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Reactions of enaminones and related compounds with *N*,*N*-dimethylacetamide dimethyl acetal. A simple one-pot metal-free synthesis of polysubstituted benzene derivatives

Benjamin Prek [b], Jure Bezenšek [a], Marta Kasunič [a], Uroš Grošelj [a], Jurij Svete [a,b], Branko Stanovnik [a,b,*]

[a] Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, PO Box 537, SI-1000 Ljubljana, Slovenia
[b] EN-FIST Centre of Excellence, Dunajska 156, SI-1000 Ljubljana, Slovenia

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ABSTRACT

Herein a simple one-pot metal-free synthesis of alkyl-, aryl-, heteroaryl- and alkoxycarbonyl substituted 1,3-bis(dimethylamino)benzene derivatives is described. The products were prepared from the corresponding methyl ketones or compounds with an α-methylene group in regard to the carbonyl group, using *N*,*N*-dimethylacetamide dimethyl acetal (DMADMA) as the reagent.

1. Introduction

Recently, alkyl-, aryl-, and heteroaryl methyl ketones **1** have been transformed by treatment with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) or *tert*-butoxy bis(dimethylamino)methane (Bredereck's reagent) into the corresponding 3-(dimethylamino)-1-substituted-prop-2-enones **2**, which afforded, via regiospecific microwave assisted [2+2] cycloaddition to dimethyl acetylenedicarboxylate (DMAD), highly functionalized buta-1,3-dienes, i.e., dimethyl 2-[(dimethylamino)methylene]-3-(2-substituted)-succinates **3**.[1–7] These highly functionalized buta-1,3-dienes proved to be useful and versatile reagents in the formation of highly substituted pyridines,[2] pyridine *N*-oxides,[2] pyrroles,[2] pyrido[3,4-*c*]pyridazine derivatives,[2] 6-substituted pyridine-3,4-dicarboxylates and their *N*-oxides,[7] as well as triazafulvalene derivatives[4] (Scheme 1).

However, when we tried to prepare 4-(dimethylamino)pent-3-en-2-one (**4a**) by treatment of acetone (**1a**) with *N*,*N*-dimethylacetamide dimethyl acetal (DMADMA) under microwave irradiation, we observed that N^1,N^1,N^3,N^3,5-pentamethylbenzene-1,3-diamine (**9a**) was formed.

Aromatic compounds play an important role in organic chemistry as functional materials and bioactive compounds. Many methods leading to benzene derivatives via cyclization of unsaturated compounds are described in the literature. These are: the Diels–Alder reaction, which due to its broad scope and simplicity of operation, is the most powerful and versatile synthetic method for construction of six-membered rings ever since its discovery in 1928,[8] Bergmann cyclization,[9] Meyers,[10] Saito,[11] and Schmittel[12] reactions.

Transition metal-catalyzed cycloadditions of alkynes provide an efficient method for constructing aromatic derivatives.[13] Recently, a cobalt-catalyzed neutral Diels–Alder reaction,[14] an AuCl-catalyzed [3+3] cycloaddition,[15] which allows excellent control of substitution at the benzene ring, and a cationic rhodium(I)/BINAP complex-catalyzed decarboxylative [2+2+2] cycloaddition[16] as a new route to substituted phenols, have been described. Additionally, Bronsted acid activated chiral oxazaborolidine complexes,[17] diarylprolinol silyl ethers as catalysts,[18a,b] chiral Indium(III) complex,[18c] [$AlCl_3$+2THF],[18d] cationic silicon Lewis acids,[18e] and also rhenium and manganese-catalyzed syntheses[18f] of aromatic compounds have also been reported. Ring-closure metathesis is also an important method. In this manner, various substituted phenol and other benzene derivatives were prepared.[19] Because of the limitations of

* Corresponding author. E-mail address: branko.stanovnik@fkkt.uni-lj.si (B. Stanovnik).

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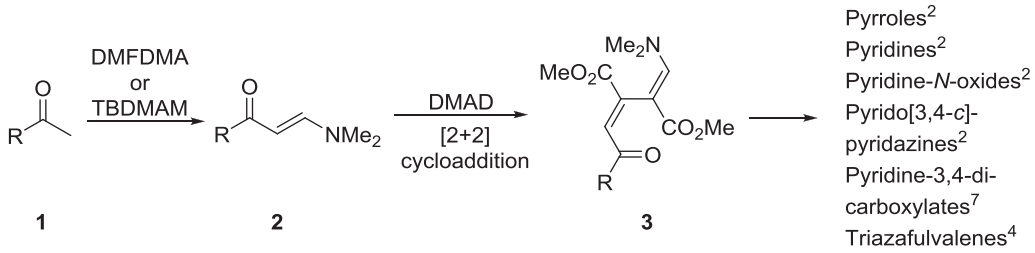


Scheme 1.

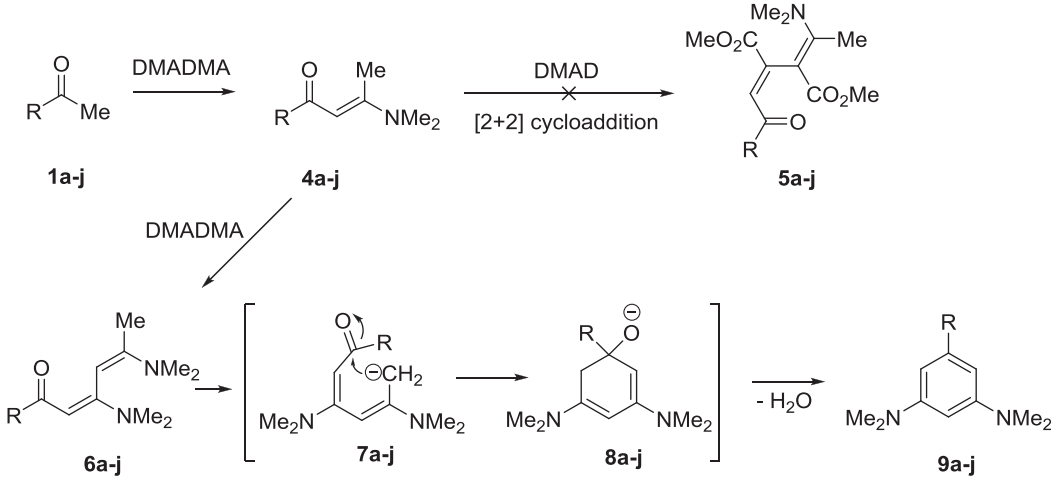
the synthetic methods most of the diaminobenzene derivatives are 1-substituted-2,4-diaminobenzene derivatives.[20] 1-Alkyl-3,5-diaminobenzene derivatives with various alkyl chain lengths have been prepared from commercially available di-*tert*-butylmalonate and 3,5-dinitrobenzyl chloride.[21]

3,5-Bis(dimethylamino)toluene was previously prepared from acetylacetone and dimethylamine via 4-*N*,*N*-dimethylamino-3-penten-2-one, which was converted with tetrakis(dimethylamino)-titanium into *N*,*N*,*N*′,*N*′-tetramethyl-1,3-pentadiene-2,4-diamine, followed by treatment with acetyl chloride and potassium *tert*-butoxide. When propionyl chloride was used, 3,5-bis(dimethylamino)-1-ethylbenzene was obtained.[22] The formation of 3,5-bis(dimethylamino)toluene was also observed in the photochemical heterolysis of 3,5-bis(dimethylamino)benzyl alcohols and esters in connection with the studies of aryl carbenium ions substituted with *meta*-π-donors.[23,24]

In this communication we report on a simple one-pot metal-free synthesis of polysubstituted aromatic compounds from polysubstituted enaminones prepared from alkyl ketones or compounds with an α-methylene group next to the carbonyl group, and *N*,*N*-dimethylacetamide dimethyl acetal (DMADMA).

2. Results and discussion

When we treated acetone (**1a**) with DMADMA instead of DMFDMA a mixture of (*E*)-4-(dimethylamino)pent-3-en-2-one (**4a**) and **9a** were formed. Compound **4a** did not react with dimethyl acetylenedicarboxylate (DMAD) to give the corresponding **5a** via [2+2] cycloaddition reaction. When we tried to improve the yield of **4a** by using excess DMADMA at elevated temperature; 3,5-bis(dimethylamino)toluene (**9a**) was isolated as the main product in a one-pot procedure (Scheme 2). Since the formation of 3,5-bis(dimethylamino)toluene is a simple one-pot procedure, we decided to examine the scope and limitations of this methodology for the construction of polysubstituted benzene derivatives. In this connection we selected several types of methyl ketones (acetyl compounds).



Scheme 2. Synthesis of N^1,N^1,N^3,N^3-tetramethyl-5-(substituted)benzene-1,3-diamines **9a**–**j**.

The first group represents simple methyl ketones, such as acetone (**1a**), pentan-2-one (**1b**), acetophenone (**1c**), 2-acetylpyridine (**1d**), 2-acetylpyrazine (**1e**), 3-acetyl-1-methylpyrrole (**1f**), 2-acetylthiophene (**1g**), 3-acetylthiophene (**1h**), 2-acetylfuran (**1i**) and 4-nitroacetophenone (**1j**). They were treated with DMADMA in 2.5 M ratio in a closed vessel under microwave conditions at temperatures between 130 and 170 °C for 12–35 min. After isolation and purification of the crude products we obtained 1-substituted 3,5-bis(dimethylamino)benzene derivatives **9a**–**j** (Scheme 2, Table 1).

Table 1
The N^1,N^1,N^3,N^3-tetramethyl-5-(substituted)benzene-1,3-diamines

Compound **9**	R	Yield [%]	Mp [°C]
a	Me	30	Oil
b	Pr	10	Oil
c	Ph	16	40–43[a]
d	Pyridyl-2	19	76–80
e	Pyrazinyl-2	19	96–101
f	1-Methyl- pyrrolyl-3	8	90–96
g	Thienyl-2	30	Oil
h	Thienyl-3	21	83–89
i	Furyl-2	49	Oil
j	4′–O_2N–C_6H_4	30	112–117

[a] The starting acetophenone (**1c**) was incorporated in the crystal structure.

The formation of the final products can be explained in the following way: the methyl group of the methyl ketones **1a**–**j** reacts with DMADMA to give the *N*,*N*-dimethylaminomethylene intermediates **4a**–**j**. The methyl group of **4a**–**j** reacts further with DMADMA to give polysubstituted butadienes **6a**–**j**, from which the corresponding anions **7a**–**j** are formed followed by rapid cyclization into **8a**–**i** and elimination of water to give the final products **9a**–**j**. The only exception is **1j** where the reaction under these conditions stops at **4j**. In order to carry out the reaction to the desired product **9j** the intermediate **4j** was heated with a large excess of DMADMA (Scheme 2).

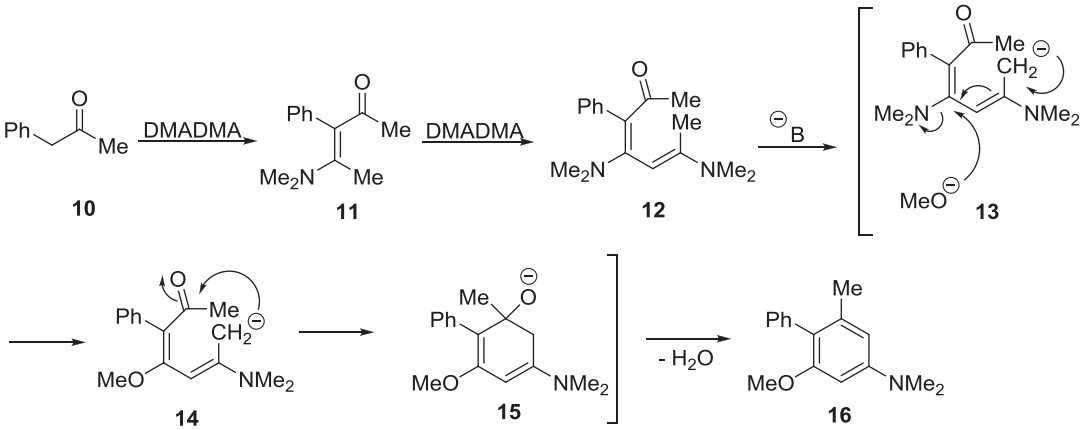
In the case of phenylacetone (**10**) the more reactive methylene group at position 1 reacts with DMADMA to form firstly 4-(dimethylamino)-3-phenylpent-3-en-2-one (**11**). The methyl group at position 4 reacts further with DMADMA to give **12**. In the next step, substitution of one dimethylamino group with a methoxy group takes place to form **14**, followed by cyclization into **15** and elimination of water to form 2-methoxy-*N*,*N*,6-trimethylbiphenyl-4-amine (**16**) as the final product (Scheme 3).

to **30a**,**b**. Intermediates **25a**,**b** can than be transformed under reaction conditions in a *retro-Claisen* reaction into **4a**,**c**, which react further with DMADMA to form **6a**,**c**. The latter intermediates can also be formed from **30a**,**b** in a *retro-Claisen reaction*. Intermediate **6a** cyclizes into **9a**. On the other hand, intermediate **6c** cyclizes in the reaction sequence **26**→**27**→**28** into **29**. The reaction path **30a**,**b**→**31a**,**b**→**9a** (and **29**) seems to be less plausible (Scheme 5).

Ethyl acetoacetate (**32**) reacts analogously via intermediates **33** and **34** to form ethyl 2,4-bis(dimethylamino)-6-methylbenzoate (**35**) (Scheme 6).

The reaction of dimethyl malonate (**36**) proceeds via intermediates **37**–**39** to afford the corresponding methyl 2,4-bis(dimethylamino)-6-methoxybenzoate (**40**). The reaction with diethyl malonate (**41**) proceeds analogously, thus leading to the corresponding ethyl 2,4-bis(dimethylamino)-6-methoxybenzoate (**42**) (Scheme 7).

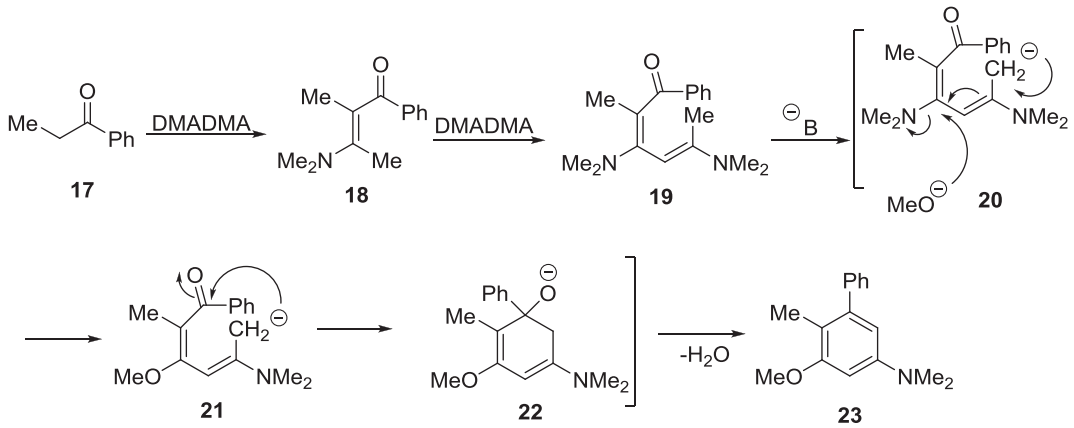
Methyl hippurate (**43**) produced *N*-[2,4-bis(dimethylamino)-6-methoxyphenyl]benzamide (**47**) via intermediates **44**–**46** (Scheme 8).



Scheme 3. Synthesis of 2-methoxy-*N*,*N*,6-trimethylbiphenyl-4-amine (**16**).

In the case of propiophenone (**17**) the reaction took place at the methylene group to form in the reaction sequence **18**→**19**→**20**→**21**→**22** the isomeric biphenyl derivative 5-methoxy-*N*,*N*,6-trimethylbiphenyl-3-amine (**23**) (Scheme 4).

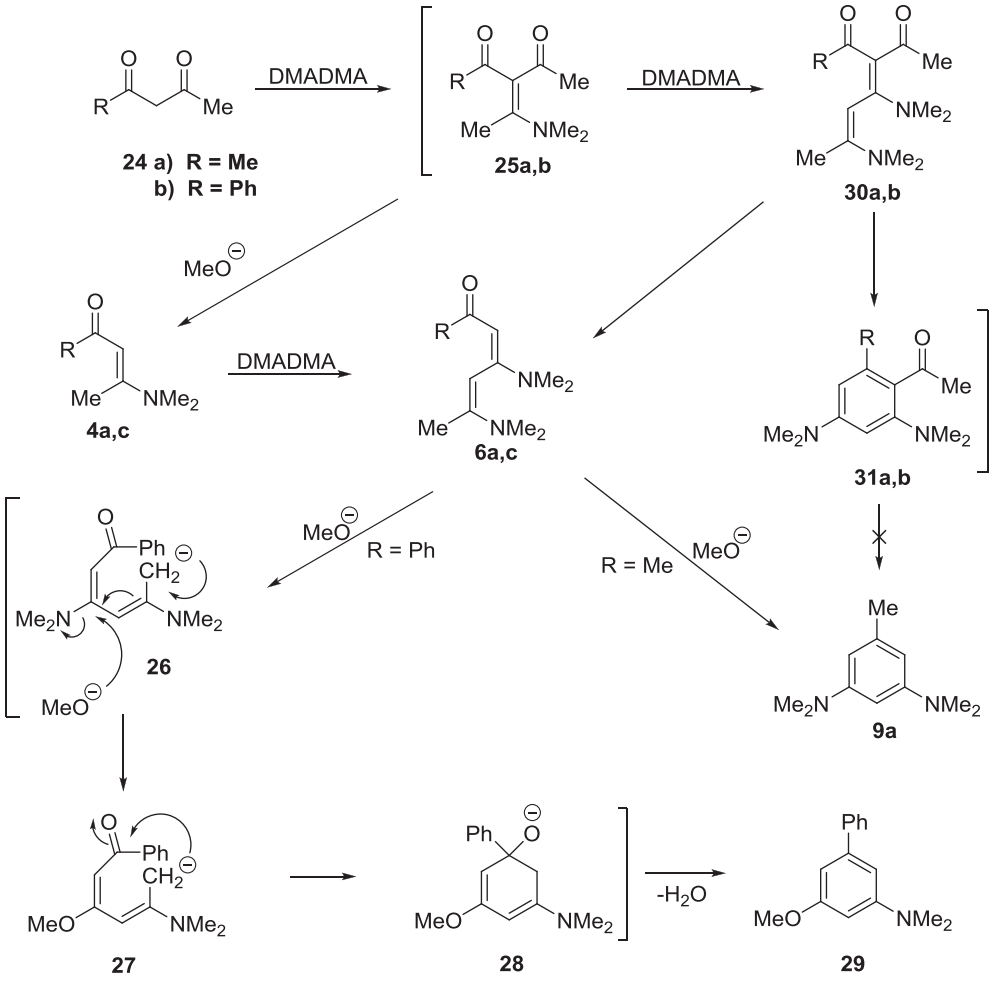
In some instances, intermediates were isolated and characterized, such as (*E*)-3-(dimethylamino)-1-phenylbut-2-ene-1-one (**4c**) and 3-(dimethylamino)-1-(4-nitrophenyl)but-2-ene-1-one (**4j**).



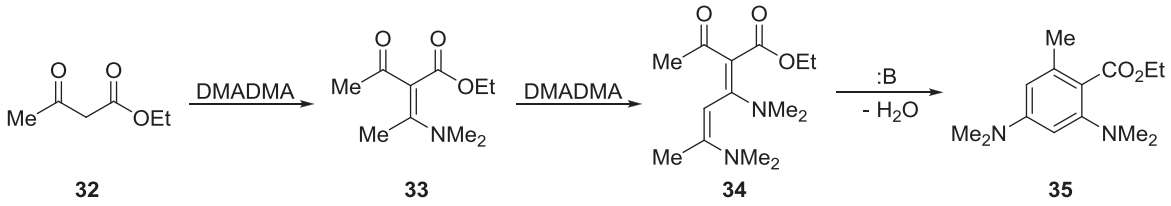
Scheme 4. Synthesis of 5-methoxy-*N*,*N*,6-trimethylbiphenyl-3-amine (**23**).

The 1,3-diketone representatives acetylacetone (**24a**) and benzoylacetone (**24b**) react with DMADMA first at the methylene group to form intermediates **25a**,**b**. These can react further with DMADMA

Methyl cyanoacetate (**48**) afforded, via intermediate **49**, (2*Z*,4*Z*)-methyl 2-cyano-3,5-bis(dimethylamino)hexa-2,4-dienoate (**50**), which did not cyclize into the benzene derivative due to



Scheme 5. Cyclization of 1,3-diketones **24a**,**b** into N^1,N^1,N^3,N^3,5-pentamethylbenzene-1,3-diamine (**9a**) and 5-methoxy-*N*,*N*-dimethylbiphenyl-3-amine (**29**).



Scheme 6. Synthesis of ethyl 2,4-bis(dimethylamino)-6-methylbenzoate (**35**).

inappropriate orientation of the methyl group in respect to the ester group (Scheme 9).

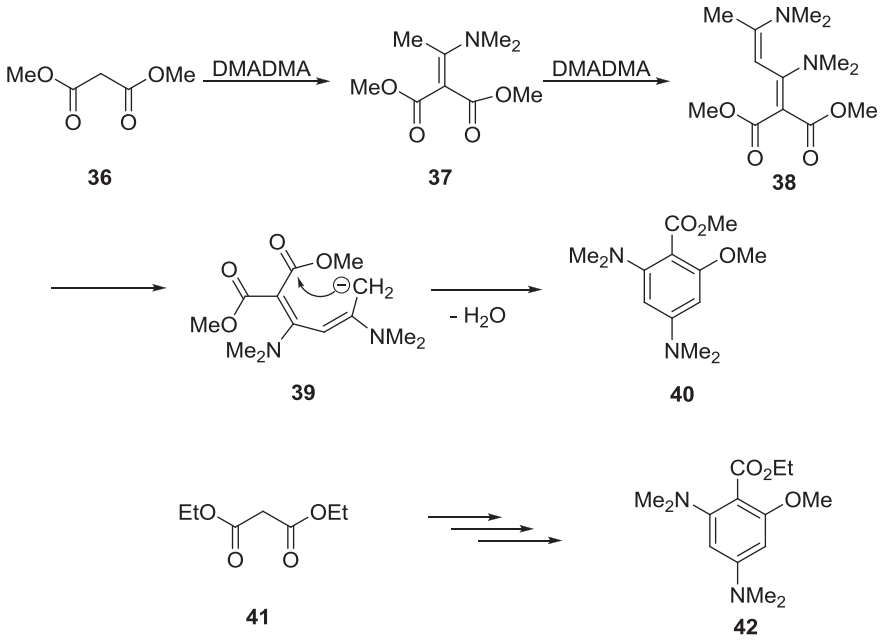
3. Structure determination

The structures of the new compounds were determined by ^{1}H and ^{13}C NMR spectroscopy, HRMS and microanalyses for C, H, and N.

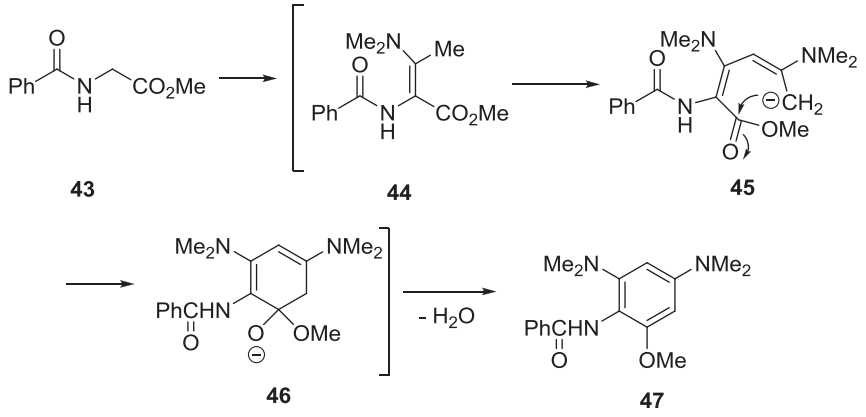
In many cases the structure of the final product was not straightforward, therefore additional methods for determination of the structures had to be applied. Two-dimensional nuclear magnetic resonance spectroscopy (2D NMR), mainly ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC, were the means of gathering the missing information, to correctly determine the structures. In the case of products **9a**–**j** the structure determination was straightforward. Because of the symmetry of the products, the ^{1}H NMR spectra showed a triplet with a *meta* coupling constant for the 4-H proton in the range between 5.95 (R=methyl) and 6.19 (R=pyrazinyl-2) and a doublet integrated for 2 for the 2-H and 6-H protons in the range between 6.03 (R=methyl) and 6.78 (R=pyrazinyl-2) (Fig. 1).

In the case of the reaction between phenylacetone (**10**) and DMADMA, more than one product could be formed. Besides the reaction path *i* that leads to the actual product via intermediates **11**–**15** (Scheme 3), reaction path *ii* could also be probable, thus five different products could be formed (Scheme 10). After careful evaluation of the information derived from the ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC NMR spectra, we were able to confirm, without a doubt that the structure of the product is **16**.

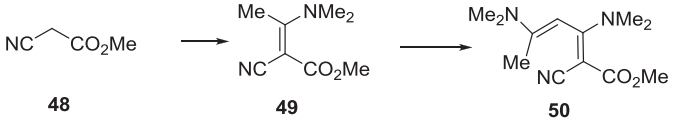
The absence of the benzyl CH_2 group signal in the ^{1}H NMR spectrum meant that structures **16c** and **16d** were not those of the product. The characteristic lower chemical shifts for the protons on the diamine bearing benzene ring, made it easy to distinguish the



Scheme 7. Synthesis of methyl 2,4-bis(dimethylamino)-6-methoxybenzoate (**40**) and ethyl 2,4-bis(dimethylamino)-6-methoxybenzoate (**42**).



Scheme 8. Synthesis of *N*-(2,4-bis(dimethylamino)-6-methoxyphenyl)benzamide (**47**).



Scheme 9. (2*Z*,4*Z*)-methyl 2-cyano-3,5-bis(dimethylaminohexa-2,4-dienoate (**50**).

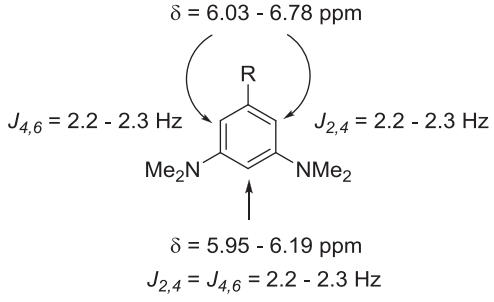
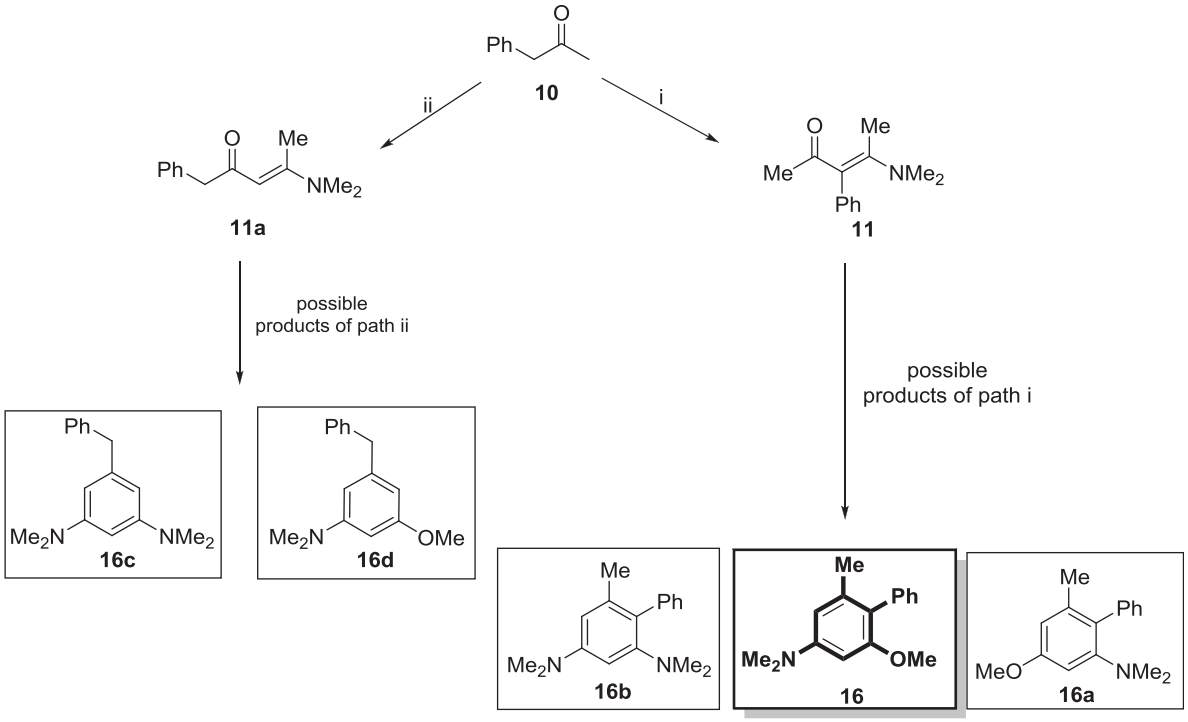


Fig. 1. Chemical shifts and coupling constants of the benzene protons of products **9a**–**j**.

H3 and H5 protons from other aromatic protons, which were at higher chemical shifts. The *meta* coupling constant J=2.5 Hz was in accordance with the expected structure (Fig. 2). The information that was needed to correctly position the substituents was collected with the before mentioned 2D NMR experiments. From $^{1}H-^{13}C$ HMBC NMR we could see the correlation of 3-H and 5-H with 1-C. The same correlation with 1-C was seen for the methyl protons and for 2′-H. The correlation of 5-H with the methyl group carbon made it possible to distinguish between 3-H and 5-H, because 3-H did not correlate with the methyl carbon. Both 3-H and 5-H showed a weak correlation through two bonds with 4-C, which was also correlated with the methyl protons of the dimethylamino



Scheme 10. Possible products of the reaction between phenylacetone (**10**) and DMADMA.

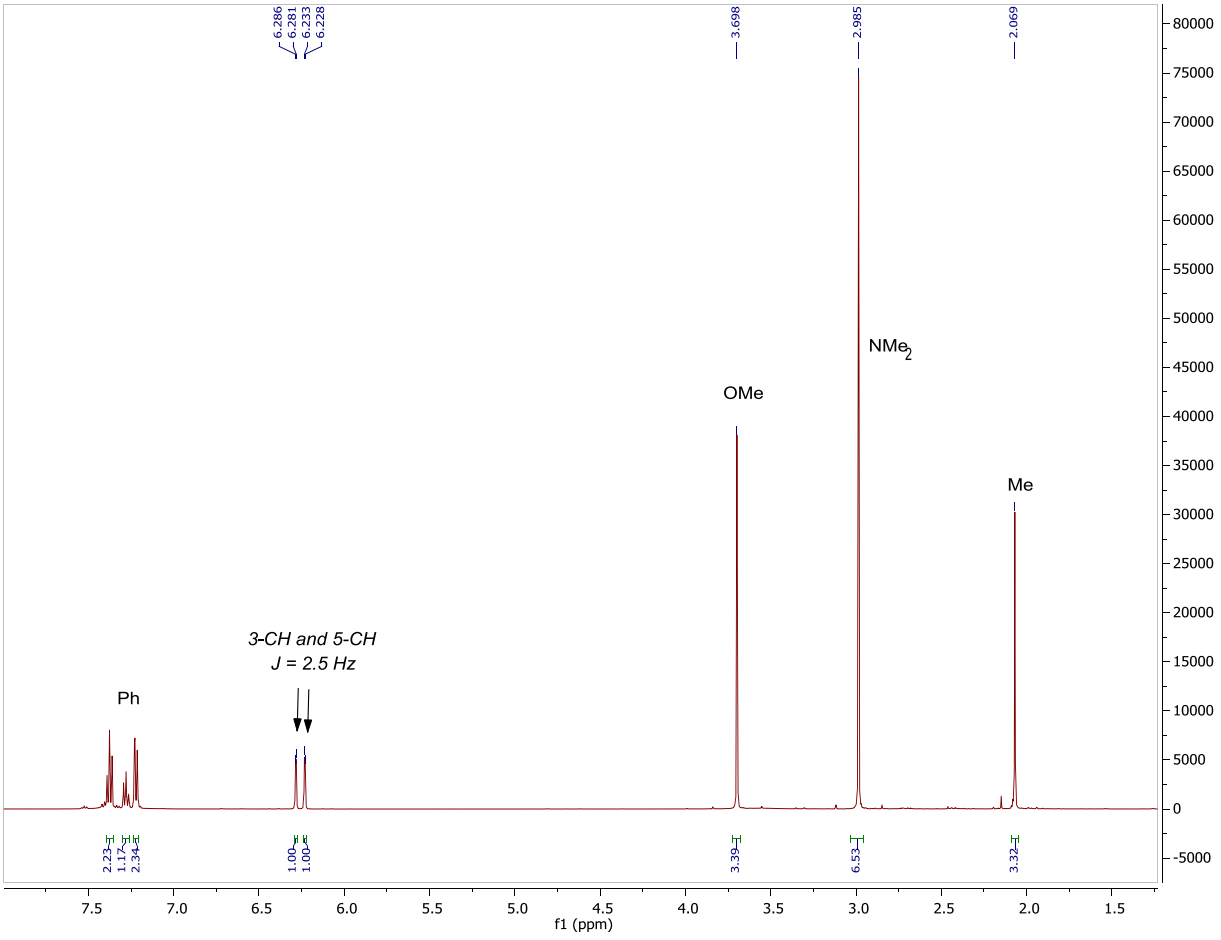


Fig. 2. ^{1}H NMR spectrum of **16**.

group. The protons on the methoxy group correlated with 2-C, and a weak correlation through two bonds between 3-H and 2-C meant that the methoxy group is positioned next to the 3-H proton. The NOESY experiment also showed the appropriate correlations. The correlation between 5-H and the methyl group carbon and the correlation between 3-H and methoxy carbon meant that these groups are closely related through space, thus confirming the structure of **16** (Fig. 3).

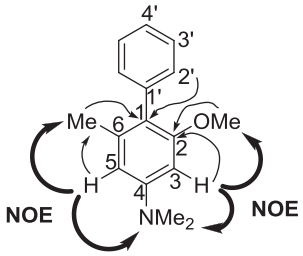


Fig. 3. Key 2D NMR correlations for compound **16**.

Other products, whose structure could be ambiguous, had their structure determined in the same manner as shown in the case of **16**. The structures of compounds **4c**, **9c**, **9d**, **9e**, **9h**, **40** and **50** were confirmed by X-ray analyses (Fig. 4).

4. Conclusion

In conclusion, this paper reports a one-pot metal-free synthesis of polyfunctional benzene derivatives, based simply on the reaction of methyl ketones or compounds with an α-methylene group next to the carbonyl group and *N*,*N*-dimethylacetamide dimethyl acetal.

5. Experimental

5.1. General

Melting points were determined on a Stanford Research Systems MPA100 OptiMelt automated melting point system. The NMR spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C and on a Bruker Avance III UltraShield 500 plus at 500 MHz for ^{1}H and 126 MHz for ^{13}C, using $CDCl_3$ and DMSO-d_6 with Me_4Si as the internal standard, as solvents. Mass spectra were recorded on an Agilent 6224 Accurate Mass TOF LC/MS spectrometer, IR spectra on a Perkin Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin–Elmer CHN Analyzer 2400 II. Column chromatography (CC) was performed on silica gel (Fluka, Silica gel 60, particle size 35–70 μm). Starting compounds **1a**–**j**, **10**, **17**, **24a**,**b**, **32**, **36**, **41** and **43** are commercially available.

5.2. General procedure for the preparation of N^1,N^1,N^3,N^3-tetramethyl 5-(substituted)benzene-1,3-diamines and related compounds

To the starting compound (3 mmol), being methyl ketones or compounds with an active methylene group, 2.5 equiv of DMADMA (*N*,*N*-dimethylacetamide dimethyl acetal) (7.5 mmol) were added. The resulting mixture was heated and stirred in a closed vessel at an automatically-controlled constant temperature (300 W) in a CEM Corporation Discover microwave unit. The reaction temperature varied from 130 °C to 170 °C, depending on the progress of the reaction, and the irradiation times were typically short—between 12 and 35 min.

*5.2.1. N^1,N^1,N^3,N^3,5-Pentamethylbenzene-1,3-diamine (**9a**).*

(a) *From acetone*: The product was prepared from acetone (**1a**; 174 mg, 3 mmol), 140 °C, 20 min; column chromatography (ethyl acetate/petroleum ether=1:7). Yield: 10% (54 mg), yellow oil. The product was identified only with ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.28 (3H, s, CH_3); 2.91 (12H, s, 2× N(CH_3)$_2$); 5.94 (1H, t, *J*=2.2 Hz, 2-C*H*); 6.03 (2H, d, *J*=2.2 Hz, 4-C*H* in 6-C*H*).

(b) *From pentane-2,4-dione (acetylacetone)*: The product was prepared from pentane-2,4-dione (**24a**; 300 mg, 3 mmol), 140 °C, 30 min; column chromatography (ethyl acetate/petroleum ether=1:5). Yield: 30% (160 mg), black oil.[22,24] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.28 (3H, s, CH_3); 2.92 (12H, s, 2× N(CH_3)$_2$); 5.95 (1H, t, *J*=2.2 Hz, 2-C*H*); 6.03 (2H, d, *J*=2.2 Hz, 4-C*H* and 6-C*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 22.7, 41.3, 95.9, 104.1, 139.5, 152.3. EI-HRMS: *m*/*z*=179.153 (MH^+) found; $C_{11}H_{19}N_2$ calculated: *m*/*z*=179.153. ν_{max} 3068, 2915, 2790, 1698, 1670, 1586, 1487, 1438, 1380, 1365, 1154, 803.

*5.2.2. N^1,N^1,N^3,N^3-Tetramethyl-5-propylbenzene-1,3-diamine (**9b**).* The product was prepared from 2-pentanone (**1b**; 258 mg, 3 mmol), 140 °C, 60 min; column chromatography (ethyl acetate/petroleum ether=1:10). The isolated yellow oil was found to be a mixture of the aromatic product and the starting 2-pentanone in approximately 1.5:1 ratio in favour of the product. The longer reaction time is a consequence of the non-polar character of the reaction mixture, which leads to longer reaction times to reach the high temperature that is needed for the reaction to proceed. With the help of HSQC and HMBC 2D NMR techniques, we were able to assign the signals, corresponding to the aromatic product. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.96 (3H, t, *J*=7.5 Hz, CH_3); 1.62–1.68 (2H, m, 2′-CH_2); 2.50 (2H, t, *J*=7.5 Hz, 1′-CH_2); 2.92 (12H, s, 2× N(CH_3)$_2$); 5.96 (1H, t, *J*=2.3 Hz, 2-C*H*); 6.04 (2H, *J*=2.3 Hz, 4-C*H* and 6-C*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.2, 24.9, 39.3, 40.9, 95.8, 103.2, 144.1, 151.74. EI-HRMS: *m*/*z*=206.1857 (MH^+) found; $C_{13}H_{23}N_2$ calculated *m*/*z*=207.1856 (MH^+). ν_{max} 2954, 2928, 2867, 2790, 1586, 1485, 1374, 1305, 1155, 1126, 1012, 806, 692.

*5.2.3. N^3,N^3,N^5,N^5-Tetramethylbiphenyl-3,5-diamine (**9c**).* The product was prepared from acetophenone (**1c**; 360 mg, 3 mmol), 140 °C, 15 min; column chromatography (ethyl acetate/petroleum ether=1:5), crystallization from ethyl acetate/heptane afforded brown crystals. Although the structure was determined by single crystal X-ray analysis, the ^{1}H and ^{13}C NMR spectrum showed the presence of the starting acetophenone. Using ^{1}H NMR we evaluated that the ratio between the starting compound and the product is approximately 1:1. The corresponding product signals in ^{1}H and ^{13}C NMR spectrums were assigned by subtracting the peaks of acetophenone. The determined melting point for the mixture: 40–43 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.99 (12H, s, 2× N(CH_3)$_2$); 6.12 (1H, br s, 4-C*H*); 6.38 (2H, d, *J*=2.2 Hz, 2-C*H* and 6-C*H*); 7.43–7.47 (2H, m, Ph); 7.49–7.54 (1H, m, Ph); 7.86–7.90 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 41.2, 96.9, 102.2, 127.2, 128.8, 132.5, 143.2, 183.5. EI-HRMS: *m*/*z*=241.1817 (MH^+) found; $C_{16}H_{21}N_2$ calculated *m*/*z*=241.1699 (MH^+). ν_{max} 2876, 2848, 2787, 1586, 1572, 1485, 1425, 1304, 1160, 1062, 1023, 812, 685.

*5.2.4. N^1,N^1,N^3,N^3-Tetramethyl-5-(pyridin-2-yl)benzene-1,3-diamine (**9d**).* The product was prepared from 2-acetylpyridine (**1d**; 363 mg, 3 mmol), 160 °C, 20 min; column chromatography (ethyl acetate/petroleum ether=1:2). Yield: 19% (82 mg), yellow-green solid; mp=76–80 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.02 (12H, s, 2× N(CH_3)$_2$); 6.18 (1H, t, *J*=2.3 Hz, 2-C*H*); 6.78 (2H, d, *J*=2.2 Hz, 4-C*H* and 6-C*H*); 7.18–7.22 (1H, m, Py); 7.68–7.74 (2H, m, Py); 8.68 (1H, dt, J_1=4.9 Hz, J_2=1.4 Hz, 4′-C*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 41.0, 98.5, 101.6, 121.0, 121.8, 136.4, 140.9, 149.3,

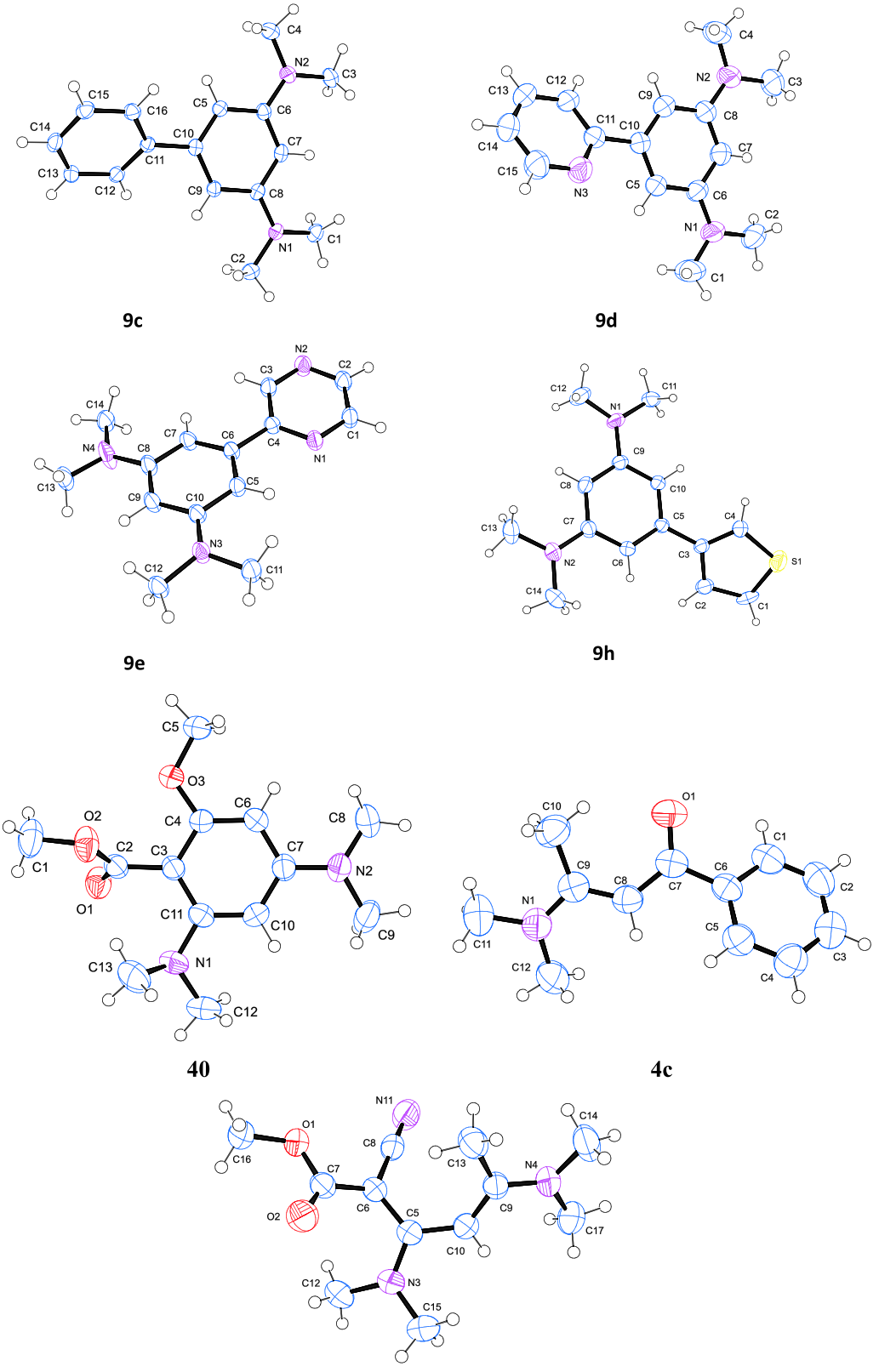


Fig. 4. ORTEP view of compounds **9c**, **9d**, **9e**, **9h**, **40**, **4c**, **50**.

152.1, 159.1. EA $C_{15}H_{19}N_3$ requires: C 74.65; H 7.94; N 17.41. Found: C 74.42; H 7.78; N 17.07. EI-HRMS: m/z=242.1652 (MH^+) found; $C_{15}H_{20}N_3$ calculated: m/z=242.1652 (MH^+). ν_{max} 3049, 2977, 2875, 2789, 1721, 1662, 1578, 1561, 1377, 1278, 1237, 1057.

*5.2.5. N^1,N^1,N^3,N^3-Tetramethyl-5-(pyrazin-2-yl)benzene-1,3-diamine (**9e**).* The product was prepared from 2-acetylpyrazine (**1e**; 366 mg, 3 mmol), 160 °C, 20 min; column chromatography (ethyl acetate/petroleum ether=1:2), crystallization from ethyl acetate/heptane. Yield: 19% (138 mg), yellow-brown crystals; mp=96–101 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.03 (12H, s, 2× N(CH_3)$_2$); 6.19 (1H, t, J=2.2 Hz, 2-C*H*); 6.78 (2H, d, J=2.2 Hz, 4-C*H* and 6-C*H*); 8.47 (1H, d, J=2.2 Hz, 3′-C*H*); 8.61 (1H, dd, J_1=2.5 Hz, J_2=1.5 Hz, 5′-C*H*); 9.00 (1H, s, 6′-C*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 40.9, 98.7, 101.0, 137.7, 142.5, 142.7, 143.8, 152.2, 154.5. EA $C_{14}H_{18}N_4$ requires: C 69.39; H 7.49; N 23.12. Found: C 69.23; H 7.47; N 22.87. EI-HRMS: m/z=243.1608 (MH^+) found; $C_{14}H_{19}N_4$ calculated: m/z=243.1604 (MH^+). ν_{max} 3046, 2880, 2848, 2797, 1747, 1589, 1571, 1393, 1304, 1141, 1013, 813.

*5.2.6. N^1,N^1,N^3,N^3-Tetramethyl-5-(1-methyl-1H-pyrrol-3-yl)benzene-1,3-diamine (**9f**).* The product was prepared from 3-acetyl-1-methylpyrrole (**1f**; 369 mg, 3 mmol), 170 °C, 25 min; column chromatography (ethyl acetate/petroleum ether=1:1). Yield: 8% (58 mg), white solid; mp=90–96 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.96 (12H, s, 2× N(CH_3)$_2$); 3.67 (3H, s, CH_3); 6.01 (1H, t, J=2.2 Hz, 2-C*H*); 6.36 (2H, d, J=2.2 Hz, 4-C*H* and 6-C*H*); 6.41 (1H, t, J=2.2 Hz, 4′-C*H*); 6.60 (1H, t, J=2.5 Hz, 5′-C*H*); 6.87 (1H, t, J=2.0 Hz, 2′-C*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 36.3, 41.1, 96.2, 100.8, 106.8, 118.7, 122.2, 126.8, 137.2, 152.0. EA $C_{15}H_{21}N_3$*1/5 MeOH requires: C 73.10; H 8.80; N 16.82. Found: C 73.31; H 8.43; N 16.41. EI-HRMS: m/z=244.1809 (MH^+) found; $C_{15}H_{22}N_3$ calculated: m/z=244.1808 (MH^+). ν_{max} 3114, 3077, 2979, 2872, 2788, 1715, 1649, 1571, 1505, 1389, 1310, 1154, 786.

*5.2.7. N^1,N^1,N^3,N^3-Tetramethyl-5-(thiophen-2-yl)benzene-1,3-diamine (**9g**).* The product was prepared from 2-acetylthiophene (**1g**; 441 mg, 3.5 mmol), 150 °C, 20 min; column chromatography (ethyl acetate/petroleum ether=1:5). Yield: 30% (258 mg), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.02 (12H, s, 2× N(CH_3)$_2$); 6.09 (1H, t, J=2.2 Hz, 2-C*H*); 6.46 (2H, d, J=2.2 Hz, 4-C*H* and 6-C*H*); 7.08 (1H, dd, J_1=5.1 Hz, J_2=3.5 Hz, 4′-C*H*); 7.26 (1H, dd, J_1=5.1 Hz, J_2=1.2 Hz, 3′-C*H*); 7.31 (1H, dd, J_1=3.6 Hz, J_2=1.2 Hz, 5′-C*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 41.3, 97.5, 101.3, 123.2, 124.4, 127.9, 136.0, 146.8, 152.4. EI-HRMS: m/z=247.1267 (MH^+) found; $C_{14}H_{19}N_2S$ calculated: m/z=247.1263 (MH^+). ν_{max} 3098, 3070, 2979, 2796, 1578, 1481, 1307, 1210, 1126, 804.

*5.2.8. N^1,N^1,N^3,N^3-Tetramethyl-5-(thiophen-3-yl)benzene-1,3-diamine (**9h**).* The product was prepared from 3-acetylthiophene (**1h**; 428 mg, 3.4 mmol), 140 °C, 12 min; column chromatography (ethyl acetate/petroleum ether=1:5). Yield: 21% (174 mg), brown crystalline solid; mp=83–89 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.01 (12H, s, 2× N(CH_3)$_2$); 6.10 (1H, t, J=2.2 Hz, 2-C*H*); 6.43 (2H, d, J=2.2 Hz, 4-C*H* and 6-C*H*); 7.34–7.42 (2H, m, 2′-C*H* and 5′-C*H*); 7.43 (1H, dd, J_1=2.8 Hz, J_2=1.5 Hz, 4′-C*H*). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 41.3, 97.3, 100.4, 101.9, 120.4, 125.8, 127.45, 137.8, 152.4. EA $C_{14}H_{18}N_2S$ requires: C 68.25; H 7.36; 11.37. Found: C 68.02; H 7.47; N 11.24. EI-HRMS: m/z=247.1267 (MH^+) found; $C_{14}H_{19}N_2S$ calculated: m/z=247.1263 (MH^+). ν_{max} 3100, 3084, 2874, 2798, 1578, 1486, 1439, 1373, 1292, 1249, 1156, 1062, 1020, 776.

*5.2.9. 5-(Furan-2-yl)-N^1,N^1,N^3,N^3-tetramethylbenzene-1,3-diamine (**9i**).* The product was prepared from 2-acetylfuran (**1i**; 235 mg, 2.14 mmol), 140 °C, 15 min; column chromatography (ethyl acetate/petroleum ether=1:1). Yield: 49% (241 mg), yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.99 (12H, s, 2× N(CH_3)$_2$); 6.06 (1H, t, J=2.2 Hz, 2-C*H*); 6.45 (1H, dd, J_1=3.2 Hz, J_2=1.8 Hz, 3′-C*H*); 6.54 (2H, d, J=2.2 Hz, 4-C*H* and 6-C*H*); 6.60–6.62 (1H, m, 4′-C*H*); 7.45 (1H, dd, J_1=1.8 Hz, J_2=0.9 Hz, 5′-C*H*). ^{13}C NMR ($CDCl_3$,125 MHz): δ 41.1, 97.4, 98.7, 104.6, 111.5, 132.0, 141.6, 152.0, 155.5. EI-HRMS: m/z=231.1494 (MH^+) found; $C_{14}H_{19}N_2O$ calculated: m/z=231.1492 (MH^+). ν_{max} 3139, 3108, 2981, 2847, 2794, 1582, 1562, 1498, 1308, 1152, 982, 794.

*5.2.10. N^3,N^3,N^5,N^5-Tetramethyl-4′-nitrobiphenyl-3,5-diamine (**9j**).* The product was prepared from 3-(dimethylamino)-1-(4-nitrophenyl)but-2-en-1-one (**4j**; 151 mg, 0.65 mmol) and a larger amount of DMADMA (6.3 equiv, 0.6 mL), 140 °C, 30 min; column chromatography (ethyl acetate/petroleum ether=1:5). Yield: 30% (57 mg), red wax; mp=112–117 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.01 (12H, s, 2× N(CH_3)$_2$); 6.13 (1H, t, J=2.2 Hz, 4-C*H*); 6.33 (2H, d, J=2.2 Hz, 2-C*H* and 6-C*H*); 7.73 (2H, d, J=8.8 Hz, 2′-C*H* and 6′-C*H*); 8.25 (2H, d, J=8.8 Hz, 3′-C*H* and 5′-C*H*). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 40.9, 97.4, 101.4, 123.8, 128.1, 140.6, 146.8, 149.8, 152.1. EI-HRMS: m/z=286.155 (MH^+) found; $C_{16}H_{20}N_3O_2$ calculated: m/z=286.155 (MH^+). ν_{max} 2916, 2849, 2799, 1576, 1510, 1482, 1441, 1383, 1336, 1315, 1277, 1240, 1159, 1107, 1023, 983, 857, 814, 751.

*5.2.11. 2-Methoxy-N,N,6-trimethylbiphenyl-4-amine (**16**).* The product was prepared from phenylacetone (**10**; 402 mg, 3 mmol), 160 °C, 35 min; column chromatography (ethyl acetate/petroleum ether=1:10). Yield: 27% (195 mg), brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.10 (3H, s, CH_3); 3.02 (6H, s, N(CH_3)$_2$); 3.73 (3H, s, OCH_3); 6.26 (1H, d, J=2.4 Hz, 3-C*H*); 6.31 (1H, d, J=2.5 Hz, 5-C*H*); 7.21–7.27 (2H, m, Ph); 7.30–7.35 (1H, m, Ph); 7.37–7.44 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 21.4, 41.1, 56.1, 94.7, 107.0, 120.5, 126.6, 128.2, 129.8, 131.2, 151.1, 158.2. EA $C_{16}H_{19}NO$*1/2H_2O requires: C 76.77; H 8.05; N 5.60. Found: C 76.87; H 7.71; N 5.25. EI-HRMS: m/z=242.1542 (MH^+) found; $C_{16}H_{20}NO$ calculated: 242.1539 (MH^+). ν_{max} 3052, 3004, 2986, 2918, 2838, 1711, 1608, 1559, 1487, 1469, 1364, 1240, 1156, 1092, 936.

*5.2.12. 5-Methoxy-N,N,6-trimethylbiphenyl-3-amine (**23**).* The product was prepared from propiophenone (**17**; 402 mg, 3 mmol), 140 °C, 15 min; column chromatography (ethyl acetate : petroleum ether=1:10). Yield: 17% (126 mg), yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.02 (3H, s, Ph-CH_3); 2.93 (6H, s, N(CH_3)$_2$); 3.86 (3H, s, OCH_3); 6.26 (1H, d, J=2.5 Hz, 2-C*H*); 6.32 (1H, d, J=2.5 Hz, 4-C*H*); 7.31–7.40 (5H, m, Ph). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 12.5, 41.1, 55.6, 95.7, 107.0, 112.9, 126.7, 128.0, 129.4, 142.9, 143.6, 149.5, 158.7. EI-HRMS: m/z=242.1541 (MH^+) found; $C_{16}H_{20}NO$ calculated m/z=242.1539 (MH^+). ν_{max} 2988, 2933, 2863, 2791, 1604, 1567, 1491, 1438, 1381, 1361, 1250, 1164, 1123, 1096, 1047, 1001, 809, 701.

*5.2.13. 5-Methoxy-N,N-dimethylbiphenyl-3-amine (**29**).* The product was prepared from 1-phenyl-1,3-butanedione (**24b**; 486 mg, 3 mmol), 140 °C, 20 min; column chromatography (ethyl acetate/petroleum ether=1:15). Yield: 13% (90 mg), yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.97 (6H, s, N(CH_3)$_2$); 3.83 (3H, s, OCH_3); 6.28 (1H, t, J=2.3 Hz, 4-C*H*); 6.50 (1H, dd, J_1=2.2 Hz, J_2=1.4 Hz, 2-C*H*); 6.54 (1H, dd, J_1=2.2 Hz, J_2=1.4 Hz, 6-C*H*); 7.37–7.44 (3H, m, Ph); 7.55–7.60 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 40.8, 55.3, 98.1, 101.2, 105.1, 127.3, 127.4, 128.6, 142.4, 143.4, 152.2, 161.1. EI-HRMS: m/z=228.1383 (MH^+) found; $C_{15}H_{18}NO$ calculated m/z=228.1383 (MH^+). ν_{max} 2992, 2935, 2838, 2803, 1684, 1586, 1573, 1490, 1440, 1367, 1269, 1207, 1147, 1062, 999, 825, 758.

*5.2.14. Ethyl 2,4-bis(dimethylamino)-6-methylbenzoate (**35**).* The product was prepared from ethyl acetoacetate (**32**; 390 mg, 3 mmol), 130 °C, 10 min; column chromatography (ethyl acetate/

petroleum ether=1:7). Yield: 8.8% (66 mg), yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.36 (3H, t, J=7.1 Hz, Et–CH_3); 2.28 (3H, s, Ph–CH_3); 2.77 (6H, s, N(CH_3)$_2$); 2.94 (6H, s, N(CH_3)$_2$); 4.34 (2H, q, J=7.1 Hz, Et–CH_2); 6.13 (1H, d, J=2.9 Hz, 3-CH); 6.14 (1H, d, J=2.9 Hz, 5-CH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.4, 20.9, 40.4, 44.4, 60.5, 99.6, 107.4, 116.0, 137.6, 151.7152.9, 170.6. EI-HRMS: m/z=251.1753 (MH^+) found; $C_{14}H_{23}N_2O_2$ calculated m/z=251.1754 (MH^+). ν_{max} 2976, 2933, 2791, 1713, 1596, 1560, 1477, 1365, 1253, 115, 1081, 814.

*5.2.15. Methyl 2,4-bis(dimethylamino)-6-methoxybenzoate (**40**).* The product was prepared from dimethyl malonate (**36**; 396 mg, 3 mmol), 160 °C, 35 min; column chromatography (ethyl acetate/petroleum ether=1:2). Yield: 40% (302 mg), brown solid; mp=84–86 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.81 (6H, s, N(CH_3)$_2$); 2.99 (6H, s, N(CH_3)$_2$); 3.82 (3H, s, OCH_3); 3.88 (3H, s, OCH_3); 5.84 (1H, d, J=2.1 Hz, CH); 5.86 (1H, d, J=2.1 Hz, CH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 40.6, 43.8, 52.2, 56.0, 88.9, 94.2, 104.6, 152.8, 153.2, 159.3, 169.6. EA $C_{13}H_{20}N_2O_3$ requires: C 61.88; H 7.99; N 11.10. Found: C 61.88; H 8.17; N 10.89. EI-HRMS: m/z=253.1547 (MH^+) found; $C_{13}H_{21}N_2O_3$ calculated: m/z=253.1547 (MH^+). ν_{max} (KBr) 2945, 2838, 2795, 1704, 1595, 1558, 1504, 1451, 1428, 1270, 1249, 1159, 1077, 1015, 978, 803.

*5.2.16. Ethyl 2,4-bis(dimethylamino)-6-methoxybenzoate (**42**).* The product was prepared from diethyl malonate (**41**; 480 mg, 3 mmol), 130 °C, 30 min; column chromatography (ethyl acetate/petroleum ether=1:5). Yield: 42%, brown solid; mp=38–44 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.35 (3H, t, J=7.1 Hz, Et–CH_3); 2.79 (6H, s, N(CH_3)$_2$); 2.96 (6H, s, N(CH_3)$_2$); 3.79 (3H, s, OCH_3); 4.34 (2H, q, J=7.1 Hz, Et–CH_2); 5.83 (1H, d, J=2.2 Hz, CH); 5.85 (1H, d, J=2.2 Hz, CH). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.4, 40.6, 43.9, 55.9, 60.8, 89.1, 34.4, 105.2, 152.7, 153.1, 159.1, 169.2. EA $C_{14}H_{22}N_2O_3$ requires: C 63.13; H 8.33; N 10.52. Found: C 62.92; H 8.18; N 10.26. EI-HRMS: m/z=555.3149 (2M+Na)$^+$ found; $C_{28}H_{44}N_4NaO_6$ calculated: m/z=555.3153 (2M+Na)$^+$. ν_{max} (KBr) 2979, 2941, 2837, 2800, 1709, 1598, 1559, 1506, 1452, 1428, 1303, 1249, 1156, 1090, 1016, 977, 806.

*5.2.17. N-(2,4-Bis(dimethylamino)-6-methoxyphenyl)benzamide (**47**).* The product was prepared from methyl hippurate (**43**; 328 mg, 1.7 mmol), 140 °C, 12 min; column chromatography (ethyl acetate/petroleum ether=1:1). Yield: 21% (112 mg), brown-white solid; mp=137–142 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.68 (6H, s, N(CH_3)$_2$); 2.96 (6H, s, N(CH_3)$_2$); 3.82 (3H, s, OCH_3); 6.03 (1H, d, J=2.6 Hz, 3′-CH); 6.05 (1H, d, J=2.6 Hz, 5′-CH); 7.30 (1H, br s, NH); 7.42–7.54 (3H, m, Ph); 7.90–7.97 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 41.0, 43.8, 56.0, 92.0, 95.8, 109.2, 127.6, 128.6, 131.4, 135.3, 150.7, 151.2, 156.4, 166.8. EA $C_{18}H_{23}N_3O_2$ requires: C 68.98; H 7.40; N 13.41. Found: C 68.33; H 6.93; N 13.02. EI-HRMS: m/z=314.1865 (MH^+) found; $C_{18}H_{24}N_3O_2$ calculated: m/z=314.1863 (MH^+). ν_{max} 3202, 3063, 2987, 2954, 2820, 2766, 1720, 1637, 1590, 1509, 1446, 1256, 1084, 981.

*5.2.18. Methyl 2-cyano-3-(dimethylamino)but-2-enoate (**49**).* To a solution of methyl cyanoacetate (**48**; 297 mg, 3 mmol) in toluene (5 mL), DMADMA (1.1 equiv, 0.482 mL) was added. The reaction was stirred at ambient temperature for 2 h. The reaction progress was monitored with thin-layer chromatography. Volatile compounds were removed under reduced pressure and the product was isolated via column chromatography (ethyl acetate/petroleum ether=1:1). Yield: 74% (373 mg), yellow oil. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.41 (3H, br s, CH_3); 3.16 (6H, br s, N(CH_3)$_2$); 3.59 (3H, s, OCH_3). ^{13}C NMR (DMSO-d_6, 125 MHz): 19.3, 43.0, 50.8, 69.0, 120.2, 166.4, 173.3. EI-HRMS: m/z=169.0973 (MH^+) found; $C_8H_{12}N_2O_2$ calculated m/z=169.0972 (MH^+). ν_{max} 2984, 2838, 2188, 1686, 1557, 1433, 1400, 1277, 1263, 1185, 1113, 1073, 1054, 1013, 936, 765.

*5.2.19. (E)-3-(Dimethylamino)-1-phenylbut-2-en-1-one (**4c**).* The product was prepared from a solution of acetophenone (**1c**; 12 g, 100 mmol) in anhydrous toluene, and 1.4 equiv of DMADMA (18.62 g, 140 mmol). The reaction mixture was heated to reflux temperature and stirred vigorously for 24 h. The solvent was removed under reduced pressure, thus affording brown crystals of the product. Yield: 46.6% (8.81 g); mp=68–70 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.66 (3H, s, CH_3); 3.07 (6H, s, N(CH_3)$_2$); 5.68 (1H, s, CH); 7.30–7.51 (3H, m, Ph); 7.79–7.94 (2H, m, Ph). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 16.5, 40.1, 92.7, 127.3, 128.0, 130.3, 143.2, 163.9, 188.3. EI-HRMS: m/z=190.1226 (MH^+) found; $C_{12}H_{16}NO$ calculated m/z=190.1226 (MH^+). ν_{max} 3042, 2951, 2873, 1533, 1480, 1419, 1382, 1358, 1223, 1178, 1153, 1063, 1027, 917, 861, 771, 705.

*5.2.20. 3-(Dimethylamino)-1-(4-nitrophenyl)but-2-en-1-one (**4j**).* The product was prepared from 4′-nitroacetophenone (**1j**; 495 mg, 3 mmol), 140 °C, 10 min; column chromatography (ethyl acetate/petroleum ether=1:1), crystallization from ethyl acetate. Yield: 8% (50 mg), brown-orange solid; mp=183–185 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.61 (3H, s, CH_3); 3.10 (6H, s, N(CH_3)$_2$); 5.65 (1H, s, CH); 8.02 (1H, d, J_1=2.2 Hz, CH); 8.04 (1H, d, J_1=2.2 Hz, CH); 8.22 (1H, d, J_1=2.1 Hz, CH); 8.24 (1H, d, J_1=2.1 Hz, CH). ^{13}C NMR (DMSO-d_6, 75.5 MHz): 17.0, 29.3, 91.9, 124.2, 129.0, 149.0, 149.5, 166.0, 183.9. EI-HRMS: m/z=235.1079 (MH^+) found; $C_{12}H_{15}N_2O_3$ calculated m/z=235.1077 (MH^+). ν_{max} 3107, 2955, 2916, 1585, 1555, 1523, 1511, 1342, 1317, 1238, 1207, 1064, 742.

*5.2.21. (2Z,4Z)-Methyl 2-cyano-3,5-bis(dimethylamino)hexa-2,4-dienoate (**50**).* The product was prepared from methyl cyanoacetate (**48**; 297 mg, 3 mmol), 100 °C, 10 min; column chromatography (ethyl acetate). Yield: 28% (201 mg), brown crystalline solid; mp=104–109 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.26 (3H, s, CH_3); 3.05 (6H, s, N(CH_3)$_2$); 3.09 (6H, s, N(CH_3)$_2$); 3.71 (3H, s, OCH_3); 4.56 (1H, s, CH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 17.9, 40.8, 43.2, 51.2, 92.0, 124.3, 162.3, 167.1, 170.5. EI-HRMS: m/z=238.1572 (MH^+) found; $C_{12}H_{20}N_3O_2$ calculated m/z=238.1550 (MH^+). ν_{max} 2949, 2935, 2176, 1657, 1548, 1528, 1395, 1265, 1181, 1071, 1016, 787, 764.

5.3. X-ray structure analysis for compounds 4c, 9c, 9d, 9e, 9h, 40 and 50

Diffraction data for the above mentioned compounds were collected on a SuperNova X-ray single crystal diffractometer equipped with an Atlas detector using monochromated Mo Kα radiation at 150 K (for **9c** and **9e**) or ambient temperature for the other five structures. Data reduction and integration were performed with the software package CrysAlis PRO.[25] The coordinates of all of the nonhydrogen atoms were found via direct methods using the SIR97 or Supeflip or Olex2 structure solution programs.[26–28] A full-matrix least-squares refinement on F^2 magnitudes with anisotropic displacement parameters for all nonhydrogen atoms using SHELXL-97 was employed.[29] All hydrogen atoms were initially located in difference Fourier maps. All H atoms attached to carbon were subsequently treated as riding atoms in geometrically idealized positions with bond lengths C–H of 0.96/0.98 Å for methyl and 0.93/0.95 Å for aromatic C–H bonds (the first number refers to ambient and the second to low temperature). The corresponding displacement parameters U_{iso}(H) were 1.5-times higher than those of the carrier methyl carbons and 1.2-times higher than all other hydrogen bearing carbon atoms. Figures depicting the structures were prepared by ORTEP3.[30] CCDC 967245–967251 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The

Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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