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Functional Group Transformations in Derivatives of 1,4-Dihydrobenzo[1,2,4]triazinyl Radical

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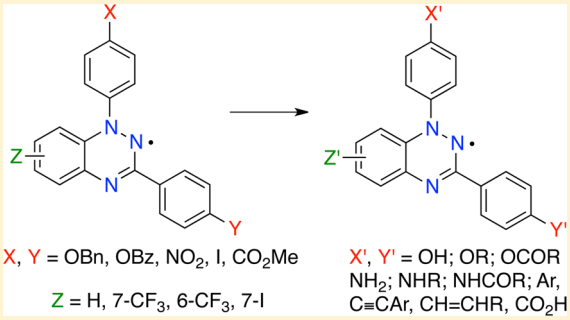
Supporting Information

ABSTRACT: Transformations of functional groups OCOPh, OCH_2Ph, I, NO_2, and CO_2Me in Blatter's radical derivatives **1**–**5** were investigated in order to develop synthetic tools for incorporation of the benzo[1,2,4]triazinyl system into complex molecular architectures. Thus, basic hydrolysis of OCOPh or Pd-catalyzed debenzylation of OCH_2Ph gave phenol functionality, which was acylated and alkylated. Pd-catalyzed Suzuki, Negishi, Sonogashira, and Heck C–C cross-coupling reactions of iodo derivatives **1c**, **1d**, and **2d** were also successful and efficient. Reduction of NO_2 in **1e** led to aniline derivative **1t**, which was reductively alkylated with hexanal and coupled to L-proline. Selected benzo[1,2,4]triazinyl radicals were characterized by EPR and electronic absorption spectroscopy, and the results were analyzed in tandem with DFT computational methods. Lastly, the mechanism for formation of the 1,4-dihydrobenzo[1,2,4]triazine ring was investigated using the B3LYP/6-31G(2d,p) method.



INTRODUCTION

Stable π-delocalized radicals are becoming important structural elements of materials for solar cells,[1] energy storage,[2] electronic,[3,4] and biological[5−8] applications.[9,10] Their incorporation into more complex molecular architectures and tuning of properties can be accomplished through functional group transformations. In this context, we recently demonstrated a number of chemical transformations on derivatives of the 1,3,5-triphenyl-6-oxoverdazyl radical (**I**, Figure 1).[11] However, the benzo[1,2,4]triazinyl radical appears even more interesting in the context of developing new materials.[12,13]

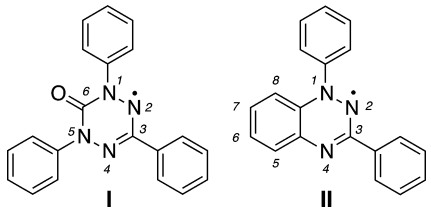


Figure 1. Structure and numbering scheme for 1,3,5-triphenyl-6-oxoverdazyl (**I**) and 1,3-diphenyl-1,4-dihydrobenzo[1,2,4]triazinyl (Blatter's radical, **II**).

1,3-Diphenylbenzo[1,2,4]triazinyl (**II**), also known as Blatter's radical,[14] is prototypical of a family of exceptionally stable organic radicals, which broadly absorb in the visible range[15,16] and exhibit reversible redox potentials with a relatively narrow electrochemical window.[17,18] Due to its inefficient and cumbersome synthesis, the radical has received little attention, and only a handful of derivatives have been reported in the literature. This situation changed several years ago when Koutentis began systematic development of synthetic access to this class of radicals. Since then, Koutentis optimized the classic synthetic routes to the benzo[1,2,4]triazinyl skeleton,[19] demonstrated Pd-catalyzed C–C cross-coupling reactions of the 7-iodo derivatives,[20−23] fused 5-membered heterocyclic rings at the 6,7 positions,[17,24] and applied benzo[1,2,4]triazinyls toward the synthesis of other heterocycles.[25] More recently, he has developed another synthetic pathway to the benzo[1,2,4]triazinyl, potentially widening the scope of substitution patterns on the heterocycle.[18] While the structural variety of benzo[1,2,4]triazinyl derivatives has increased dramatically, there still remains a need for broader investigation of functionalized derivatives of the radical and functional group transformations in the presence of the unpaired electron. Such functionalized derivatives are required for the development of advanced materials and are of interest in our research program aimed at investigation of organic semiconductors.

Herein, we report the investigation of functionalized derivatives of Blatter's radical **II** containing OCOPh (OBz), OCH_2Ph (OBn), NO_2, CO_2Me, and I groups substituted on the phenyl rings (Chart 1). We focused on 7-(trifluoromethyl)-benzo[1,2,4]triazinyl radicals **1** and also prepared 7-iodo derivatives **2a** and **2d**[26] and report an attempted synthesis of 7-fluoro analogue **3d**. We additionally describe two 7-

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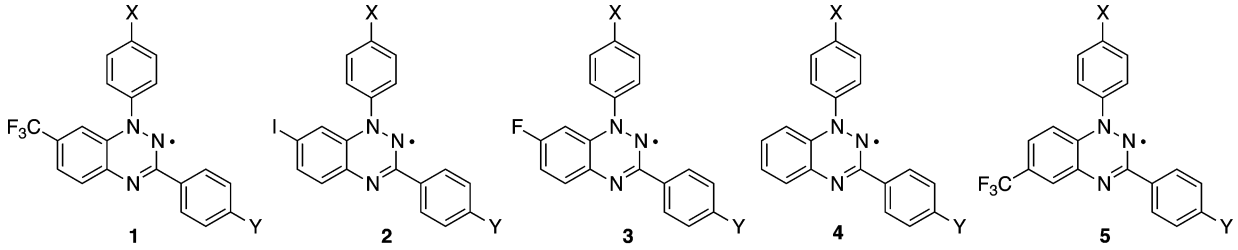
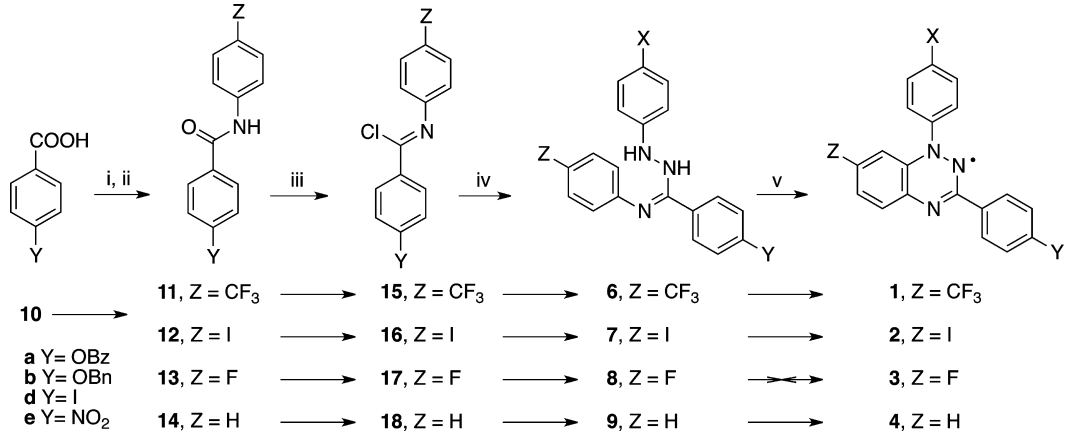
Chart 1



Scheme 1. Synthesis of Radicals 1−4[a]



[a]Reagents and conditions: (i) $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt; (ii) 4-$ZC_6H_4NH_2$, CH_2Cl_2, Et_3N, rt; (iii) $SOCl_2$ (excess), reflux; (iv) 4-$XC_6H_4NHNH_2$ (**19**: **a**, X = OBz; **b**, X = OBn; **c**, X = I; **e**, X = H), Et_3N, CH_2Cl_2/MeCN, rt; (v) air, DBU, Pd/C, CH_2Cl_2, rt.

unsubstituted derivatives **4a** and **4b** and preparation of functionalized 6-trifluoromethyl derivatives **5f** and **5h**. We investigated transformations of these functionalities to esters, ethers, amides, and alkylamines, and demonstrate Pd-catalyzed C−C coupling reactions. We also characterize selected radicals by electrochemical and spectroscopic methods and briefly investigate the effect of the substituent on the phenyl rings on electronic absorption and EPR spectra. The experimental data are augmented with DFT computational results, which also include mechanistic studies of the formation of the 1,3-diphenyl-1,4-dihydrobenzo[1,2,4]triazine.

RESULTS

Synthesis of Radicals 1-5. Benzo[1,2,4]triazinyls **1**−**4** with a substituent at the C(7) position were prepared following the classical Neugebauer route,[15] which involves oxidative cyclization of the corresponding amidrazones **6**−**9** (Scheme 1). The aerial oxidation of **6**, **7**, and **9** in the presence of catalytic amounts of Pd/C and DBU, according to a general method,[19] gave the expected radicals **1**, **2**,[26] and **4**, respectively, in yields ranging from 32% to 89%. No 7-fluorobenzo[1,2,4]triazinyl **3d** was obtained from fluoroamidrazone **8d** under these conditions, and only a complex mixture of products was observed by TLC. The low yields obtained for radicals containing the benzoyloxy group are presumably due to the low hydrolytic stability of the ester under the reaction conditions.

Radicals **1** and **2** were conveniently isolated by column chromatography on SiO_2. In contrast, radicals **4** partially decomposed under the same conditions, and pure compounds were obtained using SiO_2 passivated with Et_3N.

The requisite amidrazones **6**−**9** were obtained from 4-substituted benzoic acids **10**, which were converted to amides **11**−**14** and subsequently to imidoyl chlories **15**−**18** using $SOCl_2$ (Scheme 1). Reactions of chlorides **15**−**18** with an appropriate arylhydrazine **19**[11] gave the desired amidrazones **6**−**9**, respectively, isolated in 29−85% yield after chromatography. In general, reactions with 4-iodophenylhydrazine (**19c**) gave higher yields of amidrazones, while the lowest yield of 29% was obtained for **6a** containing the benzoyloxy group.

Reactions of benzoyloxy imidoyl chloride **15a** with hydrazines **19b** (X = OBn) and **19g** (X = CO_2H) gave complex mixtures of products from which no amidrazones **6f** and **6g** could be isolated. Amidrazones **6a**, **6b**, and **7a** were obtained conveniently by reacting appropriate imidoyl chloride with hydrazine hydrochloride **19a·HCl** (X = OBz) in the presence of an additional 1 equiv of Et_3N.[11]

Amidrazones **6**−**9** had limited stability to purification on SiO_2 and storage, which hampered complete characterization efforts. For instance, within several hours, amidrazone **6c** underwent partial oxidation in the solid state giving a number

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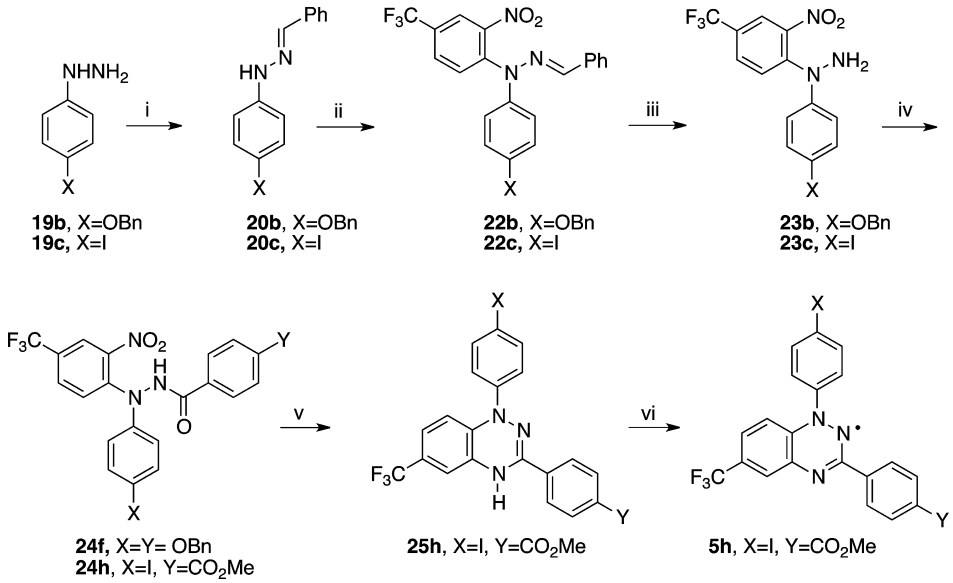
Scheme 2. Synthesis of Radicals 5[a]



[a]Reagents and conditions: (i) C_6H_5CHO, EtOH, reflux, 2h for **19c** or C_6H_5CHO, EtOH, 0 °C → rt, overnight for **19b**; (ii) 4-fluoro-3-nitro(trifluoromethyl)benzene (**21**), K_2CO_3, DMSO, rt, 16h; (iii) $NH_2OH{\cdot}\bullet HCl$, pyridine, 80 °C, 20 h; (iv) ArCOCl from **10d** or **10h**, Et_3N, CH_2Cl_2, 0 °C → rt, 20 h; (v) Sn, AcOH, rt 30 min → reflux 10 min; (vi) air, base or $NaIO_4$, rt.

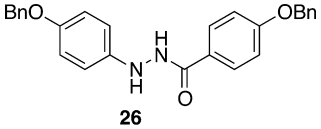
of products including radical **1c**, as demonstrated by TLC analysis. Most amidrazones underwent slow decomposition during recrystallization; however, no radicals were detected by TLC.

The overall yields for benzo[1,2,4]triazinyls **1**, **2**, and **4** range from 12% to 25% based on acid **10**. Exceptionally high overall yields of about 53% were obtained for iodo radicals **1c** and **1d**.

Benzo[1,2,4]triazinyls **5f** and **5h**, with the CF_3 substituent at the C(6) position, were obtained according to a new, recently described procedure[18] (Scheme 2). Thus, arylation of hydrazones **20b** and **20c** with 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (**21**) in DMSO containing K_2CO_3 gave the corresponding products **22b** and **22c** in 99% and 60% yield, respectively. The double activation of the fluorine atom in **21** by the NO_2 and CF_3 substituents for nucleophilic aromatic substitution permitted the arylation to be conducted at ambient temperature rather than at 100 °C.[18] Treatment of hydrazones **22** with an excess $NH_2OH{\cdot}HCl$ in hot pyridine,[18] removed the benzal group and hydrazines **23b** and **23c** was obtained in 64% and 77% yield, respectively. In both cases, the reaction was incomplete and unreacted hydrazones **22** could be separated from the crude product. A subsequent reaction of **23c** with acid chloride derived from monomethyl terephthalate (**10h**) in CH_2Cl_2 containing Et_3N at −5 °C gave the desired hydrazide **24h** in 71% yield. The reaction was incomplete, as evident from the remaining unreacted hydrazine, even when using an excess acid chloride. No reaction occurred with the acid anhydride derived from **10h**. At ambient temperatures and above, the formation of an unidentified side product was observed by TLC.

Finally, hydrazide **24h** was converted to the corresponding radical **5h** by reduction with excess tin powder in hot acetic acid followed by oxidation. The original method[18] was modified, and during workup the reaction mixture was diluted with CH_2Cl_2 and washed with aq $NaHCO_3$. Chromatography on the resulting product permitted isolation of the *leuco* **25h** in 49% yield, which was oxidized with $NaIO_4$ to the expected radical **5h** in nearly quantitative yield. Although *leuco* **25h** appeared stable in air, it undergoes quick aerial oxidation to **5h** upon treatment with 1 equiv of KOH, in analogy to the first reported synthesis of Blatter's radical **II**.[14]

The preparation of the benzyloxy hydrazide **24f** was problematic. Attempts at acylation of hydrazine **23b** with acid chloride derived from 4-benzyloxybenozic acid (**10b**) using several different reaction conditions (CH_2Cl_2 and Et_3N, neat pyridine cold or warm) resulted in the appearance of a new, unidentified major product, similar to that observed during the preparation of **24h**. Unfortunately, the expected hydrazide **24f** and the unknown side product could not be separated by chromatography, and this approach was abandoned. Another preparation of hydrazide **24f** was attempted starting with bisbenzyloxy hydrazide **26**. Unfortunately, arylation[18] of **26** with **21** in *sec*-butanol containing K_2CO_3 gave a complex mixture of products from which **24f** could not be isolated.



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Functional Group Transformations in Benzo[1,2,4]-triazinyl Derivatives. Deprotection of the phenolic functionality and formation of bisphenols **1i** and **4i** was performed by basic hydrolysis of bis-benzoates **1a** and **4a**, respectively, according to conditions used for the 6-oxoverdazyl analogue.[11] Thus, treatment of **1a** and **4a** with stoichiometric amounts of KOH in CH_2Cl_2/MeOH at ambient temperature gave the desired diphenols **1i** and **4i** in 97% and 58% yield, respectively (Schemes 3 and 4). Similarly, monophenol **1j** was obtained in 90% yield by hydrolysis of benzoate **1b** (Scheme 3). Both mono- and bisphenol radicals can be stored in the solid form at ambient temperature; however, they undergo slow decomposition in solutions, as evidenced by the appearance of a blue spot on TLC.

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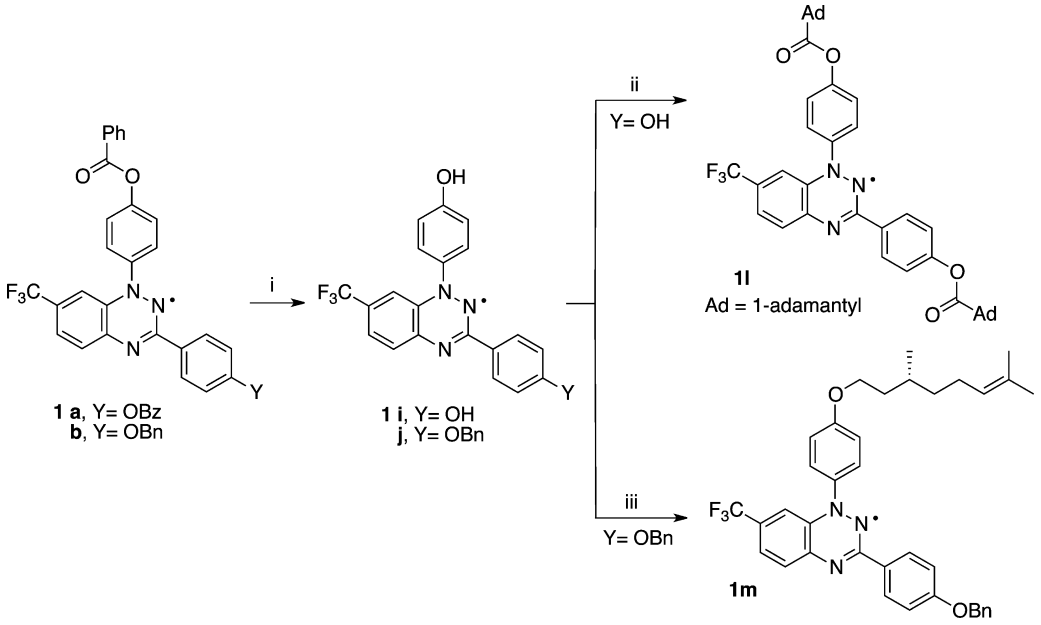
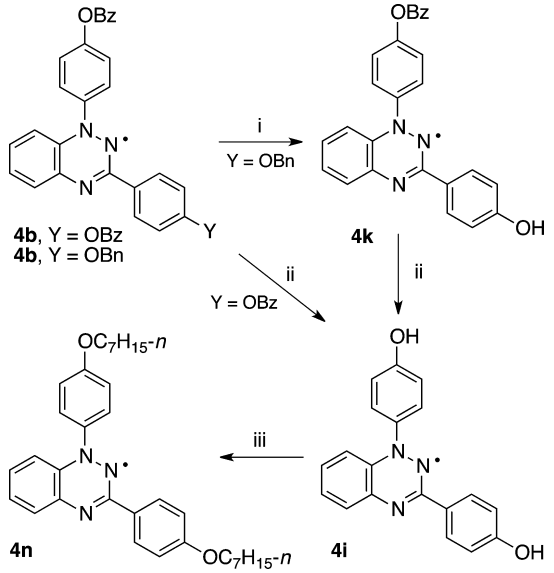
Scheme 3. Transformations of the OH Groups in 1[a]



[a]Reagents and conditions: (i) 0.1 N KOH in MeOH, CH_2Cl_2/MeOH, 1 h, rt; (ii) $C_{10}H_{15}$-1-COCl, Et_3N, CH_2Cl_2, 1 h, rt; (iii) (*S*)-(+)-citronellyl bromide, K_2CO_3, MeCN, 4 h, reflux.

Scheme 4. Transformations of the OH Groups in 4[a]

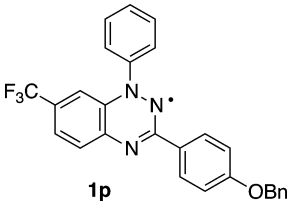


[a]Reagents and conditions: (i) H_2, 10% Pd/C, THF/EtOH, 12 h, rt; (ii) 0.1 N KOH in MeOH, CH_2Cl_2/MeOH, 1 h, rt; (iii) *n*-$C_7H_{15}I$, K_2CO_3, MeCN, 6 h, reflux.

The benzyl group in radical **4b** was removed under reductive conditions (H_2 and 10% Pd/C) giving monophenol **4k**, which opens possibilities for differentiation of the two hydroxyl groups (Scheme 4). The second hydroxy group in **4k** was deprotected under basic hydrolytic conditions giving another route to bisphenol **4i** in 87% yield. All phenols in series **1** and **4** were purified by column chromatography (SiO_2).

With access to phenolic derivatives of Blatter's radical, their reactivity was investigated under a variety conditions. Thus, a reaction of bisphenol **1i** with adamantane-1-carbonyl chloride in the presence of Et_3N provided corresponding diester **1l** in 91% yield (Scheme 3). Phenol **1j** was alkylated with (*S*)-(+)-citronellyl bromide under standard conditions (MeCN, K_2CO_3), and the resulting ether **1m** was isolated in 55% yield. Similar alkylation of **4i** with 1-iodoheptane gave diether **4n** in 56% yield (Scheme 4). Interestingly, in the former alkylation reaction with citronellyl bromide, TLC analysis showed evidence of a major polar side product appearing as a blue spot on TLC. No such side product was observed in the alkylation of **4i** with heptyl iodide.

Iodine containing benzo[1,2,4]triazinyl derivatives **1c**, **1d**, and **2d**, were tested as substrates for Pd-catalyzed C−C coupling reactions. Thus, radical **1c** reacted smoothly with 4-methoxyphenylboronic acid under Suzuki conditions[20] (refluxing toluene/water) and the coupling product **1o** was isolated in 83% yield (Scheme 5). A similar coupling reaction with potassium 4-methoxyphenyltrifluoroborate[27] under Molander conditions,[28] afforded **1o** in 51% yield accompanied by small amounts of deiodinated product **1p** (11% yield). The phenol functionality in **1o** was then deprotected under reductive conditions (H_2, 5% Pd/C) giving phenol **1q** in 90% yield (Scheme 5).



The synthetic utility of the two iodine atoms in radical **1d** was demonstrated using modified Sonogashira[29] and Negishi[30] cross-coupling reactions at ambient temperature (Scheme 6). Thus, a reaction of **1d** with phenylacetylene cleanly afforded **1r** in 80% yield. However, the Negishi reaction of **1d** with 4-(methoxyphenyl)zinc reagent was more complicated and resulted in a mixture of the expected **1s** and its *leuco* form.

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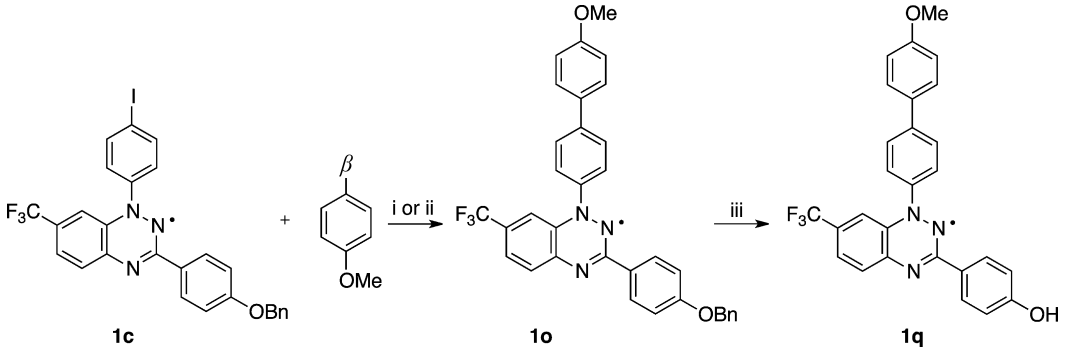
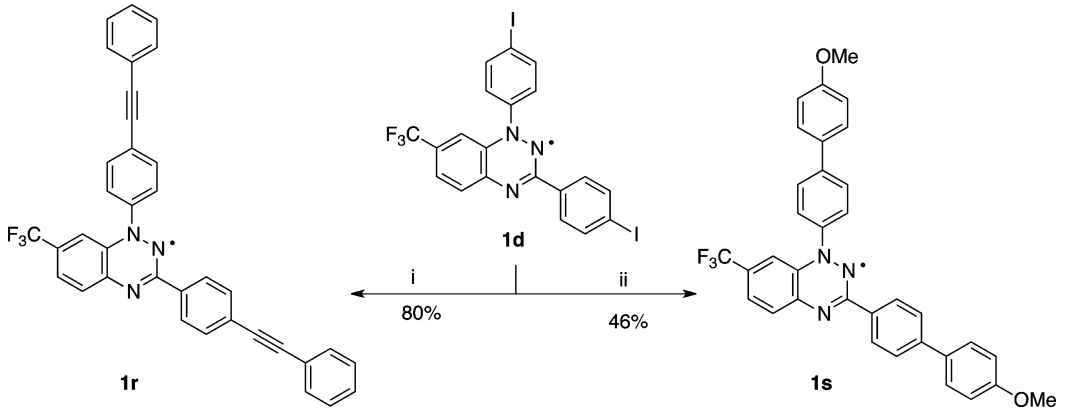
Scheme 5. Transformations of I and OH groups in 1c[a]



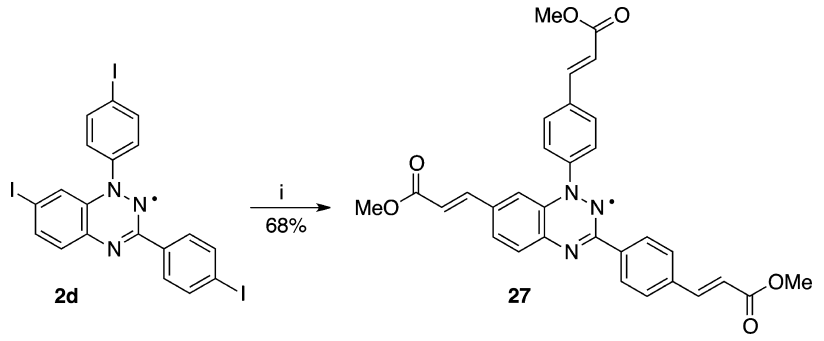
[a]Reagents and conditions: (i) β = , $Pd(OAc)_2$, K_2CO_3, toluene/H_2O, 24 h reflux; (ii) β = BF_3K, $PdCl_2(PPh_3)_2$, Cs_2CO_3, toluene/H_2O, 24 h, reflux; (iii) H_2, 10% Pd/C, THF/EtOH, 12 h, rt.

Scheme 6. Transformations of 1d[a]



[a]Reagents and conditions: (i) phenylacetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, DMF, 12 h, rt; (ii) (4-methoxyphenyl)zinc bromide, PEPPSi-IPr, THF, 4 h, rt.

Scheme 7. Transformation of 2d[a]



[a]Reagents and conditions: (i) methyl acrylate, Et_3N, $Pd(OAc)_2$, (o-$MeOC_6H_4)_3P$, DMF, 5 h, 100 °C.

Radical **1s** was isolated in 46% yield after a solution of the mixture of products was allowed to oxidize in air.

A Heck C−C cross-coupling reaction[31] was demonstrated on radical **2d** containing three iodine atoms (Scheme 7). Thus, a reaction of **2d** with methyl acrylate in DMF under typical reaction conditions in the presence of Et_3N gave the corresponding radical **27** in 68% yield after 5 h at 100 °C. Interestingly, the triester **27** crystallized with two molecules of water, which can be largely removed when CH_2Cl_2 solutions are dried with $MgSO_4$.

Transformations of benzo[1,2,4]triazinyl containing a nitro group were investigated using radical **1e** (Scheme 8). Thus, catalytic reduction of **1e** with H_2 (50 psi) in the presence of Pd/C was completed in 2 h affording the *leuco* form, which after exposure to air gave aniline derivative **1t** in 98% yield. DCC coupling of amine **1t** with *N*-Boc-protected L-proline afforded the corresponding amide **1u** in 93% yield. Amino-substituted radical **1t** was also used for the reductive amination with hexanal in the presence of $NaBH_3CN$ giving **1v**. The reductive amination reaction was incomplete, and no attempt at optimizing the reaction conditions was made. Radical **1v** undergoes partial reduction during the reaction, as evident by TLC analysis of the crude reaction mixture, but any *leuco* forms

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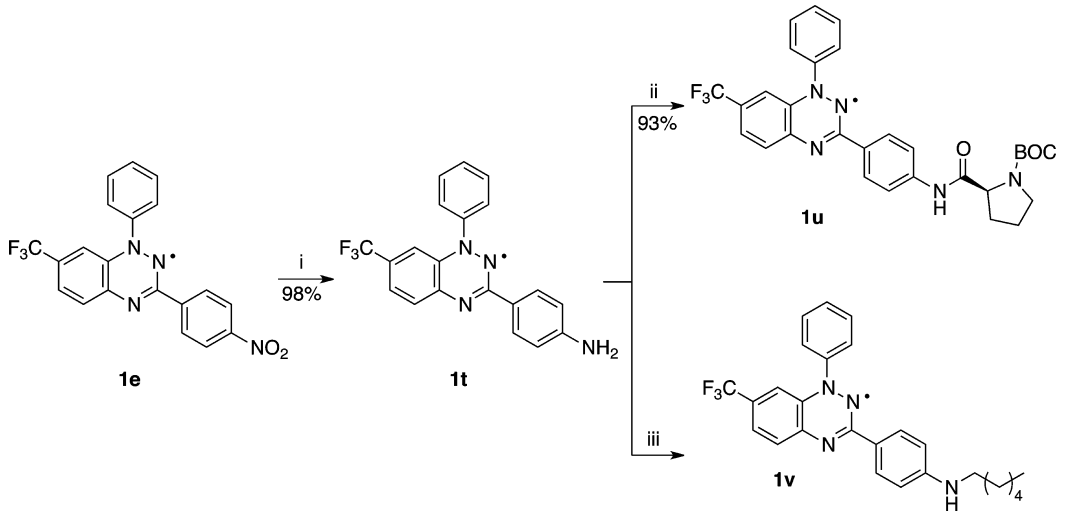
Scheme 8. Transformation of 1e[a]

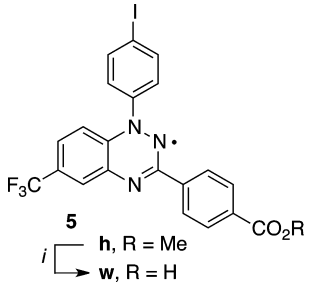


[a]Reagents and conditions: (i) H_2 (50 psi), Pd/C, THF/EtOH, 2h, rt; (ii) *N*-Boc-L-proline, DCC, DMAP, CH_2Cl_2, 12 h, rt; (iii) (1) hexanal, $NaBH_3CN$, MeOH, 24 h, rt, (2) air.

are converted to their corresponding radicals during the workup procedure.

Finally, deprotection of the carboxy group in **5h** was investigated. Thus, treatment of **5h** with 1.5 equiv of KOH in EtOH/THF at 60 °C resulted in hydrolysis of the ester group, and acid **5w** was isolated in 73% yield (Scheme 9).

Scheme 9. Transformation of 5h[a]

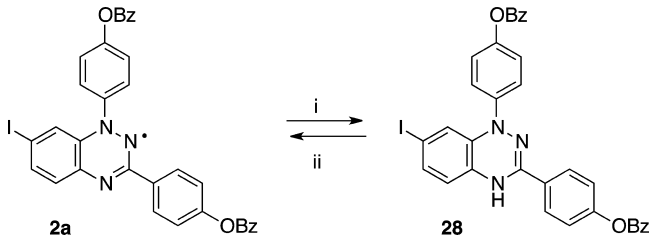


[a]Reagents and conditions: (i) KOH, EtOH/THF (1:1).

Reductive Stability of 1. The chemical stability of benzo[1,2,4]triazinyl against natural reducing reagents was qualitatively tested on radical **2a** in aqueous media. Thus, a 15 mM solution of **2a** in DMSO/H_2O (2:1) was reduced with 5 equiv of ascorbic acid after 2 h to the yellow *leuco* form **28**, which was reoxidized to **2a** with $NaIO_4$ (Scheme 10). In contrast, no reduction of **2a** with glucose was observed under identical conditions even after 24 h.

Mechanistic Studies. For a better understanding of the formation of the benzo[1,2,4]triazine skeleton, the cyclization was modeled in a CH_2Cl_2 dielectric medium using the B3LYP/6-31G(2d,p) method and PCM solvation model.[32] Analysis of 7-unsubstituted azo imino derivative **29a**, formed as the oxidation product of the corresponding amidrazone, revealed that the C(8a)···N(1) distance in the *syn*-conformer is 3.354 Å, which is close to the sum of the van der Waals radii (3.31 Å).[33] This distance contracts to 2.155 Å in the transition state $\mathbf{30}^{\ddagger}\mathbf{a}$, which is $\Delta G^{\ddagger}_{298}$ = 38.6 kcal/mol relative to **29a**, and then to 1.476 Å in the cyclic nonaromatic product **31a** (Figures 2−4).

Scheme 10. Chemical reduction and oxidation of 2a[a]



[a]Reagents and conditions: (i) ascorbic acid, DMSO/H_2O (2:1), rt; (ii) $NaIO_4$, AcOEt/H_2O, rt, 15 min.

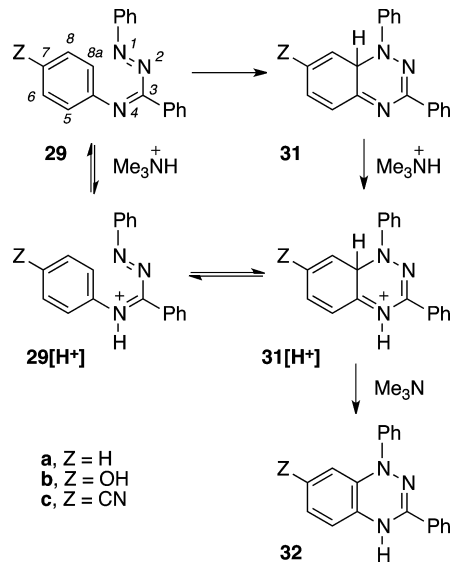


Figure 2. Proposed mechanism for the formation of 1,3-diphenyl-1,4-dihydrobenzo[1,2,4]triazine **32**.

The process is endothermic by 9.0 kcal/mol (ΔG_{298} = 11.7 kcal/mol), and stabilization occurs by tautomerization to **32a** with an exotherm of −28.2 kcal/mol (ΔG_{298} = −27.8 kcal/mol). In the 4*H* tautomer, the C(8a)−N(1) distance is 1.417 Å. The tautomerization may occur by proton transfer from the

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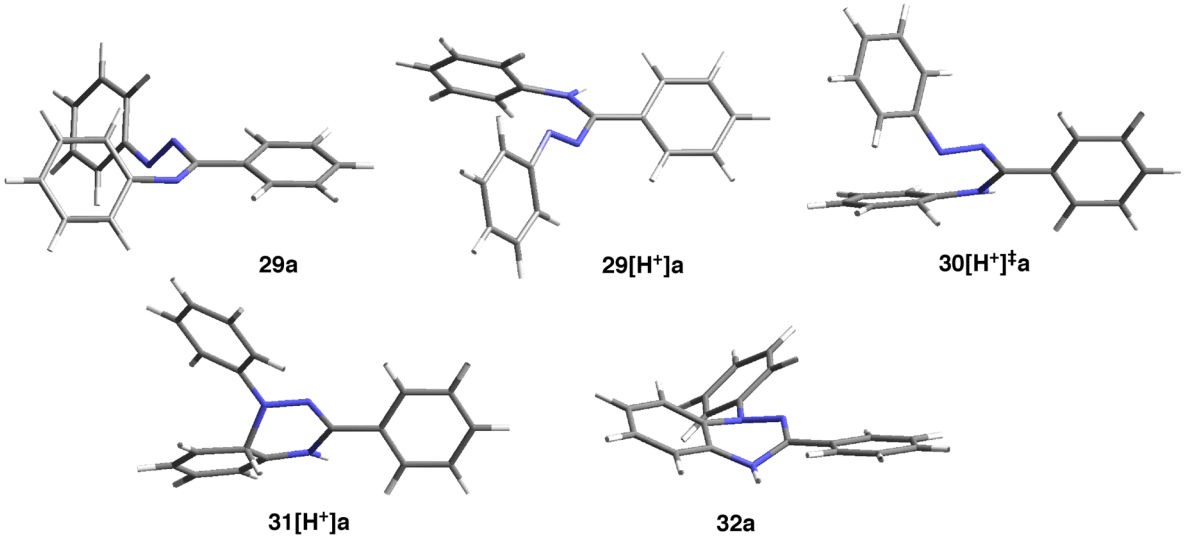

Figure 3. B3LYP/6-31G(2d,p)-optimized geometries for structures involved in formation of **32a** from **29a**.

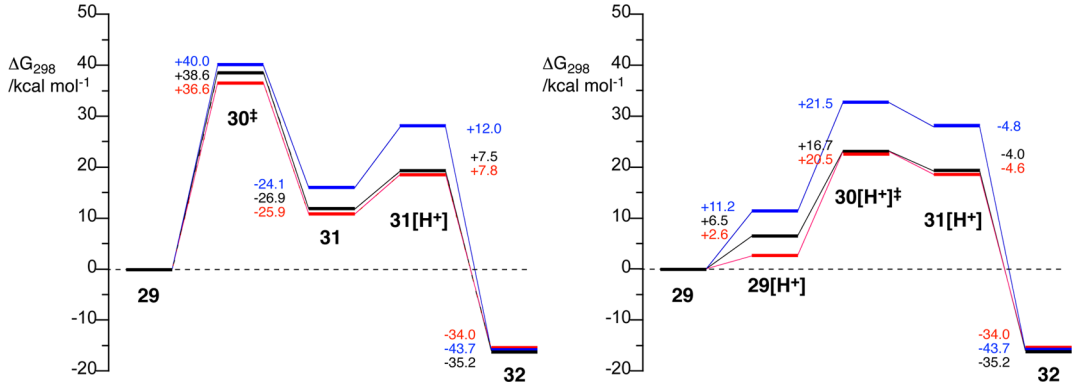

Figure 4. B3LYP/6-31G(2d,p) potential energy surface for two proposed mechanisms for the formation of **32** from **29** in Figure 2: Z = H (black), Z = OH (red), Z = CN (blue). Full thermodynamic data is provided in the Supporting Information.

reaction medium to the N(4) position to form **31**[H^+], followed by deprotonation at the C(8a) position. Since the reaction is conducted in the presence of an amine, it is reasonabe to assume for the purpose of the calculations, that an ammonium cation, such as $[HNMe_3]^+$ is the source of the proton. Such a proton transfer to **31a** and formation of **31**[H^+]**a** is endothermic by 7.1 kcal/mol, which is followed by a significant exotherm (ΔH = −35.3 kcal/mol) upon deprotonation and the formation of **32a**.

Alternatively, the protonation may occur prior to the cyclization step (Figure 2). Thus, proton transfer from ammonium $[HNMe_3]^+$ to **29a** and formation of **29**[H^+]**a** is moderately endothermic (5.7 kcal/mol). Computational modeling demonstrates that the C(8a) and N(1) atoms are significantly closer in the *syn*-conformer (2.923 Å) of the protonated **29**[H^+]**a** than in the neutral form **29a**. The cyclization to **31**[H^+]**a** proceeds through a late transition state **30**[H^+]‡**a** ($d_{C\cdots N}$ = 1.807 Å) with a low activation energy of $\Delta G^‡_{298}$ = 16.7 kcal/mol (Figures 3 and 4). The process is endothermic and, due to the relatively low $\Delta G^‡_{298}$, is reversible. The cyclic cation **31**[H^+]**a** undergoes deprotonation-aromatization to form **32a**. Thus, computational results strongly indicate the later mechanism, protonation−cyclization−deprotonation, as the most likely process leading to the benzo[1,2,4]triazine skeleton. The overall process is moderately exothermic with free energy change of 16.0 kcal/mol.

Brief investigations of the substituent effect on the cyclization energies were conducted using the OH and CN groups at the C(7) position (Figure 4).[34] The results demonstrate that the substituents have little impact on the cyclization activation energies for the neutral precursor **29**. In contrast, they have a more pronounced effect on the energetics of the protonation of **29** and its subsequent cyclization. Thus, an electron-donating substituent, OH, lowers the protonation energy and raises the cyclization activation barrier by about 4 kcal/mol. In contrast, the CN substituent increases both the protonation and cyclization activation free energy by about 5 kcal/mol.

Electronic Absorption Spectroscopy. Blatter's radicals are dark brown-red in solutions. UV−vis spectroscopic analysis of two selected radicals, **1r** and **4n**, revealed similar spectra with strong absorption bands around 300 nm (301 and 283 nm, respectively) and low to medium intensity bands in the visible range (Figure 5). The obtained spectra are qualitatively similar to that of Batter's radical (**II**).[15]

TD-DFT computational analysis of **1r** and a model dimethoxy derivative **4x** in CH_2Cl_2 dielectric medium revealed several (5 and 9, respectively) low oscillator strength excitations in the visible range. In general, all excitations involve multiple transitions and excitations in **1r** have higher oscillator strength

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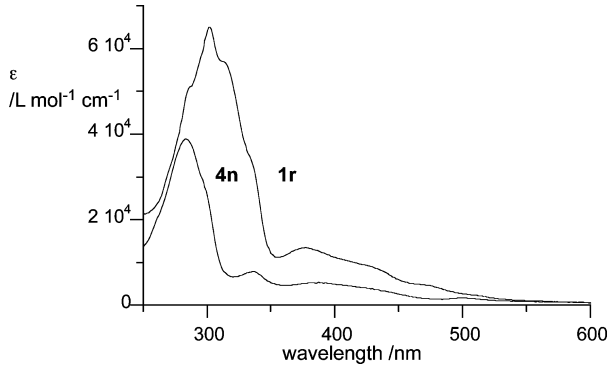

Figure 5. Electronic absorption spectra for **1r** and **4n** (CH_2Cl_2).

than those in the dimethoxy **4x**. The lowest energy excitation for the dimethoxy **4x** is calculated at 581 nm and involves mainly the α-HOMO (SOMO) → α-LUMO transition (f = 0.005), while the excitation at 499 nm is largely due to the β-HOMO → β-LUMO transition (f = 0.04). The SOMO and the β-LUMO orbitals are localized on the benzo[1,2,4]triazinyl ring, while the α-LUMO and β-HOMO are delocalized on the coplanar ring at the C(3) position (Figure 6). For the acetylene

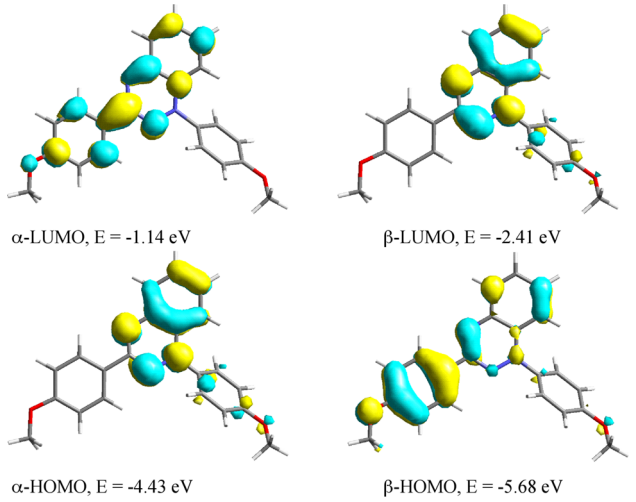

Figure 6. B3LYP/6-31G(2d,p)-derived contours and energies of frontier molecular orbitals relevant to low energy excitations for **4x** in CH_2Cl_2 dielectric medium.

derivative **1r** analogous excitations have lower energies, at 638 and 552 nm, respectively. Higher energy excitations, at 479 nm (f = 0.04) and 474 nm (f = 0.47), in **1r** involve HOMO−1 and LUMO+1 orbitals localized on the tolane substituents.[34]

EPR Spectroscopy. EPR spectra of several derivatives **1** exhibit 12 principal bands[35] due to coupling to three ^{19}F and quadrupolar ^{14}N nuclei broadened by minor coupling to ^{1}H's of the benzene rings as shown for **1t** in Figure 7. Simulation of the experimental spectra aided with DFT calculations demonstrates that the highest hfcc values, about 6.5 G, are associated with the N(1) atoms and smaller, of about 4 G with N(2), and N(4) and F atoms (Table 1). The benzo[1,2,4]trizine ring H atoms have smaller hfcc with the largest of about 1.8 G for the H(5) atom. This assignment of the largest hfcc to the N(1) atom is consistent with results of ENDOR and isotope labeling studies of the Blatter and related radicals.[15,36,37] Interestingly, the distribution of spin density in the triazinyl ring is affected by

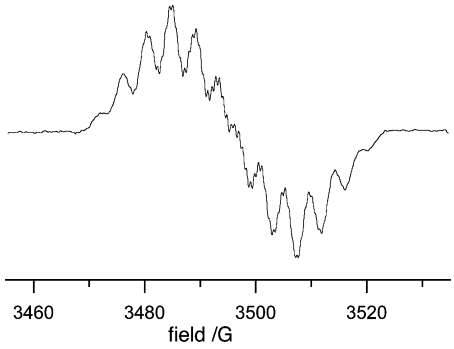

Figure 7. EPR spectrum of **1t** recorded in benzene.

electron density of the phenyl ring attached at the nodal position C(3). Thus, substitution of the NO_2 group for the NH_2 in **1t** reduces the a_{N2} hfcc in **1e** by 0.65 G (calculated 0.56 G) and increases the a_{N4} hfcc by 0.15 G (calculated 0.29 G). Although the experimental values for a_{N1} are close and about 6.8 G for the two radicals, DFT calculations show larger hfcc for this position, by 0.2 G, in nitro **1e** than in amine **1t**. This effect is consistent with polarization of electron density in the triazine ring by the substituents, and greater contribution of the polar resonance form **B** in the structure of nitro derivative **1e** than in amino analogue **1t** (Figure 8).

DISCUSSION AND CONCLUSIONS

Derivatives of Blatter's radical **II** with a wide variety of substituents are available either through classical methods involving oxidative cyclization of amidrazones (such as **6**–**9**, Scheme 1, method A) or using a recently elaborated reductive cyclization of *N*′,*N*′-diarylhydrazides (e.g., Scheme 2, method B). Due to regiochemical aspects of the cyclization, the former method is suitable for the preparation of 7-substituted benzo[1,2,4]triazinyls, while the latter method can be used for regiospecific syntheses of the radical with other substitution patterns (e.g., 6-CF_3 derivatives **5**).

Pd-catalyzed oxidation of amidrazones and formation of the benzo[1,2,4]triazinyl was generally efficient for **1**, **2**, and **4**, which were formed in yields ranging from 63% (**1d**) to 89% (**1c**). Lower yields of the radicals were obtained from amidrazones containing the benzoyloxy substituent (about 50%), presumably due to sensitivity of the ester group to the reaction conditions. Surprisingly, no expected radical was obtained in the case of Z = F (**3**, Scheme 1), and it is not clear whether the decomposition occurs at the amidrazone or at the radical stage.

While cyclization of amidrazones and hydrazides and formation of the corresponding radicals works well, both methods suffer from inconsistent and rather modest availability of the required intermediates. For instance, amidrazones are typically obtained using two general methods: from imidoyl chlorides or hydrazonoyl chlorides. The yields of amidrazones in the former method appear to depend on the substituent. For example, a moderately electron-attracting substituent in the *para* position of the hydrazine, $PhNHNH_2$, promotes the formation of the amidrazone. Thus, 4-iodophenylhydrazine (σ_p = +0.18)[38] gave the highest yields of amidrazones (58−85%), 4-(benzoyloxy)phenylhydrazine (σ_p = +0.13)[38] gave moderate yields of 30−40%, and poor yields of amidrazones were obtained with parent $PhNHNH_2$ (σ_p = 0.0). On the other hand, phenylhydrazines containing CO_2^- (σ_p = 0.0)[38] and OBn ($\sigma_p \approx$

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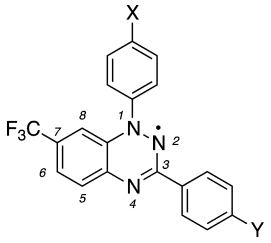
Table 1. Hyperfine Coupling Constants (G) for Selected Radicals[a]



compd	$a_{N(1)}$	$a_{N(2)}$	$a_{N(4)}$	$a_{H(5)}$	$a_{H(6)}$	$a_{H(8)}$	a_F	$a_{Ho/m}$	$a_{Ho/m}$	$a_{Ho/m}$	$a_{Ho/m}$	g
1c X = I Y = OBn	6.20	4.89	3.75	1.75	0.23	0.94	4.19	0.78	0.68	0.65	0.37	2.0040
1e X = H, Y = NO_2	6.78	3.89	4.36	1.44	0.88	0.94	4.32	0.75	0.76	0.23	0.16	2.0042
1t X = H, Y = NH_2	6.83	4.54	4.21	1.53	1.15	1.30	3.53	0.89	0.81	0.60	0.14	2.0050

[a]Assigned on the basis of B3LYP/EPR-II//B3LYP/6-31G(2d,p) results.

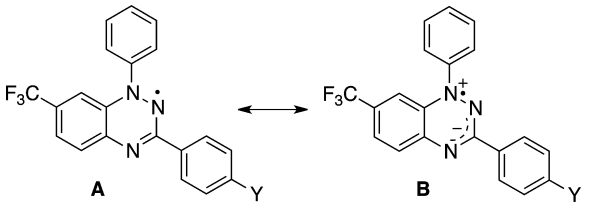


Figure 8. Two resonance forms of radical **1**.

−0.2) gave no product that could be isolated. In all cases, the preparation of amidrazones is accompanied by formation of several side products, and their purification is complicated by their tendency to oxidize in air. The formation of *N,N*-diarylhydrazines and their hydrazide intermediates (e.g., **23** and **24** in Scheme 2), in method B, is even more challenging and substituent dependent, as our results confirmed the recent findings.[18]

Using methods A and B, we prepared 11 derivatives of Blatter's radical containing five functional groups, OBn, OBz, CO_2Me, NO_2, and I, substituted on the phenyl rings. Their subsequent transformations, which involved basic hydrolysis and catalytic hydrogenation, provided access to phenol, aniline, and carboxylic acid derivatives, which were acylated and alkylated in good to excellent yields.

Investigation of iodo derivatives **1c**, **1d**, and **2d** demonstrated a broad scope of Pd-catalyzed C−C cross coupling reactions that include Suzuki, Heck, Negishi, and Sonogashira methods permitting arylation, vinylation, and ethynylation of Blatter's radical in good to excellent yields. The reported reactions complement and expand the previously reported Suzuki and Stille arylation at the C(7) position[20,23] and that of the triiodo derivative **2d**.[26]

Transformations presented here demonstrate robustness of Blatter's radical and excellent stability of the heterocycle under variety of reactions conditions that include: basic medium, catalytic hydrogenation, organometallic reagents, and prolonged heating at 100 °C. The stability of the radical to these conditions appears to be the same whether or not the shielding CF_3 group is present at the high spin position C(7). The radical is also stable in the presence of the C═C bond in citronellyl derivative **1m**.

In some reactions the benzo[1,2,4]triazinyl undergoes 1 electron reduction to the *leuco* form, which can be quickly reoxidized with air or chemically to the radical. Thus, formation of the *leuco* form is typically observed in catalytic hydrogenation (H_2/Pd and H_2/Pt), the Negishi coupling reactions, and reductive amination in the presence of $NaBH_3CN$. We also observed that the benzo[1,2,4]triazinyl is reduced with ascorbic acid in aqueous media.

The stability and scope of functional group transformations observed for Blatter's radical (**II**) is in sharp contrast to those previously found for the analogous 6-oxoverdazyl (**I**) derivatives.[11] For instance, while all attempted Pd-catalyzed C−C cross-coupling reactions involving **II** gave the expected products, none of these reactions were successful with 6-oxoverdazyl (**I**) derivatives. Also, the carboxylic acid derivative of **I** could not be isolated, while acid **5w** appears stable. Another significant difference was observed in phenol derivatives. While N(1) phenol groups of both **I** and **II** can be acylated, only N(1) phenol derivatives of the latter (compounds **1j** and **4i**) undergo efficient alkylation under basic conditions. In contrast, the N(1) phenol of 6-oxoverdazyl does not give the expected O-alkylation product and undergoes rapid decomposition in air in the presence of a base.[11] This high reactivity of the verdazyl phenolate anion was ascribed to an extensive spin delocalization onto the oxygen atom with the calculated spin density of 0.21. On the other hand, oxygen atom in the phenoxide anion of **II** has a lower spin concentration (0.17) presumably due to less efficient $\pi-\pi$ overlap of the N(1) phenyl ring and the triazinyl ring due to a high dihedral angle of about 60° observed in the solid state.[22−24,39,40]

Mechanistic investigation of the benzo[1,2,4]triazine ring formation revealed a low activation energy pathway to cyclization of the protonated imino azo intermediate, such as **29**[H^+]**a** ($\Delta G^{\ddagger}_{298}$ = 16.7 kcal/mol), which is consistent with the original report of cyclization of **29a**[41] in isopropanol in the presence of HBr at ambient temperature.[14] In contrast, electrocyclization of unprotonated **29a** requires significantly higher activation energy ($\Delta G^{\ddagger}_{298}$ = 38.6 kcal/mol) in agreement with reports of such cyclizations in hot DMSO (150 °C) in the absence of acid.[15,16] Mercury oxide appears to promote cyclization of **29a** in warm ethanol,[15] presumably by coordinating to the N(4) atom in **29** and forming a complex, such as **33**. Low-temperature formation of the benzo[1,2,4]-triazine ring was also reported in reactions of a nitrile imine **34** with iminophosphorane[42] **35a** (Z = OMe, Figure 9) or with sulfimide **35b** (Z = H).[43] Betaines **36a** and **36b**, respectively, were postulated as intermediates undergoing cyclization, although our brief investigation failed to locate the structure **36b** as a minimum on the potential energy surface. Alternatively, the betaines may undergo fragmentation with loss of neutral Ph_3P or Me_2S molecule leading to azoimine **29**,

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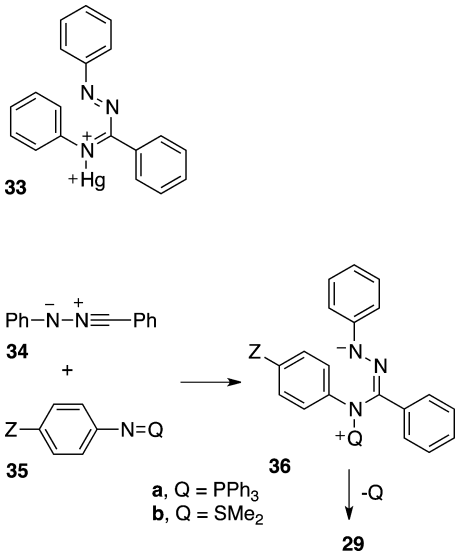
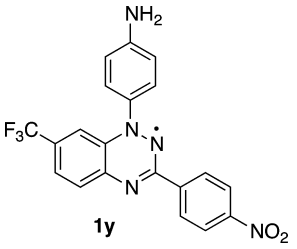


Figure 9. Proposed alternative mechanism for the formation of **29** from **36**.

which upon proton transfer from $R_3N{\cdot}HCl$, present in the reaction medium, electrocyclizes to benzo[1,2,4]triazine **32** as shown in Figure 2.

Thus, it appears that protonation of the N(4) atom or coordination with a Lewis acid dramatically accelerates cyclization of the azo imines by lowering the activation energy by about 20 kcal/mol, and such a process occurs at low temperatures. This finding is consistent with recently described examples of Lewis acid catalyzed 6-π electrocyclization of substituted 1,3,5-hexatriene, although coordination of the adjacent carbonyl group lowered the activation energy for cyclization only by about 2 kcal/mol.[44]

Overall, transformations presented here permit incorporation of Blatter's radical into complex molecular architectures using several types of functional groups. For instance, an efficient formation of proline amide derivative **1u** suggests the possibility of incorporation of **II** into biomolecules. Substitution of Blatter's radical **II** also allows for more extensive spin delocalization by placing π-conjugated groups in the C(7) position of the heterocyclic ring and *para* position of the phenyl ring at the N(1) position. Indeed, DFT modeling demonstrates significant spin delocalization in the tolane (**1r**) and acrylic ester (**27**) derivatives (Figure 10). Experimental and theoretical results indicate that spin density delocalization onto N(1) position and its substituent can be enhanced by using electron-attracting substituents at the C(3) position and electron-releasing substituents at the N(1) position. For instance, substitution of an amino group into nitro derivative **1e** increases the a_{N1} hfcc value by 0.21 G in **1y** according to DFT calculations. Spin delocalization from C(5) and C(8) is hampered by steric congestion at these positions and poor orbital overlap between the aromatic and ring and the heterocycle.



SUMMARY

Benzo[1,2,4]triazinyl is an exceptionally robust radical stable under a number of typical reaction conditions that include ester hydrolysis, *O*- and *N*-alkylation, *O*- and *N*-acylation, catalytic reduction, and Pd-catalyzed C−C cross-coupling reactions. In some reactions, the radical is reduced to the *leuco* form, which can be easily oxidized to the radical. These reactions permit incorporation of Blatter's radical into complex molecular architectures and expansion of the spin delocalization by placing π substituents at high spin density positions through Heck, Sonogashira, or Suzuki reactions of appropriate iodo derivatives.

Mechanistic analysis indicates that the formation of the benzo[1,2,4]triazine ring of the Blatter's radical proceeds through a 6π electrocyclization process of a protonated (or Lewis acid coordinated) azo imine with the activation energy of $\Delta G^{\ddagger}_{298}$ = 16.7 kcal/mol.

COMPUTATIONAL DETAILS

Quantum-mechanical calculations were carried out at the B3LYP/6-31G(2d,p) level of theory using the Gaussian 09 suite of programs.[45] Geometry optimizations were undertaken using tight convergence limits and without symmetry constraints. No conformational search was attempted. Electronic excitation energies for **1r** and **4x** in CH_2Cl_2 dielectric medium were obtained at the UB3LYP/6-31G(2d,p) level using the time-dependent DFT method[46] and PCM solvation model[32] supplied in the Gaussian package.

EXPERIMENTAL SECTION

Reagents and solvents were obtained commercially. Reactions were carried out under argon, and subsequent manipulations were conducted in air. NMR spectra were obtained at 400 MHz (^{1}H) and 100 MHz (^{13}C) in $CDCl_3$ or DMSO-d_6 and referenced to the solvent, unless otherwise specified. UV−vis spectra were recorded in

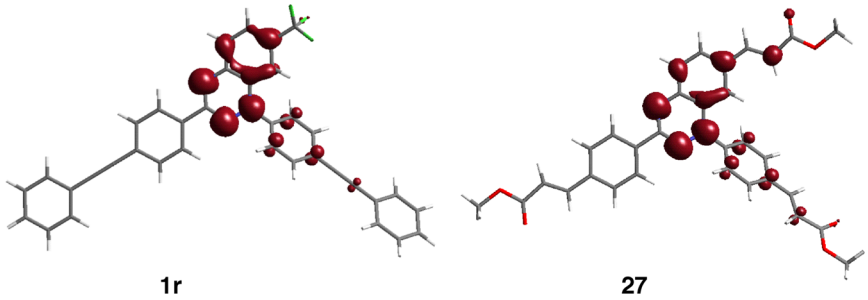


Figure 10. Total spin density map for **1r** and **27** (B3LYP/6-31G(2d,p)).

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spectroscopic grade CH_2Cl_2 at concentrations of (1−10) × 10^{-5} M. Extinction coefficient were obtained by fitting the maximum absorbance at about 350 nm against concentration in agreement with Beer's law.

X-band EPR spectra were taken using modulation amplitude 0.10 G and spectral width of 100 G. Solutions in distilled benzene were degassed by three freeze/pump/thaw cycles. The *g* value for radicals was obtained from experimental parameters using WinEPR Sinfonia 1.26 program. Simulation of the EPR spectra was done with PEST program (EPR-winSim.2002 version 0.98 for Windows using results of B3LYP/EPR-II/B3LYP/6-31G(2d,p) for initial input. The resulting *hfcc* values were perturbed until the global minimum for the fit was achieved. Spectra used for simulation were generated by reflection of the left half of each spectrum.

General Procedures for Synthesis of Radicals 1, 2, and 4. Following a general procedure,[19] a solution of DBU (0.1 mmol) and amidrazone **6**, **7**, or **9** (1.0 mmol) in dry CH_2Cl_2 (2 mL) containing 10% Pd/C (1.6 mol %) was stirred overnight at rt. After evaporation of the solvent, the crude product was purified by flash chromatography (hexane/CH_2Cl_2, 1:1). Analytically pure radicals **1**, **2**, or **4**, respectively, were obtained by recrystallization from either hexane or AcOEt.

*7-(Trifluoromethyl)-1,3-bis(4-(benzoyloxy)phenyl)-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**1a**).* Radical **1a** (0.308 g, 52% yield) was obtained from 0.590 g of **6a**: R_f = 0.80 (CH_2Cl_2); mp 195−196 °C; IR (KBr) 1737 (C═O), 1266, 1200, 1062, 709 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{22}F_3N_3O_4$ 593.1557, found 593.1530. Anal. Calcd for $C_{34}H_{21}F_3N_3O_4$: C, 68.92; H, 3.57; N, 7.09. Found: C, 68.73; H, 3.69; N, 6.93.

*7-(Trifluoromethyl)-1-(4-(benzoyloxy)phenyl)-3-(4-(benzyloxy)phenyl)-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**1b**).* Radical **1b** (0.283 g, 49% yield) was obtained from 0.580 g of **6b**: R_f = 0.90 (CH_2Cl_2); mp 186−187 °C; IR (KBr) 1735 (C═O), 1319, 1264, 1203, 1064, 707 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{24}F_3N_3O_3$ 579.1764, found 579.1751. Anal. Calcd for $C_{34}H_{23}F_3N_3O_3$: C, 70.58; H, 4.01; N, 7.26. Found: C, 70.55; H, 3.95; N, 7.11.

*7-(Trifluoromethyl)-3-(4-(benzyloxy)phenyl)-1-(4-iodophenyl)-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**1c**).* Radical **1c** (0.583 g, 89% yield) was obtained from 0.519 g of **6c**: R_f = 0.95 (CH_2Cl_2); mp 209−210 °C; IR (KBr) 1604, 1481, 1402, 1362, 1319, 1262, 1169, 1106, 823 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M]^+$ calcd for $C_{27}H_{18}F_3IN_3O$ 584.0441, found 584.0440. Anal. Calcd for $C_{27}H_{18}F_3IN_3O$: C, 55.50; H, 3.10; N, 7.19. Found: C, 54.92; H, 2.97; N, 6.94.

*7-(Trifluoromethyl)-1,3-bis(4-iodophenyl)-1,4-dihydrobenzo-[1,2,4]triazin-4-yl (**1d**).* Radical **1d** (1.121 g, 74% yield) was obtained from 1.502 g of **6d**: R_f = 0.96 (CH_2Cl_2); mp 247−248 °C dec (DSC); IR (KBr) 1582, 1484, 1319, 1261, 1111, 1066, 823 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{12}F_3I_2N_3$ 604.9067, found 604.9104. Anal. Calcd for $C_{20}H_{11}F_3I_2N_3$: C, 39.76; H, 1.84; N, 6.96. Found: C, 39.55; H, 1.69; N, 6.84.

*7-(Trifluoromethyl)-3-(4-nitrophenyl)-1-phenyl-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**1e**).* Radical **1e** (0.732 g, 74% yield) was obtained from 1.003 g of **6e**: R_f = 0.85 (CH_2Cl_2); mp 109−111 °C; IR (KBr) 1534, 1354, 1311, 1264, 1126, 700 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{13}F_3N_4O_2$ 398.0985, found 398.0996.

*7-Iodo-1,3-bis(4-(benzoyloxy)phenyl)-1,4-dihydrobenzo[1,2,4]-triazin-4-yl (**2a**).* Radical **2a** (0.637 g, 32% yield) was obtained from 2.013 g of **7a**: R_f = 0.73 (CH_2Cl_2); mp 185−187 °C; IR (KBr) 1739 (C═O), 1502, 1395, 1264, 1204, 1058, 704 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M]^+$ calcd for $C_{33}H_{21}IN_3O_4$ 650.0571, found 650.0577. Anal. Calcd for $C_{33}H_{21}IN_3O_4$: C, 60.94; H, 3.25; N, 6.46. Found: C, 61.00; H, 3.53; N, 6.43.

*7-Iodo-1,3-bis(4-iodophenyl)-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**2d**).* Radical **2d** (0.825 g, 55% yield) was obtained from 1.514 g of **7d**: R_f = 0.93 (CH_2Cl_2); mp 175−178 °C; IR (KBr) 1473, 1394 cm^{-1}. Anal. Calcd for $C_{19}H_{11}I_3N_3$: C, 34.47; H, 1.67; N, 6.35. Found: C, 34.63; H, 1.63; N, 6.27.

*1,3-Bis(4-(benzoyloxy)phenyl)-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**4a**).* Radical **4a** (0.486 g, 34% yield) was obtained from 1.211 g of **9a**: R_f = 0.59 (CH_2Cl_2); mp 171−173 °C; IR (KBr) 1733 (C═O), 1501, 1398, 1266, 1207, 1061, 710 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{33}H_{23}N_3O_4$ 525.1683, found 525.1684. Anal. Calcd for $C_{33}H_{22}N_3O_4$: C, 75.56; H, 4.23; N, 8.01. Found: C, 75.54; H, 4.19; N, 7.98.

*1-(4-(Benzoyloxy)phenyl)-3-(4-(benzyloxy)phenyl)-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**4b**).* Radical **4b** (0.504 g, 36% yield) was obtained from 1.405 g of **9b**: R_f = 0.76 (CH_2Cl_2); mp 118−120 °C; IR (KBr) 1736 (C═O), 1605, 1503, 1395, 1250, 1200, 707 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M]^+$ calcd for $C_{33}H_{24}N_3O_3$ 510.1812, found 510.1833. Anal. Calcd for $C_{33}H_{24}N_3O_3$: C, 77.63; H, 4.74; N, 8.23. Found: C, 77.39; H, 4.99; N, 7.93.

6-(Trifluoromethyl)-1-(4-iodophenyl)-3-(4-(methoxycarbonyl)phenyl)-1,4-dihydrobenzo[1,2,4]triazin-4-yl (5h). Tin powder (153 mg, 1.28 mmol) was added to a vigorously stirred solution of hydrazide **24h** (188 mg, 0.321 mmol) in glacial acetic acid (5 mL). The resulting mixture was stirred at rt for 30 min and then heated at ca. 118 °C for 10 min. After cooling, the mixture was diluted with CH_2Cl_2, and the organic phase was washed with water (2 × 20 mL), saturated $NaHCO_3$ (20 mL), and water (20 mL) and dried (Na_2SO_4). After evaporation of the solvent, the crude product was purified by flash chromatography (CH_2Cl_2; R_f = 0.87) giving 85 mg (49% yield) of *leuco* **25h** as a red solid: mp 180−182 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.87 (s, 3H), 6.52 (d, *J* = 8.4 Hz, 1H), 6.97 (bs, 1H), 7.02 (d, *J* = 9.0 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 8.05 (d, *J* = 8.5 Hz, 2H), 9.17 (s, 1H); IR (KBr) 3376 (NH), 1708 (C═O), 1487, 1335, 1288, 1114 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M]^+$ calcd for $C_{22}H_{15}F_3IN_3O_2$ 537.0156, found 537.0150.

A solution of $NaIO_4$ (0.123 mmol, 26 mg) in H_2O (0.5 mL) was added to a solution of crude *leuco* **25h** (30 mg, 0.056 mmol) in CH_2Cl_2/MeOH (1:1, 1 mL). The resulting mixture was stirred for 30 min at rt, diluted with CH_2Cl_2, and washed with H_2O, and the organic solution was dried (Na_2SO_4). Evaporation of the solvent gave 29 mg (99% yield) of radical **5h** as a black green solid, which was purified further by recrystallization from hexane: mp 220−222 °C; IR (KBr) 1718 (C═O), 1277, 1116, 712 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M]^+$ calcd for $C_{22}H_{14}F_3IN_3O_2$ 536.0077, found 536.0108. Anal. Calcd for $C_{22}H_{14}F_3IN_3O_2$: C, 49.27; H, 2.63; N, 7.84. Found: C, 49.34; H, 2.70; N, 7.79.

1,4-Dihydrobenzo[1,2,4]triazinyls through Functional Group Transformations. *General Procedure for Deprotection of the Phenolic Functionality. Method A. Hydrolysis of Benzoate Esters.* A solution of benzoate ester (0.5 mmol) in CH_2Cl_2/MeOH (3:1, 4 mL) was treated with 0.1 M solution of KOH in MeOH (1 equiv). The resulting mixture was stirred at rt for 0.5 h until TLC (CH_2Cl_2) showed the absence of starting material. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (3 × 5 mL). The organic layer was dried (Na_2SO_4), and solvents were evaporated. The crude product was purified by flash chromatography (CH_2Cl_2).

Method B. Hydrogenation of Benzyl Ethers. A solution of benzyloxy derivative (0.15 mmol) in THF/EtOH (1:1, 5 mL) containing 10% Pd/C (5 mol %) was stirred at rt under positive pressure of H_2 until the starting material was completely consumed (by TLC analysis). The reaction mixture was filtered through Celite, solvents were evaporated, and crude product was purified by flash chromatography.

*7-(Trifluoromethyl)-1,3-bis(4-(adamantane-1-carbonyloxy)-phenyl)-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**1l**, through Esterification).* Bisphenol **1i** (0.096 g, 97% yield) was obtained from 0.153 g of **1a** according to method A (R_f = 0.05 (CH_2Cl_2): mp 222−224 °C; IR (KBr) 3415 (OH), 1610, 1507, 1338, 1270, 1169, 1134, 832 cm^{-1}; HRMS (ESI-TOF) *m*/*z* $[M]^+$ calcd for $C_{20}H_{13}F_3N_3O_2$ 384.0954, found 384.0960). A solution of radical **1i** (70 mg, 0.18 mmol), adamantane-1-carbonyl chloride (72 mg, 0.36 mmol), and Et_3N (0.05 mL, 0.36 mmol) in dry CH_2Cl_2 (5 mL) was stirred at rt until all starting bisphenol **1i** was consumed (TLC, CH_2Cl_2, ∼1 h). The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with H_2O (2 × 5 mL). The organic layer was dried (Na_2SO_4), and solvents were evaporated. The resulting crude product was purified by recrystallization (MeCN) giving 117 mg (91% yield) of diester **1l** as

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a black brown solid: mp >260 °C; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{42}H_{42}F_3N_3O_4$ 709.3122, found 709.3121. Anal. Calcd for $C_{42}H_{41}F_3N_3O_4$: C, 71.17; H, 5.83; N, 5.93. Anal. Calcd for $C_{42}H_{41}F_3N_3O_4 \cdot H_2O$: C, 69.41; H, 5.96; N, 5.78. Found: C, 69.49; H, 5.81; N, 5.73.

*7-(Trifluoromethyl)-3-(4-benzyloxyphenyl)-1-((S)-4-citronellyloxyphenyl)-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**1m**, through O-Alkylation).* Phenol **1j** (0.085 g, 90% yield) was obtained from 0.117 g of benzoate **1b** according to method A in 90% yield (R_f = 0.23 (CH_2Cl_2): mp 110−112 °C; IR (KBr) 3343 (OH), 1605, 1506, 1324, 1256, 1119, 834 cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ calcd for $C_{27}H_{19}F_3N_3O_2$ 474.1424, found 474.1433.) A solution of phenol **1j** (45 mg, 0.095 mmol) and (*S*)-(+)-citronellyl bromide (22 mg, 0.02 mL, 0.1 mmol) in dry MeCN (3 mL) containing K_2CO_3 (14 mg, 0.1 mmol) was refluxed for 4 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with AcOEt. The extract was washed with water and dried (Na_2SO_4). Solvents were evaporated, and the residue was purified by flash chromatography (SiO_2, hexanes/CH_2Cl_2, 1:1; R_f = 0.65, CH_2Cl_2) giving 32 mg (55% yield) of **1m** as a dark brown solid: mp 101−104 °C; IR (KBr) 2926, 1605, 1508, 1324, 1252, 1119, 837 cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ calcd for $C_{37}H_{37}F_3N_3O_2$ 612.2832, found 612.2815.

*7-(Trifluoromethyl)-3-(4-(benzyloxy)phenyl)-1-[4-(4-methoxyphenyl)phenyl]-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**1o**, through Suzuki Cross-Coupling Reaction). Method A.* A solution of radical **1c** (200 mg, 0.342 mmol) in degassed toluene (6 mL) and water (0.5 mL) were added via a syringe to a mixture of $Pd(OAc)_2$ (4 mg, 5 mol %), *p*-methoxyphenylboronic acid (157 mg, 1.03 mmol), and K_2CO_3 (142 mg, 1.03 mmol). The resulting mixture was refluxed for 12 h, cooled, and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes/CH_2Cl_2, 2:1, R_f = 0.90; CH_2Cl_2) giving 160 mg (83% yield) of **1o** as a dark brown solid: mp 154−155 °C; IR (KBr) 1607, 1495, 1397, 1251, 1125 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{34}H_{26}F_3N_3O_2$ 565.1972, found 565.1983. Anal. Calcd for $C_{34}H_{25}F_3N_3O_2$: C, 72.33; H, 4.46; N, 7.44. Found: C, 72.03; H, 4.43; N, 7.31.

Method B. A solution of radical **1c** (58 mg, 0.1 mmol) in degassed toluene (3 mL) and water (0.75 mL) was added via syringe to a mixture of $PdCl_2(PPh_3)_2$ (4 mg, 5 mol %), potassium *p*-methoxyphenyltrifluoroborate (22 mg, 0.105 mmol), and Cs_2CO_3 (98 mg, 0.3 mmol). The resulting mixture was refluxed for 24 h. After cooling, the solution was filtered through Celite, diluted with H_2O, and extracted into AcOEt. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, hexanes/CH_2Cl_2, 2:1) giving 28 mg (51% yield) of **1o** as the second fraction. The first fraction (5 mg, 11% yield) was identified as deiodinatined product **1p**: mp 181−182 °C; IR (KBr) 1606, 1495, 1398, 1250, 1124, 826 cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ calcd for $C_{27}H_{19}F_3N_3O$ 458.1475, found 458.1461.

*7-(Trifluoromethyl)-3-(4-hydroxyphenyl)-1-[4-(4-methoxyphenyl)phenyl]-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**1q**, through Catalytic Debenzylation).* Phenol **1q** (0.063g, 90% yield) was obtained from 0.083 g of **1o** according to method B as a black solid: mp 232−235 °C; IR (KBr) 1609, 1496, 1397, 1274, 1261, 1174, 1107, 823 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{20}F_3N_3O_2$ 475.1502, found 475.1507.

*7-(Trifluoromethyl)-1,3-bis[4-(phenylethynyl)phenyl]-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**1r**, through Sonogashira Cross-Coupling Reaction).* A solution of **1d** (100 mg, 0.166 mmol) in degassed DMF (2 mL) was treated with phenylacetylene (34 mg, 0.332 mmol), $PdCl_2(PPh_3)_2$ (9 mg, 4 mol %), CuI (2.5 mg, 4 mol %), and Et_3N (0.07 mL, 0.50 mmol). The resulting mixture was stirred at rt for 24 h under an Ar atmosphere. The solution was filtered through Celite, diluted with H_2O, and extracted into AcOEt. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2, R_f = 0.99) giving 73 mg (80% yield) of **1r** as a black brown solid: mp 220−222 °C dec (DSC); IR (KBr) 2209 (C≡C), 1605, 1510, 1393, 1317, 1262, 1116, 1064, 846, 756, 690 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{36}H_{22}F_3N_3$ 553.1760, found 553.1779. Anal. Calcd for $C_{36}H_{21}F_3N_3$: C, 78.25; H, 3.83; N, 7.60. Anal. Calcd for $C_{36}H_{21}F_3N_3 \cdot H_2O$: C, 75.78; H, 4.06; N, 7.36. Found: C, 76.01; H, 4.08; N, 7.07.

*7-(Trifluoromethyl)-1,3-bis[4-(4-methoxyphenyl)phenyl]-1,4-dihydro-benzo[1,2,4]triazin-4-yl (**1s**, through Negishi Cross-Coupling Reaction).* A suspension of dry $ZnCl_2$ (412 mg, 3.03 mmol) in dry THF (3 mL) at 0 °C was treated with a solution of (4-methoxyphenyl)magnesium bromide (533 mg, 2.53 mmol) in THF (4 mL). The reaction mixture was stirred at 0 °C for 15 min and then at rt for 20 min. PEPPSI-Ipr (9 mg, 10 mol %) was added, and the reaction mixture was stirred for 10 min, followed by addition of radical **1d** (76 mg, 0.126 mmol). The reaction mixture was then stirred for 4 h and quenched with NH_4Cl, and products were extracted into AcOEt. The organic extracts were washed with H_2O and brine and dried (Na_2SO_4). The solvent was evaporated, and the crude product was purified on silica gel (CH_2Cl_2, R_f = 0.95) giving 33 mg (46% yield) of radical **1s** as a dark brown solid: mp 159−161 °C; IR (KBr) 2924, 1606, 1496, 1398, 1315, 1248, 1108, 826 cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ calcd for $C_{34}H_{25}F_3N_3O_2$ 564.1893, found 564.1906. Anal. Calcd for $C_{34}H_{25}F_3N_3O_2$: C, 72.33; H, 4.46, N, 7.44. Found: C, 71.79; H. 4.81; N, 7.04.

*7-(Trifluoromethyl)-3-(4-aminophenyl)-1-phenyl-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**1t**, through Reduction of the NO_2 Group).* A solution of radical **1e** (160 mg, 0.4 mmol) in THF/EtOH (1:1, 10 mL) containing 10% Pd/C (42 mg, 10 mol %) was hydrogenated at 50 psi until starting material was no longer detectable (TLC). The green reaction mixture was stirred in air (ca. 30 min), and the resulting dark brown solution was passed through Celite. Solvents were evaporated, and the resulting crude product was purified by flash column chromatography (SiO_2, CH_2Cl_2, R_f = 0.30) giving 140 mg (98% yield) of **1t** as a dark brown solid: mp 178−180 °C; IR (KBr) 3470 and 3323 (NH), 1618, 1397, 1316, 1113 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{15}F_3N_4$ 368.1249, found 368.1284. Anal. Calcd for $C_{20}H_{14}F_3N_4$: C, 65.39; H, 3.84; N, 15.25. Found: C, 65.16; H, 3.98; N, 15.02.

*7-(Trifluoromethyl)-3-(4-(N-BOC-pyrrolidine-2-carboxamido)-phenyl)-1-phenyl-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**1u**, through Amidation Reaction).* DCC (96 mg, 0.465 mmol) and catalytic amounts of DMAP were added to a solution of *N*-BOC-L-proline (73 mg, 0.342 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was stirred at rt for 30 min. Amine **1t** (114 mg, 0.311 mmol) in CH_2Cl_2 (2 mL) was added, and the mixture was stirred for 24 h. The reaction mixture was diluted with CH_2Cl_2, washed with H_2O, and dried (Na_2SO_4). Solvents were evaporated, and the resulting crude product was purified by flash column chromatography (SiO_2, hexane/AcOEt, 2:1) giving 163 mg (93% yield) of radical **1u** as a dark brown solid: mp 177−179 °C; IR (KBr) 3327 (NH), 1701 (C═O), 1604, 1546, 1394, 1317, 1162, 1121 cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ calcd for $C_{30}H_{29}F_3N_5O_3$ 564.2217, found 564.2234. Anal. Calcd for $C_{30}H_{29}F_3N_5O_3$: C, 63.82; H, 5.18; N, 12.40. Calcd for $C_{30}H_{29}F_3N_5O_3 \cdot {}^1/_2H_2O$: C, 62.32; H, 5.27; N, 12.21. Found: C, 62.87; H, 5.37; N, 11.84.

*7-(Trifluoromethyl)-3-(4-(hexylamino)phenyl)-1-phenyl-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**1v**, through Reductive Amination).* Freshly distilled hexanal (58 mg, 0.583 mmol) and amine **1t** (214 mg, 0.53 mmol) in a solution of MeOH (5 mL) was stirred at rt for 15 min. The reaction mixture was then treated with a solution of $NaBH_3CN$ (55 mg, 0.874 mmol) in MeOH (0.5 mL), and stirring was continued for 24 h. Saturated aqueous $NaHCO_3$ was added, the organic products were extracted with AcOEt, and the extracts were dried (Na_2SO_4), while kept open to the air. Solvents were removed, and the residue was separated by flash column chromatography (SiO_2, CH_2Cl_2, R_f = 0.90) giving 62 mg (24% yield) of radical **1v** as the first fraction: mp 91−92 °C; IR (KBr) 3408 (NH), 2924, 1609, 1397, 1316, 1113 cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ calcd for $C_{26}H_{26}F_3N_4$ 451.2104, found 451.2108. Anal. Calcd for $C_{26}H_{26}F_3N_4$: C, 69.16; H, 5.80; N, 12.41. Found: C, 69.31; H, 5.87; N, 12.23.

The unreacted amine **1t** was isolated as the second fraction (125 mg).

*1,3-Bis(4-heptyloxyphenyl)-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**4n**, O-Alkylation).* The phenol functionality in **4b** (0.206 g) was

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deprotected according to method B giving 0.107 g (63% yield) of **4k**: mp 188−190 °C; IR (KBr) 3423 (OH), 1735 (C═O), 1608, 1492, 1396, 1262, 1204, 1172, 1062, 706 cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ calcd for $C_{26}H_{18}N_3O_3$ 420.1343, found 420.1364. Subsequent hydrolysis of the benzoate group according to method A gave dihydroxy derivative **4i** in 87% yield: mp 176−179 °C; HRMS (ESI-TOF) m/z $[M]^+$ calcd for $C_{19}H_{14}N_3O_2$ 316.1081, found 316.1091.

A suspension of phenol **4i** (93 mg, 0.294 mmol), K_2CO_3 (89 mg, 0.647 mmol), and *n*-iodoheptane (0.1 mL, 0.647 mmol) in dry MeCN (6 mL) was refluxed for 6 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with AcOEt. The organic extract was washed with H_2O and dried (Na_2SO_4). Solvents were removed, and the resulting crude product was purified by flash chromatography (SiO_2, hexanes/CH_2Cl_2, 1:1) giving 85 mg (56% yield) of **4n** as a brown solid: mp 65−66 °C. Anal. Calcd for $C_{33}H_{42}N_3O_2$: C, 77.31; H, 8.26; N, 8.20. Found: C, 77.39; H, 8.27; N, 8.07.

*6-(Trifluoromethyl)-1-(4-iodophenyl)-3-(4-(hydroxycarbonyl)-phenyl)-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**5w**, through Methyl Ester Hydrolysis).* A solution of radical **5h** (57 mg, 0.106 mmol) in THF/H_2O (9:1, 1.1 mL) was treated with 0.1 N KOH in EtOH (1.59 mL, 0.159 mmol). The reaction mixture was stirred for 48 h at 60 °C and poured into 10% HCl (2 mL). The resulting mixture was extracted with AcOEt, and the organic layer was washed with H_2O and dried (Na_2SO_4). The solvents were removed, and the resulting crude product was purified by flash chromatography (SiO_2, AcOEt) giving 40 mg (73% yield) of **5w** as a brown solid: mp >260 °C; IR (KBr) 1687 (C═O), 1392, 1338, 1270, 1127, 712 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{13}F_3IN_3O_2$ 523.0004, found 522.9985. Anal. Calcd for $C_{21}H_{12}F_3IN_3O_2$: C, 48.30; H, 2.32; N, 8.05. Found: C, 48.13; H, 2.40; N, 7.93.

*7-(2-(Methoxycarbonyl)ethenyl)-1,3-bis(4-(2-(methoxycarbonyl)-ethenyl)phenyl)-1,4-dihydrobenzo[1,2,4]triazin-4-yl (**27**, through Heck Coupling).* Methyl acrylate (77 mg, 0.9 mmol) was added to mixture of triiodo derivative **2d** (100 mg, 0.15 mmol), Et_3N (91 mg, 0.9 mmol), $Pd(OAc)_2$ (5 mg, 0.0225 mmol), and tris(*o*-methoxyphenyl)phosphine (10 mol %, 16 mg, 0.045 mmol) in DMF (5 mL). The resulting mixture was heated for 5 h at 100 °C and cooled, H_2O was added, and the products were extracted into AcOEt. The solvents were removed, and the crude product was purified by flash chromatography (SiO_2, AcOEt/hexane, 3:1; R_f = 0.68, CH_2Cl_2) giving 55 mg (68% yield) of radical **27** as a brown solid: mp 163−165 °C; IR (KBr) 3061, 3033, 1717 (C═O), 1633, 1598, 1507, 1324, 1278, 1205, 1171 cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ calcd for $C_{31}H_{26}N_3O_6$ 536.1816, found 536.1832. Anal. Calcd for $C_{31}H_{26}N_3O_6$: C, 69.39; H, 4.88; N, 7.83. Calcd for $C_{31}H_{26}N_3O_6 \cdot 1/2H_2O$: C, 68.25; H, 4.99; N, 7.70. Found: C, 68.66; H, 5.37; N, 7.49.

Intermediates to 1,4-Dihydrobenzo[1,2,4]triazinyls. *General Procedures for Synthesis of Amidrazones **6**−**9**. Method A.* A solution of benzimidoyl chloride **15**, **16**, **17**, or **18** (1.0 mmol) in dry CH_2Cl_2 (3 mL) and Et_3N (1.0 mmol) was added to hydrazine **19** (1 mmol) in a solution of dry CH_2Cl_2 (3 mL). The mixture was stirred overnight at rt under Ar. A 1% solution of HCl was added, and the organic products were extracted (CH_2Cl_2). The combined extracts were dried (Na_2SO_4) and solvents evaporated. The crude products **6**, **7**, **8**, or **9**, respectively, were partially purified by flash chromatography (SiO_2, hexane/CH_2Cl_2, 3:1) and due to limited stability quickly used in subsequent reactions.

Method B. In preparation of amidrazones **6a**, **6b**, **7a**, **9a**, and **9b**, hydrazine **19a** was generated in situ from hydrochloride **19a·HCl** by using an additional equivalent of Et_3N.

*N′-(4-(Benzoyloxy)phenyl)-N-[4-(trifluoromethyl)phenyl]-4-(benzoyloxy)benzenecarbohydrazonamide (**6a**).* Amidrazone **6a** (2.34 g, 29% yield) was obtained from 5.52 g of **15a**: mp 101−103 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.81 (br s, 1H), 6.76 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 9.0 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 7.46−7.54 (m, 5H), 7.62−7.68 (m, 4H), 7.78 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 8.4 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) major signals δ 113.8, 115.3, 121.8, 122.2, 122.6, 126.7, 126.7 (q, J = 4 Hz), 127.4, 128.4, 128.5, 129.1, 129.4, 130.0, 130.1, 131.5, 133.4, 133.6, 142.3, 144.2, 151.4, 165.0, 165.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{34}H_{25}F_3N_3O_4$ 596.1792, found 596.1806.

*N′-(4-(Benzoyloxy)phenyl)-N-[4-(trifluoromethyl)phenyl]-4-benzyloxybenzenecarbohydrazonamide (**6b**).* Amidrazone **6b** (2.56 g, 43% yield) was obtained from 4.05 g of **15b**: mp 78−80 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.09 (s, 2H), 5.86 (br s, 1H), 6.75 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.15 (d, J = 9.1 Hz, 2H), 7.43−7.33 (m, 5H), 7.52−7.46 (m, 5H), 7.60−7.69 (m, 3H), 8.19 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) major signals δ 70.2, 114.0, 115.2, 115.8, 119.8, 122.4, 126.9 (q, J = 4 Hz), 127.6, 128.1, 128.2, 128.7, 128.8, 128.9, 129.2, 129.8, 130.3, 133.6, 136.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{34}H_{27}F_3N_3O_3$ 582.1999, found 582.1991.

*N′-(4-Iodophenyl)-N-[4-(trifluoromethyl)phenyl]-4-benzyloxybenzenecarbohydrazonamide (**6c**).* Amidrazone **6c** (1.81 g, 60% yield) was obtained from 2.12 g of **15c**: mp 57−59 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.09 (s, 2H), 5.71 (br s, 1H), 6.73 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 7.33−7.50 (m, 8H), 7.52 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) major signals δ 70.0, 81.6, 115.0, 115.4, 115.5, 126.8 (q, J = 4 Hz), 127.4, 127.9, 128.1, 128.6, 136.4, 137.8, 144.1, 144.4, 159.9.

*N′-(4-Iodophenyl)-N-[4-(trifluoromethyl)phenyl]-4-iodobenzenecarbohydrazonamide (**6d**).* Amidrazone **6d** (3.78 g, 85% yield) was obtained from 3.04 g of **15d**: mp 182−183 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.63 (br s, 1H), 6.72 (d, J = 8.3 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 7.66 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 82.3, 95.2, 115.0, 115.4, 127.0 (q, J = 4 Hz), 127.7, 133.5, 135.0, 137.8, 137.9, 143.8, 144.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{15}F_3I_2N_3$ 607.9302, found 607.9280. Anal. Calcd for $C_{20}H_{14}F_3I_2N_3$: C, 39.56; H, 2.32; N, 6.92. Found: C, 39.50; H, 2.22; N, 6.86.

*N′-Phenyl-N-[4-(trifluoromethyl)phenyl]-4-nitrobenzenecarbohydrazonamide (**6e**).* Amidrazone **6e** (1.16 g, 19% yield) was obtained from 5.02 g of **15e**: mp 163−165 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.72 (br s, 1H), 6.74 (d, J = 8.2 Hz, 2H), 6.97 (t, J = 7.2 Hz, 1H), 7.17 (d, J = 7.8 Hz, 2H), 7.32 (t, J = 7.7 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.85 (d, J = 8.7 Hz, 2H), 8.10 (br s, 1H), 8.19 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 113.8, 114.8, 121.8, 123.1 (q, J = 33 Hz), 124.1, 126.3, 127.3 (q, J = 4 Hz), 127.9 (q, J = 271 Hz), 129.6, 132.2, 140.8, 143.5, 144.5, 147.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{16}F_3N_4O_2$ 401.1220, found 401.1218.

*N′-(4-(Benzoyloxy)phenyl)-N-(4-iodophenyl)-4-(benzoyloxy)-benzenecarbohydrazonamide (**7a**).* Amidrazone **7a** (2.47 g, 58% yield) was obtained from 3.11 g of **16a**: mp 87−90 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.71 (br s, 1H), 6.49 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 9.1 Hz, 2H), 7.15 (d, J = 9.1 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 7.49−7.54 (m, 6H), 7.61−7.67 (m, 3H), 7.75 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 8.5 Hz, 4H); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{33}H_{25}IN_3O_4$ 654.0884, found 654.0870.

*N,N′-Bis(4-iodophenyl)-4-iodobenzenecarbohydrazonamide (**7d**).* Amidrazone **7d** (3.71 g, 58% yield) was obtained from 4.52 g of **16d**; mp 189−190 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.49 (br s, 1H), 6.46 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 7.58 (br s, 1H), 7.69 (d, J = 8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 82.0, 83.0, 95.1, 115.4, 117.9, 127.9, 133.7, 135.9, 137.7, 137.9, 138.3, 140.8, 144.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{15}I_3N_3$ 665.8395, found 665.8400. Anal. Calcd for $C_{19}H_{14}I_3N_3$, C, 34.31; H, 2.21; N, 6.32. Found: C, 34.53; H, 2.14; N, 6.27.

*N′-(4-Fluorophenyl)-N-(4-iodophenyl)-4-iodobenzenecarbohydrazonamide (**8d**).* Amidrazone **8d** (1.49 g, 32% yield) was obtained from 3.03 g of **17d**: mp 199−201 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.52 (br s, 1H), 6.62−6.65 (m, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.93 (t, J = 8.6 Hz, 2H), 7.40 (d, J = 8.6 Hz, 2H), 7.47 (s, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.6 Hz, 2H). HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{19}H_{15}FI_2N_3$ 557.9334, found 557.9345.

*N′-(4-(Benzoyloxy)phenyl)-N-phenyl-4-(benzoyloxy)benzenecarbohydrazonamide (**9a**).* Amidrazone **9a** (1.45 g, 37% yield) was obtained from 2.52 g of **18a**: mp 87−90 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.70 (br s, 1H), 6.73 (d, J = 7.8 Hz, 2H), 6.94 (t, J = 7.4 Hz,

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1H), 7.11 (d, J = 9.0 Hz, 2H), 7.15 (d, J = 9.1 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 7.26 (t, J = 8.0 Hz, 1H), 7.49−7.53 (m, 4H), 7.61−7.66 (m, 3H), 7.79 (d, J = 8.7 Hz, 2H), 8.20 (d, J = 8.5 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 113.8, 116.0, 121.0, 121.8, 122.2, 127.6, 128.4, 128.5, 129.3, 129.5, 129.7, 130.06, 130.14, 132.5, 133.4, 133.6, 141.1, 142.8, 144.2, 151.4, 164.9, 165.6; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{33}H_{26}N_3O_4$ 528.1918, found 528.1930.

*N′-(4-(Benzoyloxy)phenyl)-N-phenyl-4-(benzyloxy)benzenecarbohydrazonamide (**9b**).* Amidrazone **9b** (1.66 g, 26% yield) was obtained from 4.03 g of **18b**; mp 179−182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.08 (s, 2H), 5.71 (br s, 1H), 6.72 (d, J = 7.7 Hz, 2H), 6.92 (t, J = 8.2 Hz, 1H), 6.95 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 9.0 Hz, 2H), 7.13 (d, J = 9.2 Hz, 2H), 7.22−7.26 (m, 1H), 7.33−7.52 (m, 8H), 7.61−7.63 (m, 1H), 7.65 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 70.0, 113.7, 114.8, 116.4, 120.9, 122.1, 127.4, 128.0, 128.1, 128.4, 128.6, 129.4, 129.8, 130.1, 133.3, 136.6, 138.4, 141.2, 143.2, 143.9, 159.6, 165.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{33}H_{28}N_3O_3$ 514.2125, found 514.2151.

*General Procedure for Synthesis of Amides **11**−**14**.* A solution of 4-trifluoromethylaniline, 4-iodoaniline, 4-fluoroaniline or aniline (10 mmol) in CH_2Cl_2 (20 mL), and dry Et_3N (10 mmol) was treated with acid chloride (prepared from appropriate acid **10** and oxalyl chloride, 10 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 2 h at rt, the resulting white precipitate was filtered, and recrystallized from AcOEt or EtOH.

*4-Benzoyloxy-N-(4-(trifluoromethyl)phenyl)benzamide (**11a**).* Amide **11a** (8.91 g, 93% yield) was obtained from 5.06 g of chloride derived from acid **10a**: mp 285−286 °C DSC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.49 (d, J = 8.6 Hz, 2H), 7.63 (t, J = 7.7 Hz, 2H), 7.72−7.77 (m, 3H), 8.02 (d, J = 8.6 Hz, 2H), 8.08 (d, J = 8.6 Hz, 2H), 8.16 (d, J = 7.2 Hz, 2H), 10.64 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 120.5, 122.5, 124.0 (q, J = 32 Hz), 124.9 (q, J = 272 Hz), 126.3 (q, J = 4 Hz), 129.0, 129.4, 129.9, 130.3, 132.6, 134.6, 143.2, 153.7, 164.7, 165.7; IR (KBr) 3350 (NH), 1734 (C═O), 1654 (C═O), 1116, 705 cm^{-1}. Anal. Calcd for $C_{21}H_{14}F_3NO_3$: C, 65.46; H, 3.66; N, 3.63. Found: C, 65.55; H, 3.76; N, 3.61.

*4-Benzyloxy-N-(4-(trifluoromethyl)phenyl)benzamide (**11b**).* Amide **11b** (7.04 g, 98% yield) was obtained from 4.75 g of chloride derived from acid **10b**: mp 219−220 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.20 (s, 2H), 7.14 (d, J = 8.9 Hz, 2H,), 7.33 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.3 Hz, 2H), 7.46 (d, J = 7.1 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 7.97 (d, J = 8.6 Hz, 2H), 8.01 (d, J = 8.6 Hz, 2H), 10.45 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 69.8, 114.9, 120.4, 123.6 (q, J = 32 Hz), 124.8 (q, J = 274 Hz), 126.2 (q, J = 4 Hz), 127.0, 128.2, 128.4, 128.9, 130.2, 137.0, 143.4, 161.6, 165.7; IR (KBr) 3226 (NH), 1645 (C═O), 1605, 1246, 1173, 754 cm^{-1}. Anal. Calcd for $C_{21}H_{16}F_3NO_2$: C, 67.92; H, 4.34; N, 3.77. Found: C, 67.69; H, 4.20; N, 3.75.

*4-Iodo-N-(4-(trifluoromethyl)phenyl)benzamide (**11d**).* Amide **11d** (6.96 g, 95% yield) was obtained from 5.03 g of chloride derived from acid **10d**: mp 228−230 °C DSC; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.72 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.3 Hz, 2H), 7.99 (d, J = 8.5 Hz, 2H), 10.61 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 100.1, 120.6, 124.1 (q, J = 32 Hz), 124.7 (q, J = 271 Hz), 126.2 (q, J = 4 Hz), 130.1, 134.2, 137.7, 143.0, 165.7; IR (KBr) 3330 (NH), 1657 (C═O), 1529, 1331, 1127, 833 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{10}F_3INO$ 391.9754, found 391.9754. Anal. Calcd for $C_{14}H_9F_3INO$: C, 42.99; H, 2.32; N, 3.58. Found: C, 42.89; H, 2.34; N 3.53.

*4-Nitro-N-(4-(trifluoromethyl)phenyl)benzamide (**11e**).*[47] Amide **11e** (5.07 g, 99% yield) was obtained from 3.12 g of chloride derived from acid **10e**: mp 213−214 °C DSC (lit.[47] mp 194−196 °C); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.73 (d, J = 8.6 Hz, 2H,), 8.00 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 8.9 Hz, 2H), 8.37 (d, J = 8.9 Hz, 2H), 10.86 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 120.5, 123.9, 124.5 (q, J = 32 Hz), 124.7 (q, J = 271 Hz), 126.3 (q, J = 4 Hz), 129.9, 140.3, 142.8, 149.7, 164.8; IR (KBr) 3414 (NH), 1680 (C═O), 1603, 1535, 1516, 1347, 1323, 1120, 1065 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{10}F_3N_2O_3$ 311.0638, found 311.0638. Anal. Calcd for $C_{14}H_9F_3N_2O_3$: C, 54.20; H, 2.92; N, 9.03. Found: C, 54.47; H, 2.88; N, 9.03.

*4-(Benzoyloxy)-N-(4-iodophenyl)benzamide (**12a**).* Amide **12a** (6.89 g, 94% yield) was obtained from 4.31 g of chloride derived from acid **10a**: mp >260 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.47 (d, J = 8.2 Hz, 2H), 7.62−7.71 (m, 6H), 7.76 (t, J = 7.0 Hz, 1H), 8.06 (d, J = 8.2 Hz, 2H), 8.16 (d, J = 7.5 Hz, 2H), 10.40 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) major signals δ 122.4, 122.9, 129.4, 129.7, 130.3, 137.7; IR (KBr) 3348 (NH), 1729 (C═O), 1649 (C═O), 1502, 1281, 815, 706 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{15}INO_3$ 444.0091, found 444.0084. Anal. Calcd for $C_{20}H_{14}INO_3$: C, 54.20; H, 3.18; N, 3.16. Found: C, 53.95; H, 3.20; N, 3.06.

*4-Iodo-N-(4-iodophenyl)benzamide (**12d**).* Amide **12d** (7.43 g, 88% yield) was obtained from 5.02 g of chloride derived from acid **10d**: mp >260 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.62 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H), 7.90 (d, J = 8.6 Hz, 2H), 10.39 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 87.9, 99.9, 122.9, 130.0, 134.4, 137.7 (2C), 139.3, 165.3; IR (KBr) 3327 (NH), 1649 (C═O), 1589, 1519, 818 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{10}I_2NO$ 449.8846, found 449.8838. Anal. Calcd for $C_{13}H_9I_2NO$: C, 34.77; H, 2.02; N, 3.12. Found: C, 34.95; H, 1.99; N, 3.14.

*4-Iodo-N-(4-fluorophenyl)benzamide (**13d**).* Amide **13d** (4.02 g, 90% yield) was obtained from 3.52 g of chloride derived from acid **10d**: mp 218−219 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.18 (t, J = 8.9 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.75 (dd, J = 9.1 Hz, J = 5.1 Hz, 2H), 7.91 (d, J = 8.4 Hz, 2H), 10.33 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 99.7, 115.6 (d, J = 22 Hz), 122.6 (d, J = 8 Hz), 130.0, 134.5, 135.7 (d, J = 3 Hz), 137.7, 158.7 (d, J = 240 Hz), 165.1; IR (KBr) 3328 (NH), 1649 (C═O), 1530, 1513, 832 cm^{-1}. Anal. Calcd for $C_{13}H_9FINO$: C, 45.77; H, 2.66; N, 4.11. Found: C, 45.87; H, 2.75; N 4.10.

*4-Benzoyloxybenzanilide (**14a**).* Amide **14a** (3.94 g, 77% yield) was obtained from 4.24 g of chloride derived from acid **10a**: mp 215−217 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.11 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.9 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H), 7.62 (t, J = 7.8 Hz, 2H), 7.74−7.78 (m, 3H), 8.05 (d, J = 8.7 Hz, 2H), 8.15 (d, J = 7.2 Hz, 2H), 10.31 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 120.8, 122.4, 124.2, 129.02, 129.04, 129.4, 129.7, 130.3, 133.1, 134.6, 139.4, 153.4, 164.8, 165.2; IR (KBr) 3352 (NH), 1733 (C═O), 1649 (C═O), 1599, 1530, 1504, 1440, 1279, 705 cm^{-1}. Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41. Calcd for $C_{20}H_{15}NO_3 \cdot {}^1/_2H_2O$: C, 73.61; H, 4.94; N, 4.29. Found: C, 73.43; H, 4.95; N, 4.21.

*4-Benzyloxybenzanilide (**14b**).* Amide **14b** (5.29 g, 86% yield) was obtained from 5.07 g of chloride derived from acid **10b**: mp 210−211 °C (DSC); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.19 (s, 2H), 7.07 (t, J = 7.4 Hz, 1H), 7.12 (d, J = 8.9 Hz, 2H), 7.30−7.35 (m, 3H), 7.39 (t, J = 7.8 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 9.4 Hz, 2H), 7.95 (d, J = 8.9 Hz, 2H), 10.12 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 69.8, 114.8, 120.7, 123.8, 127.5, 128.2, 128.4, 128.88, 128.93, 130.0, 137.0, 139.7, 161.3, 165.3. Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.19; H, 5.65; N, 4.62. Found: C, 79.21; H, 5.47; N 4.56.

*General Procedure for Synthesis of Benzimidoyl Chlorides (**15**−**18**).* Amide **11**−**14** (1 mmol) was dissolved in excess $SOCl_2$, and the mixture was refluxed overnight. Excess $SOCl_2$ was evaporated to give crude imidoyl chloride as a pale yellow solid, which was used for the next step without additional purification.

*4-Benzoyloxy-N-(4-(trifluoromethyl)phenyl)benzimidoyl Chloride (**15a**).* Chloride **15a** (6.29 g, 98% yield) was obtained from 6.05 g of **11a**: mp 175−177 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.8 Hz, 2H), 7.54 (t, J = 7.7 Hz, 2H), 7.66−7.71 (m, 3H), 8.23 (d, J = 8.0 Hz, 2H), 8.26 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 120.5; 121.9, 126.2 (q, J = 3 Hz), 127.0 (q, J = 32 Hz), 128.6, 129.0, 130.2, 130.9, 132.4, 133.9, 150.5, 154.3, 164.6 (the CF_3 signal was not located); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{14}ClF_3NO_2$ 404.0665, found 404.0659.

*4-(Benzyloxy)-N-(4-(trifluoromethyl)phenyl)benzimidoyl Chloride (**15b**).* Chloride **15b** (7.33 g, 99% yield) was obtained from 7.04 g of **11b**: mp 129−130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.16 (s, 2H),

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7.04−7.06 (m, 4H), 7.40−7.43 (m, 5H), 7.64 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 70.2, 114.7, 120.7, 124.2 (q, J = 272 Hz), 126.1 (q, J = 4 Hz), 126.7 (q, J = 33 Hz), 127.4, 127.5, 128.2, 128.7, 131.4, 136.1, 144.2, 150.8, 162.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{16}ClF_3NO$ 390.0872, found 390.0866.

*4-Iodo-N-(4-(trifluoromethyl)phenyl)benzimidoyl Chloride (**15d**).* Chloride **15d** (6.19 g, 91% yield) was obtained from 6.51 g of **11d**: mp 101−103 °C; ^{1}H NMR (CD_3CN, 400 MHz) δ 7.14 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.3 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 100.1, 120.5, 124.2 (q, J = 272), 126.2 (q, J = 4 Hz), 127.2 (q, J = 33 Hz), 130.8, 134.4, 137.8, 144.2, 150.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_9ClIF_3N$ 409.9420, found 409.9416.

*4-Nitro-N-(4-(trifluoromethyl)phenyl)benzimidoyl Chloride (**15e**).* Chloride **15e** (5.24 g, 99% yield) was obtained from 5.03 g of **11e**: mp 132−134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.11 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 8.4 Hz, 2H), 8.35 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 120.2, 123.4, 123.8 (q, J = 272 Hz), 126.0 (q, J = 4 Hz), 127.2 (q, J = 33 Hz), 130.3, 140.0, 142.0, 149.7 (*C*-NO_2 not observed); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_9ClF_3N_2O_2$ 329.0304, found 329.0316.

*4-(Benzoyloxy)-N-(4-iodophenyl)benzimidoyl Chloride (**16a**).* Chloride **16a** (3.64 g, 99% yield) was obtained from 3.51 g of **12a**: mp 156−158 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.79 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.54 (t, J = 7.7 Hz, 2H), 7.67 (t, J = 9.1 Hz, 1H), 7.72 (d, J = 8.6 Hz, 2H), 8.21−8.25 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 89.2, 121.8, 122.6, 128.6, 129.0, 130.2, 130.9, 132.7, 133.9, 137.9, 143.0, 147.1, 154.1, 164.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{14}ClINO_2$ 461.9758, found 461.9766.

*4-Iodo-N-(4-iodophenyl)benzimidoyl Chloride (**16d**).* Chloride **16d** (6.55 g, 90% yield) was obtained from 7.04 g of **12d**: mp 104−107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.78 (d, J = 8.6 Hz, 2H), 7.72 (d, J = 8.6 Hz, 2H), 7.83 (d, J = 8.9 Hz, 2H), 7.86 (d, J = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 100.1, 120.4, 126.17, 126.20, 130.8, 134.4, 137.8, 144.2, 150.3. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 89.4, 99.8, 122.5, 130.7, 134.7, 137.7, 137.9, 143.2, 146.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_9ClI_2N$ 467.8513, found 467.8528.

*4-Iodo-N-(4-fluorophenyl)benzimidoyl Chloride (**17d**).* Chloride **17d** (3.64 g, 99% yield) was obtained from 3.53 g of **13d**: mp 209−212 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (dd, J = 9.0 Hz, J = 4.9 Hz, 2H), 7.10 (t, J = 8.7 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 7.87 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 99.5, 115.6 (d, J = 23 Hz), 122.2 (d, J = 8 Hz), 128.5, 130.7, 134.9, 137.7, 138.0, 160.4 (d, J = 245 Hz); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{13}H_9ClIFN$ 359.9452, found 359.9460.

*4-Benzoyloxy-N-phenylbenzimidoyl Chloride (**18a**).* Chloride **18a** (3.66 g, 99% yield) was obtained from 3.51 g of **14a**: mp 119−120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (d, J = 7.3 Hz, 2H), 7.22 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.9 Hz, 2H), 7.42 (t, J = 7.9 Hz, 2H), 7.54 (t, J = 7.7 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 8.23 (d, J = 9.6 Hz, 2H), 8.26 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 120.4, 122.7, 125.1, 128.6, 128.8, 129.1, 130.0, 130.8, 133.0, 133.8, 142.2, 147.5, 153.9, 164.6; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}ClNO_2$ 336.0791, found 336.0783.

*4-Benzyloxy-N-phenylbenzimidoyl Chloride (**18b**).* Chloride **18b** (5.24 g, 99% yield) was obtained from 5.02 g of **14b**: mp 98−100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.17 (s, 2H), 7.04−7.07 (m, 4H), 7.24 (t, J = 9.3 Hz, 1H), 7.37−7.47 (m, 6H), 8.17 (d, J = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 70.1, 114.5, 120.5, 124.7, 127.4, 128.1, 128.2, 128.6, 128.7, 131.2, 136.2, 142.8, 147.7, 161.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{17}ClNO$ 322.0999, found 322.0986.

*General Procedure for Synthesis of Hydrazones **22**.* A mixture of benzaldehyde hydrazone **20** (1 mmol), 4-fluoro-3-nitro-(trifluoromethyl)benzene (**21**, 1.1 mmol), and K_2CO_3 (1.1 mmol) in DMSO (1 mL) and H_2O (0.01 mL) was stirred overnight at rt. The mixture was diluted with AcOEt (20 mL) and washed with H_2O (20 mL), 10% HCl (20 mL), 10% NaOH (20 mL), and brine. The organic phase was separated and dried (Na_2SO_4), and the solvent was removed giving crude product **22** as an orange oil, which was purified by flash chromatography (SiO_2, CH_2Cl_2). Recrystallization from hexane gave analytically pure hydrazone **22** as yellow crystals.

*2-Benzylidene-1-(4-(benzyloxy)phenyl)-1-(2-nitro-4-(trifluoromethyl)phenyl)hydrazine (**22b**).* Hydrazone **22b** (0.601 g, 60% yield) was obtained from 0.620 g of hydrazone **20b**: mp 132−134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.16 (s, 2H), 6.85 (d, J = 8.8 Hz, 1H), 7.20 (d, J = 9.0 Hz, 2H), 7.25 (d, J = 9.0 Hz, 2H), 7.30−7.50 (m, 12H), 7.87 (d, J = 1.3 Hz, 1H); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.19 (s, 2H), 7.01 (d, J = 9.0 Hz, 2H), 7.24 (d, J = 9.0 Hz, 2H), 7.32−7.41 (m, 4H), 7.43 (t, J = 7.3 Hz, 2H), 7.48−7.53 (m, 4H), 7.75 (dd, J = 9.0 Hz, J = 2.0 Hz, 1H), 8.18 (d, J = 1.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) major signals δ 70.1, 117.6, 120.6, 127.1, 128.4, 128.5, 129.0, 129.2, 129.9, 130.9, 134.5, 136.9, 140.3, 140.6, 151.4, 159.4; IR (KBr) 1622, 1532, 1502, 1324, 1280, 1130 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{27}H_{21}F_3N_3O_3$ 492.1530, found 492.1518. Anal. Calcd for $C_{27}H_{20}F_3N_3O_3$: C, 65.98; H, 4.10; N, 8.55. Found: C, 65.68; H, 4.06; N, 8.38.

*2-Benzylidene-1-(4-iodophenyl)-1-(2-nitro-4-(trifluoromethyl)-phenyl)hydrazine (**22c**).* Hydrazone **22c** (1.052 g, 80% yield) was obtained from 0.823 g of hydrazone **20c**: mp 117−119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.97 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 8.6 Hz, 2H), 7.29 (s, 1H), 7.32−7.38 (m, 3H), 7.48 (dd, J = 8.0 Hz, J = 1.9 Hz, 2H), 7.59 (dd, J = 8.8 Hz, J = 1.8 Hz, 1H), 7.91 (d, J = 8.6 Hz, 2H), 7.98 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 93.8, 122.3, 123.0 (q, J = 272 Hz), 123.2 (q, J = 4 Hz), 124.4 (q, J = 34 Hz), 126.9, 128.6 (q, J = 4 Hz), 128.7, 129.3, 129.7, 133.9, 138.7, 140.0, 141.1, 141.6, 141.9; IR (KBr) 1623 (C═N), 1537, 1324, 1281, 1124 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{14}F_3IN_3O_2$ 512.0077, found 512.0094. Anal. Calcd for $C_{20}H_{13}F_3IN_3O_2$: C, 46.99; H, 2.56; N, 8.22. Found: C, 47.29; H, 2.77; N, 8.20.

*General Procedure for Synthesis of Hydrazine **23**.* Following a general procedure,[18] a mixture of hydrazone **22** (1 mmol) and H_2NOH·HCl (10 mmol) in pyridine (7 mL) was heated at ca. 80 °C for 20 h. Pyridine was removed in vacuo, the residue was treated with CH_2Cl_2, and the resulting suspension was filtered to remove excess H_2NOH·HCl. The filtrate was diluted with additional portion of CH_2Cl_2 (20 mL) and washed with 2 M KOH (20 mL), 10% HCl (20 mL), and H_2O (20 mL). The organic phase was separated and dried (Na_2SO_4), and after evaporation of the solvent, the crude product was purified by flash chromatography (SiO_2, hexane/CH_2Cl_2, 3:1). Analytically pure hydrazine **23** was obtained by recrystallization from hexane.

*1-(4-(Benzyloxy)phenyl)-1-(2-nitro-4-(trifluoromethyl)phenyl)-hydrazine (**23b**).* Hydrazine **23b** (0.298 g, 64% yield) was obtained from 0.551 g of **22b**: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.09 (s, 2H), 5.40 (s, 2H), 7.01 (d, J = 9.0 Hz, 2H), 7.24 (d, J = 9.0 Hz, 2H), 7.32−7.46 (m, 6H), 7.67 (dd, J = 9.0 Hz, J = 2.2 Hz, 1H), 7.95 (d, J = 1.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 69.8, 115.9, 118.7 (q, J = 34 Hz), 120.8, 123.50 (q, J = 4 Hz), 123.7, 124.0 (q, J = 271 Hz), 128.1, 128.2, 128.8, 129.2 (q, J = 3 Hz), 137.4, 139.1, 140.3, 146.1, 156.0. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{16}F_3N_3O_3$•Na 426.1036, found 426.1036.

*1-(4-Iodophenyl)-1-(2-nitro-4-(trifluoromethyl)phenyl)hydrazine (**23c**).* Hydrazine **23c** (0.383 g, 77% yield) was obtained from 0.603 g of **22c**: mp 86−88 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.36 (bs, 2H), 6.90 (d, J = 8.9 Hz, 2H), 7.50 (d, J = 8.7 Hz, 1H), 7.61 (d, J = 9.0 Hz, 2H), 7.65 (dd, J = 8.4 Hz, J = 1.8 Hz, 1H), 8.06 (d, J = 1.5 Hz, 1H); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.50 (s, 2H), 7.03 (d, J = 8.9 Hz, 2H), 7.61 (d, J = 8.9 Hz, 2H), 7.65 (d, J = 8.8 Hz, 1H), 7.81 (dd, J = 8.9 Hz, J = 2.1 Hz, 1H), 8.08 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) major signals δ 86.4, 120.0, 123.8 (q, J = 4 Hz), 124.6, 129.3 (q, J = 3 Hz), 138.4, 142.0, 144.4, 146.6; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 86.5, 121.15, 121.17 (q, J = 34 Hz), 123.2 (q, J = 4 Hz), 123.4 (q, J = 272 Hz), 123.6, 129.4 (q, J = 3 Hz), 137.6, 140.7, 144.5, 146.7. Anal. Calcd for $C_{13}H_9F_3IN_3O_2$: C, 36.90; H, 2.14; N, 9.93. Found, C, 36.99; H, 2.26; N, 9.85.

*Methyl 4-(2-(4-(benzyloxy)phenyl)-2-(2-nitro-4-(trifluoromethyl)-phenyl)hydrazinecarbonyl)benzoate (**24h**).* A solution of hydrazine **23c** (358 mg, 0.846 mmol) and Et_3N (0.26 mL, 1.86 mmol) in dry

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CH_2Cl_2 (6 mL) at −5 °C was treated with a solution of acid chloride, derived from acid **10h** (368 mg, 1.86 mmol), in CH_2Cl_2 (4 mL). The resulting mixture was slowly warmed to rt and stirred overnight. The reaction mixture was diluted with CH_2Cl_2, washed with H_2O (2 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting mixture of products was fractionated by flash chromatography (SiO_2, hexane/CH_2Cl_2, gradient) giving 65 mg of recovered hydrazine **23c** as the first fraction and 353 mg (71% yield) of hydrazide **24h** as the more polar yellow compound: mp 207−209 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.96 (s, 3H), 6.80 (d, J = 8.2 Hz, 2H), 7.60 (d, J = 7.9 Hz, 2H), 7.84 (s, 4H), 8.14 (d, J = 7.7 Hz, 2H), 8.25 (s, 1H), 8.60 (s, 1H); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.88 (s, 3H), 6.94 (d, J = 8.9 Hz, 2H), 7.63 (d, J = 6.4 Hz, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.94−7.99 (m, 3H), 8.07−8.12 (m, 3H), 8.23 (d, J = 1.4 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 52.9, 88.6, 121.9, 123.6 (q, J = 271 Hz), 123.8 (q, J = 4 Hz), 124.1, 128.5, 129.8, 130.2 (q, J = 32 Hz), 130.8 (q, J = 3.3 Hz), 133.2, 135.8, 138.4, 140.8, 141.5, 144.4, 165.4, 165.9; IR (KBr) 3169 (NH), 1716 (C═O), 1673 (C═O), 1531, 1327, 1291, 1120 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{16}F_3IN_3O_5$ 586.0087, found 586.0058. Anal. Calcd for $C_{22}H_{15}F_3IN_3O_5$: C, 45.15; H, 2.58; N, 7.18. Found: C, 45.27; H, 2.71; N, 6.89.

*4-(Benzyloxy)-N′-(4-(benzyloxy)phenyl)benzohydrazide (**26**).* A suspension of hydrazine **19b** (850 mg, 3.4 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (0.95 mL, 6.8 mmol) followed by a solution of acid chloride, derived from **10b** (836 mg, 3.4 mmol), in CH_2Cl_2. The resulting mixture was stirred overnight at rt, diluted with CH_2Cl_2, and washed with H_2O (3 × 20 mL) and the organic phase dried (Na_2SO_4). The crude product was purified by flash column chromatography (SiO_2, hexane/AcOEt, 3:1) giving 450 mg (31% yield) of **26** as a white solid: mp 162−164 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.98 (s, 2H), 5.18 (s, 2H), 6.72 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 7.29−7.41 (m, 8H), 7.46 (d, J = 7.2 Hz, 2H), 7.53 (d, J = 3.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 10.19 (d, J = 3.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 69.7, 70.0, 114.1, 114.9, 115.7, 125.8, 127.9, 128.0, 128.1. 128.3, 128.7, 128.9, 129.5, 137.1, 138.0, 144.2, 152.1, 161.3, 166.1. HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{27}H_{25}N_2O_3$ 425.1860, found 425.1885.

■ ASSOCIATED CONTENT

Supporting Information

1D ^{1}H and ^{13}C NMR spectra, complete thermodynamic data for Figures 2 and 3, partial TD-DFT output data, MO contours for **1r**, theoretical hfcc for selected radicals, experimental and simulated ESR spectra, and archive of DFT equilibrium geometries for selected molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Nishide, H.; Suga, T.; Ito, M. Jpn. Kokai Tokkyo Koho. JP 2011124567 A, 2011. Oka, H.; Tanabe, J.; Hintermann, T.; Takahashi, R.; Nesvadba, P.; Nakamichi, S. PCT Int. Appl. WO 2010121900 A1, 2010.

(2) Suga, T.; Ohshiro, H.; Sugita, S.; Oyaizu, K.; Nishide, H. *Adv. Mater.* **2009**, *21*, 1627−1630.

(3) Sanvito, S. *Chem. Soc. Rev.* **2011**, *40*, 3336−3355.

(4) Wang, Y.; Wang, H.; Liu, Y.; Di, C.; Sun, Y.; Wu, W.; Yu, G.; Zhang, D.; Zhu, D. *J. Am. Chem. Soc.* **2006**, *128*, 13058−13059.

(5) Dane, E. L.; Swager, T. M. *J. Org. Chem.* **2010**, *75*, 3533−3536.

(6) Haze, O.; Corzilius, B.; Smith, A. A.; Griffin, R. G.; Swager, T. M. *J. Am. Chem. Soc.* **2012**, *134*, 14287−14290.

(7) Michaelis, V. K.; Smith, A. A.; Corzilius, B.; Haze, O.; Swager, T. M.; Griffin, R. G. *J. Am. Chem. Soc.* **2013**, *135*, 2935−2938.

(8) Frantz, D. K.; Walish, J. J.; Swager, T. M. *Org. Lett.* **2013**, *15*, 4782−4785.

(9) *Stable Radicals: Fundamentals and Applied Aspects of Odd-Electron Compounds*; Hicks, R. G., Ed.; Wiley & Sons: New York, 2010.

(10) Ratera, I.; Veciana, J. *Chem. Soc. Rev.* **2012**, *41*, 303−349.

(11) Jasiński, M.; Gerding, J. S.; Jankowiak, A.; Gębicki, K.; Romański, J.; Jastrzębska, K.; Sivaramamoorthy, A.; Mason, K.; Evans, D. H.; Celeda, M.; Kaszyński, P. *J. Org. Chem.* **2013**, *78*, 7445−7454.

(12) Hicks, R. G. Reference 9 , pp 245−280 and references therein.

(13) For recent applications, see: (a) Zheng, Y.; Miao, M.; Kemei, M. C.; Seshadri, R.; Wudl, F. *Isr. J. Chem.* **2014**, *54*, 774−778. (b) Morgan, I. S.; Peuronen, A.; Hänninen, M. M.; Reed, R. W.; Clérac, R.; Tuononen, H. M. *Inorg. Chem.* **2014**, *53*, 33−35. (c) Demetriou, M.; Berezin, A. A.; Koutentis, P. A.; Krasia-Christoforou, T. *Polym. Int.* **2014**, *63*, 674−679.

(14) Blatter, H. M.; Lukaszewski, H. *Tetrahedron Lett.* **1968**, *9*, 2701−2705.

(15) Neugebauer, F. A.; Umminger, I. *Chem. Ber.* **1980**, *113*, 1205−1225.

(16) Neugebauer, F. A.; Umminger, I. *Chem. Ber.* **1981**, *114*, 2423−2430.

(17) Berezin, A. A.; Constantinides, C. P.; Mirallai, S. I.; Manoli, M.; Cao, L. L.; Rawson, J. M.; Koutentis, P. A. *Org. Biomol. Chem.* **2013**, *11*, 6780−6795.

(18) Berezin, A. A.; Zissimou, G.; Constantinides, C. P.; Beldjoudi, Y.; Rawson, J. M.; Koutentis, P. A. *J. Org. Chem.* **2014**, *79*, 314−327.

(19) Koutentis, P. A.; Lo Re, D. *Synthesis* **2010**, 2075−2079.

(20) Constantinides, C. P.; Koutentis, P. A.; Loizou, G. *Org. Biomol. Chem.* **2011**, *9*, 3122−3125.

(21) Constantinides, C. P.; Koutentis, P. A.; Rawson, J. M. *Chem.—Eur. J.* **2012**, *18*, 15433−15438.

(22) Constantinides, C. P.; Koutentis, P. A.; Rawson, J. M. *Chem.—Eur. J.* **2012**, *18*, 7109−7116.

(23) Constantinides, C. P.; Carter, E.; Murphy, D. M.; Manoli, M.; Leitus, G. M.; Bendikov, M.; Rawson, J. M.; Koutentis, P. A. *Chem. Commun.* **2013**, *49*, 8662−8664.

(24) Berezin, A. A.; Constantinides, C. P.; Drouza, C.; Manoli, M.; Koutentis, P. A. *Org. Lett.* **2012**, *14*, 5586−5589.

(25) Berezin, A. A.; Koutentis, P. A. *Org. Biomol. Chem.* **2014**, *12*, 1641−1648.

(26) Synthesis and Suzuki C−C cross coupling of **2d** was reported independently: Takahashi, Y.; Miura, Y.; Yoshioka, N. *Chem. Lett.* **2014**, DOI: 10.1246/cl.140335.

(27) Molander, G. A.; Trice, S. L. J.; Kennedy, S. M.; Dreher, S. D.; Tudge, M. T. *J. Am. Chem. Soc.* **2012**, *134*, 11667−11673.
(28) Fleury-Brégeot, N.; Presset, M.; Beaumard, F.; Colombel, V.; Oehlrich, D.; Rombouts, F.; Molander, G. A. *J. Org. Chem.* **2012**, *77*, 10399−10408.
(29) Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411−1414.
(30) Valente, C.; Belowich, M. E.; Hadei, N.; Organ, M. G. *Eur. J. Org. Chem.* **2010**, 4343−4354.
(31) Heck, R. F. *Org. React.* **1982**, *27*, 345−390.
(32) Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43−54 and references cited therein.
(33) Rowland, R. S.; Taylor, R. *J. Phys. Chem.* **1996**, *100*, 7384−7391.
(34) For more details, see the Supporting Information.
(35) Constantinides, C. P.; Koutentis, P. A.; Krassos, H.; Rawson, J. M.; Tasiopoulos, A. J. *J. Org. Chem.* **2011**, *76*, 2798−2806.
(36) Neugebauer, F. A.; Rimmler, G. *Magn. Reson. Chem.* **1988**, *26*, 595−600.
(37) Kadirow, M. K.; Buzykin, B. I.; Gazetdinova, N. G. *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 1796−1799.
(38) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.
(39) Mukai, K.; Inoue, K.; Achiwa, N.; Jamali, J. B.; Krieger, C.; Neugebauer, F. A. *Chem. Phys. Lett.* **1994**, *224*, 569−575.
(40) Gubaidullin, A. T.; Buzykin, B. I.; Litvinov, I. A.; Gazetdinova, N. G. *Russ. J. Gen. Chem.* **2004**, *74*, 939−943.
(41) Barton, D. H. R.; Ducker, J. W.; Lord, W. A.; Magnus, P. D. *J. Chem. Soc., Perkin Trans. 1* **1976**, 38−42.
(42) Huisgen, R.; Wulff, J. *Chem. Ber.* **1969**, *102*, 1848−1858.
(43) Gilchrist, T. L.; Harris, C. J.; Rees, C. W. *Chem. Commun.* **1974**, 485−486.
(44) Bishop, L. M.; Barbarow, J. E.; Bergman, R. G.; Trauner, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8100−8103.
(45) Gaussian 09, Revision A.02: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford, CT, 2009.
(46) Stratmann, R. E.; Scuseria, G. E.; Frisch, M. J. *J. Chem. Phys.* **1998**, *109*, 8218−8224.
(47) Hu, W.-P.; Chen, Y.-K.; Liao, C.-C.; Yu, H.-S.; Tsai, Y.-M.; Huang, S.-M.; Tsai, F.-Y.; Shen, H.-C.; Chang, L.-S.; Wang, J.-J. *Bioorg. Med. Chem.* **2010**, *18*, 6197−6207.