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The Synthesis and Resolution of 2,2′-, 4,4′-, and 6,6′-Substituted Chiral Biphenyl Derivatives for Application in the Preparation of Chiral Materials

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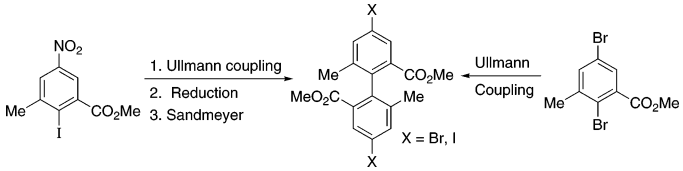

Various routes were examined for the synthesis of chiral biphenyl species that are substituted at the 2,2′, 4,4′ and 6,6′ positions. Because the biaryl bond is tetrasubstituted, many coupling reactions were not suitable. The most reliable coupling reaction proved to be the Ullmann, which gave the desired product in 82% yield. The products were required as the starting point for the preparation of chiral materials using these as the monomer. For this reason, a route was required that produced large quantities of both enantiomers. The two enantiomers were resolved at the penultimate step by the use of chiral HPLC. A complicating feature proved to be the necessity to have a reactive group at the 4,4′ positions, which would permit polymerization though this point. Ultimately, we employed an Ullmann coupling on a dibrominated arene, which occurred selectively at the more hindered bromine by virtue of the directing effect of an ortho ester substituent.

Introduction

Although the largest application of chiral organic compounds is in the synthesis of pharmaceutical compounds, chiral auxiliaries, and chiral ligands, the need for chiral molecules/monomers in materials chemistry is growing. For example, small quantities of chiral organic compounds can induce technologically important bulk properties in soft materials such as polymers, self-assembled monolayers, and liquid crystals. The propagation of chirality from the chiral dopant to the bulk of the material is a function of dopant−host complementarity and molecular recognition. Axially chiral binaphthyl and biphenyl structures are particularly effective at inducing chiral bulk properties in a range of materials[1,2] and, at the same time, are widely known as chiral ligands for some of the most efficient asymmetric catalysts developed to date.

In terms of chiral ligands, axially chiral binaphthyl compounds BINOL (**1**)[3] and BINAP (**2**)[4] are two of the most generally useful ligands developed to date (Figure 1). In addition to binaphthyls, chiral ligands based on *biphenyl* architectures have also been developed, providing some of the most highly enantioselective catalysts known.[4b] For example, SEGPHOS (**3**) and its derivatives have been used as chiral ligands in Cu(I)-catalyzed cross-aldol type reactions,[5] Ru-mediated hydrogenation of ketones and alkenes,[6] and Pd-catalyzed allene formation.[7] Biphenyl (**4**) as well as derivatives of **2** are the key components of asymmetric Mo-catalyzed ring closing metathesis catalysts.[8]

Derivatives of BINOL are also employed in materials chemistry, where they can induce helical structures in certain nematic liquid crystals. They are particularly effective in liquid crystals with complementary biphenyl structures, which promote

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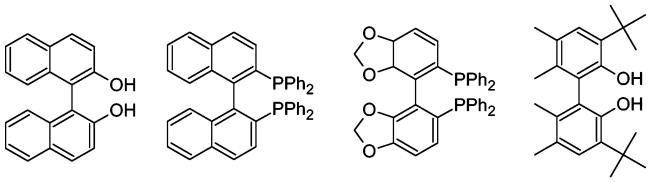


BINOL (**1**) BINAP (**2**) SEGPHOS (**3**) (**4**)

FIGURE 1.

the propagation of chirality through noncovalent core−core interactions.[9] One of us has shown that axially chiral biphenyl dopants are very effective at inducing polar order in smectic liquid crystals with complementary biaryl core structures via intermolecular chirality transfer.[1] For example, a biaryl dopant has been shown to induce some of the highest ferroelectric polarizations ever reported in achiral smectic C liquid crystals with 2-phenylpyrimidine cores. This type of behavior is particularly relevant to the development of fast switching ferroelectric liquid crystal microdisplays.[10]

As part of a project directed toward the synthesis of chiral materials based on biaryl compounds, we required access to large quantities of highly functionalized tetra-*ortho*-substituted biphenyls of the general structure of **5**, Scheme 1. Polar, hydrogen-bonding groups are required around the axis to facilitate the organization of the material and as a handle for further synthetic manipulations. Most critical is the presence of halogen substituents *para* to the ring juncture, because these sites will be employed to incorporate the chiral biphenyl into various materials. As shown in Scheme 1, using **5** as the starting point, we will be able to introduce aryl, vinyl, siloxyl, and a variety of other groups by Pd- or Rh-catalyzed coupling reactions.

Because large amounts of the target compound were required, the route to these species has to be efficient and scalable. In addition, a resolution should be possible as close to the final target as possible, providing access to both enantiomers. Finally, the synthesis should be modular to permit the introduction of a variety of substituents.

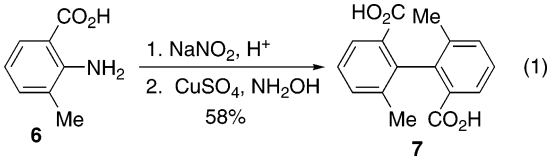
Synthetic Routes

Despite the large number of coupling reactions that can be used in the synthesis of biaryls,[11−14] only a few are effective at forming tetra-substituted biaryls. The majority of methods that are used to prepare these hindered compounds require the presence of a tether, effectively preorganizing the two aryl groups.[14] Although asymmetric syntheses have been developed using chiral tethers or chiral catalysts, most suffer from insufficient generality, cost, or are too lengthy to be employed for the production of large quantities of the final product.[13,14]

Certain Pd-catalyzed aryl−aryl coupling reactions can be employed in the synthesis of sterically hindered biaryls. Fu and Dai[15] developed a Negishi cross coupling using P(*t*-Bu)$_3$ as the ligand of choice. This was quickly followed by other examples of hindered biaryl syntheses via Negishi,[16] Suzuki−Miyaura,[17] and Stille couplings.[18] More recently, organocuprate oxidation has been used to couple hindered Grignard reagents,[19] as well as organolithium reagents,[20] with encouraging results.

Historically, the classical Ullmann coupling[11] and the reductive coupling of diazonium salts[21−23] have been most effective in the synthesis of hindered biaryls. Neither of these reactions require the presence of special ligands or expensive reagents. The apparent simplicity of these last two reactions and the presence of closely related structures in the literature convinced us to explore synthetic pathways involving both of these reactions in the key coupling step.

Route 1: Diazonium Coupling of Bromoaniline Derivative. Denmark and Matsuhashi[21] reported the synthesis of compound **7** via a reductive coupling of diazonium salts generated from amine **6**.



6 **7**

For our route, precursor **11**, in which the *para* position is substituted with a bromine atom, was required. This species was initially synthesized via isatin intermediate **9**,[24−26] which was prepared from *o*-toluidine, in two steps (Scheme 2). Importantly, bromination of **9** occurred exclusively *para* to the amide moiety. Hydrolysis of **10** provided substrate **11** for the key coupling step.

Although the coupling of **6** in which the key *para* position is unsubstituted could be reliably reproduced using the Denmark procedure,[21] compound **11** gave the desired compound **12** in extremely low yield. Although the ^{1}H NMR spectrum and weight of the crude product suggested a clean reaction with a fairly high yield (about 70%), it soon became obvious that a large amount of spectroscopically invisible material accompanied the product, complicating purification. When purification was finally achieved, the yield of the coupling reaction was at best 13%.

Because the only difference between substrates **6** and **11** is the *para*-bromo substituent, we hypothesized that activation of

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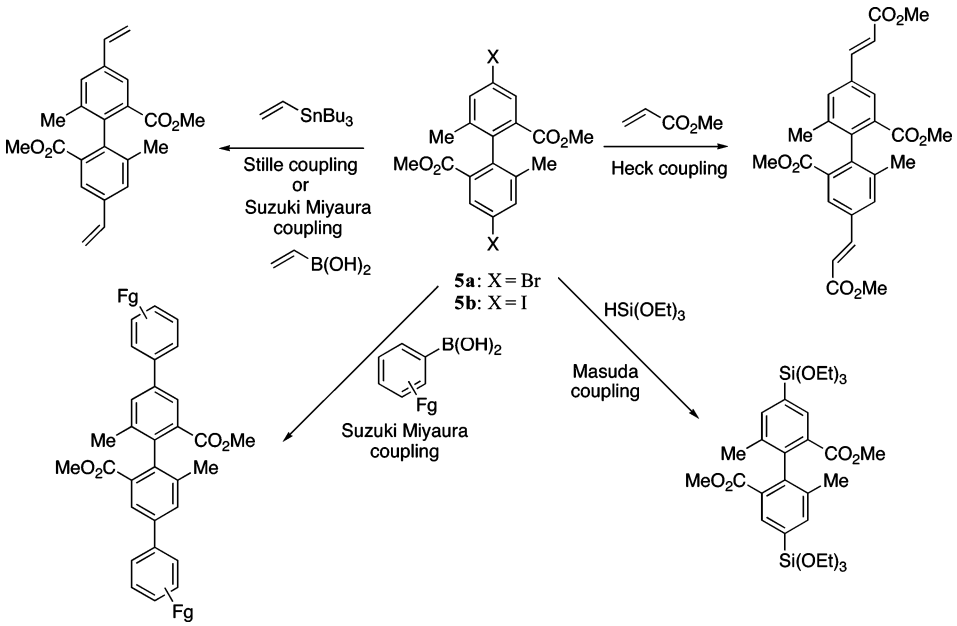
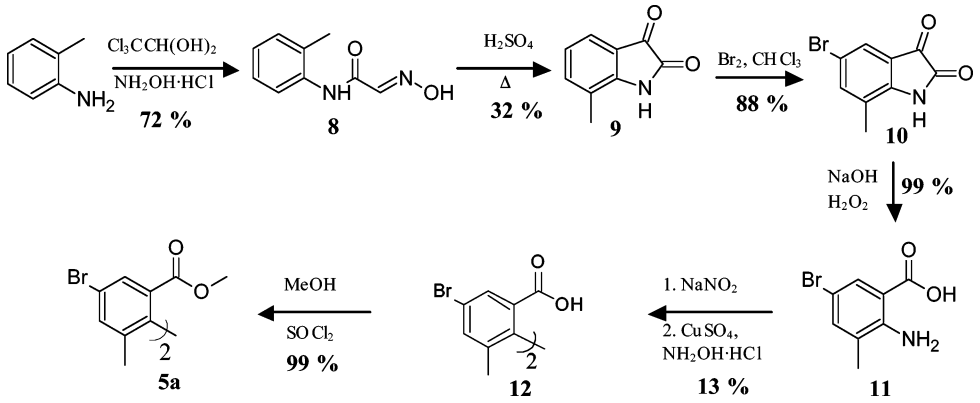
SCHEME 1. Introduction of Polymerizable Groups on the Biaryl Framework



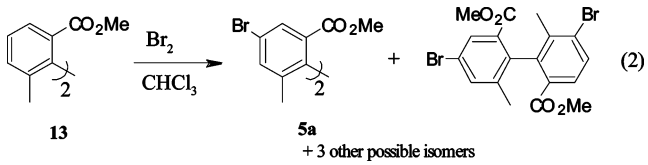
SCHEME 2



the C−Br bond and subsequent reaction with the amine from another molecule[27] in a Hartwig−Buchwald-type might be responsible for the polymeric contaminants observed.

In an attempt to simplify the purification, the crude biphenyl, **12**, was taken through to the next step, esterified,[28] and then purified on flash silica. This method of purification, while successful, proved unsatisfactory as we planned to resolve the biphenyl atropisomers at the acid stage by salt formation with quinine. The purified diester would, thus, have to be hydrolyzed (88% yield), resolved, and then re-esterified (85% yield), in effect adding two unwanted steps to the pathway.

In lieu of the apparent incompatibility of the *para*-bromo substituent under coupling conditions, we attempted to introduce the halogen *after* the coupling by an electrophilic bromination (eq 2). Unfortunately, this reaction proved highly unselective, with the crude ^{1}H NMR showing the presence of at least three other isomers, all in greater yield than the desired product. The directing power of the phenyl group is obviously not strong enough to out-compete that of the methyl group.



Route 2: Diazonium Coupling of Nitroaniline Derivative. Re-evaluating our synthetic route, we decided to employ a nitro group as a synthon for the bromo substituent. Even though conversion of the NO_2 group into Br requires two steps (reduction and Sandmeyer reaction), the improved behavior of the substrate at problem steps more than compensated for the additional steps. Furthermore, this route would provide facile access to the *para*-diiodo biphenyl derivative, **5b**, which would be the most reactive substrate for a slate of future metal-catalyzed coupling reactions.

Nitration of methyl isatin **9** proceeded smoothly, as did the hydrolysis of **14**, yielding 2-amino-3-methyl-5-nitrobenzoic acid **15** (Scheme 3).[29] As expected, the coupling step proceeded with higher but still unsatisfactory yields (47%). The crude product showed the presence of both unreacted starting material as well

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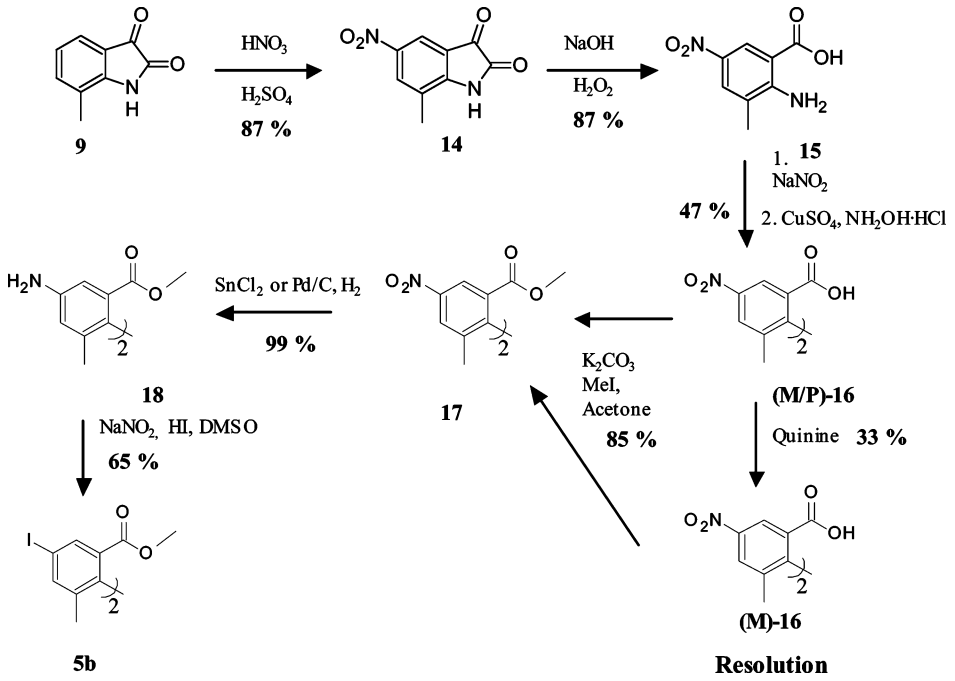
SCHEME 3



as a small amount of 2-hydroxy-3-methyl-5-nitrobenzoic acid. The former could be removed by trituration with ether, but final purification still required exhaustive silica gel chromatography, which was not desirable on a large scale.

Compound **16** could be resolved by selective crystallization of one of the diastereomeric salts with quinine. The enantiomeric excess of the *M*-isomer was determined both by chiral SFC and ^{1}H NMR shift reagents (europium tris-3-(heptafluoropropyhydroxymethylene)-(+)-camphorate in a 3:1 ratio with **(*M*)-17**) to be >95%. However, the yields after resolution were less than satisfactory, normally being on the order of 30% for high purity material. The supernatant afforded an enriched solution of *P*-isomer that could not be further resolved, as quinine has no natural enantiomers (resolution of racemic **16** with quinidine, a diastereomer of quinine, was not successful). This was problematic because both enantiomers are ultimately required for the preparation of chiral materials of both handedness.

Carrying on with the rest of the route, the reduction of nitro ester **17** with $SnCl_2$ proceeded smoothly and in quantitative yield. However, the workup of the $SnCl_2$ reduction proved tedious due to the formation of emulsions. Reduction with Pd/C and H_2 was faster, just as high yielding, and the workup was trivial. Some care had to be taken in storing the diamino biphenyl **18**, which became oxidized, most likely to the *N*-oxide, if left exposed to air. However, the amine could be stored under nitrogen or argon in the fridge for up to two weeks without any noticeable degradation.

The final step in the synthesis, conversion of the diamine to diiodo biphenyl ester **5b** was also problematic. Normal aqueous conditions for the Sandmeyer reaction provided very little product (10%). This could have been due to the insolubility of **18**, as well as the possible loss of product due to the unwanted hydrolysis of the esters to acids, but no free iodinated acids were detected. Furthermore, using the free acid as the starting material still gave poor results. Nonaqueous methods using *iso*-amyl nitrite[30] and *tert*-butyl nitrite[31] were attempted with moderate success (yields < 10% for the former and in the 50% range for the latter). The main difficulty in purification was that the product was always contaminated with small amounts of monoiodinated product resulting from reduction of one of the two diazonium salts. This byproduct had a very similar R_f as di-iodinated species **5b**, making it difficult to remove.

Not content with the extent of time and labor required to perform this reaction, we examined other options. Moore and co-workers[32−34] have effectively used 1-aryl-3,3-dialkyltriazenes as masking groups for aryl iodides in the synthesis of phenylacetylene macrocycles.[33] Unfortunately, the yield of the triazene derivatives from aromatic amine **18** was quite low. Finally, a recently reported procedure[35] using DMSO, $NaNO_2$, and HI gave the highest yield we have obtained to date in this reaction (65%) along with little to no byproduct, fast reaction times, and facile workup. It is worth noting that the conversion of aromatic diamines to the corresponding aromatic dihalogens is often a poor reaction, and yields below 50% are common.

Although this route provided access to the desired compound, a critical look at the synthetic pathway revealed two major problems that still had to be addressed. First, the isatin route to **15** did not have a very high overall yield (17%), and the acquisition of large quantities of chloral hydrate was complicated, as it is a controlled substance. Substitution of the chloral hydrate with the brominated analogue gave slightly lower yields of the isonitrosoacetanilide. In addition, scale-up of the coupling reaction was anticipated to be problematic because the reaction requires low temperatures, carefully controlled addition of concentrated HCl to the reaction to form the diazonium salt, followed by another controlled addition of the latter, and the

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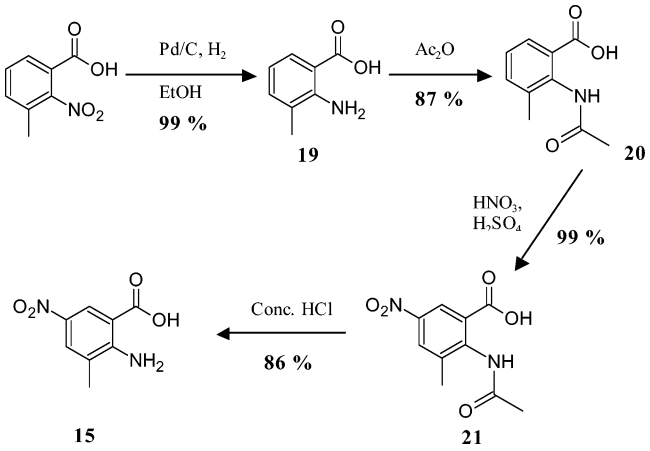
SCHEME 4



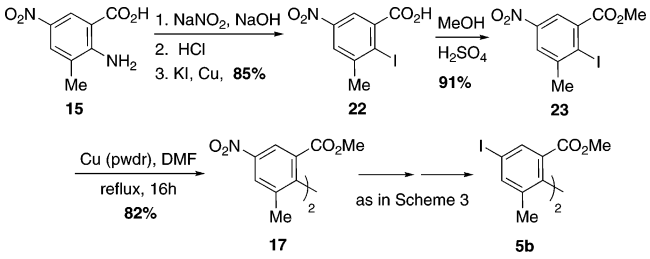
subsequent evolution of large quantities of gas. With these considerations in mind, in addition to literature evidence[36,37] suggesting that the Ullmann coupling would occur in high yield, we attempted the synthesis of **5** via an Ullmann coupling.

Route 3: Ullmann Coupling of Iodonitro Derivative. Our success in the reduction of the nitro group in **17** to the corresponding amine led us to attempt the reduction of commercially available 2-nitro-3-methyl benzoic acid (NMBA) to 2-amino-3-methyl benzoic acid **19** (Scheme 4). The reduction, using Pd/C and H_2, proceeded smoothly and in quantitative yield. Direct nitration of **19** is complicated by the protonation of the amine with concentrated HNO_3, so **19** was first protected as an acetamide. During nitration, the reaction temperature could not be allowed to rise above 10 °C, otherwise two regioisomers were observed corresponding to nitration *para* to the amine and *ortho* to the carboxyl substituent,[38] respectively (9:1). At 0 °C, the reaction was selective for the *para*-nitro isomer, but significant decreases in rate were observed. Ultimately, we found that increasing the concentration of the nitrating reagent by using fuming nitric acid and keeping the reaction temperature at 0 °C gave a selective and fast reaction, providing **21** in 99% yield.

Poor yields in the deprotection of the acetamide were observed under basic conditions (50−66%).[39] However, refluxing **21** in concentrated HCl resulted in efficient removal of the amide, and **15** precipitated out of solution in high yield. Although we expected to isolate compound **15** as the HCl salt, an infrared spectrum of the material shows both the presence of a primary amine (two peaks at 3473 and 3362 cm^{-1}) as well as hydrogen bonding between this amine and the carboxylic acid (very broad peak at 3000 cm^{-1}), implying that internal hydrogen bonding takes place between the acid and the amine.

Conversion of the amine group in **15** into an iodide via a Sandmeyer reaction proceeded smoothly (85% yield, Scheme 5). It was necessary to initially add the $NaNO_2$ in a basic solution of **15**, before acidifying, to ensure that no significant hydroxylation side product of the diazonium salt occurred. Fisher esterification of the acid yielded the Ullmann coupling precursor **23**. Protection of the carboxylic acid as an ester was necessary

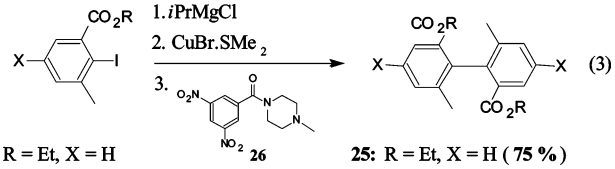
SCHEME 5



at this stage, because acids are known to interfere with the coupling reaction. Remarkably, the Ullmann coupling proved to be far superior to our previous coupling attempts in terms of yield (82%), ease of reaction, reproducibility, and scalability.

The only complication in this route is that hydrolysis of the ester to the corresponding acid was necessary to perform the resolution with quinine, as previously described. Rather than add more steps to the synthesis, chiral chromatography was examined. In fact, diamino biphenyl **18** could be resolved on Chiralpak AS column *even as the ester.* Although the maximum amount of the amine that could be separated in a given run was limited by the solubility of **18**, this method enabled us to perform the separation at the penultimate step, without additional synthetic steps. In addition, complete baseline separation was achieved, providing both enantiomers in pure form. Thus, using a column of 5 × 50 cm, we were able to obtain 100 mg of each enantiomer in 100 minutes.

As one final alternative for the coupling reaction, we examined the recently published organocuprate oxidation of Grignard reagents.[19] Reported yields for the reaction (**24** to **25**, eq 3) are comparable to that of the Ullmann (75%), and the reaction time is much shorter (30 min). However, our substrate (**23**) reacted with very low yield (10%), illustrating the sensitivity of the reaction to variations in substrate. In addition, the requirement for one full equivalent of Grignard reagent and oxidant **26**, as well as low temperatures, make this method unappealing for large scale applications.



24: R = Et, X = H
23: R = Me, X = NO_2
25: R = Et, X = H (75 %)
17: R = Me, X = NO_2 (10 %)

Route 4: Ullmann Coupling of Dibromo Derivative. One final pathway investigated for the synthesis of **5a** takes advantage of the observation that Ullmann reactions take place preferentially at halogens that are *ortho* to an electron-withdrawing group such as methoxycarbonyl. Thus, if it were possible to differentiate between the two bromines in compound **28**, we would have a significantly shorter route to the desired compound, as outlined in Scheme 6.

The synthesis of **28** begins with selective bromination of **19** without prior protection of the latter, using DMSO and HBr.[40] The second bromine is then added via the modified Sandmeyer reaction, and the crude acid is finally esterified. Gratifyingly the Ullmann coupling proceeded with high selectivity giving

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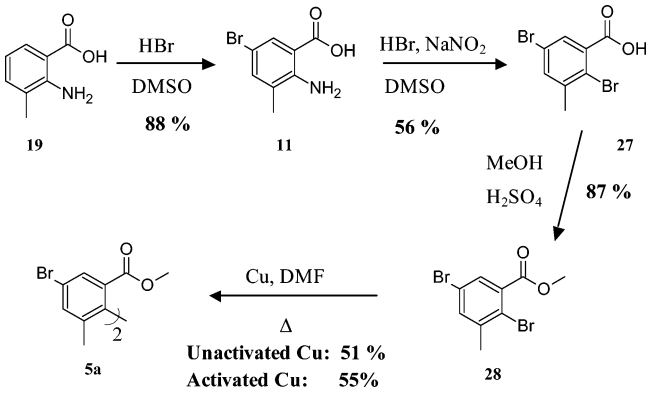
SCHEME 6



only the desired coupled product. Although the yield is moderate (55% with activated Cu), the shortness of the route compensates for this.

Comparison of Routes

The various synthetic routes that have been examined for the synthesis of **5** are compared in Table 1. The first route examined, which involves the coupling of *para*-bromo aniline (**11**) as the key step, is only six steps, but the low yield in the coupling step makes this route untenable, with an overall yield of 2.7%. Proceeding through the nitro derivative **15**, even though it adds an additional two steps, gives an average yield per step of 68%, but the overall yield is still only 4.6%. The big improvement in the synthesis came with the use of NMBA as the starting material instead of chloral hydrate. The diazonium coupling in this route is still the lowest yielding step, but the overall yield increases to 18.9%. The initial Ullmann route is longer by one step but is the most scalable and highest yielding, with an overall yield of 30.2% and an average yield per step of 87%. Finally, the Ullmann route using precursor **28** is only five steps long but suffers from two low yielding steps, giving an overall yield that is lower (21.1%) than the previous pathway, with an average yield of 77.2%.

Conclusions

In conclusion, the synthesis of chiral biphenyl **5** has been achieved by a variety of routes. Difficulties were encountered in the coupling and iodination steps. The most reliable coupling reaction proved to be the Ullmann, which gave the desired product in 82% yield. The overall yield for this sequence was 30.2%, with an average yield per step of 87.5%. The two enantiomers were resolved at the penultimate step by the use of chiral HPLC. The preparation of analogues of **5** and conversion of these compounds into chiral materials is currently underway in our lab.

Experimental Section

General. All nonhydrolytic reactions were performed in oven- or flame-dried glassware under a dry nitrogen or argon atmosphere. The ^{1}H and ^{13}C NMR spectra were recorded using 300-, 400-, 500-, and 600-MHz spectrometers. Proton chemical shifts are given relative to those of internal standards chloroform, methanol, DMSO, and acetone: δ = 7.26, 3.30, 2.50, or 2.05 ppm, respectively. Carbon chemical shifts are given relative to those of chloroform, methanol, DMSO, and acetone: 77.0, 49.0, 39.5, or 29.8 ppm, respectively. Mass spectra were obtained using a QStar XL spectrometer. TLC was performed using glass- or aluminum-backed Silica Gel 60 F_{254}. Column purification was achieved through normal flash silica or using the flash chromatography cartridges. Analytical SFC chromatography was performed on a SFC HPLC using a Daicel ChiralPak AD-H column and methanol as the co-eluent. Preparative chiral stationary-phase HPLC separations were performed using a 5 × 50 cm Chiralpak AS column. Melting points (uncorrected) were determined using a Fisher-Jones melting point apparatus.

Materials. All reagents and chemicals were used without further purification unless otherwise noted.

Synthesis of *o*-Isonitrosoacetotoluidide (8).[26] A three-neck 2-L round-bottom flask was charged with chloral hydrate (39.9 g, 241 mmol, 1.1 equiv), anhydrous sodium sulfate (312.2 g, 1.75 mol, 8 equiv), and 880 mL of H_2O. The solution was stirred with a mechanical stirrer and heated to 40 °C until the mixture became clear.

Solution **A**: Distilled *o*-toluidine (23.4 g, 219 mmol) was dissolved in 135 mL of H_2O and concentrated HCl (22.7 g, 19.0 mL, 230 mmol, 1.05 equiv).

Solution **B**: Hydroxylamine (50.2 g, 723 mmol, 3.3 equiv) was dissolved in 225 mL of H_2O.

Solutions **A** and **B** were added to the mixture in order, under vigorous stirring. The resulting solution was heated to reflux, allowed to reflux for 2 min, and then cooled to room temperature. The product precipitated out of solution, and after standing for 16 h, the solid was collected and dried: 28.8 g (74%); mp 117−118 °C (lit.[41] 119−121 °C). ^{1}H NMR ($CDCl_3$): δ 8.21 (s, 1H), 8.01 (s, 1H), 7.97 (d, J = 8 Hz, 1H), 7.62 (s, 1H), 7.24 (t, J = 8 Hz, 1H), 7.21 (d, J = 8 Hz, 1H), 7.10 (t, J = 8 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 160.5, 144.6, 134.6, 130.6, 129.2, 126.9, 125.7, 122.8, 17.4.

Synthesis of 7-Methyl-1*H*-indole-2,3-dione (9).[26] To a preheated (50 °C) solution of concentrated sulfuric acid (33 mL), under rapid stirring, compound **8** (8.40 g, 0.053 mol) was slowly added, keeping the temperature of the reaction between 60 and 70 °C. Once the addition was complete, the reaction mixture was heated to 80 °C and stirred for 20 min. The reaction mixture was then allowed to cool to rt and poured over crushed ice (200 g), yielding a crude rust-colored precipitate that was collected by suction filtration. The crude product was purified by initial suspension in 15 mL of hot water, followed by dissolution in NaOH (1.4 g in 5 mL of H_2O). This solution was then acidified using 4 M HCl until a slight precipitate appeared (around pH 3−4), at which point it was filtered and the filtrate was acidified below pH 0. The pure product precipitated out as an orange solid that was collected and air-dried: 3.185 g (32%); mp 273 °C (lit.[26,41] 270−273 and 266−268 °C, respectively). ^{1}H NMR (DMSO-d_6): δ 11.09 (s, 1H), 7.43 (d, J = 8 Hz), 7.34 (d, J = 8 Hz, 1H), 6.98 (t, J = 8 Hz, 1H), 2.19 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 185.2, 160.4, 149.7, 140.0, 123.1, 122.5, 122.1, 117.9, 15.9.

Synthesis of 5-Bromo-7-methyl-1*H*-indole-2,3-dione (10). To a solution of 7-methyl-1*H*-indole-2,3-dione, **9** (2.15 g, 0.013 mol), in $CHCl_3$ (200 mL) was added dropwise to a solution of Br_2 (2.6 g) in 30 mL of $CHCl_3$. The resulting solution was heated to reflux and stirred for 24 h. It was then cooled to 0 °C (ice bath), which resulted in the precipitation of the product as a red solid. The precipitate was collected by suction filtration and dried under vacuum to yield 3.75 g of **10** (88%): mp 262 °C dec (lit.[42] 180 °C). ^{1}H NMR (DMSO-d_6): δ 11.20 (s, 1H), 7.64 (s, 1H), 7.48 (s, 1H), 2.20 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 184.0, 160.0, 148.9, 141.2, 124.8, 124.6, 119.5, 114.7, 15.7. MS (EI^+): m/z 239 [M^+]; HRMS calcd for $C_9H_6O_2NBr$, 238.9582; found, 238.9590.

Synthesis of 2-Amino-5-bromo-3-methylbenzoic Acid (11). Method 1. Compound **10** (7.6 g, 0.032 mol), NaCl (4.2 g, 0.073

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TABLE 1. Comparison of Various Synthetic Pathways

coupling precursor/ starting material	coupling method	number of steps	lowest yielding step (%)	overall yield (%)	yield per step (%)
Br (**11**)/toluidine	diazonium	6	13	2.66	54.6
NO_2 (**15**)/toluidine	diazonium	8	47	4.61	68.1
NO_2 (**15**)/NMBA	diazonium	8	47	18.9	81.2
NO_2 (**15**)/NMBA	Ullmann	9	65	30.2	87.5
Br (**28**)/NMBA	Ullmann	5	55	21.1	77.2

mol), and NaOH (2.9 g, 0.073 mol) were dissolved in water (75 mL) with stirring to give a yellow solution after 0.5 h. This mixture was cooled to 0 °C, to which a solution made up of 30% H_2O_2 (5.5 mL) and NaOH (4.9 g) in water (65 mL) was slowly added. The reaction mixture was stirred for another 1.5 h and then quenched with glacial acetic acid, yielding the product as a tan precipitate. The solid was collected by suction filtration, washed thoroughly with cold water, and dried under vacuum to yield 7.20 g (99%).

Method 2. To a solution of compound **19** (1.36 g, 9.00 mmol) in 10 mL of DMSO was added 48% HBr (5 equiv, 3.64 g, 2.44 mL, 45 mmol), and the resulting mixture was stirred for 16 h. A white precipitate formed during the course of the reaction. The reaction was quenched with $NaCO_{3(satd)}$, yielding a white solid that was filtered and dried under vacuum to yield 1.83 g of product (88%): mp 218−220 °C. IR (KBr): 3511, 3379 (NH_2), 2800 (br, OH), 1680 (C═O). ^{1}H NMR (DMSO-d_6): δ 7.68 (s, 1H), 7.32 (s, 1H), 2.10 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 168.8, 149.0, 136.3, 130.6, 126.2, 111.0, 104.5, 17.2. MS (EI$^+$): *m*/*z* 229 [M$^+$]; HRMS calcd for $C_8H_8O_2NBr$, 228.9738; found, 228.9747.

General Synthetic Procedure for Biphenyl Compounds (12) and (16).[21] The requisite amine (10 mmol) was taken up in 18 mL of 2.5 M NaOH (4.5 equiv), followed by 18 mL of H_2O, to give a fine suspension. This suspension was stirred and cooled in an ice bath (0−4 °C) for 10 min, then $NaNO_2$ (2.5 equiv, 1.71 g, 25 mmol) was added. After an additional 15 min of stirring, the dropwise addition of cold 4 M HCl (33 equiv, 94 mL), while keeping the temperature between 0 and 5 °C, was performed. The solution was stirred for an additional 1.5 h to ensure formation of the diazonium species. In a separate flask, $CuSO_4$ (1.7 equiv, 4.25 g, 17 mmol) was dissolved in 40 mL of H_2O and stirred for 10 min in an ice bath. NH_4OH (230 equiv, 30 mL) was then added to the solution, and the resulting deep purple solution was stirred at 0 °C for an additional 1.5 h. A solution of NH_2OH, prepared by dissolving NH_2-OH·HCl (1.9 equiv, 1.32 g, 19 mmol) in 2.5 M NaOH (2 equiv, 15.2 mL), was then added to the copper solution. The diazonium solution was then added dropwise into the copper solution, at all times maintaining the temperature below 10 °C. Once the addition was complete, the reaction solution was stirred for 5 min then heated at reflux for 0.5 h. The reaction was cooled to room temperature, had 37.5 mL of 12 M HCl added dropwise, and then was stirred for 12 h. The crude brown product precipitate was collected by suction filtration, washed with H_2O, and dried in vacuo.

Purification of 4,4′-Dibromo-6,6′-dimethyl[1,1′-biphenyl]-2,2′-dicarboxylic Acid (12). Using the general procedure, 5.19 g of amine **11** (22.6 mmol) afforded 3.51 g of crude biphenyl **12**. Trituration of the crude product in ether, followed by filtration and removal of the solvent, yielded 2.80 g of still impure product. Final purification was achieved by column chromatography using an ether/hexanes/acetic acid (29.75:70:0.25) solvent mixture. The impure product was added as a silica plug (5 g) to a 60 g silica column affording 0.617 g of pure product (13%): mp 151−152 °C. IR (KBr): 3000 (br, OH), 1687 (C═O). ^{1}H NMR (CD_3COCD_3): δ 7.99 (d, J = 1.6 Hz, 2H), 7.69 (d, J = 1.6 Hz, 2H), 1.92 (s, 6H). ^{13}C NMR (CD_3COCD_3): δ 166.7, 140.6, 140.2, 136.8, 132.6, 131.3, 121.0, 19.9. MS (ES$^-$): *m*/*z* 427 [M − H]$^-$; HRMS calcd for $C_{16}H_{11}O_4Br_2$, 424.9024; found, 424.9019.

Purification of 4,4′-Dinitro-6,6′-dimethyl[1,1′-biphenyl]-2,2′-dicarboxylic Acid (16). Using the general procedure, 7.42 g of amine **15** (37.8 mmol) afforded 5.32 g of crude biphenyl **16**. Trituration of the crude in ether, followed by filtration and removal of the solvent, yielded 4.21 g of still impure product. Final purification was achieved by column chromatography using an ether/hexanes/acetic acid (59.5:40:0.5) solvent mixture. The impure product was added as a silica plug (10 g) to a 200 g silica column, affording 3.17 g of pure product (47%): mp 84−185 °C. IR (KBr): 3000 (br, OH), 1712 (C═O). ^{1}H NMR (CD_3COCD_3): δ 8.76 (s, 2H), 8.42 (s, 2H), 2.10 (s, 6H). ^{13}C NMR (CD_3COCD_3): δ 165.1, 147.1, 147.0, 139.0, 130.6, 127.8, 123.0, 19.3. MS (EI$^-$): *m*/*z* 358.9 [M − H]$^-$; HRMS calcd for $C_{16}H_{11}O_8N_2$, 359.0514; found, 359.0530.

Classical Resolution of 16.[43] To **12** (1.81 g, 5.02 mmol), dissolved in 25 mL of acetone, was added quinine (1.81 g, 5.02 mmol, 1 equiv), and then the mixture was refluxed for 30 min. Once the solution had cooled, the precipitated salt was collected, washed once with cold acetone, and dried under vacuum to yield 1.71 g. This salt was dissolved into 10 mL of 4 N HCl solution that was subsequently extracted with ether (3 × 10 mL). The organic solvent was dried with $MgSO_4$, filtered, and concentrated to yield 594 mg of (+)-**12** (33%), mp 187−191 °C, $[\alpha]_D = +2.5°$ (*c* 1.7, MeOH). The supernatant was concentrated, treated with HCl, and subsequently extracted with ether, yielding enriched (−)-**12**, upon concentration, 853 mg (47%).

Synthesis of Dimethyl 4,4′-Dibromo-6,6′-dimethyl[1,1′-biphenyl]-2,2′-dicarboxylate (5a).[28] **Method 1.** Compound **5** (26 mg, 0.610 mmol) was dissolved in 2 mL of methanol, resulting in a homogeneous solution, and cooled to 0 °C. $SOCl_2$ (0.026 mL, 1.83 mmol, 6 equiv) was then added dropwise to the reaction mixture, which was heated at reflux for 2 h. The reaction was cooled to room temperature and concentrated in vacuo. The resulting solid was triturated with EtOAc and discarded. The organic solution was washed with H_2O, dried with $MgSO_4$, and concentrated to afford 27.8 mg of a white solid (99%).

Method 2. A mixture of **27** (1.444 g, 4.69 mmol) and activated Cu powder (1.2 g, 18.8 mmol, 4 equiv) in 20 mL of dry DMF was refluxed with stirring for 16 h. Once the solution was cool, it was filtered, and the residue was washed with ethyl acetate (50 mL). The filtrate was washed successively with 1 M HCl (3 × 20 mL), H_2O (3 × 20 mL), and satd $NaHCO_3$ (3 × 20 mL), dried with $MgSO_4$, and concentrated to give a crude brown solid. The product was purified by column chromatography (Biotage) using a gradient solvent system (3% EtOAc/hexanes to 25% EtOAc/hexanes). The isolated yield of **5a** was 0.591 g (55%): mp 163−164 °C. IR (KBr): 1737, 1715 (C═O). ^{1}H NMR ($CDCl_3$): δ 8.01 (d, J = 1.5 Hz, 1H), 7.58 (d, J = 1.5 Hz, 1H), 3.63 (s, 3H), 1.88 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 165.9, 139.3, 138.8, 136.5, 130.8, 121.0, 52.2, 19.9. MS (EI$^+$): *m*/*z* 455 [M$^+$]; HRMS calcd for $C_{18}H_{16}O_4Br_2$, 455.9396; found, 455.9410.

Synthesis of 7-Methyl-5-nitro-1*H*-indole-2,3-dione (14). Compound **9** (10.9 g, 67.7 mmol) was added to a cooled (6 °C) solution of concentrated H_2SO_4 (60 mL) and stirred for 5 min. A solution of concentrated HNO_3 (5 mL) and H_2SO_4 (0.5 mL) was then added dropwise, keeping the temperature between 10 and 14 °C. Once the addition was complete, the reaction was stirred for another 10 min and poured onto 360 g of crushed ice. The resulting orange

(43) Williams, V. E.; Lemieux, R. P. *Chem. Commun.* **1996**, 2259−2260.

precipitate was filtered, washed with H_2O (3 × 20 mL), and dried under vacuum, 12.21 g (87%): mp 255−256 (lit.[29] 256−257 °C). ^{1}H NMR (CD_3COCD_3): δ 10.68 (br s, 1H), 8.38 (s, 1H), 8.16 (s, 1H), 3.44 (br s, 2H), 2.45 (s, 3H). ^{13}C NMR (CD_3COCD_3): δ 183.5, 160.3, 154.9, 144.3, 134.4, 124.1, 118.4, 118.2, 15.7. MS (EI^+): *m*/*z* 206 [M^+]; HRMS calcd for $C_9H_6O_4N_2$, 206.0328; found, 206.0336.

Synthesis of 2-Amino-3-methyl-5-nitrobenzoic Acid (15). Method 1. Compound **14** (4.00 g, 34 mmol) was dissolved in 500 mL of a freshly made 0.90 M NaOH (18 g) solution and stirred at rt for 1.5 h. Then 193 mL of 3% H_2O_2 in H_2O was added to the solution, and it was stirred for an additional hour at rt. The reaction was quenched by adding 50 mL of glacial acetic acid, yielding a yellow precipitate that was collected via filtration, washed with H_2O (2 × 50 mL), and dried under vacuum, 5.79 g (87%).

Method 2. Concentrated HCl (150 mL) was added to compound **21** (10.0 g, 42.0 mmol), and the resulting solution was refluxed for 2 h. Toward the end of the reaction, the product started to precipitate out as a yellow solid. The solution was cooled, added to a beaker containing crushed ice (100 g), and filtered once the ice had melted. The solid was then washed with H_2O (3 × 50 mL) and dried to yield 6.70 g. The supernatant was diluted by adding 50% more water and allowed to stand for 24 h, at which point the second crop of product was filtered and washed with H_2O, 0.408 g. Overall yield: 7.11 g (86%). Mp 268−269 (lit.[29] 268 °C). ^{1}H NMR (CD_3COCD/DMSO): δ 8.65 (s, 1H), 8.02 (s, 1H), 7.50 (br s, 1H), 2.27 (s, 3H). ^{13}C NMR (CD_3COCD/DMSO): δ 169.8, 155.6, 136.4, 129.2, 127.4, 124.8, 109.4, 17.6. MS (ESI^+): *m*/*z* 197 [M + H]$^+$, 219 [M + Na]$^+$; HRMS calcd for $C_8H_9NO_4$, 197.0562; found, 197.0555.

Synthesis of 2-Amino-3-methyl-benzoic Acid (19). An autoclave was charged with 2-nitro-3-methylbenzoic acid (25.0 g, 0.14 mol) in ethanol (160 mL). Palladium on activated carbon (10% Pd, 2.5 g) was then added. After sequentially evacuating and purging with hydrogen three times, the autoclave was charged to approximately 500 psi, and the reaction mixture was stirred at ambient temperature until further hydrogen uptake ceased. Once the reaction was finished, the catalyst was removed by filtration through a sintered-glass funnel containing a pad of Celite, which was washed with 500 mL of ethanol. The solvent was removed under reduced pressure, and the product was then further dried under vacuum, yielding a pinkish-white solid, 20.5 g (99%): mp 175−176 °C (lit.[44] 174−176 °C). ^{1}H NMR (CD_3COCD_3): δ 7.76 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.53 (t, J = 8.0 Hz), 2.17 (s, 3H). ^{13}C NMR (CD_3COCD_3): δ 169.7, 150.1, 134.7, 129.4, 123.0, 114.7, 109.3, 16.7. MS (ESI^-): *m*/*z* 150 [M − H]$^-$.

Synthesis of 2-Acetylamino-3-methyl-benzoic Acid (20). 2-Amino-3-methylbenzoic acid **19** (37.3 g, 0.25 mol) and acetic anhydride (70 mL, 0.75 mol) were added to a 300-mL round-bottom flask, and the resulting suspension was heated to reflux for 2 h under constant stirring. The hot solution was then poured into a flask containing 500 g of crushed ice, resulting in a white precipitate. The suspension was stirred for an additional 10 h, and then the beige-white solid was collected by suction filtration, washed with cold water, and further dried under vacuum, 41.4 g (87%): mp 204−205 °C (lit.[45] 204−205 °C). ^{1}H NMR (CD_3COCD_3): δ 9.47 (s, 1H), 7.59 (d, J = 7.2 Hz, 1H), 7.42 (d, J = 6.8 Hz, 1H), 7.21 (t, J = 7.2 Hz, 1H), 2.20 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (CD_3COCD_3): δ 168.8, 168.4, 136.1, 136.0, 133.9, 129.5, 128.0, 126.1, 23.5, 18.5. MS (TOF^-): *m*/*z* 192 [M − H]$^-$; HRMS calcd for $C_{10}H_{10}NO_3$, 192.0661; found, 192.0660.

Synthesis of 2-Acetylamino-3-methyl-5-nitrobenzoic Acid (21). 2-Acetylamino-3-methyl-benzoic acid **20** (5.95 g, 31.0 mmol) was dissolved in concentrated H_2SO_4 (75 mL), and the resulting mixture was cooled to 0 °C. Fuming HNO_3 (90%, 186 mmol, 6 equiv) was slowly added, under constant stirring, so that the temperature of the reaction was kept between 0 and 5 °C. Once the addition was complete, the resulting mixture was kept between 0 and 5 °C for another 8 h. The resulting yellow solution was then poured into a flask containing 300 g of crushed ice. The flask was shaken vigorously, resulting in an off-white solid precipitate. The solid was collected by suction filtration, washed thoroughly with cold water, and further dried under vacuum to give pure product, 9.19 g (99%): mp 201−202 °C. IR (KBr): 3258 (NH), 1700, 1665 (C═O). ^{1}H NMR (CD_3COCD_3): δ 9.54 (s, 1H), 8.59 (s, 1H), 8.34 (s, 1H), 2.43 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (CD_3COCD_3): δ 168.1, 166.1, 144.3, 142.8, 137.3, 128.5, 126.3, 123.2, 22.8, 18.4. MS (ESI^-): *m*/*z* 237 [M − H]$^-$, 475 [M_2 − H]$^-$, 712 [M_3 − H]$^-$; HRMS (ESI^+) calcd for $C_{10}H_{11}N_2O_5$, 239.0668 [M + H]$^+$; found, 237.0664.

Synthesis of 2-Iodo-3-methyl-5-nitrobenzoic Acid (22). Compound **15** (4.02 g, 20.5 mmol) and $NaNO_2$ (2 equiv, 41 mmol, 2.83 g) were added to 20 mL of 2 M NaOH and 20 mL of H_2O that was cooled in an ice bath to 4 °C. HCl (4 M) in the amount of 25 mL was then added dropwise, ensuring that the temperature did not surpass 8 °C. This was then followed by the dropwise addition of 50 mL of 12 M HCl, once again ensuring that the temperature stayed below 8 °C. The solution was then left stirring, at 4 °C, for 90 min. Urea (2.00 g) was then added to the solution until all the excess nitrite had been consumed (tested using starch iodide paper). A solution of KI (5 equiv, 200 mmol, 17 g), with a small amount of Cu (2 mg), in 15 mL of H_2O was added to the reaction carefully (vast quantities of N_2 evolved) under vigorous stirring. The reaction was allowed to reach room temperature and left stirring overnight. The brown precipitate was collected, washed with water (2 × 50 mL), and dried to yield 5.25 g (85%) of product: mp 198 °C (lit.[29] 199 °C). ^{1}H NMR (CD_3OD/$CDCl_3$): δ 8.20 (s, 1H), 8.15 (s, 1H), 2.62 (s, 3H). ^{13}C NMR (CD_3OD/$CDCl_3$): δ 168.4, 147.3, 145.9, 140.6, 124.5, 120.9, 107.8, 29.2. MS (EI^-): *m*/*z* 305.8 [M − H]$^-$; HRMS calcd for $C_8H_5O_4NI$, 305.9263; found, 305.9265.

Synthesis of Methyl 2-Iodo-3-methyl-5-nitrobenzoate (23). Acid **22** (5.25 g, 17.1 mmol) was added to a solution containing 60 mL of MeOH and 6 mL of concentrated H_2SO_4, and the mixture was refluxed for 16 h. Once the solution was cooled (ice bath), the product began to precipitate out. The precipitate was collected by filtration and washed with H_2O (3 × 50 mL). The supernatant had another 100 mL of H_2O added to induce another crop of product. This was also collected and added to the second crop, 5.02 g (91%): mp 108−109 °C. IR (KBr): 1737 (C═O). ^{1}H NMR ($CDCl_3$): δ 8.23 (s, 1H), 8.16 (s, 1H), 3.99 (s, 3H), 2.65 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 30.0, 53.2, 108.6, 121.6, 125.1, 139.7, 145.9, 147.3, 166.8. MS (CI^+): *m*/*z* 322 [M + 1]$^+$; HRMS calcd for $C_9H_9NO_4I$, 321.9576; found, 321.9576.

Synthesis of Dimethyl 6,6′-Dimethyl-4,4′-dinitro[1,1′-biphenyl]-2,2′-dicarboxylate (17). Method 1. To a solution of acid **16** (75 mg, 0.208 mmol) and K_2CO_3 (173 mg, 1.25 mmol, 6 equiv) in 10 mL of dry acetone was added MeI (177 mg, 1.25 mmol, 6 equiv). The mixture was heated to reflux and stirred for 16 h. The solvent was then removed, under reduced pressure, and EtOAc was added. This solution was washed with H_2O, dilute HCl, and brine and dried with $MgSO_4$. It was then filtered and concentrated to yield 69 mg of pure product (85%).

Method 2. A mixture of **23** (0.559 g, 1.74 mmol) and Cu powder (1.10 g, 17.4 mmol, 10 equiv) in 5 mL of dry DMF was refluxed with stirring for 16 h. Once the solution was cool, it was filtered, and the residue was washed with ethyl acetate (50 mL). The filtrate was washed successively with 1 M HCl (3 × 20 mL), H_2O (3 × 20 mL), and satd $NaHCO_3$ (3 × 20 mL), dried with $MgSO_4$, and concentrated to give a crude brown solid (313.3 mg). The product was purified by column chromatography (Biotage) using a gradient solvent system (3% EtOAc/hexanes to 25% EtOAc/hexanes). The reduced starting material and the product **18** have R_f values of 0.64 and 0.54 (1:3 EtOAc/hexanes), respectively. The isolated yields of

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(45) Cremin, D. J.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2* **1978**, *3*, 208−212.

18 and the reduced starting material were 247 mg (73%) and 26 mg, respectively.

This method was improved by activating the copper powder using the following procedure. Cu in the amount of 10 g was stirred into a solution of iodine (2 g) in 50 mL of acetone. As soon as the mixture became colorless, the liquid was decanted and the copper powder was washed once with $HCl_{(concd)}$/acetone (1:1), followed by acetone (5 × 50 mL). The copper powder was then dried in a vacuum at 170 °C for 2 h and used immediately. The reaction requires 2.5 times less Cu than the unactivated version, and the final yield is increased to 82% (with an 8% yield of deaminated product): mp 136−137 °C. IR (KBr): 1736 (C═O). ^{1}H NMR ($CDCl_3$): δ 8.79 (d, 2H, J = 2.5 Hz), 8.35 (d, 2H, J = 2.5 Hz), 3.72 (s, 6H), 2.04 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 164.9, 147.1, 146.6, 138.5, 129.9, 128.2, 123.4, 52.6, 19.9. MS (TOF EI$^+$): *m*/*z* 388 [M]$^+$; HRMS calcd for $C_{18}H_{16}N_2O_8$, 388.0907; found, 388.0908.

Synthesis of Dimethyl 4,4′-Diamino-6,6′-dimethyl[1,1′-biphenyl]-2,2′-dicarboxylate (18). Method 1. A mixture of **17** (0.218 g, 0.561 mmol) and $SnCl_2 \cdot 2H_2O$ (10 equiv, 5.61 mmol, 1.26 g) in 10 mL of absolute ethanol was heated at 70 °C for 2.5 h. Once the solution was cool, it was poured onto 50 g of crushed ice, and the pH of the solution was adjusted to 7−8 by adding satd $NaHCO_3$. It was then extracted with EtOAc (4 × 50 mL), and the organic layer was washed with brine (1 × 50 mL), dried over $MgSO_4$, and concentrated to give a pale yellow solid (184 mg, 100%).

Method 2. Compound **17** (4.33 g, 11.2 mmol) was dissolved in 300 mL of a mixture of deoxygenated 95% EtOH/EtOAc (1:1). 500 mg of 10% Pd/C was then added to the solution and set up on a Parr hydrogenater. The system was charged with H_2 (40 PSI) and shaken until no more was being absorbed (3 h). The solution was then filtered through a bed of Celite, and the solvent was removed to yield the product as a pale yellow solid, 3.65 g (99%): mp 136−138 °C: ^{1}H NMR ($CDCl_3$): δ 7.26 (s, 2H), 6.72 (s, 2H), 3.67 (br s, 4H), 3.55 (s, 6H), 1.84 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 168.1, 144.8, 138.5, 131.1, 130.9, 120.1, 113.8, 51.6, 20.2. MS (TOF EI$^+$): 329 [M + H]$^+$; 351 [M + Na]$^+$; 367 [M + K]$^+$; HRMS calcd for $C_{18}H_{21}N_2O_4$, 329.15013; found, 329.1512.

Chiral Column Resolution of 18. A 20 mL loop containing 200 mg of racemic **18** dissolved in 60:40 EtOH/hexanes was injected into the preconditioned Chiralpak AS using an 18:82 EtOH/hexanes solvent mixture. At a flow rate of 50 mL min^{-1}, (−)-**18** (100 mg) and (+)-**18** (95 mg) had retention times of 64 and 85 min, respectively. $[\alpha]_D$ for (−)-**18**: −32.2° (*c* 1.3, MeOH); mp 153−154 °C. $[\alpha]_D$ for (+)-**18**: +32.2° (*c* 1.2, MeOH); mp 153−154 °C.

Synthesis of Dimethyl 4,4′-Diiodo-6,6′-dimethyl[1,1′-biphenyl]-2,2′-dicarboxylate (5b). Method 1.[31] Compound **18** (0.500 g, 1.52 mmol) and I_2 (3 equiv, 1.16 g, 4.57 mmol) were dissolved in 75 mL of dry benzene, then the solution was cooled in an ice bath to 0−4 °C, under constant stirring to prevent the benzene from freezing. Freshly distilled *tert*-butyl nitrite (3 equiv, 0.471 g, 0.543 mL, 4.57 mmol) was then added to the solution, it was allowed to reach rt, and stirred for 16 h. The solution was then heated to 70 °C for 1.5 h, then allowed to cool to rt. Once cool, H_2O (75 mL) was added, and the two layers were separated. The aqueous layer was washed with EtOAc (3 × 75 mL). The organic layers were combined and washed with $NaHSO_3$ (3 × 50 mL), dried with $MgSO_4$, and the solvent was removed under vacuo to yield the crude product. Final purification was achieved by column chromatography (gradient elution of toluene/hexanes 96:4 to 100%), yielding 0.410 g (49%) of product.

Method 2.[35] A solution made up of dissolved **18** (1.67 g, 5.08 mmol) and $NaNO_2$ (8 equiv, 2.80 g, 40.6 mmol) in 35 mL of DMSO was heated to 40 °C, under constant stirring. A freshly made solution containing HI (8 equiv, 55%, 5.56 mL, 40.6 mmol), CuI (0.2 equiv, 0.193 g, 1.02 mmol), and 25 mL of DMSO was then added, and the mixture was stirred for 30 min. It was then poured into a flask containing satd $NaCO_3$/crushed ice, and the crude product precipitate was collected via filtration, washed with H_2O, and the redissolved in EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under vacuum. Final purification was achieved by gradient elution (1 to 20% EtOAc/hexanes) on the Biotage, 1.816 g (65%): mp 123−125 °C. IR (KBr): 1734, 1714 (C═O). ^{1}H NMR ($CDCl_3$): δ 8.19 (s, 2H), 7.78 (s, 2H), 3.62 (s, 6H), 1.85 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 165.7, 142.4, 140.0, 138.7, 136.7, 130.7, 92.5, 52.2, 19.7. MS (TOF EI$^+$): 550 [M]$^+$; HRMS calcd for $C_{18}H_{16}I_2O_4$, 550.9216; found, 550.9194. $[\alpha]_D$ for (+)-**5b**: +8.15° (*c* 0.91, EtOAc); mp 82−83 °C. $[\alpha]_D$ for (−)-**5b**: −8.15° (*c* 1.1, EtOAc); mp 82−83 °C.

Synthesis of Methyl 2,5-Dibromo-3-methylbenzoic Acid (27). To a solution of **19** (0.575 g, 2.50 mmol), $NaNO_2$ (4 equiv, 0.690 g, 10 mmol), and CuBr (1 equiv, 0.360 g, 2.5 mmol) in 12.5 mL of DMSO was added dropwise a solution of 48% HBr (4 equiv, 1.86 g, 1.25 mL, 10 mmol), and this solution was left to stir at 40 °C for 3 h. The reaction was quenched with $NaHCO_3$/ice, and the green copper residue was filtered off through a pad of Celite. The filtrate was reacidified to yield a white precipitate that was filtered and dried under vacuum to give 0.404 g of product (55%): mp 170−171 °C. IR (KBr): 3000 (br, OH), 1718, 1684 (C═O). ^{1}H NMR ($CDCl_3$/CD_3OD): δ 7.67 (s, 1H), 7.46 (s, 1H), 4.01 (br s, 1H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$/CD_3OD): δ 167.7, 141.7, 135.6, 130.9, 122.0, 120.4, 23.5. MS (TOF$^-$): *m*/*z* 292.8 [M − H]$^-$; HRMS calcd for $C_8H_5O_2Br_2$, 290.8656; found, 290.8645.

Synthesis of Methyl 2,5-Dibromo-3-methylbenzoate (28). Compound **28** (0.404 g, 1.37 mmol) was dissolved in a solution of 1:6 MeOH/H_2SO_4 (6.6 mL) and heated to reflux for 16 h. After most of the MeOH was then removed under reduced pressure, water was added, followed by EtOAc. The organic layer was then separated, dried with brine, followed by $MgSO_4$, filtered, and concentrated to give 0.367 g of product as a white solid: mp 34−35 °C. IR (KBr): 1737 (C═O). ^{1}H NMR ($CDCl_3$): δ 7.61 (s, 1H), 7.49 (s, 1H), 3.93 (s, 3H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 166.3, 141.8, 135.7, 135.2, 130.8, 122.1, 120.5, 52.8, 23.7. MS (EI$^+$): *m*/*z* 307.9 [M$^+$]; HRMS calcd for $C_9H_8Br_2O_2$, 305.8891; found, 305.8882.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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