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Full Paper

Facile Synthesis of Triarylmethanimine Promoted by a Lewis Acid–Base Pair: Theoretical and Experimental Studies

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An efficient method for triarylmethanimine synthesis promoted by a Lewis acid–base pair ($AlCl_3$–Et_3N) was designed using mechanistic analysis with the aid of density functional theory. A series of triarylmethanimines were successfully prepared under mild conditions in good to excellent yields with a simple work-up procedure. The promoter, the Lewis acid–base pair ($AlCl_3$–Et_3N), is inexpensive, efficient, and shows good functional group tolerance. The experimental results show that the electronic effect played a significant role, i.e. the reactions proceeded smoothly when electron-sufficient arylamines and electron-deficient ketones were used as substrates.

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Introduction

Schiff bases[1] are an important class of biologically active compounds.[2,3] They play an important role in the biosynthesis of amino acids[4] and aza-aromatic heterocycles.[5] Moreover, Schiff bases have proved to be attractive building blocks for creating new active and selective sites in coordination chemistry. Nowadays Schiff bases are still considered 'privileged ligands' by modern chemists.[6,7]

Unlike the condensation of alkylarylketones (such as acetophenone) and arylamines,[8–10] the direct condensation of diarylketones with arylamines is very difficult and a high temperature and/or catalysts are required.[11,12] Brønsted or Lewis acids, such as $AlCl_3$[13] $ZnCl_2$,[14] HBr,[14] $POCl_3$,[15] BF_3,[16] $PhN(MgBr)_2$,[17] $EtAlCl_2$,[18] $TiCl_4$,[19–21] or $Pd(OAc)_2$[22] have been used to promote the reaction by enhancing the activity of the electrophile. It is also essential to add either the dehydration agent, tetraethyl orthosilicate ($Si(OEt)_4$),[23] or activated molecular sieves[24,25] in order to facilitate the reaction. Other methods, such as the hydroamination of alkynes have also been reported.[26] Metathesis of oximes with arylboronic acids is another alternative method.[27] In spite of their potential usefulness, the methods mentioned above all suffer from one or more drawbacks such as low yields, long reaction times, high temperatures, expensive substrates, toxic reagents, poor functional group tolerance, or limited scopes.

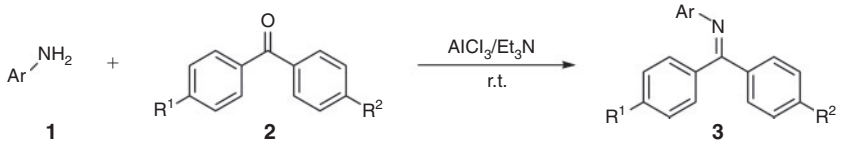
$AlCl_3$ acting as a promoter for the imine synthesis from ammonia and acetophenone was first reported by Strain.[13] However, high temperature and a long reaction time are needed and the yield was very low (less than 40 %). Based on Strain's report,[13] a computational design[28–30] and our own theoretical analysis, herein an improved synthesis for triarylmethanimines promoted by an $AlCl_3$–Et_3N pair, is reported (Scheme 1).

Results and Discussion

Theoretical Results

The density functional theory (DFT) results show that the atomic polar tensor (APT) charge on the carbonyl carbon in $Ph_2C{=}O$ is $+1.142\,e^-$ and the carbonyl carbon becomes more positive ($+1.565\,e^-$) in the presence of $AlCl_3$. The charge analysis shows that $AlCl_3$ acts as a promoter to enhance the electrophilicity of the carbonyl carbon.

In terms of the mechanism, the reaction proceeds by a nucleophilic addition giving a hemiaminal –C(OH)(NHR)– intermediate, followed by an elimination of water to yield the imine. There are two possible transition states (TS) through



Ar = Ph, *p*-NO_2-C_6H_5, *o*-X-C_6H_5, m-X-C_6H_4, *p*-X-C_6H_5, 3, 5-di-NO_2-C_6H_4, 1-naphthyl,
R_1, R_2 = H, F, MeO, NO_2

Scheme 1

which the hemiaminal intermediate can be obtained, a) the hydrogen on the amine directly migrates to the oxygen (four-membered ring transition state) and b) the H migrates with a transfer (six-membered ring transition state). The results are depicted in Fig. 1. The energy of the barrier for the nucleophilic addition step, which occurs through a four-membered TS, is 54.2 kcal mol^{-1} (Fig. 1a) and is 15.3 kcal mol^{-1} higher than that promoted by $AlCl_3$ (Fig. 1b). The high barrier of the four-membered TS can be attributed to ring strain. In order to reduce the calculation resource, ammonia was used in place of arylamine to act as a proton transfer agent. It was found that ammonia is a better transfer agent than water in the six-membered ring transition state (Fig. 1c, d). In the case of ammonia, the energy barrier of the TS is at 38.1 kcal mol^{-1}, which is 4.3 kcal mol^{-1} lower than that of water. Therefore, in the following study, a six-membered transition state with ammonia as the transfer agent was chosen as the optimized transition state.

The total energy profile of the reaction is shown in Fig. 2. The activation energy of the $AlCl_3$-promoted hemiaminal intermediate formation step is 16.8 kcal mol^{-1} (Fig. 2, TS-1), which is 21.3 kcal mol^{-1} lower than that without the Lewis acid (Fig. 1d) and 19.5 kcal mol^{-1} higher than the barrier of the four-membered TS. Although the entropy change through a six-membered TS is 106.4 J mol^{-1} · K^{-1} higher than that of the four-membered TS, the enthalpy barrier of the six-membered TS is only 6.0 kcal mol^{-1} compared with the 33.1 kcal mol^{-1} of the enthalpy barrier of the four-membered TS. As a result, the $AlCl_3$-promoted process through the six-membered TS is still feasible. The hydroxy leaving barrier is only 8.5 kcal mol^{-1} which is 8.3 kcal mol^{-1} lower than the hemiaminal formation step, i.e. the first step is the rate determining step, in which the hemiaminal intermediate (INT-1) forms after a nucleophilic attack and there is a H transfer with the aid of another molecule of amine.

HO–$AlCl_3^-$ then leaves through TS-2 followed by Et_3N capturing a hydrogen on the nitrogen atom which has a low barrier; the whole process is an exergonic process (−16.5 kcal mol^{-1}). Finally the strongly exergonic reaction between Et_3NH^+ and $HOAlCl_3^-$ occurs to form very stable Et_3NHCl and $HOAlCl_2$, and this makes the whole process irreversible (see Supplementary Material Fig. S11). The low activation energy indicates that the reaction occurs at low temperature.

The solvent effect of $CHCl_3$ was also taken into consideration. The energy profile of the process showing the solvent effect is shown in Fig. S12 (Supplementary Material).

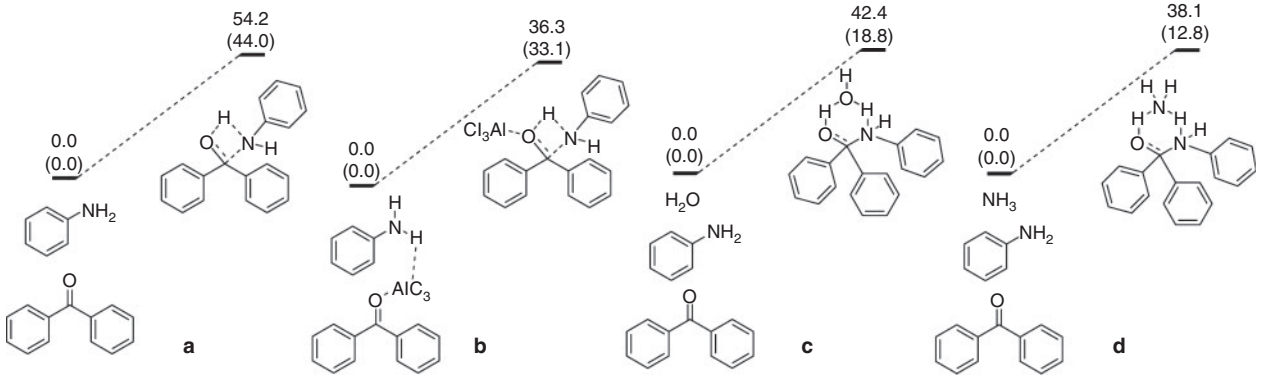


Fig. 1. Energy profiles of the comparative study with different mechanisms. The relative free energies and electronic energies (in parentheses) are given in kcal mol^{-1}.

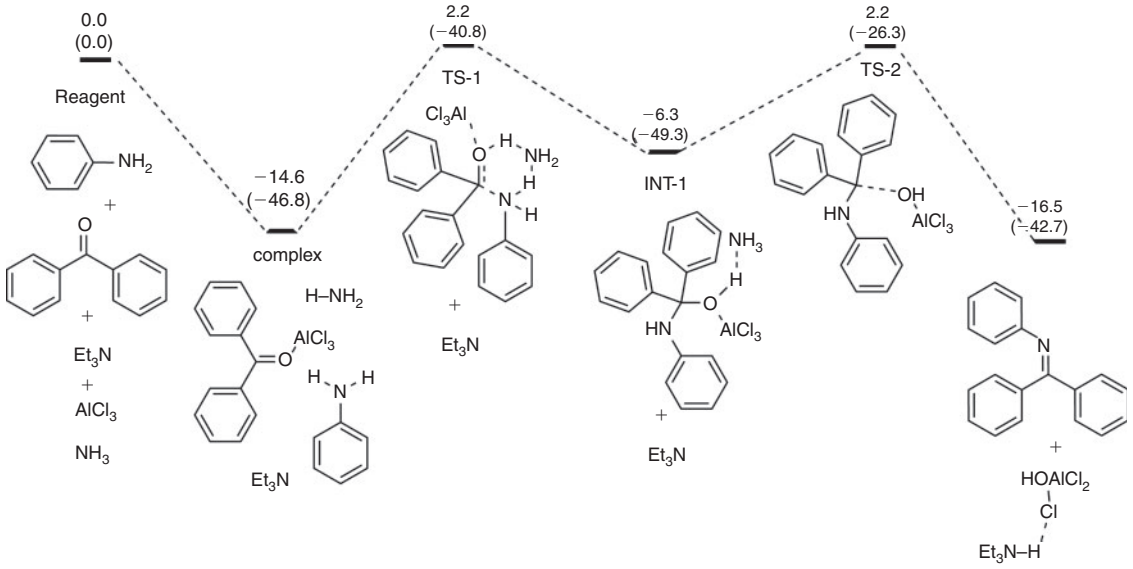


Fig. 2. Energy profile of the whole reaction process. The relative free energies and electronic energies (in parentheses) are given in kcal mol^{-1}.

Table 1. Effect of solvent
$Ph_2CO/PhNH_2/AlCl_3/Et_3N = 1:2:1.7:5.1$, room temperature

Entry	Solvent	Time [h]	Yield [%]
1	CH_2Cl_2	20	83.9
2	$CHCl_3$	5	92.3
3	CCl_4	24	59.9
4	Benzene	24	70.9
5	Chlorobenzene	8	85.4

Table 2. Optimization of the reaction conditions at room temperature

Entry	Diarylketone [equiv.]	Arylamine [equiv.]	$AlCl_3$ [equiv.]	Et_3N [equiv.]	Yield [%]
1	1.0	1.0	1.7	5.1	53.3
2	1.0	1.2	1.7	5.1	89.7
3	1.0	1.4	1.7	5.1	90.6
4	1.0	1.6	1.7	5.1	98.7
5[A]	1.0	1.6	1.7	5.1	98.2
6	1.0	1.8	1.7	5.1	95.4
7	1.0	2.0	1.7	5.1	92.3
8	1.0	1.6	1.0	3.0	74.3
9	1.0	1.6	1.35	4.05	77.1
10	1.0	1.6	2.05	6.15	97.3
11	1.0	1.6	2.4	7.2	95.5
12	1.0	1.6	0	0	–[B]

[A]Reaction was refluxed for 5 h. [B]No reaction.

The $CHCl_3$ solvent effect lowered the barrier of the whole process from 16.8 to 13.6 kcal mol^{-1}.

In conclusion, an imine formation reaction promoted by the $AlCl_3$–Et_3N pair was verified through the DFT method. The computational results show that the Lewis acid $AlCl_3$ lowers the barrier of the process, and an additional base Et_3N makes the whole process irreversible. The thermodynamic viability of the assumed process was also confirmed by the theoretical method.

Experimental Results

Based on the calculated results, a series of experiments were performed. The reaction between benzophenone and aniline was selected as the model reaction. Experiments to optimize the solvent for the condensation of benzophenone and aniline were conducted and the results are shown in Table 1. Chloroform was found to be the best solvent which gives an excellent yield of 92.3 %. The mole ratio of the reactants was also optimized, and the results are given in Table 2. The best ratio of $Ph_2C{=}O/PhNH_2/AlCl_3/Et_3N$ was 1 : 1.6 : 1.7 : 5.1 (5 h gave a yield of 98.7 %). When the temperature was elevated to reflux for 5 h, no further enhancement of the yield was obtained (Table 2). Obviously, room temperature is the best selection.

In order to broaden the substrate scope, a series of arylamines were selected and the results are listed in Table 3. Arylamines with electron donating groups (EDGs) and halogens gave excellent yields under the optimized conditions (Table 3), whereas those with electron withdrawing groups (EWGs) gave unsatisfactory results (Table 3). For example, an aniline with MeO or F, Cl or Br at the *para*-position shortened the reaction time, whereas a NO_2 or CF_3 group prolonged it. Owing to the electron withdrawing character of thiazolyl, 2-aminothiazole also gave a low yield (Table 3). In addition, the steric effect plays a significant role. The reaction times for substrates with EDGs at the *ortho*-positions were prolonged to more than 10 h and the yields were low (Table 3). Among these, 2,6-dimethylaniline gave the lowest yield. In the case of 2-nitroaniline, no reaction product was isolated (Table 3). This suggests that both the steric effect and the electron withdrawing character of the nitro group hinder the condensation.

Next, the effect of substituents on the diarylketones was studied and the results are listed in Table 4. The electronic effect of the diarylketones was opposite to that of the arylamine, i.e. an electron-deficient diarylketone facilitated the reaction (Table 4) whereas an electron-sufficient one hindered the reaction (Table 4). Excellent yields were obtained for 9-fluorenone and 9,10-anthraquinone and this may be attributed to the instability of both substrates which is caused by the anti-aromatic cyclopentadienone and quinone moieties (Table 4). In conclusion, the condensation is facilitated by EDGs and halogen on arylamines, and EWGs on diarylketones.

Conclusions

Using Strain's report as a basis, an improved method to synthesize triarylmethanimines was theoretically designed and then the method was performed experimentally. The reaction between arylamine and diarylketone was promoted by a Lewis acid–base pair, $AlCl_3$–Et_3N, and the preferred solvent was chloroform. Electron-sufficient arylamines and electron-deficient diarylketones facilitated the reaction whereas the steric effect hindered the reaction.

Experimental

Computational Details

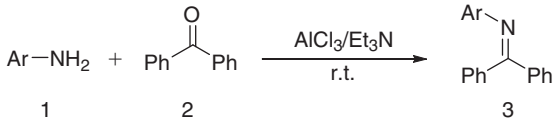
Molecular geometries of model complexes were optimized using the Restricted Becke3LYP (rB3LYP)[31,32] functional. Frequency calculations at the same level of theory were also performed to identify all the stationary points as minima (zero imaginary frequencies) or transition states (one imaginary frequency). Intrinsic reaction coordinates (IRC)[33,34] were calculated for the transition states to confirm that such structures indeed connect two relevant minima. The 6-31G(d) basis set was used for C, N, and O atoms, and 6-31G(d, p) was used for H. The effective core potentials (ECPs) of Hay and Wadt with a double-ξ basis set (LanL2DZ)[35–37] were used for Al and Cl atoms. Polarization functions were added for Cl ($\xi_d = 0.514$).[38] The effect of solvent was examined by performing single-point self-consistent reaction field (SCRF) calculations based on the polarizable continuum model (PCM)[39,40] for all of the gas-phase-optimized species. The solvent calculations were carried out by using the SCFVAC keyword to obtain the free energies of solvation then adding the relevant thermal corrections RTln(RT/P), which is followed by adding the energies to gas phase energies.[41] $CHCl_3$ was chosen as the solvent, using the default parameter in *Gaussian03*, $\varepsilon = 4.9$, solvent radius = 2.48 Å, and the atomic radii are taken from the UFF. To reduce computational costs, the $PhNH_2$ which acts as a H transfer medium was replaced by NH_3. All calculations were performed with the *Gaussian 03* software package.[42]

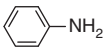
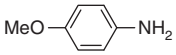
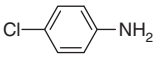
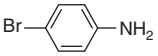
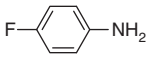
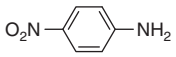
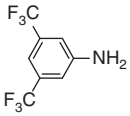
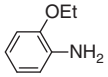
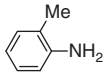
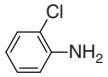
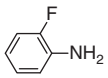
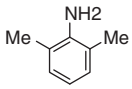
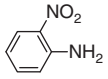
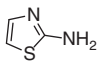
Experimental Details

General

Melting points were determined by an X-6 micro-melting point apparatus and were uncorrected. High resolution mass spectra (HRMS) were obtained on a micrOTOF-Q II 10204 instrument. ^1H NMR spectra were obtained in $CDCl_3$ on a

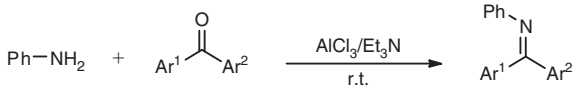
Table 3. Scope of arylamine subtrates



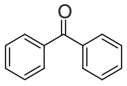
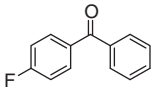
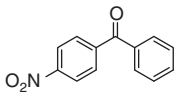
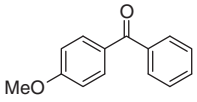
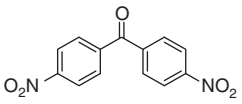
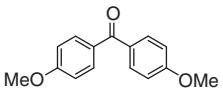
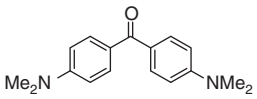
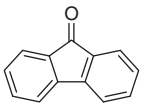
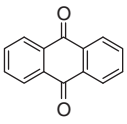
Entry	$ArNH_2$	Product	Time [h]	Yield [%]	Yield of $ArN(MgBr)_2$[12] [%]	Yield of $ZnCl_2$[9] or HBr[9] [%]	Yield of $POCl_3$[10] [%]	m.p. [°C]
1		**3a**	5	98.2	68.0	81	86.0	104–106
2		**3b**	4	96.2	72.0	78.5	–	70–72
3		**3c**	3	97.3	–	80	–	88–89
4		**3d**	3	96.4	–	–	–	82–83
5		**3e**	4	96.7	–	–	–	102–104
6[A]		**3f**	20	77.5	–	–	–	152–153
7		**3g**	18	69.1	–	–	–	115–116
8		**3h**	16	94.1	–	–	–	–
9[A]		**3i**	10	94.2	–	–	–	50–51
10[A]		**3j**	10	93.3[B]	–	–	–	93–95
11[A]		**3k**	14	92.8[B]	–	–	–	100–101
12		**3l**	20	38.0	–	–	–	90–92
13		**3m**	20	Trace	–	–	–	–
14[A]		**3n**	16	59.7	–	74.0	–	130–132
15[A]		**3o**	24	38.2	–	–	–	83–84

[A] Reactions under reflux. [B] Yield obtained by HPLC.

Table 4. Scope of diarylketone substrates



1 **2** **3**

Entry	Diarylketones	Product	Time [h]	Yield [%]	Yield of $ArN(MgBr)_2$[12] [%]	Yield of $ZnCl_2$[9] or HBr[9] [%]	m.p. [°C]
1		**3a**	5	98.2	–	–	104–106
2		**3p**	4	82.4	–	–	118–120
3		**3q**	4	91.8	–	–	125–126
4		**3r**	6	89.7	39.0		66–67
5		**3s**	4	98.0	–	–	158–160
6		**3t**	8	78.0	–	76.0	105–106
7[A]		**3u**	24	81.1[B]	–	–	123–125
8		**3v**	2.5	98.4	82.0[D]	75.0	80–82
9[C]		**3w**	2	97.2	–	–	192–194

[A]Reaction under reflux. [B]Yield obtained by HPLC. [C]Reaction conditions: anthraquinone/aniline/$AlCl_3$/Et_3N = 1 : 3.2 : 3.4 : 10.2, room temperature. [D]The amine is 4-methoxyaniline in the literature.

Varian 400 spectrometer. If not otherwise noted, chemical shifts are reported as values in ppm relative to tetramethylsilane (TMS) using the residual $CDCl_3$ peak in the $CDCl_3$ solution as the internal standard ($\delta = 7.26$ relative to TMS).

Procedure

A flask was charged with a substituted benzophenone (**1**, 2.0 mmol), $AlCl_3$ (3.4 mmol), and 20 mL chloroform. A solution of arylamines (**2**, 3.2 mmol) in Et_3N (10.2 mmol) was then added dropwise with stirring. The resulting reaction mixture was stirred for the desired time at room temperature or at reflux. After completion of the reaction (monitored by TLC), the mixture was treated with 4 M NaOH solution and then extracted three times with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The crude product was further purified by column chromatography and the yield was calculated based on the weight of pure product. Selected data for typical compounds follow.

*Compound **3a***. δ_H (400 MHz, $CDCl_3$) 7.77–7.71 (m, 2H), 7.50–7.43 (m, 1H), 7.40 (t, *J* 7.3, 2H), 7.24 (s, 2H), 7.17–7.08

(m, 5H), 6.91 (t, *J* 7.3, 1H), 6.72 (d, *J* 7.6, 2H). *m*/*z* (HRMS) Calc. for $C_{19}H_{16}N^+$ ($[M+H]^+$): 258.1277. Found: 258.1278.

Compound ***3b***. δ_H (400 MHz, $CDCl_3$) 7.73 (d, *J* 7.3, 2H), 7.51 – 7.33 (m, 3H), 7.30 – 7.23 (m, 3H), 7.12 (d, *J* 5.2, 2H), 6.68 (s, 4H), 3.72 (s, 3H).

Compound ***3f***. *m*/*z* (HRMS) Calc. for $C_{19}H_{15}N_2O_2^+$ ($[M+H]^+$): 303.1128. Found: 303.1126.

Compound ***3i***. δ_H (400 MHz, $CDCl_3$) 7.79 (d, *J* 7.3, 2H), 7.49–7.45 (m, 1H), 7.41 (t, *J* 7.3, 2H), 7.24 (d, *J* 5.8, 3H), 7.12–7.04 (m, 3H), 6.91 (t, *J* 7.4, 1H), 6.83 (t, *J* 7.3, 1H), 6.43 (d, *J* 7.6, 1H), 2.18 (s, 3H).

Compound ***3j***. δ_H (400 MHz, $CDCl_3$) 7.73 (d, *J* 7.3, 2H), 7.48 (t, *J* 7.2, 1H), 7.40 (t, 2H), 7.35–7.16 (m, 5H), 7.10 (d, *J* 6.4, 2H), 6.59 (d, *J* 8.5, 2H).

Compound ***3o***. δ_H (400 MHz, $CDCl_3$) 7.78 (s, 2H), 7.55–7.27 (m, 7H), 7.20 (s, 2H), 6.90 (d, *J* 3.2, 1H).

Compound ***3u***. δ_H (400 MHz, $CDCl_3$) 7.57 (d, *J* 8.5, 2H), 7.07 (t, *J* 7.5, 2H), 6.91 (d, *J* 8.3, 2H), 6.80 (t, *J* 7.2, 1H), 6.69 (d, *J* 7.6, 2H), 6.56 (d, *J* 8.5, 2H), 6.38 (d, *J* 8.4, 2H), 3.33 (q, *J* 6.8, 4H), 3.23 (q, *J* 6.9, 4H), 1.11 (t, *J* 6.9, 6H), 1.05 (t, *J* 6.9, 6H). *m*/*z* (HRMS) Calc. for $C_{27}H_{34}N_3^+$ ($[M+H]^+$): 400.2747. Found: 400.2753.

Compound ***3v***. δ_H (400 MHz, $CDCl_3$) 7.92 (d, *J* 7.3, 1H), 7.57 (d, *J* 6.9, 2H), 7.49–7.16 (m, 6H), 6.99 (d, *J* 7.3, 2H), 6.90 (t, *J* 7.6, 1H), 6.56 (d, *J* 7.5, 1H).

Supplementary Material

NMR spectra, HRMS spectra, and computational Cartesian coordinates and energies are available on the Journal's website.

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