JOC The Journal of Organic Chemistry

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Pinacolborane as the Boron Source in Nitrogen-Directed Borylations of Aromatic *N,N*-Dimethylhydrazones

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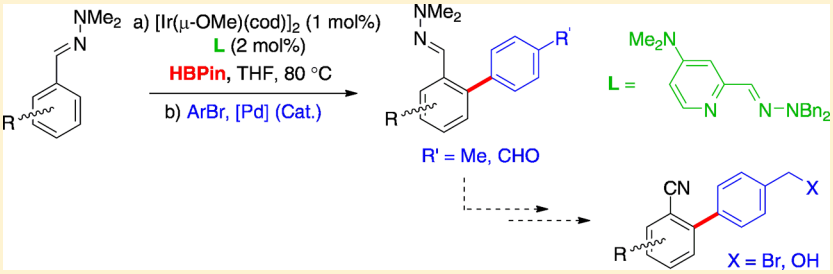
Supporting Information

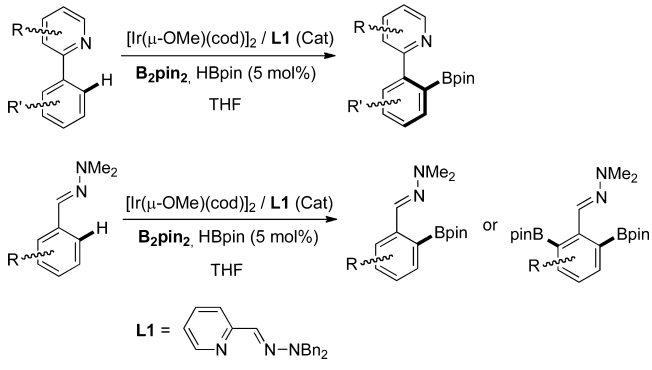


ABSTRACT: A mild procedure for the Ir(III)-catalyzed nitrogen-directed *ortho* borylation of aromatic *N,N*-dialkylhydrazones using pinacolborane as the boron source has been developed. The methodology relies on a modified, hemilabile N,N ligand built on a 4-*N,N*-dimethylaminopyridine unit that provides high reactivity while maintaining exclusive *ortho*-selectivity. This procedure can be combined with Suzuki–Miyaura cross-couplings in a 'one-pot' fashion to afford functionalized biaryl derivatives that, upon subsequent 'one-pot', high yielding transformations, provide a convenient entry for the preparation of advanced benzonitrile intermediates for the synthesis of Sartan-type drugs.

The Ir-catalyzed borylation of arenes combined with cross-coupling methodologies has emerged as a powerful tool for the direct functionalization of aromatic compounds.[1] After the seminal work by Smith, Hartwig, and Miyaura groups, the catalytic system made by the combination of $[Ir(\mu\text{-OMe})(cod)]_2$ (COD = cyclooctadiene) and 4,4′-di-*tert*-butylbipyridine (dtbpy) has enabled reactions to proceed at low temperatures with high turnover numbers.[2] Unfortunately, the reaction usually requires the use of expensive bis(pinacolate)diboron (B_2pin_2) as the borylating agent to take place efficiently, while the use of pinacolborane (HBPin), a cheaper and more 'atom-economic' boron source,[3] requires, with a few exceptions,[4] elevated temperatures and a higher excess of arene to give satisfactory results.[2b,c,5] This reaction is typically controlled by steric factors, but recently, new methodologies for the *ortho*-directed borylation of arenes employing modified Ir,[6] Rh,[7] or Pd[8] based catalysts have been developed. With no exceptions, these methods have made use of B_2pin_2 as the borylating agent. We wish to report herein the development of a catalytic system for the nitrogen-directed borylation of arenes using HBpin as the borylating reagent under mild conditions.

Our approach for the nitrogen-directed iridium-catalyzed *ortho*-borylation of 2-aryl pyridines(isoquinolines) and aromatic hydrazones,[9] and for the *ortho,orthó′*-diborylation of the latter,[10] relies on the use of a hemilabile pyridine-hydrazone N,N ligand **L1** (Scheme 1) as the central strategy to generate a coordination vacancy, thereby facilitating the formation of a preorganized catalyst–substrate complex prior to the C–H activation step. In this paper, we show that structural modifications of this pyridine-hydrazone ligand allows an increase of catalytic activity up to the level required to perform these directed borylations using HBpin as the boron source. Toward this goal, we reasoned that the introduction of electron-donating groups[11] at the para position of the pyridine fragment should help stabilize the proposed Ir(V) intermediates, an effect that was also observed in the classic dtbpy-based catalyst. Moreover, increasing the basicity of the pyridine ligand should facilitate the temporary decoordination of the hydrazone terminus, thus enhancing the hemilabile character

Scheme 1. Nitrogen-Directed Arene Borylations Mediated by *N,N*-Hemilabile Ligand L1

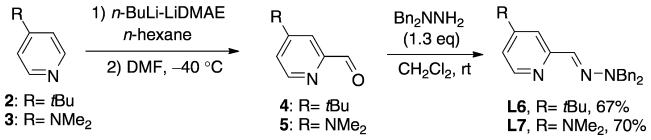


Received: September 10, 2012
Published: October 16, 2012

   dx.doi.org/10.1021/jo301965v | *J. Org. Chem.* 2012, 77, 9915–9920

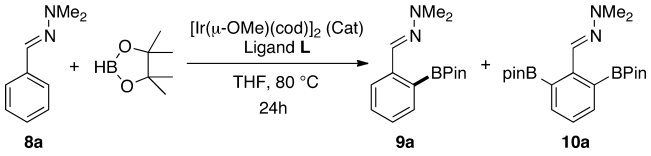
of the ligand presumably required to achieve an exclusive *ortho*-selectivity. According to this idea, we decided to incorporate *tert*-butyl (**L6**) and dimethylamino (**L7**) groups in the para position of the pyridine ring of ligand **L1**. The synthesis was readily accomplished from pyridines **2** and **3** by selective formylation at the 2-position (→**4** and **5**) according to a known procedure,[12] followed by condensation with *N,N*-dibenzylhydrazine to afford **L6** and **L7** in 67 and 70% yield respectively (Scheme 2).

Scheme 2. Synthesis of Modified Ligands L6 and L7 (DMAE: 2-(*N,N*-Dimethylamino)ethanol)



With these new ligands in hand, the relative activity of the catalysts formed *in situ* from $[Ir(\mu\text{-OMe})(cod)]_2$, the N,N ligand (**L1**, **L6**, or **L7**), and HBpin was investigated using the borylation of benzaldehyde *N,N*-dimethylhydrazone **8a** as a model reaction (Table 1). Preliminary experiments were carried out in THF at

Table 1. Screening of Ligands in the Borylation of 8a with HBpin[a]



entry	L	[Ir] (mol %)	L (mol %)	HBpin (equiv)	yield **9a** (%)[b]	yield of **10a** (%)[b]
1	**L1**	1	2	1	20	–
2	**L6**	1	2	1	30	–
3	**L7**	1	2	1	75	~5%
4	**L7**	1	2	1.2	75	~5%
5	**L7**	1	2	1.4	**85**	~5%
6	**L7**	1.5	3	1	75	8
7	**L7**	1.5	3	1.2	78	8
8	**L7**	1.5	3	1.4	80	12
9	**L7**	1.5	3	1.6	74	20

[a]Reactions were performed at 0.25 mmol scale. [b]Estimated by ^{1}H NMR.

80 °C using initially stoichiometric amounts of HBpin. Under these conditions, the unmodified catalytic system based on ligand **L1** showed a poor performance, leading to only a 20% yield of **9a** after 24 h (estimated by ^{1}H NMR, entry 1). The *tert*-butyl-substituted derivative **L6** provided a slightly better 30% yield (entry 2) and maintained exclusive *ortho* selectivity, in line with the expectations but still unsatisfactory. Finally, the more basic DMAP-derived ligand **L7** afforded a much higher activity, leading to a much higher yield of **9a** (*ca.* 75%, entry 3), along with a minor amount (*ca. 5%)* of the 2,6-diborylated product **10a**. However, no trace of regioisomers was detected in the crude mixtures. Further experiments aimed to optimize the reactions conditions (entries 4–9) were therefore conducted with ligand **L7**. No significant improvement was observed when 1.2 equiv of HBPin were used (entry 4), but increasing the amount of reagent up to 1.4 equiv provided a higher 85% yield (entry 5). On the other hand, increasing the catalyst loading to 1.5 mol % did not result in any improvement. Thus, similar conversions were obtained when 1–1.2 equiv of HBPin were used (entries 6 and 7), whereas considerable amounts (12–20%) of diborylation product **10a** were observed for reactions carried out with 1.4–1.6 equiv (entries 8–9). All these preliminary results showed that the best conditions in terms of activity and mono- versus diborylation selectivity are achieved with 1 mol % of the Ir precatalyst, 2 mol % of the ligand **L7**, and 1.4 equiv of HBpin.

The method was then extended to a variety of aromatic *N,N*-dialkylhydrazones **8b–j** (Scheme 3). The selected examples demonstrate that the reaction has a broad substrate scope, affording the desired *ortho* borylation products **9b–j** in good to excellent conversions. Due to their relative instability, a partial decomposition of these products was regularly observed during chromatographic purification.[13] However, given the high degree of purity of the crude reaction mixtures and considering that the main application of these products is their use as coupling partners in metal-catalyzed cross-coupling reactions, the crude borylation products **9a–j** were used in Suzuki-Miyaura couplings without any further purification. In this manner, the desired *ortho* arylation products **11** and **12** were obtained in moderate to excellent yields (56–99%) in a two-step, 'one-pot' reaction. The overall procedure tolerates both electron-donating (**8b,e,f,h,j**) and -withdrawing (**8c,d,g,i**) groups in *ortho*, *meta*, and *para* positions of the phenyl ring, as well as disubstituted derivatives.

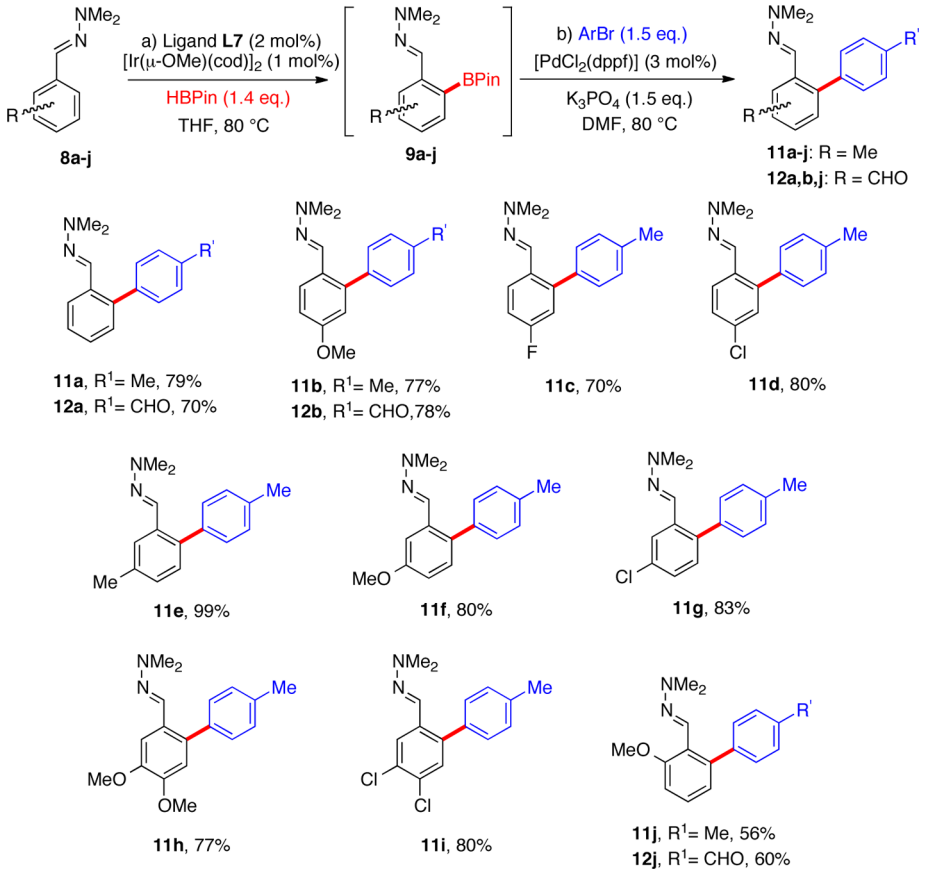
With the coupling products in hand, we decided to explore their synthetic utility for the obtention of advanced intermediates toward the synthesis of *Sartan* type drugs, well established modulators of the renin-angiotensin system (RAS).[14] The efficient aza-Cope type oxidative cleavage of the hydrazone moiety by magnesium monoperoxyphthalate (MMPP)[15] was applied for the high yielding transformation of compounds **11a–j** into the corresponding nitriles **13a–j** (Scheme 4). While the transformation of **11b,e,f,h–j** into nitriles **13b,e,f,h–j** was accomplished with excellent (70–99%) yields, the high purity of the crude products **13** (see crude spectra in the Supporting Information) was exploited to combine this transformation with a radical bromination of the benzylic position[16] to afford bromomethyl derivatives **14** without purification of the former. In this manner, representative hydrazones **11a,c,d,g** were transformed into products **14a,c,d,g** in good 78–84% overall yields after a two-step reaction sequence. These compounds have been used as intermediates in the synthesis of angiotensin II antagonist compounds (Sartan drugs).[14a] Alternatively hydrazones **12a,b,j** can be used for a 'one-pot' quantitative aldehyde reduction/hydrazone-to-nitrile transformation to afford benzyl alcohols **15a,b,j**, which are also suitable precursors for modified Sartan drugs.

■ CONCLUSIONS

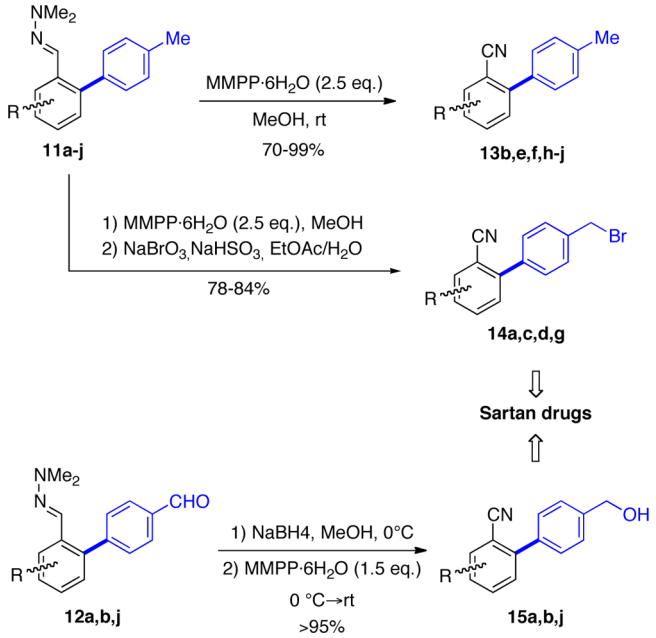
In summary, it has been shown that the activity of the Ir(III) borylation catalysts based on pyridine-hydrazone ligands can be substantially increased without compromising the ortho selectivity. Using modified ligand **L7**, the nitrogen-directed borylation reaction can be achieved using cheap and readily available pinacolborane with a broad reaction scope, excellent conversions, and complete regioselectivity in all cases. This reaction, combined with Suzuki–Miyaura cross-couplings in a 'one-pot' fashion, afforded functionalized biphenyl derivatives that have been transformed into valuable intermediates for the synthesis of modified *Sartan* type drugs upon high yielding, 'one-pot' functional group transformations in a very efficient manner.

dx.doi.org/10.1021/jo301965v | *J. Org. Chem.* 2012, 77, 9915–9920

Scheme 3. One-Pot Directed Borylation/S-M Cross-Coupling Reaction



Scheme 4. One-Pot Hydrazone Transformation: Application to the Sartan Type Drugs Synthesis



EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz; ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz with the solvent peak used as the internal reference (7.26 and 77.0 ppm for ^{1}H and ^{13}C respectively). Column chromatography was performed on silica gel (Merck Kieselgel 60). Analytical TLC was performed on aluminum backed plates (1.5 cm × 5 cm) precoated (0.25 mm) with silica gel (Merck, Silica Gel 60 F_{254}). Compounds were visualized by exposure to UV light or by dipping the plates in a solution of 5% $(NH_4)_2Mo_7O_{24}{\cdot}4H_2O$ in 95% EtOH (w/v) or Mostain reagent [ceric sulfate (1% (w/v) and ammonium molybdate (2.5% (w/v) in 10% (v/v) aqueous sulfuric acid] followed by heating. Borylation reactions were carried out in oven-dried Schlenk tubes under an argon atmosphere employing standard manifold techniques. Anhydrous THF was obtained using Grubbs-type solvent drying columns. Pinacolborane (HBpin), $[Ir(\mu\text{-OMe})(cod)]_2$, $[PdCl_2(dppf)]$, pyridines **2** and **3**, aryl bromides, and *N*,*N*-dibenzylhydrazine were purchased from commercial suppliers and used without further purification. Hydrazones **8** were synthesized according to a previously reported procedure.[9,10,17]

General Procedure for the Synthesis of Aldehydes 4 and 5. Following a described methodology,[12] *n*-BuLi (1.7 M in *n*-hexane, 28 mL, 48 mmol) was added dropwise to a cooled (−10 °C) solution of 2-dimethylaminoethanol (2.4 mL, 24 mmol) in dry *n*-hexane (30 mL). The mixture was stirred at this temperature for 30 min, and then the corresponding pyridine **2** or **3** (12 mmol) was added at once as a solid. After stirring at 0 °C for 1 h, the reaction was cooled to −40 °C and a solution of dry DMF (1.39 mL, 18 mmol) in dry THF (45 mL) was added. After 30 min at −40 °C, the mixture was quenched with 60 mL of 1 M HCl, the organic layer was separated, and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to dryness, and the resulting residue was purified by flash chromatography. Methods used for purification, yields, and characterization data for products **4** and **5** are as follows:

4-(tert-Butyl)picolinaldehyde (4). Following the general procedure, flash chromatography (*n*-10:1 hexane/EtOAc) afforded **4** as a yellow viscous oil. Product was obtained contaminated with an impurity, and the yield was estimated by NMR (~28%); aldehyde was used in the next reaction step. A pure sample for the characterization of **4** was obtained by purification on preparative TLC (20:1 toluene/EtOAc). ^{1}H NMR

dx.doi.org/10.1021/jo301965v | J. Org. Chem. 2012, 77, 9915−9920

(400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.67 (d, 1H, *J* = 5.2 Hz), 7.96 (d, 1H, *J* = 2.2 Hz), 7.49 (dd, 1H, *J* = 5.2, 2.2 Hz), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 161.6, 152.8, 150.1, 125.0, 118.7, 35.0, 30.4. HRMS(EI) calcd for $C_{10}H_{13}NO$ (M^+) 163.0997. Found 163.0999.

*4-(Dimethylamino)picolinaldehyde (**5**).* Following the general procedure, flash chromatography (EtOAc) afforded **5** (594 mg, 33%) as a yellow viscous oil. ^1H NMR (500 MHz, $CDCl_3$): δ 9.97 (s, 1H), 8.37 (d, 1H, *J* = 6.0 Hz), 7.17 (d, 1H, *J* = 2.5 Hz), 6.64 (dd, 1H, *J* = 6.0, 3.0 Hz), 3.06 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 194.6, 154.8, 153.1, 150.1, 109.9, 104.4, 39.3. HRMS(EI) calcd for $C_8H_{10}N_2O$ (M^+) 150.0793. Found 150.0795.

General Procedure for the Synthesis of Ligands L6 and L7. *N,N*-Dibenzylhydrazine (2.2 mmol) was added to a solution of aldehyde **4** or **5** (2 mmol) in MeOH (4 mL), and the mixture was stirred overnight at rt. The solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography. Methods used for purification, yields, and characterization data for products **L6** and **L7** are as follows:

*4-(tert-Butyl)picolinaldehyde N,N-dibenzylhydrazone **L6**.* Following the general procedure, flash chromatography (8:1 *n*-hexane/EtOAc) afforded **L6** (480 mg, 67%) as a light yellow solid. Mp 102−104 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.35 (d, 1H, *J* = 5.0 Hz), 7.82 (d, 1H, *J* = 1.2 Hz), 7.33−7.25 (m, 11H), 7.08 (dd, 1H, *J* = 5.0, 1.5 Hz), 4.61 (s, 4H), 1.33 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.9, 155.7, 148.6, 137.0, 131.6, 128.5, 127.5, 127.2, 118.9, 115.4, 57.7, 34.8, 30.5. HRMS(EI) calcd for $C_{24}H_{27}N_3$ (M^+) 357.2205. Found 357.2205.

*4-(Dimethylamino)picolinaldehyde N,N-dibenzylhydrazone **L7**.* Following the general procedure, flash chromatography (8:1 CH_2Cl_2/MeOH) afforded **L7** (482 mg, 70%) as a light yellow solid. Mp 98−100 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, 1H, *J* = 6.0 Hz), 7.29−7.22 (m, 11H), 7.02 (d, 1H, *J* = 2.7 Hz), 6.35 (dd, 1H, *J* = 6.0, 2.7 Hz.), 4.57 (s, 4H), 3.00 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.4, 154.7, 148.6, 137.1, 131.9, 128.5, 127.6, 127.2, 105.5, 100.8, 57.6, 39.2. HRMS(EI) calcd for $C_{22}H_{24}N_4$ (M^+) 344.2001. Found 344.1990.

General Procedure for Sequential *ortho*-Borylation/Suzuki−Miyaura Coupling Reactions. 0.5 mL of the catalyst stock solution[18] and HBPin (51 μL, 0.35 mmol) were added to a dried Schlenk tube charged with the substrate **8a−j** (0.25 mmol). The reaction mixture was stirred at 80 °C until consumption of the starting material (^1H NMR monitoring), then cooled to rt, and concentrated to dryness. [$PdCl_2$(dppf)] (7.5 μmol, 6.2 mg), K_3PO_4 (0.375 mmol, 79.6 mg), 4-bromotoluene (0.375 mmol, 65.5 mg) or 4-bromobenzaldehyde (0.375 mmol, 70.1 mg), and dry DMF (2 mL) were added under Ar. The reaction mixture was stirred at 80 °C overnight, cooled to rt, diluted with Et_2O (20 mL), washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and concentrated to dryness. The resulting residue was purified by flash chromatography using *n*-hexane/Et_2O or acetone/toluene mixtures as solvents. Methods used for purification, yields, and characterization data for products **10a−j** and **11a,b,j** are as follows:

*4′-Methyl-[1,1′-biphenyl]-2-carbaldehyde N,N-dimethylhydrazone (**11a**).* Following the general procedure, flash chromatography (160:1→50:1 toluene/acetone) afforded **11a** (47 mg, 79%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, 1H, *J* = 7.6 Hz), 7.30 (dt, 1H, *J* = 8.0, 1.0 Hz), 7.29−7.22 (m, 7H), 2.85 (s, 6H), 2.40 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$): δ 140.3,137.6, 136.7, 134.0, 132.8, 130.1, 129.6, 128.8, 127.3, 127.2, 124.9, 42.9, 21.2. HRMS(EI) calcd for $C_{16}H_{18}N_2$ (M^+) 238.1470. Found 238.1473.

*(E)-2′-[(2,2-Dimethylhydrazono)methyl]-[1,1′-biphenyl]-4-carbaldehyde (**12a**).* Following the general procedure, flash chromatography (1:6→1:5 Et_2O/*n*-hexane) afforded **12a** (45 mg, 70%) as a yellow solid. Mp 95−97 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 10.08 (s, 1H), 8.01 (d, 1H, *J* = 7.7 Hz), 7.94 (d, 2H, *J* = 7.7 Hz), 7.57 (d, 2H, *J* = 7.6 Hz), 7.39 (t, 1H, *J* = 7.3 Hz), 7.31 (t, 1H, *J* = 7.2 Hz), 7.27−7.24 (m, 1H), 7.14 (s, 1H), 2.87 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.9, 147.3, 138.7, 135.1, 134.1, 130.7, 130.4, 129.8, 129.6, 128.3, 127.2, 125.2, 42.7. HRMS(EI) calcd for $C_{16}H_{16}N_2O$ (M^+) 252.1263. Found 252.1259.

*5-Methoxy-4′-methyl-[1,1′-biphenyl]-2-carbaldehyde N,N-Dimethylhydrazone (**11b**).* Following the general procedure, flash chromatography (60:1 toluene/acetone) afforded **11b** (52 mg, 77%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, 1H, *J* = 8.7 Hz), 7.27 (d, 2H, *J* = 7.8 Hz), 7.24 (s, 1H), 7.21 (d, 2H, *J* = 7.5 Hz), 6.89 (dd, 1H, *J* = 8.6, 2.1 Hz), 6.77 (d, 1H, *J* = 2.2 Hz), 3.81 (s, 3H), 2.81 (s, 6H), 2.40 (s, 3H, Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 141.7, 137.5, 136.9, 133.6, 129.5, 128.8, 127.0, 126.5, 114.6, 113.7, 55.4, 43.1, 21.2. HRMS(EI) calcd for $C_{17}H_{20}N_2O$ (M^+) 268.1576. Found 268.1571.

*(E)-2′-[(2,2-Dimethylhydrazono)methyl]-5′-methoxy-[1,1′-biphenyl]-4-carbaldehyde (**12b**).* Following the general procedure, flash chromatography (1:2 Et_2O/*n*-hexane) afforded **12b** (55 mg, 78%) as a yellow solid. Mp 81−83 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 10.07 (s, 1H), 7.94−7.92 (m, 3H), 7.55 (d, 2H, *J* = 8.0 Hz), 7.11 (s, 1H), 6.95 (dd, 1H, *J* = 8.8, 2.5 Hz), 6.76 (d, 1H, *J* = 2.6 Hz), 3.83 (s, 3H), 2.81 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.9, 158.9, 147.0, 140.1, 135.2, 131.7, 130.3, 129.5, 127.0, 126.8, 114.6, 114.5, 55.4, 42.9. HRMS(EI) calcd for $C_{17}H_{18}N_2O_2$ (M^+) 282.1368. Found 282.1373.

*5-Fluoro-4′-methyl-[1,1′-biphenyl]-2-carbaldehyde N,N-Dimethylhydrazone (**11c**).* Following the general procedure, flash chromatography (170:1 toluene/acetone) afforded **11c** (45 mg, 70%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.92 (dd, 1H, *J* = 8.6, 6.2 Hz), 7.24−7.17 (m, 4H), 7.17 (s, 1H), 6.98 (td, 1H, *J* = 8.6, 2.5 Hz), 6.93 (dd, 1H, *J* = 9.5, 2.4 Hz), 2.82 (s, 6H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.0 (d, $^1J_{C,F}$ = 245 Hz), 142.0 (d, $^3J_{C,F}$ = 8 Hz), 137.3, 136.5, 132.1, 130.4, 129.4, 129.0, 126.9 (d, $^3J_{C,F}$ = 8 Hz), 116.4 (d, $^2J_{C,F}$ = 21 Hz), 114.5 (d, $^2J_{C,F}$ = 21 Hz), 42.9, 21.1. HRMS(EI) calcd for $C_{16}H_{17}FN_2$(M^+) 256.1376. Found 256.1373.

*5-Chloro-4′-methyl-[1,1′-biphenyl]-2-carbaldehyde N,N-Dimethylhydrazone (**11d**).* Following the general procedure, flash chromatography (1:8 Et_2O/*n*-hexane) afforded **11d** (54 mg, 80%) as a pale solid. Mp 70−72 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, 1H, *J* = 8.5 Hz), 7.26−7.19 (m, 6H), 7.14 (s, 1H), 2.84 (s, 6H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.6, 137.3, 136.4, 132.7,132.6, 131.1, 129.9, 129.4, 129.0, 127.4, 126.3, 42.8, 21.2. HRMS(EI) calcd for $C_{16}H_{17}ClN_2$ (M^+) 272.1080. Found 272.1078.

*4,4′-Dimethyl-[1,1′-biphenyl]-2-carbaldehyde N,N-Dimethylhydrazone (**11e**).* Following the general procedure, flash chromatography (110:1 toluene/acetone) afforded **11e** (63 mg, 99%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.25−7.24 (m, 3H), 7.19 (d, 2H, *J* = 7.5 Hz), 7.14 (d, 1H, *J* = 7.5 Hz), 7.09 (d, 1H, *J* = 7.5 Hz), 2.84 (s, 6H), 2.38 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.8, 137.6, 136.9, 136.5, 133.6, 133.2, 130.1, 129.6, 128.7, 128.3, 125.3, 42.9, 21.2, 21.1. HRMS(EI) calcd. for $C_{17}H_{20}N_2$ (M^+) 252.1626. Found 252.1620.

*4-Methoxy-4′-methyl-[1,1′-biphenyl]-2-carbaldehyde N,N-Dimethylhydrazone (**11f**).* Following the general procedure, flash chromatography (130:1 toluene/acetone) afforded **11f** (54 mg, 80%) as a pale solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.24−7.22 (m, 2H), 7.19 (d, 2H, *J* = 8.0 Hz), 7.15 (d, 2H, *J* = 8.5 Hz), 6.85 (dd, 1H, *J* = 8.0, 2.0 Hz), 3.87 (s, 3H), 2.86 (s, 6H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 137.4, 136.3, 134.9, 133.4, 131.3, 131.3, 129.7, 128.8, 114.5, 108.3, 55.4, 42.9, 21.1. HRMS(EI) calcd for $C_{17}H_{20}N_2O$ (M^+) 268.1576. Found 268.1575.

*4-Chloro-4′-methyl-[1,1′-biphenyl]-2-carbaldehyde N,N-Dimethylhydrazone (**11g**).* Following the general procedure, flash chromatography (1:15 Et_2O/*n*-hexane) afforded **11g** (56 mg, 83%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, 1H, *J* = 1.9 Hz), 7.23−7.21 (m, 5H), 7.15 (d, 2H, *J* = 8.0 Hz), 2.88 (s, 6H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 137.0, 136.5, 135.6, 133.4, 131.4, 130.3, 129.4, 128.9, 126.9, 124.5, 42.7, 21.2. HRMS(EI) calcd for $C_{16}H_{17}ClN_2$ (M^+) 272.1080. Found 272.1087.

*4,5-Dimethoxy-4′-methyl-[1,1′-biphenyl]-2-carbaldehyde N,N-Dimethylhydrazone (**11h**).* Following the general procedure, flash chromatography (1:15 Et_2O/*n*-hexane) afforded **11h** (57 mg, 77%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.25−7.24 (m, 3H), 7.22 (s, 2H, *J* = 7.5 Hz), 6.73 (s, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 2.82 (s, 6H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.5, 148.4, 137.3, 136.5, 133.6, 129.6, 128.8, 128.1, 126.6, 112.7, 107.1, 55.8, 55.8, 43.1, 21.1. HRMS(EI) calcd for $C_{18}H_{22}N_2O_2$ (M^+) 298.1681. Found 298.1674.

*4,5-Dichloro-4′-methyl-[1,1′-biphenyl]-2-carbaldehyde N,N-Dimethylhydrazone (**11i**).* Following the general procedure, flash chromatography (1:15 Et_2O/*n*-hexane) afforded **11i** (61 mg, 80%) as a pale solid. Mp 95−97 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.06 (s, 1H),

dx.doi.org/10.1021/jo301965v | *J. Org. Chem.* 2012, 77, 9915−9920

7.31 (s, 1H), 7.22 (s, 4H), 7.04 (s, 1H), 2.89 (s, 6H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.5, 137.5, 135.4, 134.2, 131.6, 131.5, 130.2, 129.3, 129.1, 128.9, 126.3, 42.7, 21.2. HRMS(EI) calcd for $C_{16}H_{16}Cl_2N_2$ (M^+) 306.0691. Found 306.0692.

*3-Methoxy-4′-methyl-[1,1′-biphenyl]-2-carbaldehyde N,N-Dimethylhydrazone (**11j**).* Following the general procedure, flash chromatography (70:1 toluene/acetone) afforded **11j** (37 mg, 56%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24−7.17 (m, 4H), 7.13 (d, 2H, J = 7.8 Hz), 6.88 (d, 2H, J = 8.0 Hz), 3.86 (s, 3H), 2.71 (s, 6H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.6, 142.7, 138.8, 136.1, 131.3, 129.7, 128.3, 127.9, 123.7, 123.0, 110.2, 56.0, 42.7, 21.1. HRMS(EI) calcd for $C_{17}H_{20}N_2O$(M^+) 268.1576. Found 268.1576.

*(E)-2′-[(2,2-Dimethylhydrazono)methyl]-3′-methoxy-[1,1′-biphenyl]-4-carbaldehyde (**12j**).* Following the general procedure, flash chromatography (1:2 Et_2O/*n*-hexane) afforded **12j** (42 mg, 60%) as a yellow solid. Mp 88−90 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.00 (s, 1H), 7.81 (d, 2H, J = 8.1 Hz), 7.42 (d, 2H, J = 8.0 Hz), 7.31 (s, 1H), 7.24−7.23 (m, 1H), 6.91 (d, 1H, J = 8.0 Hz), 6.84 (d, 1H, J = 8.2 Hz), 3.86 (s, 3H), 2.61 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.2, 157.7, 149.8, 140.7, 134.3, 130.2, 129.1, 128.2, 127.9, 123.8, 122.9, 110.5, 55.8, 42.4. HRMS(EI) calcd for $C_{17}H_{18}N_2O_2$ (M^+) 282.1368. Found 282.1367.

General Procedure for Hydrazone-to-Nitrile Transformation.[15] A solution of magnesium monoperoxyphthalate hexahydrate (MMPP·6H_2O, 0.38 mmol, 186 mg) in MeOH (0.75 mL) was added dropwise to a stirred suspension of **11b,e,f,h−j** (0.15 mmol) in MeOH (0.75 mL). After consumption of the starting material (∼20 min at rt, TLC monitoring), CH_2Cl_2 (15 mL) and H_2O (15 mL) were added. The organic layer was washed with brine (2 × 10 mL), dried over $MgSO_4$, and concentrated to dryness. Purification was carried out by flash chromatography using acetone/toluene or EtOAc/*n*-hexane mixtures as solvents. Methods used for purification, yields, and characterization data for products **13b,e,f,h-j** are as follows:

*5-Methoxy-4′-methyl-[1,1′-biphenyl]-2-carbonitrile (**13b**).* Following the general procedure, flash chromatography (1:10 EtOAc/*n*-hexane) afforded **13b** (34 mg, 99%) as a pale solid. Mp 116−118 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, 1H, J = 9.0 Hz), 7.46 (d, 2H, J = 7.5 Hz), 7.29 (d, 2H, J = 8.0 Hz), 6.97 (d, 1H, J = 1.5 Hz), 6.92 (dd, 1H, J = 8.5, 2.0 Hz), 3.88 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.6, 147.6, 138.7, 135.3, 135.3, 129.3, 128.4, 119.2, 115.3, 113.2, 103.0, 55.6, 21.2 . HRMS(EI) calcd for $C_{15}H_{13}NO$ (M^+) 223.0997. Found 223.0996.

*4,4′-Dimethyl-[1,1′-biphenyl]-2-carbonitrile (**13e**).* Following the general procedure, flash chromatography (1:20 EtOAc/*n*-hexane) afforded **13e** (28 mg, 89%) as a light yellow solid. Mp 53−55 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.45−7.42 (m, 3H), 7.39 (d, 1H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.0 Hz), 2.42 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.7, 138.3, 137.3, 135.2, 133.9, 133.7, 129.8, 129.3, 128.5, 119.0, 110.9, 29.7, 21.2, 20.7. HRMS(EI) calcd for $C_{15}H_{13}N$ (M^+) 207.1048. Found 207.1046.

*4-Methoxy-4′-methyl-[1,1′-biphenyl]-2-carbonitrile (**13f**).* Following the general procedure, flash chromatography (1:200 acetone/toluene) afforded **13f** (33 mg, 98%) as a white solid. Mp 108−110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43−7.40 (m, 3H), 7.28 (d, 2H, J = 8.0 Hz), 7.23 (d, 1H, J = 3.0 Hz), 7.17 (dd, 1H, J = 8.5, 2.5 Hz), 3.86 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.4, 138.1, 135.0, 131.2, 129.3, 128.7, 128.5, 119.6, 118.7, 117.7, 111.7, 55.6, 21.2. HRMS(EI) calcd for $C_{15}H_{13}NO$ (M^+) 223.0997. Found 223.0995.

*4,5-Dimethoxy-4′-methyl-[1,1′-biphenyl]-2-carbonitrile (**13h**).* Following the general procedure, flash chromatography (1:3 EtOAc/*n*-hexane) afforded **13h** (35 mg, 92%) as a yellow solid. Mp 87−89 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.0 Hz), 7.15 (s, 1H), 6.92 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.5, 148.0, 140.2, 138.3, 135.3, 129.3, 128.4, 119.2, 114.9, 112.3, 102.2, 56.2, 56.0, 21.1. HRMS(EI) calcd for $C_{16}H_{15}NO_2$ (M^+) 253.1103. Found 253.1102.

*4,5-Dichloro-4′-methyl-[1,1′-biphenyl]-2-carbonitrile (**13i**).* Following the general procedure, flash chromatography (1:10 EtOAc/*n*-hexane) afforded **13i** (28 mg, 70%) as a yellow solid. Mp 131−133 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (s, 1H), 7.60 (s, 1H), 7.43 (d, 2H, J = 8.0 Hz), 7.31 (d, 2H, J = 7.5 Hz), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 139.7, 137.8, 134.8, 133.1, 131.9, 131.8, 129.7, 128.4, 117.0, 110.7, 21.3. HRMS(EI) calcd for $C_{14}H_9Cl_2N$ (M^+) 261.0112. Found 261.0113.

*3-Methoxy-4′-methyl-[1,1′-biphenyl]-2-carbonitrile (**13j**).* Following the general procedure, flash chromatography (1:10 EtOAc/*n*-hexane) afforded **13j** (32 mg, 96%) as a yellow solid. Mp 118−120 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (t, 1H, J = 8.0 Hz),7.43 (d, 2H, J = 7.0 Hz), 7.26 (d, 2H, J = 7.5 Hz), 7.03 (d, 1H, J = 8.0 Hz), 6.91 (d, 1H, J = 8.5 Hz), 3.95 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.2, 147.3, 138.7, 135.2, 133.6, 129.3, 128.6, 121.8, 116.1, 109.3, 100.9, 56.2, 21.2. HRMS(EI) calcd for $C_{15}H_{13}NO$(M^+) 223.0997. Found 223.0994.

General Procedure for Sequential Hydrazone-to-Nitrile Transformation/Radical Bromination. A solution of magnesium monoperoxyphthalate hexahydrate (MMPP·6H_2O, 0.25 mmol, 124 mg) in methanol (0.5 mL) was added dropwise to a stirred suspension of **11a,c,d,g** (0.1 mmol) in MeOH (0.5 mL). After consumption of the starting material (∼20 min at rt, TLC monitoring), CH_2Cl_2 (15 mL) and H_2O (15 mL) were added. The organic layer was washed with brine (2 × 10 mL), dried over $MgSO_4$, and concentrated to dryness to give crude **13a,c,d,g** products in >95% yield (estimated by ^{1}H NMR). Reaction crudes were used directly in the next bromination reaction.[16] A solution of $Na_2S_2O_5$ (0.15 mmol, 28.5 mg) in H_2O (0.3 mL) was added to a cooled (0 °C) biphasic mixture composed by a solution of $NaBrO_3$ (0.15 mmol, 22.6 mg) in H_2O (0.15 mL) and the reaction crude containing **14a,c,d,g** in EtOAc (0.2 mL). The reaction mixture was stirred at rt until consumption of the starting material (4−10 h, TLC monitoring). EtOAc (10 mL) and H_2O (10 mL) were added, and the organic layer was washed with brine (2 × 10 mL), dried over $MgSO_4$, and concentrated to dryness. Purification was carried out by flash chromatography using Et_2O/*n*-hexane or EtOAc/*n*-hexane mixtures as solvents. Methods used for purification, yields, and characterization data for products **14a,c,d,g** are as follows:

*4′-(Bromomethyl)-[1,1′-biphenyl]-2-carbonitrile (**14a**).* Following the general procedure, flash chromatography (Et_2O/*n*-hexane 1:15) afforded **14a** (33 mg, 80%) as a white solid. Spectroscopic and physical data matched those reported in the literature.[19]

*4′-(Bromomethyl)-5-fluoro-[1,1′-biphenyl]-2-carbonitrile (**14c**).* Following the general procedure, flash chromatography (EtOAc/*n*-hexane 1:12) afforded **14c** (34 mg, 78%) as a white solid. Mp 122−124 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (dd, 1H, J = 8.6, 5.5 Hz), 7.54 (s, 4H), 7.22 (dd, 1H, J = 9.0, 2.8 Hz), 7.17 (td, 1H, J = 7.6, 2.8 Hz), 4.55 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.8 (d, $^1J_{C,F}$ = 255 Hz), 147.7 (d, $^3J_{C,F}$ = 9 Hz), 138.9, 136.9, 136.1 (d, $^3J_{C,F}$ = 10 Hz), 129.5, 129.0, 117.8, 117.3 (d, $^2J_{C,F}$ = 23 Hz), 115.4 (d, $^2J_{C,F}$ = 23 Hz), 107.3, 32.5. HRMS(EI) calcd for $C_{14}H_9BrFN$(M^+) 288.9902. Found 288.9900.

*4′-(Bromomethyl)-5-chloro-[1,1′-biphenyl]-2-carbonitrile (**14d**).* Following the general procedure, flash chromatography (Et_2O/*n*-pentane 1:10) afforded **14d** (39 mg, 84%) as a white solid. Mp 95−97 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, 1H, J = 8.3 Hz), 7.53 (s, 4H), 7.52 (d, 1H, J = 1.9 Hz), 7.44 (dd, 1H, J = 8.3, 1.8 Hz), 4.54 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.3, 139.5, 139.0, 136.8, 134.9, 130.3, 129.6, 129.1, 128.2, 117.8, 109.6, 32.5. HRMS(EI) calcd for $C_{14}H_9BrClN$ (M^+) 304.9602. Found 304.9603.

*4′-(Bromomethyl)-4-chloro-[1,1′-biphenyl]-2-carbonitrile (**14g**).* Following the general procedure, flash chromatography (Et_2O/*n*-pentane 1:10) afforded **14g** (38 mg, 82%) as a white solid. Mp 127−129 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, 1H, J = 2.0 Hz), 7.63 (dd, 1H, J = 8.4, 2.1 Hz), 7.56 (s, 4H), 7.45 (d, 1H, J = 8.4 Hz), 4.54 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 138.7, 137.0, 134.0, 133.3, 131.3, 129.6, 129.1, 117.3, 112.6, 32.6. HRMS(EI) calcd for $C_{14}H_9BrClN$ (M^+) 304.9602. Found 304.9598.

General Procedure for Sequential Formyl Reduction/Hydrazone-to-Nitrile Transformation. To a cooled (0 °C) suspension of substrate **12a,b,j** (0.15 mmol) in MeOH (0.5 mL), $NaBH_4$ (0.15 mmol, 5.7 mg) was added, and the reaction mixture was stirred at this temperature until consumption of the starting material (∼30 min, TLC monitoring). Then, a solution of MMPP·6H_2O (0.23 mmol, 111 mg) in methanol (0.5 mL) was added dropwise at 0 °C, and reaction mixture

dx.doi.org/10.1021/jo301965v | J. Org. Chem. 2012, 77, 9915−9920

was stirred at rt for 30 min. CH_2Cl_2 (20 mL) and H_2O (20 mL) were added, and the organic layer was washed with brine (2 × 10 mL), dried over $MgSO_4$, and concentrated to dryness. Purification was carried out by flash chromatography using *n*-hexane/Et_2O mixtures as solvents. Methods used for purification, yields, and characterization data for products **15a,b,j** are as follows:

4′-(Hydroxymethyl)-[1,1′-biphenyl]-2-carbonitrile (15a). Following the general procedure, flash chromatography (Et_2O/*n*-hexane 2:1) afforded **15a** (31 mg, 99%) as a pale solid. Spectroscopic and physical data matched those reported in the literature.[20]

4′-(Hydroxymethyl)-5-methoxy-[1,1′-biphenyl]-2-carbonitrile (15b). Following the general procedure, flash chromatography (Et_2O/*n*-hexane 3:1) afforded **15b** (36 mg, 99%) as a pale solid. Mp 128−130 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, 1H, J = 8.5 Hz), 7.55 (d, 2H, J = 8.0 Hz), 7.49 (d, 2H, J = 8.5 Hz), 6.98 (d, 1H, J = 2.0 Hz), 6.94 (dd, 1H, J = 9.0, 2.5 Hz), 4.76 (s, 2H), 3.89 (s, 3H), 1.89 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.7, 147.3, 141.6, 137.5, 135.4, 128.8, 127.2, 119.1, 115.5, 113.4, 103.1, 64.9, 55.6. HRMS(EI) calcd for $C_{15}H_{13}NO_2$ (M^+) 239.0946. Found 239.0939.

4′-(Hydroxymethyl)-3-methoxy-[1,1′-biphenyl]-2-carbonitrile (15j). Following the general procedure, flash chromatography (Et_2O/*n*-hexane 3:1) afforded **15j** (35 mg, 99%) as a pale solid. Mp 124−126 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57−7.54 (m, 3H), 7.47 (d, 2H, J = 7.5 Hz), 7.05 (d, 1H, J = 7.5 Hz), 6.96 (d, 1H, J = 8.5 Hz), 4.74 (s, 2H), 3.97 (s, 3H), 1.96 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.2, 147.0, 141.5, 137.4, 133.8, 129.0, 127.1, 121.9, 116.1, 109.6, 101.0, 64.9, 56.3. HRMS(EI) calcd for $C_{15}H_{13}NO_2$ (M^+) 239.0946. Found 239.0940.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Spanish 'Ministerio de Ciencia e Innovación' (Grants CTQ2010-15297, CTQ2010-14974 and fellowship to R.L-R.), the European FEDER funds, and the Junta de Andalucía (Grants 2008/FQM-3833 and 2009/FQM-4537) for financial support. A.R. thanks the European Union for a Marie Curie Reintegration Grant (FP7-PEOPLE-2009-RG-256461) and the CSIC for a JAE Postdoctoral Fellowship. R.L.-R. thanks the CSIC for a JAE Predoctoral Fellowship.

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