Efficient Synthesis of Symmetrical 2,5-Disubstituted Benzoquinones via Palladium-Catalyzed Double Negishi Coupling

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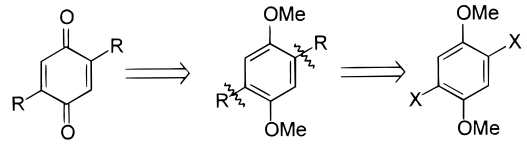
Introduction

Current synthetic methodology in organic synthesis is heavily directed toward rapid ways of preparing new molecules with increased concern about the efficiency of the chosen route.[1,2] A wealth of reactions have been designed to accomplish these goals, exemplified by various cascade and tandem reactions.[3] An alternative approach to increase synthetic efficiency is the simultaneous two-directional synthesis of molecules pioneered by Schreiber.[4] Benzoquinones[5] are a class of compounds found in nature as subunits in many natural products.[6] In addition, benzoquinones have found use in organic synthesis, as oxidizing and dehydrogenation agents,[7,8] and as reactive dienophiles in [4 + 2] cycloadditions.[9] Several palladium(II)-catalyzed oxidations have been designed that employ 1,4-benzoquinone as a stoichiometric oxidant or as a catalytic electron carrier.[10−12] One role of the benzoquinone in the latter reactions is to regenerate the catalytic species by reoxidation of palladium(0) to palladium(II). Another role of the quinone is to act as a ligand for palladium(II).

Previous investigations, in which a wide range of quinones were tested, have shown that the reaction rate, the selectivity, and the yield in these reactions are remarkably dependent upon the quinone substituents and electronic properties.[12] In an ongoing program aimed at the design of an asymmetric palladium-catalyzed 1,4-oxidation of dienes, a range of new benzoquinone structures were needed.[13] In particular, access to chiral C_2-symmetric quinones that could function as ligands was desirable. In the literature, there is only one previous procedure reported on the synthesis of symmetrical 2,5-disubstituted 1,4-benzoquinones.[14] In that procedure, quinones were synthesized by addition of organolithium reagents to 2,5-diethoxybenzoquinones followed by hydrolyses. Our strategy was to introduce chains in the 2- and 5-positions of a quinone skeleton utilizing the two-directional chain synthesis.[4] The functional group tolerance of many transition-metal-catalyzed reactions would allow the connection of the two arms to a protected hydroquinone in a single operation. We have focused on the Negishi coupling,[15] a palladium(0)-catalyzed carbon−carbon bond-forming reaction between an organohalide and an organozinc reagent. The zinc reagents are compatible with a large number of functional groups[16] and tolerate esters, amines, and cyanides, thus fulfilling our goals for synthetic flexibility. In this paper, we have examined the scope and generality of the Negishi-type bis cross-coupling for the preparation of symmetrical 2,5-disubstituted benzoquinones.

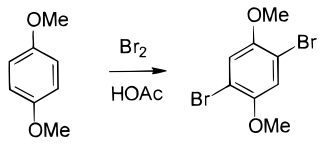
Results and Discussion

The retrosynthetic analysis for the preparation of symmetrical 2,5-disubstituted benzoquinones utilizing a Negishi bis cross-coupling revealed that 2,5-dibromo-1,4-dimethoxybenzene (**1**) was required as the central unit in the coupling reactions (eq 1). The quinone structure is then accessible by oxidative demethylation with ceric ammonium nitrate (CAN).[17]



(1)

The desired core unit was prepared by a modification of a literature procedure[18] by dibromination of dimethoxybenzene in acetic acid (eq 2). The dibromination could be carried out on a large scale, allowing easy preparation of multiple grams of **1**.



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Preparation of Organozinc Reagents.[19] Several methods have been used to prepare organozinc compounds.[16] We have focused mainly on two different methods for the conversion of aryl and alkyl halides to the corresponding zinc reagent. In the first procedure, activated Rieke-zinc[20] was reacted with an aryl or alkyl halide. Reaction of the activated zinc suspension with the appropriate aryl or alkyl halide afforded the corresponding organozinc derivatives. The reaction was run to 100% completion as judged by GC. In the case of aryl bromides, a substantially larger amount of Rieke-zinc was needed (3−4 equiv).

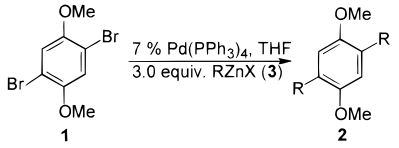
In the second method,[21] an organolithium compound was allowed to react with anhydrous zinc chloride, which afforded the corresponding zinc reagent. The organolithium compounds employed were either commercially available or prepared from the organohalide by a metal−halogen exchange with *tert*-butyllithium in THF at −78 °C. Irrespective of the method employed for the preparation, it was important that a complete conversion of the alkyl or aryl halide had occurred as judged by GC.

Palladium-Catalyzed Bis-coupling of Dibromides with Organozinc Reagents. The appropriate zinc reagent was added to a solution of 7 mol % of $Pd(PPh_3)_4$ and 1,4-dibromo-2,5-dimethoxybenzene (**1**) in THF. All the coupling reactions were carried out under an atmosphere of argon due to the sensitivity of the palladium(0) reagents, and the reaction mixture was allowed to stir at 55 °C for 12 h. To obtain good yields of the bis-coupled product, an excess of the zinc reagent was required (1.5 equiv). The results of the double Negishi coupling to give symmetrical 2,5-disubstituted benzoquinones are given in Table 1. Good to excellent yields were obtained with several aryl- and vinylzinc reagents (Table 1, entries 1 and 3−6). The (*p*-cyanophenyl)zinc reagent gave a slightly lower yield (Table 1, entry 2), which may be due to a lower reactivity of this electron-deficient aryl. On the other hand, the *ortho*-ester aryl (Table 1, entry 4) gave an excellent yield (93%) of the bis-coupling product **2d**, probably due to a favored coordination by the *ortho*-ester group. Primary alkylzinc reagents also gave the desired bis-coupling product, but only in moderate yields (Table 1, entries 7 and 8).

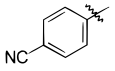
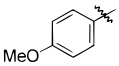
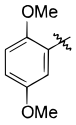
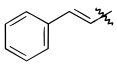
The mechanism of the bis-coupling reaction involves an oxidative addition followed by transmetalation and reductive elimination (Scheme 1). Although we cannot exclude that the oxidative addition, transmetalation, and reductive elimination occur as separate sequences in the 2- and 5-position, respectively, of **1**, we have outlined a double addition for simplicity.

Interestingly, when the secondary butylzinc reagent **3i** was employed in the palladium-catalyzed coupling with **1**, the product isolated was the bis-*n*-butyl product **2g** (Scheme 2), which is identical to the product obtained from coupling with the *n*-butylzinc reagent (Table 1, entry 7). An explanation for the formation of **2g** in the cross-coupling reaction of **3i** with **1** is that the *sec*-butylpalladium intermediate (**4**) initially formed isomerizes to the *n*-butyl derivative (**5**) (Scheme 2). This isomerization involves a β-hydride elimination−readdition sequence. The facile β-elimination from alkylpalladium intermediates also explains the low yield obtained with alkylzinc derivatives. In these reactions, the β-elimination will compete with the desired reductive elimination.

Table 1. Pd(0)-Catalyzed Bis-Couplings[a]



1 2

Entry	R	Procedure[b]	Product	Yield (%)[c]
1		A	**2a**	76
2		B[d]	**2b**	53
3		C	**2c**	84
4		B[e]	**2d**	93
5		C	**2e**	65
6		B[e,f]	**2f**	80
7	n-Butyl-	A	**2g**	30
8	$EtO_2C(CH_2)_2CH_2$-	B	**2h**	42

[a] The reactions were run at 55 °C for 12 h. [b] General procedure for the preparation of the zinc reagents: (A) commercially available lithium reagent was added to 1 equiv of anhydrous $ZnCl_2$ at −78 °C; (B) the organobromide was added to activated zinc, and the mixture was then refluxed; (C) the organobromide was lithiated with *tert*-butyllithium and then added to 1 equiv of anhydrous $ZnCl_2$ at rt. The coupling with **1** was performed in the presence of 0.07 equiv of $Pd(PPh_3)_4$. [c] Isolated yields. [d] 4 equiv of activated zinc was used for the preparation of the zinc reagent. [e] 3 equiv of activated zinc was used for the preparation of the zinc reagent. [f] The organozinc reagent was prepared by stirring overnight at rt.

Oxidative Demethylation of Coupling Products. Selected coupling products were deprotected by oxidative demethylation employing ceric ammonium nitrite (CAN) (Table 2). The oxidation was performed by addition of a water solution of CAN to the dimethoxy compound in acetonitrile at room temperature. The reaction required only a few minutes to reach completion. The selectivity and the mildness of the reaction was illustrated by the fact that a variety of functional groups were tolerated. In most cases good yields were obtained.

Bis-arylbenzoquinones as a Core for Chiral C_2-Symmetric Quinones. Numerous functional groups have been demonstrated to have affinity for palladium(II). The exploration of two such groups, sulfoxide and amides, has resulted in the first report of an asymmetric palladium-catalyzed 1,4-oxidation of 1,3-dienes.[13] C_2-Symmetric quinones of the general structure **6** have the potential to act as chelating ligands to palladium(II).

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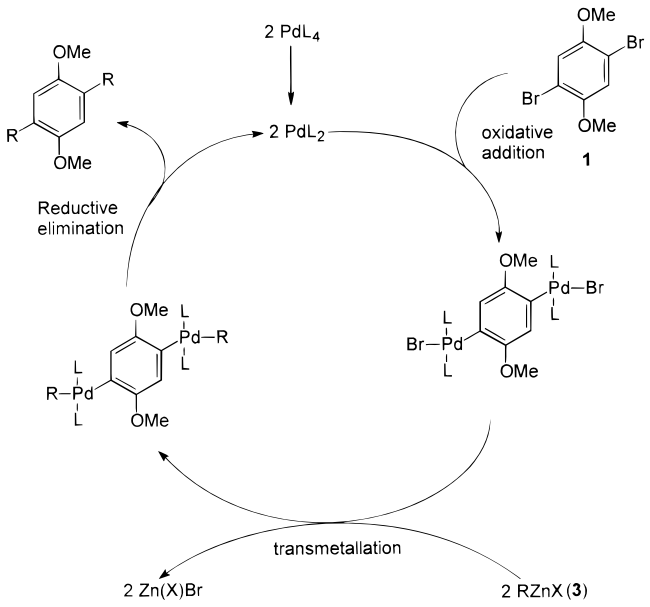
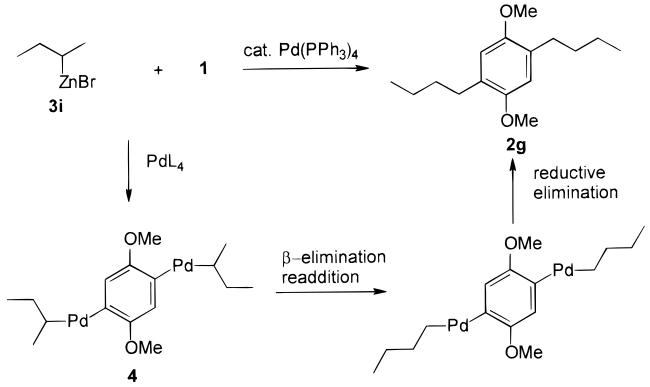
Scheme 1. Mechanism of Bis-Coupling Reaction (L = PPh_3)



Scheme 2. Proposed Mechanism for the Formation of 2g from 3i



Ligand **6** is available by the present methodology and is obtained from **2d** according to Scheme 3.

As mentioned before, this type of chiral quinones could be useful as ligands in the asymmetric 1,4-oxidation.[22]

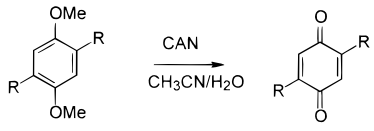
In summary, we have developed an efficient two-step synthesis of 2,5-disubstituted 1,4-benzoquinones. This procedure provides an entry into a range of structurally different C_2-symmetric quinones, which are potential ligands in palladium(II)-catalyzed oxidations.

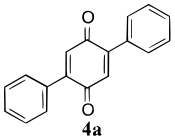
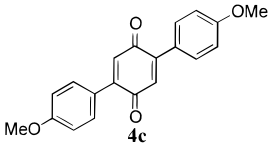
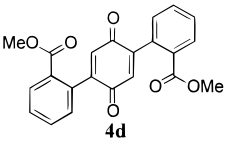
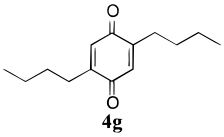
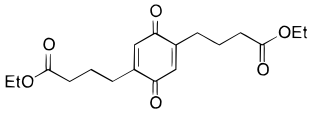
Experimental Section

General Methods. Tetrakis(triphenylphosphine)palladium[23] and 2-phenyl-1,3-cyclohexadiene[24] were prepared according to literature procedures. $ZnCl_2$ was dried under vacuum at 70 °C for 1 h and then overnight at 100 °C.

2,5-Dibromo-1,4-dimethoxybenzene (1). 1,4-Dimethoxybenzene (20.0 g, 0.149 mol) was dissolved in acetic acid (40 mL), and bromine (46.3 g, 0.289 mol, 2.0 equiv) in acetic acid (15 mL) was slowly added at room temperature. The reaction was stirred for 2 h, and during this time the desired dibromide crystallized out. The reaction mixture was cooled to 0 °C, which induced

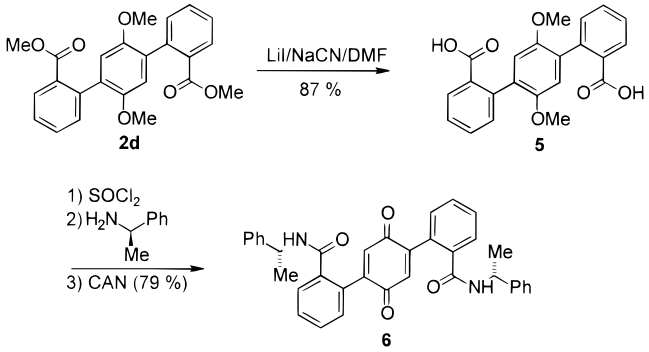
Table 2. Oxidative Demethylation of Selected Coupling Products



Entry	Starting material	Product	Yield (%)[a]
1	**2a**	 **4a**	80
2	**2c**	 **4c**	80
3	**2d**	 **4d**	81
4	**2g**	 **4g**	65
5	**2h**	 **4h**	95

[a] Isolated yields.

Scheme 3



(22) Subjecting ligand **6** to the standard conditions[13] for the 1,4-oxidation of 2-phenyl-1,3-cyclohexadiene (**7**) afforded 3,6-diacetoxy-1-phenylcyclohexane (**8**) in moderate yield (43%) with a cis/trans ratio of 86/14. Disappointingly, the cis and the trans product were obtained as racemates. The interesting observation is that the cis/trans selectivity (86/14) is reversed compared to any previously employed ligands in the reaction under chloride-free conditions (see: Grennberg, H.; Langer, V.; Bäckvall, J. E. *J. Chem. Soc., Chem. Commun*. **1991**, 1190). This high cis selectivity in the oxidation indicates a bis-chelation of the ligand to palladium during the activation of the π-allyl complex. The bis-coordination prevents coordination of acetate to palladium, and as a result, mainly external attack by acetate occurs, affording the *cis*-product.

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crystallization. The white crystals were collected by filtration and washed with cooled (0 °C) methanol. The mother liquid was diluted with water (0.5 L) and extracted with EtOAc (0.2 L), washed with 2 N NaOH (0.3 L), dried ($MgSO_4$), filtered, and concentrated in vacuo to give a second crop. The combined crude product was recrystallized from MeOH to afford 37.7 g (88%) of the dibromomethoxybenzene **1** as a white crystalline solid: mp 146 °C [recrystalliized from EtOH (lit.[25] mp 144−145 °C)].

2,5-Diphenyl-1,4-dimethoxybenzene (2a). General Procedure A for the Coupling Reaction. Phenyllithium (1.39 mL, 2.51 mmol) was added to anhydrous $ZnCl_2$ (0.347 g, 2.70 mmol) dissolved in THF (5 mL) at −78 °C under argon. The reaction mixture was stirred for 1 h, warmed to room temperature, and stirred for an additional 1 h. To a solution of 1,4-dibromo-2,5-dimethoxybenzene (0.241 g, 0.83 mmol) and $Pd(PPh_3)_4$ (0.067 g, 0.058 mmol) in THF (5 mL) was added the phenylzinc chloride reagent under an argon atmosphere. The reaction mixture was warmed to 55 °C and stirred for 12 h. The reaction was then diluted with saturated NH_4Cl (20 mL) and extracted with a 1:1 mixture of Et_2O/CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica gel chromatography (pentane/CH_2Cl_2 70:30) to afford 0.182 g (76%) of white crystals: mp 149 °C [recrystallized from ethanol (lit.[26] mp 154 °C)]; ^{1}H NMR δ 7.63−7.61 (m, 4 H), 7.48−7.44 (m, 4 H), 7.39−7.34 (m, 2 H), 7.01 (s, 2 H) 3.81 (s, 6 H); ^{13}C NMR δ 150.7, 138.3, 130.4, 129.5, 128.1, 127.1, 114.8, 56.5; IR (KBr) 1484, 1211 cm^{-1}.

2,5-Bis(5-cyanophenyl)-1,4-dimethoxybenzene (2b). General Procedure B for the Coupling Reaction. Freshly cut lithium metal (0.152 g, 22.0 mmol) and naphthalene (2.83 g, 22.0 mmol) were stirred in THF (5 mL) under an argon atmosphere. The resulting dark green solution was stirred for 12 h. Zinc chloride (dried under vacuum at 100 °C overnight, 1.49 g, 10.9 mmol) dissolved in THF (5 mL) was added dropwise over 15 min to the lithium naphthalide to give a black solution of suspended zinc metal. *p*-Bromobenzonitrile (0.50 g, 2.75 mmol) dissolved in THF (5 mL) was added to the active zinc at room temperature, and the reaction mixture was refluxed for 3 h. The solution was then transferred via a cannula to a stirred solution of $Pd(PPh_3)_4$ (0.0716 g, 0.062 mmol) and 2,5-dibromo-1,4-dimethoxybenzene (0.255 g, 0.88 mmol) in THF (5 mL) under argon. The dark solution was stirred at 55 °C for 12 h. The reaction was then diluted with saturated NH_4Cl and extracted with Et_2O/CH_2Cl_2 (1:1, 2 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica gel chromatography (CH_2Cl_2/Et_2O 98:2) to give 0.159 g (53%) of white crystals: mp 278 °C (recrystallized from EtOAc); ^{1}H NMR δ 7.74−7.67 (m, 8 H), 6.95 (s, 2 H), 3.81 (s, 6 H); ^{13}C NMR δ 150.7, 142.7, 131.9, 130.1, 129.6, 118.9, 114.4, 111.0, 56.4; IR (KBr) 2224, 1606, 1490 cm^{-1}.

2,5-Bis(5-methoxyphenyl)-1,4-dimethoxybenzene (2c). General Procedure C for the Coupling Reaction. To a solution of *p*-bromoanisole (1.00 g, 5.35 mmol) in THF (10 mL) at −78 °C under argon was added *tert*-butyllithium (7.60 mL, 10.7 mmol). The reaction was stirred for 1 h at − 78 °C and then slowly warmed to room temperature over 2 h. The lithium reagent was added to anhydrous zinc chloride (0.802 g, 5.88 mmol) in THF (10 mL). The solution was stirred for 1 h at room temperature. To a solution of 2,5-dibromo-1,4-dimethoxybenzene (0.492 g, 1.70 mmol) and $Pd(PPh_3)_4$ (0.137 g, 0.119 mmol) in THF (10 mL) was added the zinc reagent. The reaction was stirred for 12 h at 55 °C. The reaction was then quenched by the addition of saturated NH_4Cl (50 mL). The mixture was extracted with CH_2Cl_2/EtOAc (1:1, 2 × 50 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was recrystallized from EtOAc/pentane to give 0.496 g (84%) of white crystals: mp 193 °C (recrystallized from EtOAc and pentane); ^{1}H NMR δ 7.53−7.52 (m, 4 H) 6.99−6.97 (m, 4 H) 6.95 (s, 2 H) 3.86 (s, 6 H), 3.79 (s, 6 H); ^{13}C NMR δ 158.8, 150.6, 130.7, 130.5, 129.6, 114.6, 113.6, 56.5, 55.3; IR (KBr) 1609 cm^{-1}.

2,5-Bis[2-(carbomethoxy)phenyl]-1,4-dimethoxybenzene (2d). The reaction of 2-(bromomethyl)benzoate was performed according to procedure B. The crude product was purified by silica gel chromatography (CH_2Cl_2/Et_2O 98:2), affording 3.51 g (93%) of **2d** as white crystals: mp 172 °C [recrystallized from HOAc (lit.[27] mp 174−175 °C)].

2,5-Bis(2,5-dimethoxyphenyl)-1,4-dimethoxybenzene (2e). The reaction of 2-bromo-1,4-dimethoxybenzene was performed according to general procedure C. The crude product was recrystallized from EtOAc to give 0.202 g (65%) of white crystals.

2,5-Bis-*trans*-(2-phenylethenyl)-1,4-dimethoxybenzene (2f). The reaction of (2-bromovinyl)benzene was performed according to procedure B, except that the organohalide was stirred with the active zinc at room temperature overnight. The crude product was purified by silica gel chromatography (pentane/CH_2Cl_2 70:30) to yield 0.317 g (80%) of **2f** as yellow crystals (80%).

2,5-Dibutyl-1,4-dimethoxybenzene (2g). The reaction of 4-bromobutyric acid ethyl ester was performed according to general procedure A. The crude product was purified by silica gel chromatography (pentane/Et_2O 95:5) to give 0.047 g (30%) of a colorless oil.

2,5-Bis(3-carbethoxypropyl)-1,4-dimethoxybenzene (2h). The reaction was performed according to procedure B. The crude product was purified by silica gel chromatography (CH_2Cl_2/Et_2O 96:4) to give 0.265 g (42%) of a colorless oil.

2,5-Diphenyl-1,4-benzoquinone (4a). General Procedure for Oxidative Demethylation. Ceric ammonium nitrite (CAN)-(0.594 g, 1.09 mmol) in water (1 mL) was added dropwise over 5 min to a solution of 2,5-diphenyl-1,4-dimethoxybenzene (0.173 g, 0.405 mmol) dissolved in hot acetonitrile. A disappearing blue-black color was observed. The reaction was stirred for another 5 min and then quenched with water, which resulted in precipitation of the product. The precipitate was collected and dried to give 0.084 g (80%) of yellow crystals: mp 215−216 °C [recrystallized from pentane/CH_2Cl_2 (lit.[28] mp 217−218 °C)]; ^{1}H NMR δ 7.57−7.54 (m, 4 H) 7.48−7.46 (m, 6 H), 6.97 (s, 2 H); ^{13}C NMR δ 186.9, 145.6, 133.1, 132.5, 130.1, 129.3, 128.5; IR (KBr), 1641, 1604, 1440 cm^{-1}.

2,5-Bis(5-methoxyphenyl)-1,4-benzoquinone (4c). The oxidative demethylation was performed according to the general procedure. The crude product was purified by silica gel chromatography (pentane/CH_2Cl_2 70:30), affording 0.085 g (92%) of **4c** as deep red crystals.

2,5-Bis(2-carbomethoxyphenyl)-1,4-benzoquinone (4d). The oxidative demethylation was performed according to the general procedure. The reaction was quenched with water, which resulted in precipitation of the product. The precipitate was collected and dried to give 0.076 g (81%) of yellow crystals.

2,5-Dibutyl-1,4-benzoquinone (4g). The oxidative demethylation was performed according to the general procedure. The reaction was quenched with water, which resulted in precipitation of the product. The precipitate was collected and dried to give 0.048 g (65%) of yellow crystals.

2,5-Bis(3-carbethoxypropyl)-1,4-benzoquinone (4h). The oxidative demethylation was performed according to the general procedure. The reaction was quenched with water, and the reaction mixture was extracted with CH_2Cl_2/Et_2O (1:1, 3 × 15 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by silica gel chromatography (CH_2Cl_2/Et_2O 94:6), affording 0.089 g (95%) of **4c** as a deep red oil.

1,4-Dimethoxy-2,5-bis(2-carboxyphenyl)benzene (5). A solution of the bis-ester (1.90 g, 4.67 mmol), lithium iodide (6.24 g, 46.7 mmol), and sodium cyanide (0.457 g, 9.33 mmol) in DMF (130 mL) was heated at reflux for 24 h, during which time a large amount of precipitate formed. The mixture was cooled to room temperature and was made acidic with HCl (red to litmus), which dissolved all the precipitate. *Note: Potentially toxic HCN can be formed under those conditions, and this should therefore only be performed in a well-ventilated hood.* The mixture was diluted with water (2 L), and the solid was collected by filtration to afford 1.53 g (87%) of **5**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74−7.35 (m, 8 H), 6.85 (s, 2 H), 3.63 (s, 6 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.9, 149.8, 137.5, 133.1, 131.2, 130.9, 129.5,

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128.7, 127.0, 112.9, 55.5; IR (KBr) 3567, 1675, 1594 cm^{-1}. Anal. Calcd for $C_{22}H_{18}O_6$: C, 69.83; H, 4.79. Found: C, 69.93; H, 4.96.

(+)-1,4-Bis[diphenyl-[(1-(*R*)-1-azaphenylethyl)-2-carboxylic]amide]-2,5-benzoquinone (6). To a solution of bis-acid **5** (0.800 g, 2.11 mmol) in THF (50 mL) was added pyridine (0.34 mL, 4.22 mmol), followed by the addition of thionyl chloride (0.77 mL, 10.55 mmol). The reaction was stirred for 5 h, residual solid was filtered off, and the solvent was removed in vacuo. (Note: it is very important that the acid is completely dissolved before the addition of the thionyl chloride). The residue was partially dissolved in THF (75 mL), (*R*)-phenylethylamine (1.20 mL, 9.28 mmol) was added, and the resulting solution was stirred at room temperature for 12 h. The reaction was diluted with CH_2Cl_2, and the organic phase was washed with 2 N HCl, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by multiple silica gel chromatography (CH_2Cl_2/MeOH 1:0, 19:1) to afford 0.467 g (38%) of the amide.

To a solution of the amide in acetonitrile (26 mL) was added a solution of CAN (1.14 g, 2.07 mmol) in water (26 mL). The reaction was stirred at room temperature for 10 min, during which time the reaction changed color from white to purple and then to orange. The mixture was diluted with CH_2Cl_2, washed with water, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel chromatography (CH_2Cl_2/MeOH 19:1) to afford 0.351 g (79%) of (+)-**6** as a brown solid that was heat and light sensitive: mp 141−144 °C; ^{1}H NMR δ 7.60−7.28 (m, 8 H), 6.75 (s, 2 H), 6.28 (d, 2 H, J = 7.6 Hz), 5.17 (quint, 2 H, J = 7.1 Hz), 1.58 (d, 6 H, J = 6.9 Hz); ^{13}C NMR δ 185.7, 167.8, 148.6, 142.6, 136.4, 132.9, 132.3, 130.9, 130.6, 129.6, 128.7, 127.4, 126.6, 126.4, 49.4, 21.4; IR (KBr) 3304, 1625, 1635, 1592 cm^{-1}; $[\alpha]^{20}_D$ +110.7° ($CHCl_3$, c = 0.29).

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Supporting Information Available: Characterization data for **1, 2a**−**h**, **4a**−**h**, **5**, **6**, and **8** together with copies of ^{1}H and ^{13}C spectra of **1, 2a**−**h**, **4a**,**c**,**d**,**g**,**h**, **5**, **6**, and **8** (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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