44).

(*R*)-4-Nitro-3-trifluoromethylbenzylic acid (6e): 64% yield; pale yellow powder; mp 121−124 °C (EtOAc); $[\alpha]^{25}_D$ −60.2 (*c* 0.71, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.38 (5H, br s), 7.81 (1H, d, J = 8.5 Hz), 7.85 (1H, dd, J = 8.5, 1.5 Hz), 8.07(1H, br s); ^{13}C NMR ($CDCl_3$) δ 80.3 (C), 121.9 (C, q, J_{C-F} = 272 Hz), 123.4 (C, q, J_{C-F} = 34 Hz), 124.7 (CH), 126.7 (CH), 127.0 (CH, q, J_{C-F} = 5.5 Hz), 129.0 (CH), 129.3 (CH), 132.4 (CH), 140.4 (C), 146.2 (C), 147.6 (C), 175.4 (C); HRMS (EI) *m*/*z* 296.0539

($M^+ - CO_2H$, 69) ($C_{14}H_9NO_3F_3$ requires 296.0535), 295 (100), 276 (33), 265 (49), 249 (11), 188 (14).

(*R*)-2-Methoxyethoxymethoxymethyl-4-nitrobenzylic acid (6f): 80% yield; oil; $[\alpha]^{25}_D$ +19.3 (*c* 0.60, MeOH); ^{1}H NMR ($CDCl_3-CD_3OD$ 9:1) δ 3.31 (3H, s), 3.47 (2H, d, J = 3.8 Hz), 3.59 (2H, d, J = 3.8 Hz), 4.63 (4H, m), 7.26−7.30 (4H, m), 7.44 (2H, m), 7.91 (1H, d, J = 8.7 Hz), 8.40 (1H, br s); ^{13}C NMR ($CDCl_3-CD_3OD$ 9:1) δ 58.7 (CH_3), 66.2 (CH_2), 66.8 (CH_2), 71.6 (CH_2), 81.2 (C), 95.0 (CH_2), 121.3 (CH), 123.5 (CH), 126.8 (CH), 128.2 (CH), 129.4 (CH), 140.5 (C), 141.4 (C), 147.2 (C), 147.5 (C), 175.9 (C); HRMS (EI) *m/z* 346.1303 ($M^+ - CO_2H$, 0.2) ($C_{18}H_{20}NO_6$ requires 346.1291), 240 (100), 226 (49), 194 (31), 105 (18), 77 (19).

(*R*)-2-Chloro-4-nitrobenzylic acid (6 g): 81% yield; pale yellow powder; mp 169−172 °C (EtOAc); $[\alpha]^{25}_D$ −62.4 (*c* 0.60, MeOH); ^{1}H NMR ($CDCl_3-CD_3OD$ 9:1) δ 7.00 (1H, d, J = 8.4 Hz), 7.29 (3H, br s), 7.57 (2H, br s), 7.80 (1H, d, J = 8.4 Hz), 8.15 (1H, br s); ^{13}C NMR ($CDCl_3-CD_3OD$ 9:1) δ 80.4 (C), 121.1 (CH), 125.7 (CH), 126.7 (CH), 128.7 (CH), 129.2 (CH), 131.5 (CH), 135.3 (C), 137.8 (C), 145.9 (C), 147.9 (C), 176.9 (C); HRMS (EI) *m/z* 261.0185 ($M^+ - CO_2H_2$, 33) ($C_{13}H_8NO_3Cl$ requires 261.0193), 263 (10.2), 231 (11), 154 (17), 105 (100), 77 (39).

(*R*)-5-Methyl-2-nitrobenzylic acid (6i): 79% yield; pale yellow powder; mp 162−169 °C (EtOAc); $[\alpha]^{25}_D$ −290.8 (*c* 0.73, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s), 6.75 (1H, br s), 7.22 (1H, d, J = 8.1 Hz), 7.38 (3H, m), 7.57 (2H, m), 7.76 (1H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6 (CH_3), 80.0 (C), 125.3 (CH), 126.8 (CH), 128.6 (CH), 128.9 (CH), 129.8 (CH), 132.3 (CH), 136.2 (C), 138.7 (C), 144.0 (C), 146.7 (C), 175.7 (C); HRMS (EI) *m/z* 242.0835 ($M^+ - CO_2H$, 66) ($C_{14}H_{12}NO_3$ requires 242.0817), 208 (59), 180 (100), 164 (43), 152 (46), 105 (59), 77 (72).

(*R*)-5-Methoxy-2-nitrobenzylic acid (6j): 73% yield; oil; $[\alpha]^{25}_D$ −245.9 (*c* 0.66, MeOH); ^{1}H NMR ($CDCl_3$) δ 3.64 (3H, s), 6.43 (1H, br s), 6.83 (1H, dd, J = 9.2, 2.4 Hz), 7.36 (3H, br s), 7.57 (2H, br s), 7.95 (1H, d, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$) δ 55.7 (CH_3), 80.2 (C), 113.0 (CH), 118.2 (CH), 126.8 (CH), 128.1 (CH), 128.6 (CH), 129.0 (CH), 138.5 (C), 139.5 (C), 141.8 (C), 162.9 (C), 175.5 (C); HRMS (EI) *m/z* 258.0773 ($M^+ - CO_2H$, 100) ($C_{14}H_{12}NO_4$ requires 258.0766), 224 (23), 182 (45), 154 (21), 105 (30), 77 (40).

(*R*)-2-Nitro-4-trifluoromethylbenzylic acid (6k): 84% yield; yellow powder; mp 161−163 °C (EtOAc); $[\alpha]^{25}_D$ −222.1 (*c* 1.01, MeOH); ^{1}H NMR ($CDCl_3-CD_3OD$ 9:1) δ 7.12−7.14 (3H, m), 7.18 (1H, d, J = 8.4 Hz), 7.35−7.38 (2H, m), 7.43 (1H, d, J = 8.4 Hz), 7.72 (1H, br s); ^{13}C NMR ($CDCl_3-CD_3OD$ 9:1) δ 81.2 (C), 120.8 (CH, q, J_{C-F} = 3.5 Hz), 122.6 (C, q, J_{C-F} = 271.3 Hz), 126.9 (CH), 127.6 (CH, q, J_{C-F} = 3.5 Hz), 127.9 (CH), 128.0 (CH), 130.5 (C, q, J_{C-F} = 34 Hz), 133.1 (CH), 141.7 (C), 141.9 (C), 149.3 (C), 176.5 (C); HRMS (EI) *m/z* 295.0437 ($M^+ - CO_2H_2$, 2) ($C_{14}H_8NO_3F_3$ requires 295.0456), 279 (40), 264 (89), 235 (44), 201 (45), 149 (68), 105 (65), 77 (100).

(*R*)-4-(*N*-Benzoyl-*N*-methylamino)-2-nitrobenzylic acid (6m): 70% yield; oil; $[\alpha]^{25}_D$ −164.3 (*c* 0.67, MeOH); ^{1}H NMR ($CDCl_3$) δ 3.46 (3H, s), 6.76 (1H, d, J = 8.6 Hz), 7.00 (1H, dd, J = 8.6, 2.0 Hz), 7.16−7.35 (8H, m), 7.49 (2H, br s), 7.56 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 38.3 (CH_3), 79.6 (C), 122.0 (CH), 126.8 (CH), 128.2 (CH), 128.5 (CH), 128.7 (CH), 129.4 (CH), 130.5 (CH), 132.3 (CH), 134.1 (C), 134.4 (C), 139.4 (C), 144.9 (C),-149.0 (C), 171.2 (C), 175.1 (C); HRMS (EI) *m/z* 360.1106 ($M^+ - CO_2H_2$, 5) ($C_{21}H_{16}N_2O_4$ requires 360.1110), 344 (10), 328 (10), 105 (100), 77 (43).

General Procedure for the Oxidative Decarboxylation of α-Hydroxy Acid Moiety. A solution of α-hydroxy acid **6** (0.22 mmol), Co(III)-Me_2opba complex (5.3 mg, 0.013 mmol), and pivalaldehyde (74 μL, 0.66 mmol) in 0.9 mL of acetonitrile was stirred under an oxygen atmosphere until consumption of the α-hydroxy acid **6** as indicated by TLC. Water was added, the mixture was extracted with ethyl ether, and the organic layer was washed with brine and dried. The reaction products were purified by flash chromatography to give nitrobenzophenones **7**.

4-Nitrobenzophenone (7a): 82% yield; pale yellow powder; mp 133−135 °C (hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.51 (2H, t, J = 8.0 Hz), 7.64 (1H, t, J = 8.0 Hz), 7.78 (2H, d, J = 8.0 Hz), 7.91 (2H, d, J = 8.5 Hz), 8.31 (2H, d, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 123.5 (CH), 128.7 (CH), 130.1 (CH), 130.7 (CH), 133.5 (CH), 136.3 (C), 142.9 (C), 149.8 (C), 194.8 (C); HRMS (EI) *m/z* 227.0527 (M^+, 63) ($C_{13}H_9NO_3$ requires 227.0582), 150 (15), 105 (100).

2-Nitrobenzophenone (7b): 90% yield; pale yellow powder; mp 105−106 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.42−7.51 (3H, m), 7.59 (1H, tt, J = 7.6, 1.1 Hz), 7.68 (1H, td, J = 8.2, 1.3 Hz), 7.73−7.81 (3H, m), 8.23 (1H, dd, J = 8.2, 1.3 Hz); ^{13}C NMR ($CDCl_3$) δ 124.4 (CH), 128.7 (CH), 128.9 (CH), 129.2 (CH), 130.5 (CH), 133.8 (CH), 134.1 (CH), 135.9 (C), 136.2 (C), 146.7 (C), 193.4 (C); HRMS (EI) *m/z* 227.0580 (M^+, 29) ($C_{13}H_9$-NO_3 requires 227.0582), 152 (22), 150 (18), 134 (81), 105 (100).

3-Methyl-4-nitrobenzophenone (7c): 87% yield; oil; ^{1}H NMR ($CDCl_3$) δ 2.63 (3H, s), 7.50 (2H, t, J = 7.5 Hz), 7.62 (1H, t, J = 7.5 Hz), 7.60−7.79 (4H, m), 7.99 (1H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 20.2 (CH_3), 124.5 (CH), 128.2 (CH), 128.6 (CH), 130.1 (CH), 133.3 (CH), 133.7 (C), 133.9 (CH), 136.4 (C), 141.3 (C), 151.2 (C), 194.9 (C); HRMS (EI) *m/z* 241.0727 (M^+, 79) ($C_{14}H_{11}NO_3$ requires 241.0739), 224 (66), 164 (24), 105 (100).

3-Methoxy-4-nitrobenzophenone (7d): 80% yield; oil; ^{1}H NMR ($CDCl_3$) δ 3.98 (3H, s), 7.33 (1H, dd, J = 8.4, 1.8 Hz), 7.47−7.52 (3H, m), 7.63 (1H, tt, J = 7.8, 1.5 Hz), 7.78 (2H, dd, J = 7.8, 1.5 Hz), 7.85 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 56.8 (CH_3), 114.5 (CH), 121.8 (CH), 125.1 (CH), 128.6 (CH), 130.0 (CH), 133.3 (CH), 136.4 (C), 141.8 (C), 142.3 (C), 152.7 (C), 194.6 (C); HRMS (EI) *m/z* 257.0681 (M^+, 76) ($C_{14}H_{11}NO_4$ requires 257.0688), 226 (2), 211 (2), 180(15), 105 (100), 77 (35).

4-Nitro-3-trifluoromethylbenzophenone (7e): 95% yield; oil; ^{1}H NMR ($CDCl_3$) δ 7.53 (2H, t, J = 7.5 Hz), 7.67 (1H, t, J = 7.5 Hz), 7.77 (2H, d, J = 7.5 Hz), 7.95 (1H, d, J = 8.1 Hz), 8.08 (1H, dd, J = 8.1, 1.0 Hz), 8.21 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 121.5 (C, q, J_{C-F} = 272.0 Hz,), 124.0 (C, q, J_{C-F} = 34.0 Hz), 125.0 (CH), 128.9 (CH), 129.2 (CH, q, J_{C-F} = 5.0 Hz), 130.1 (CH), 133.9 (CH), 134.2 (CH), 135.8 (C), 149.7 (C), 193.2 (C); HRMS (EI) *m/z* 295.0459 (M^+, 100) ($C_{14}H_8NO_3F_3$ requires 295.0456), 218 (8), 105 (100), 77 (26).

2-Methoxyethoxymethoxymethyl-4-nitrobenzophenone (7f): 65% yield; oil; ^{1}H NMR ($CDCl_3$) δ 3.31 (3H, s), 3.45 (2H, m), 3.57 (2H, m), 4.63 (2H, s), 4.70 (2H, s), 7.44−7.50 (3H, m), 7.61 (2H, tt, J = 7.6, 1.2 Hz), 7.74 (2H, dd, J = 7.6, 1.2 Hz), 8.19 (1H, dd, J = 8.4, 2.1 Hz), 8.43 (1H, d, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 58.9 (CH_3), 66.4 (CH_2), 67.2 (CH_2), 71.6 (CH_2), 95.4 (CH_2), 122.1 (CH), 123.4 (CH), 128.7 (CH), 129.1 (CH), 130.0 (CH), 134.0 (CH), 136.2 (C), 139.6 (C), 143.3 (C), 148.7 (C), 195.8 (C); HRMS (EI) *m/z* 345.1220 (M^+, 0.2) ($C_{18}H_{19}$-NO_6 requires 345.1212), 299 (0.4), 270 (8), 240 (100), 194 (26), 165 (29), 105 (9), 77 (13).

2-Chloro-4-nitrobenzophenone (7g): 91% yield; oil; ^{1}H NMR ($CDCl_3$) δ 7.51 (2H, t, J = 7.5 Hz), 7.57 (1H, d, J = 8.5 Hz), 7.66 (1H, t, J = 7.5 Hz), 7.77 (2H, dd, J = 7.5, 1.1 Hz), 8.24 (1H, dd, J = 8.5, 2.0 Hz), 8.35 (1H, d, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 121.9 (CH), 125.2 (CH), 128.9 (CH). 129.6 (CH), 129.9 (CH), 132.5 (C), 134.5 (CH), 135.2 (C), 144.4 (C), 148.8 (C), 193.2 (C); HRMS (EI) *m/z* 261.0182 (M^+, 85) ($C_{13}H_8$-NO_3Cl requires 261.0193), 263 (29), 184 (20), 105 (100), 77 (34).

Hydroxyphthalide (7h): 77% yield from **4h**; oil; ^{1}H NMR (DMSO-d_6) δ 7.33−7.41 (3H, m), 7.51 (2H, dd, J = 8.1, 1.3 Hz), 7.57 (1H, d, J = 8.4 Hz), 8.31 (1H, d, J = 2.1 Hz), 8.38 (1H, dd, J = 8.4, 2.1 Hz), 9.71 (1H, s); ^{13}C NMR (DMSO-d_6) δ 87.6 (C), 118.1 (CH), 124.8 (CH), 125.9 (CH), 128.2 (CH), 128.7 (CH), 128.8 (CH), 132.4 (C), 141.0 (C), 148.9 (C), 156.6 (C), 166.5(C); HRMS (EI) *m/z* 253.0361 ($M^+ - H_2O$, 20) ($C_{14}H_7NO_4$ requires 253.0376), 206 (11), 193 (30), 175 (11), 105 (16).

5-Methyl-2-nitrobenzophenone (7i): 90% yield; mp 96−97 °C (hexane−diethyl ether); ^{1}H NMR ($CDCl_3$) δ 2.48 (3H, s), 7.24 (1H, d, J = 1.0 Hz), 7.40−7.45 (3H, m), 7.56 (1H, tt, J = 7.7, 1.0 Hz), 7.73 (2H, dd, J = 7.7, 1.0 Hz), 8.12 (1H, d, J =

8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5 (CH_3), 124.5 (CH), 128.7 (CH), 129.1 (CH), 130.9 (CH), 133.7 (CH), 136.0 (C), 136.3 (C), 144.4 (C), 145.9 (C), 193.7 (C); HRMS (EI) *m*/*z* 241.0743 (M^+, 25) ($C_{14}H_{11}NO_3$ requires 241.0739), 164 (31), 148 (100), 105 (87), 77 (37).

5-Methoxy-2-nitrobenzophenone (7j): 88% yield; oil; ^{1}H NMR ($CDCl_3$) δ 3.90 (3H, s), 6.86 (1H, d, J = 2.7 Hz), 7.06 (1H, dd, J = 9.1, 2.7 Hz), 7.42 (2H, td, J = 7.5, 1.5 Hz), 7.56 (1H, tt, J = 7.5, 1.5 Hz), 7.73 (2H, dd, J = 7.5, 1.5 Hz), 8.22 (1H, d, J = 9.1 Hz); ^{13}C NMR ($CDCl_3$) δ 56.2 (CH_3), 113.3 (CH), 115.3 (CH), 127.0 (CH), 128.7 (CH), 139.1 (CH), 133.7 (CH), 135.7 (C), 138.8 (C), 139.3 (C), 164.2 (C), 193.2 (C); HRMS (EI) *m*/*z* 257.0693 (M^+, 47) ($C_{14}H_{11}NO_4$ requires 257.0688), 211 (21.2), 180 (10), 105 (100), 77 (47).

2-Nitro-4-trifluoromethylbenzophenone (7k): 84% yield; oil; ^{1}H NMR ($CDCl_3$) δ 7.45 (2H, t, J = 7.5 Hz), 7.61 (1H, t, J = 7.5 Hz), 7.63 (1H, d, J = 8.0 Hz), 7.72 (2H, dd, J = 7.5, 1.3 Hz), 8.02 (1H, d, J = 8.0 Hz), 8.49 (1H, s); ^{13}C NMR ($CDCl_3$) δ 121.9 (CH, q, J_{C-F} = 3.8 Hz), 122.5 (C, q, J_{C-F} = 271.0 Hz), 129.0 (CH), 129.3 (CH), 129.9 (CH), 130.8 (CH, q, J_{C-F} = 3.4 Hz), 133.0 (C, q, J_{C-F} = 34.0 Hz), 134.3 (CH), 135.2 (C), 139.4 (C), 146.7 (C), 191.9 (C); HRMS (EI) *m*/*z* 295.0457 (M^+, 31) ($C_{14}H_8NO_3F_3$ requires 295.0456), 218 (8), 202 (59), 172 (25), 105 (100), 77 (43).

4-(*N*-Benzoyl-*N*-methylamino)-2-nitrobenzophenone (7m): 56% yield; oil; ^{1}H NMR ($CDCl_3$) δ 3.58 (3H, s), 7.26−7.39 (7H, m), 7.42 (2H, tt, J = 7.2, 2.1 Hz), 7.57 (1H, tt, J = 7.2, 1.2 Hz), 7.65 (2H, dd, J = 7.2, 1.5 Hz), 7.94 (1H, d, J = 2.1, Hz); ^{13}C NMR ($CDCl_3$) δ 38.2 (CH_3), 121.5 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 129.5 (CH), 130.7 (CH), 131.5 (CH), 133.9 (CH), 133.1 (C), 134.7 (C), 135.7 (C), 146.8 (C), 147.1 (C), 170.7 (C), 192.6 (C); HRMS (EI) *m*/*z* 360.1168 (M^+, 22) ($C_{21}H_{16}N_2O_4$ requires 360.1110), 105 (100), 77 (37).

2,4-Dinitrobenzophenone (7n): 63% yield from **4n**; yellow-orange powder; mp 146−147 °C (hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.45 (2H, t, J = 7.8 Hz), 7.62 (1H, tt, J = 7.8, 1.6 Hz), 7.77 (2H, dd, J = 7.8, 1.6 Hz), 7.86 (1H, d, J = 8.1 Hz), 8.11 (1H, d, J = 2.3 Hz), 8.65 (1H, dd, J = 8.1, 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 110.1 (CH), 128.6 (CH), 128.9 (CH), 129.6 (CH), 130.3 (CH), 134.5 (CH), 136.4 (C), 142.0 (C), 149.0 (C), 160.5 (C), 194.0 (C); HRMS (EI) *m*/*z* 272.0453 (M^+, 3.0) ($C_{13}H_8N_2O_5$ requires 272.0433), 256 (42), 240 (26), 193 (29), 166 (39), 105 (79), 77 (100).

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Supporting Information Available: General experimental methods description and ^{1}H NMR and ^{13}C NMR spectra of **c**ompounds **4a**−**n**, **5b**, **5i**−**m**, **6a**−**g**, **6i**−**k**, **6m**, **7a**−**k**, and **7m**−**n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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