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Organocatalyzed Solvent-Free Aza-Henry Reaction: A Breakthrough in the One-Pot Synthesis of 1,2-Diamines

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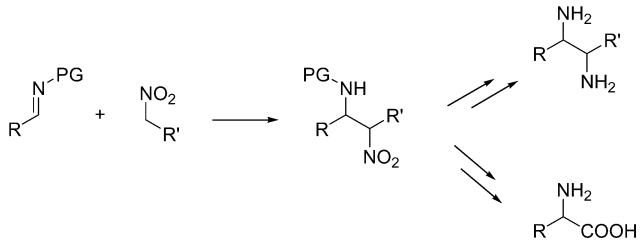
Abstract: A nitrogen-containing superbase such as TMG was found to be an effective catalyst for the reaction between *N*-diphenylphosphinoyl imines and nitroalkanes. Exploiting a protocol that avoids the use of any solvent also during workup procedure, we synthesized a series of β-nitroamines in excellent yields and high diastereomeric ratios. These results, combined with the capability of the indium in conjunction with Zn as the stoichiometric reducing agent to perform in aqueous medium reduction of the nitro group under mild reaction conditions, led us to devise a three-step, one-pot synthesis of a range of 1,2-diamines, making use of environmentally friendly procedures in the various steps.

Among the classical name reactions in organic synthesis, the Henry or nitroaldol reaction[1] is easily recognizable as one of the most important tools for carbon−carbon bond formation and has been used for the synthesis of a vast array of β-amino alcohols, which are valuable intermediates for the synthesis of many pharmaceutically active compounds.[2] On the other hand, the 1,2-diamine structural motif is important in biologically active natural products, in medicinal chemistry, and more recently as a core unit in chiral auxiliaries and chiral ligands for use in asymmetric catalysis.[3] In the past few years, this has prompted significant research to be directed toward the nitro-Mannich (aza-Henry) reaction, the nucleophilic addition of nitroalkanes to imines to give β-nitroamine derivatives.[4] The reduction to 1,2-diamines[5] and the Nef reaction to produce α-amino acids[6] highlight several important synthetic applications of these compounds (Scheme 1).[7]

SCHEME 1



Over the past few years, significant interest has been focused on the development of new protocols for environmentally benign processes that are both economically and technologically feasible,[8] and an important area of green chemistry deals with solvent minimization.[9] Whereas it has been found that the nitroaldol reaction can be performed under solvent-free conditions,[10] the application of this methodology to the aza-Henry reaction appears to be unexplored. These reactions are in most cases catalyzed or promoted by metal salts,[11] and several drawbacks lie in the cost and the toxicity of the metal species and in the use of organic solvents that are often ecologically harmful. To face these problems, only recently the first general asymmetric organocatalyzed aza-Henry reactions have been developed by Johnston's and Takemoto's groups.[12]

Herein we report a new and significantly simplified and environmentally friendly approach to the catalytic aza-Henry reaction using new solvent- and metal-free conditions.

With the aim of using an organocatalytic approach to the reaction, we reasoned that an organic base should be capable of activating the nitroalkane through deprotonation, but due to the lack of strong Lewis or Brønsted acidic sites, it might not give significant interactions with

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the imine moiety. Following this working hypothesis, we decided to focus on the use of *N*-diphenylphosphinoyl imines **1** for the development of a solvent-free aza-Henry reaction, as the diphenylphosphinoyl moiety, easily removable at the end of the synthetic sequence,[13] should also guarantee a sufficient reactivity toward nucleophilic species.

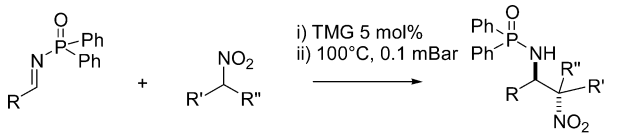
After a brief screening of different organic bases, we found 1,1,3,3-tetramethylguanidine (TMG) to be particularly effective as a catalyst in the reaction between imine **1a** and 1-nitropropane (1.25 equiv) under solvent-free conditions,[14] in line with the previous reports on the parent Henry reaction.[2,15] Use of only 5 mol % TMG afforded a clean and fast reaction. After dilution with CH_2Cl_2, acidic workup to remove the catalyst, and evaporation of the organic solvent and excess 1-nitropropane, the corresponding nitroamine **2a** was obtained in almost quantitative yield with good diastereoselectivity (94:6), favoring the anti isomer.[16] Heating the reaction mixture or performing the reaction under ultrasound or microwave irradiation did not result in any considerable enhancement in the reaction rate.[17]

However, for a truly solvent-free process, solvents need to be avoided also during workup procedure. To this purpose, we found that the nitroalkane in excess and the relatively volatile TMG catalyst could be efficiently removed by Kugelrhor distillation directly from the reaction mixture (0.1 mBar, 100 °C). This protocol furnished the β-nitroamine **2a** in nearly quantitative yield and in a spectroscopically (>95%, ^{1}H NMR) pure form. Furthermore, no epimerization at the α-carbon to the nitro moiety was observed during distillation. Silica gel chromatography afforded the analytically pure compound **2a**.

The scope of the solvent-free aza-Henry reaction was then investigated varying both the imine and the nitroalkane partners (Table 1).

Aromatic *N*-diphenylphosphinoyl imines **1a**−**e** and imine **1f** derived from pivalaldehyde were reacted with 1-nitropropane under the optimized reaction conditions (1.25 equiv of nitroalkane, 5 mol % TMG), all furnishing nitroamines **2a**−**f** in excellent yields. Unsubstituted aromatic imine **1a** (entry 1) and heteroaromatic imines **1d** (entry 4) and **1e** (entry 5), as well as imine **1b** (entry 2) bearing an electron-withdrawing group, reacted smoothly under standard conditions with 1-nitropropane affording after 2 h the expected products in almost quantitative yields, whereas the presence of an electron-releasing group in **1c** slowed considerably the reaction rate (entry 3). Also the sterically crowded imine **1f**, derived from pivalaldehyde, was poorly reactive, the corresponding nitroamine **2f** being produced in high yield only after prolonged reaction time (entry 6).[18] Increasing the length (entries 7 and 8) or the branching (entry 10) of the nitroalkane chain had only a slight effect on the reaction rate. With one exception (entry 2), very good diastereoselectivities were observed.

TABLE 1. Solvent-Free Aza-Henry Reaction of *N*-Phosphinoylimines Catalyzed by TMG[a]



1a-f **2a-j**

entry	R	R′	R″	adduct	*t* (h)	yield %[b]	anti:syn[c]
1	Ph (**1a**)	CH_3CH_2	H	**2a**	2	96	94:6
2	*p*-ClC_6H_4 (**1b**)	CH_3CH_2	H	**2b**	2	95	84:16
3	*p*-(MeO)-C_6H_4 (**1c**)	CH_3CH_2	H	**2c**	24	92	95:5
4	2-furyl (**1d**)	CH_3CH_2	H	**2d**	2	90	95:5
5	2-thienyl (**1e**)	CH_3CH_2	H	**2e**	2	92	95:5
6	*tert*-butyl (**1f**)	CH_3CH_2	H	**2f**	170	95	>98:2
7	**1a**	$CH_3(CH_2)_4$	H	**2g**	24	90	>98:2
8	**1a**	$PhCH_2$	H	**2h**	26	95	>98:2
9	**1a**	H	H	**2i**	1	90	
10	**1a**	CH_3	CH_3	**2j**	3	96	

[a] Reaction was conducted with **1a**−**f** (0.2 mmol), nitroalkane (0.25 mmol), and TMG (0.01 mmol) at room temperature. [b] After chromatography on silica gel. [c] Determined by ^{1}H NMR spectroscopy.

The relative configuration of the aza-Henry adduct **2a** was assigned as anti by comparison of the ^{1}H and ^{13}C NMR spectra of the free diamine **5** (vide infra) with literature data.[11a] The configuration of the other nitroamines **2b**−**h** was tentatively given as anti on the basis of the similarities between their ^{1}H NMR spectra with the one relative to compound **2a**. As a matter of fact, ^{1}H NMR analysis of adducts **2a**−**e**, which are all present in both diastereomeric forms, shows the signal relative to the proton α to the nitro moiety of the minor isomer invariably shifted downfield with respect to its counterpart in the major anti isomer. Similarly, the signal of the amidic proton of the minor isomer of these compounds always appears shifted upfield with respect to the signal of the corresponding proton of the major anti isomer. Furthermore, the two geminal protons of the methylene moiety are superimposed in the ^{1}H NMR spectrum in the minor isomer, while the same protons in the major isomer invariably show two distinct resonances ($\Delta\delta \approx 0.20$ ppm).

Although the conversion of some of the β-nitroamines **2** to the corresponding vicinal diamines has already been reported using SmI_2, this reducing agent [11c,d] presents drawbacks due to high cost and low stability. Therefore, we planned the development of an alternative, user-friendly procedure for the reduction of the nitro group.[19] In the past few years the reduction of aliphatic and aromatic nitro compounds by metallic indium has emerged

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(14) ,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) were equally effective in promoting the reaction.

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(16) High diastereselectivity observed is not a result of a thermodynamic equilibration in the presence of a strong base such as TMG, as β-nitroamine **2a** with a 55:45 diastereomeric ratio (obtained from a reaction catalyzed by DABCO) was recovered with the same anti/syn ratio after several hours in the presence of 5 mol % TMG.

(17) For the sake of comparison with the usual solution-phase chemistry, we also carried out the reaction in a few organic solvents such as THF, CH_2Cl_2, and toluene, observing a remarkable drop in the rate of the reaction, presumably due to dilution effects.

(18) Other imines derived from enolizable aliphatic aldehydes were not tested in the reaction due to the lack of methods for the preparation of these compounds.

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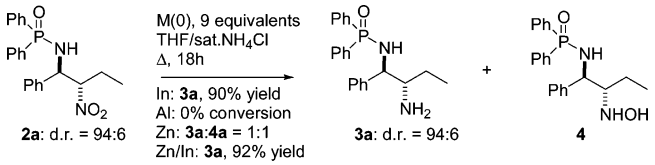
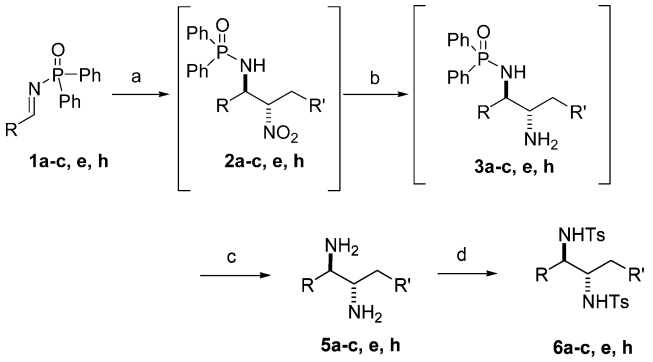
SCHEME 2. Reduction of *N*-(2-Nitro-1-phenylbutyl)diphenylphosphinic Amide (2a) with Metals



as a suitable method, tolerant to a series of functional groups and performable also in aqueous medium.[20] Furthermore, the reduction of a β-nitro-*N*-diphenylphosphinoylamine by Zn metal has already been reported in a particular case by the group of Shibasaki.[11e] Hence, we decided to investigate the possibility of using a metallic system for the conversion of the aza-Henry adducts **2** into the corresponding diamines **3** in aqueous solvent. Using 9 mol equiv of metallic indium as the reducing agent, we were able to convert nitroamine **2a** into the corresponding monoprotected 1,2-diamine **3a** in 90% yield, in refluxing THF and using AcOH or a saturated NH_4Cl aqueous solution as a proton source (Scheme 2). Switching to less expensive metals, Al did not furnish any reduced product under the same reaction conditions, whereas powdered Zn was only moderately active, affording a mixture of diamine **3a** and hydroxylamine **4** (Scheme 2). Indium(0) therefore appeared to be the metal of choice for this transformation. However, due to its cost, the stoichiometric protocol was converted into catalytic combining a small amount of indium with a less expensive metal. Following this strategy, efficiently applied to Barbier-type allylations[21] and, more recently, to the reduction of hydroxylamines,[22] we performed the reduction of **2a** with Zn as the stoichiometric reducing agent in the presence of a small amount (25 mol %) of indium. To our delight, the reduction proceeded smoothly, affording the corresponding N-protected diamine **3a** in very good yield and with the same diastereomeric ratio of the starting nitroamine **2a** (Scheme 2).

One of the important directions in sustainable organic synthesis is the development of one-pot processes, i.e., combined reactions without intermediate recovery steps.[23] We envisioned that a one-pot protocol from the *N*-diphenylphosphinoyl imine to the corresponding free diamine could be devised. We also anticipated that the Kugelrhor distillation step could be avoided, since excess nitroalkane and the TMG catalyst should not interfere with the subsequent reduction and deprotection steps.[24] Indeed, we were able to carry out the whole synthetic process in a one-pot fashion in a very effective way, simply adding

TABLE 2. One-Pot Synthesis of Vicinal Diamines and Their Derivatization to Disulfonamides[a]



entry	R	R′	product	yield[b]	anti:syn[c]
1	Ph	CH_3	6a	65%	94/6
2	*p*-ClC_6H_4-	CH_3	6b	68%	84/16
3	*p*-$MeOC_6H_4$-	CH_3	6c	60%	95/5
4	2-Thienyl	CH_3	6e	58%	95/5
5	Ph	Ph	6h	55%	>98/2

[a] Reagents and conditions: (a) nitroalkane (1.25 equiv), TMG (5 mol %); (b) In (0.25 equiv), Zn (10 equiv), THF/NH_4Cl_{sat}, Δ, 18 h; (c) 6 M HCl, Δ, 4 h; (d) TsCl (2.2 equiv), Na_2CO_3 (4.4 equiv), THF/H_2O, 18 h. [b] Isolated yield over four steps with respect to imines **1**. [c] Determined by ^1H NMR spectroscopy.

the reagents at the appropriate time in the same reaction vessel. The final free 1,2-diamine **5** could be isolated in good yield and purity (>90%, ^1H NMR) after acidic hydrolysis aimed at removing the diphenylphosphinoyl protection at nitrogen (Table 2). The obtainment of the free 1,2-diamine **5** allowed the assignment of its relative configuration as anti, by comparison of its ^1H and ^{13}C NMR spectra with literature data.[11a] Similar reactions of *N*-diphenylphosphinoyl imines **1b**,**c**,**e**,**h**, performed according to this one-pot, three-step protocol afforded the corresponding amines **5b**,**c**,**e**,**h** in 60−90% yields, thus confirming the general character of this procedure. The diamines were converted into the more stable disulfonamides **6a**−**c**,**e**,**h**, which were isolated by silica gel chromatography and fully characterized.

In summary, the results presented in this paper provide a new metal- and solvent-free procedure for the aza-Henry reaction. The reaction proceeds smoothly for a range of different imines and nitroalkanes, in the presence of a catalytic amount of TMG. Furthermore, the use of solvents is avoided also during workup, as the adducts can be obtained in a highly spectroscopically pure form by simply distilling off the catalyst from the crude reaction mixture. A user-friendly protocol based on the use of zinc in conjunction with a catalytic amount of indium in aqueous medium was also developed for the conversion of nitroamines into the corresponding monoprotected diamines. Exploiting this reductive protocol, a range of free 1,2-diamines could be synthesized from the parent imines in a one-pot, three-step procedure that furnishes the final compounds in good yield and high purity.

Experimental Section

General Procedure for the Solvent-Free Aza-Henry Reaction. A nitroalkane (0.25 mmol) was added to a test tube followed by TMG (1.3 μL, 0.01 mmol) and *N*-diphenylphosphinoyl

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(23) Bruggink, A.; Schoevaart, R.; Kieboom, T. *Org. Proc. Res. Dev.* **2003**, *7*, 622.

(24) In the one-pot protocol, 10 equiv of zinc should be used instead of 9 equiv due to the consumption of the reducing agent for excess 1-nitropropane.

imine **1a**−**f** (0.2 mmol). The resulting white solid was magnetically stirred at room temperature until disappearance of the starting material (TLC, $CHCl_3$/MeOH 9/1). The residual nitroalkane and the TMG catalyst were then removed on a Kugelrhor apparatus (0.1 mBar, 100 °C), obtaining >95% spectroscopically pure nitroamines **2a**−**j** as white solids. The nitroamines were further purified by chromatography on silica gel ($CHCl_3$/MeOH mixtures).

***N*-(2-Nitro-1-phenylbutyl)diphenylphosphinic Amide (2a).** Following the general procedure for the solvent-free aza-Henry reaction, we obtained compound **2a** as a white solid in 96% yield (76 mg) and in a 94:6 diastereomeric ratio (^{1}H NMR) favoring the anti isomer: ^{1}H NMR (400 MHz) δ 7.85−7.78 (m, $2H_{maj}$, $2H_{min}$), 7.72−7.64 (m, $2H_{maj}$, $2H_{min}$), 7.58−7.38 (m, $4H_{maj}$, $4H_{min}$), 7.34−7.26 (m, $5H_{maj}$, $5H_{min}$), 7.16−7.12 (m, $2H_{maj}$), 7.09−7.06 (m, $2H_{min}$), 4.80 (ddd, J = 10.4, 6.6, 3.7 Hz, $1H_{min}$), 4.64 (ddd, 10.5, 6.6, 4.1m Hz, $1H_{maj}$), 4.58−4.44 (m, $1H_{maj}$, $1H_{min}$), 4.15 (dd, J = 11.1, 7.3 Hz, $1H_{maj}$), 3.82 (dd, J = 11.6, 8.4 Hz, $1H_{min}$), 2.20−2.05 (m, $1H_{maj}$), 2.10−1.95 (m, $2H_{min}$), 1.86−1.74 (m, $1H_{maj}$), 0.94 (t, J = 7.2 Hz, $3H_{maj}$, $3H_{min}$); ^{13}C NMR (100 MHz) [anti isomer] δ 138.8, 132.4, 132.3, 132.2, 131.9, 131.2, 131.1, 129.6, 129.0, 128.7, 128.5, 128.4, 128.3, 126.4, 95.4, 95.3, 57.3, 25.2, 10.4; IR ν_{max} (thin layer, NaCl plate) 3376, 1555, 1206 cm^{-1}; HRMS *m/z* calcd for $C_{22}H_{23}N_2NaO_3P^+$ 417.1338, found 417.1337 ($M + Na^+$). Anal. Calcd for $C_{22}H_{23}N_2O_3P$: C, 67.00; H, 5.88; N, 7.10. Found: C, 67.08; H, 5.84; N, 7.16.

General Procedure for the Synthesis of 1,2-Diamines 5a−c,e,h. A nitroalkane (0.25 mmol) was added to a test tube followed by TMG (1.3 μL, 0.01 mmol) and *N*-diphenylphosphinoyl imine **1a**−**c**,**e**,**h** (0.2 mmol). The resulting white solid was magnetically stirred at room temperature for 2−24 h. The tube was then equipped with a condenser; THF (2 mL) and a saturated aqueous NH_4Cl solution (0.7 mL) were added, followed by In powder (5.8 mg, 0.05 mmol) and Zn powder (130 mg, 2 mmol). The mixture was heated to reflux with stirring for 18 h and cooled to room temperature; then, 6 M HCl was added (1.0 mL), and the resulting solution was heated to reflux with stirring. After 4 h, the reaction mixture was cooled to room temperature and then H_2O (1 mL) was added; the aqueous phase was washed with EtOAc (3 × 2 mL), basified with solid NaOH (pH > 12), and then extracted with EtOAc (4 × 4 mL). The organic extracts were dried over $MgSO_4$, filtered, and evaporated, affording crude amines **5a**−**c**,**e**,**h** in very good yields as pale yellow oils. The purity of the products was judged to be >90%, according to ^{1}H NMR analysis of the crude products.

1-Phenyl-1,2-butanediamine (5a).[11a] Following the general procedure for the synthesis of 1,2-diamine, we obtained crude compound **5a** as a pale yellow oil in 97% yield (31 mg) in a 94:6 diastereomeric ratio (^{1}H NMR), favoring the anti isomer: ^{1}H NMR (400 MHz) δ 7.36−7.22 (m, $5H_{maj}$, $5H_{min}$), 3.83 (d, J = 5.9 Hz, $1H_{min}$), 3.71 (d, J = 6.2 Hz, $1H_{maj}$), 2.83−2.77 (m, $1H_{min}$), 2.77−2.72 (m, $1H_{maj}$), 1.58 (br s, $4H_{maj}$, $4H_{min}$), 1.50−1.36 (m, $1H_{maj}$, $1H_{min}$), 1.28−1.16 (m, $1H_{maj}$, $1H_{min}$), 0.98 (t, J = 7.4 Hz, $3H_{min}$), 0.93 (t, J = 7.4 Hz, $3H_{maj}$); ^{13}C NMR (100 MHz) [anti isomer] δ 144.7, 128.4, 127.0, 126.8, 60.6, 58.8, 27.3, 10.8; IR ν_{max} (thin layer, NaCl plate) 3384, 3290 cm^{-1}; ESI-MS *m/z* 165 ($M + H^+$).

General Procedure for the Synthesis of Bis-4-methylbenzensulfonamides 6a−c,e,h. To a stirred solution of crude diamines **5a**−**c**,**e**,**h** in H_2O/THF (1/2 v/v, 0.6 mL) were sequentially added Na_2CO_3 (4.4 equiv) and TsCl (2.2 equiv). After 18 h of stirring at room temperature, the resulting biphasic mixture was diluted with Et_2O and H_2O. The layers were separated, and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed twice with H_2O, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude products were then purified by chromatography on silica gel (Hex/AcOEt mixtures).

4-Methyl-*N*-(2-[(4-methylphenyl)sulfonyl]amino-1-phenylbutyl)benzenesulfonamide (6a). Following the general procedure for the synthesis of bis-sulfonamides, we obtained compound **6a** as a white solid in 65% yield (61 mg) and in a 94:6 diastereomeric ratio (^{1}H NMR) favoring the anti isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.70 (m, $2H_{maj}$, $2H_{min}$), 7.56−7.46 (m, $2H_{maj}$, $2H_{min}$), 7.33−7.27 (m, $2H_{maj}$, $2H_{min}$), 7.19−7.11 (m, $5H_{maj}$), 7.10−7.05 (m, $5H_{min}$), 6.97−6.93 (m, $2H_{maj}$, $2H_{min}$), 6.06 (d, J = 8.5 Hz, $1H_{min}$), 5.40 (d, J = 6.5 Hz, $1H_{maj}$), 4.51 (d, J = 8.7 Hz, $1H_{maj}$), 4.42 (d, J = 6.8 Hz, $1H_{min}$), 4.21−4.19 (m, $1H_{min}$), 4.15 (t, J = 7.4 Hz, $1H_{maj}$), 3.43−3.34 (m, $1H_{maj}$), 3.30−3.21 (m, $1H_{min}$), 2.44 (s, $3H_{min}$), 2.43 (s, $3H_{maj}$), 2.36 (s, $3H_{maj}$), 2.34 (s, $3H_{min}$), 1.51−1.39 (m, $1H_{maj}$, $1H_{min}$), 1.04−0.91 (m, $1H_{maj}$, $1H_{min}$), 0.53 (t, J = 7.3 Hz, $3H_{maj}$), 0.50−0.48 (m, $3H_{min}$); ^{13}C NMR (100 MHz) [anti isomer] δ 143.6, 143.2, 137.6, 137.2, 136.9, 129.7, 129.3, 128.5, 127.9, 127.3, 127.2, 60.7, 59.1, 29.7, 24.2, 21.5, 21.4; ESI-MS *m/z* 473 ($M + H)^+$, 495 ($M + Na^+$); IR ν_{max} (thin layer, NaCl plate) 3380, 1334, 1160 cm^{-1}. Anal. Calcd for $C_{24}H_{28}N_2O_4S_2$: C, 60.99; H, 5.97; N, 5.93; Found: C, 61.04; H, 5.92; N, 5.98.

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Supporting Information Available: Experimental details and characterization data for compounds **2b**−**j**, **3a**, **5b**, **5c**, **5e**, **5h**, **6b**, **6c**, **6e**, and **6h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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