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o-Amine-Assisted Cannizzaro Reaction of Glyoxal with New 2,6-Diaminoanilines

Yuhki Irie,[a] Yuji Koga,[a] Taisuke Matsumoto,[b] and Kouki Matsubara*[a]

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The preparation of several new *o*-amine-substituted anilines was achieved according to a new bifunctional molecular design, and their reactions with glyoxal were conducted. Cannizzaro reactions of glyoxal proceeded using specifically designed anilines, such as 2,6-dipyrrolidinyl-, 2,6-dipiperidinyl-, 2,6-dimorpholinyl-, and 2-pyrrolidinyl-aniline, which are new and can easily be synthesized by substitution of halogen-substituted nitrobenzene with amines and subsequent reduction with hydrogen, to form α-hydroxy acetamide and α-amino acetamide derivatives, as a result of the Cannizzaro reaction. In comparison with the reaction of glyoxal with *p*-pyrrolidinylaniline to form a common diimine product, the reaction with *o*-pyrrolidinylaniline leads only to α-hydroxy amides, strongly suggesting that the abnormal Cannizzaro reactions are attributed to the existence of basic nitrogen atoms at the *o*-positions, which suppress diimine formation and assist the generation of acetamides.

Introduction

Reactions of aromatic amines are well known as the nucleophilic addition and substitution of olefins, aromatic compounds, and carbonyl compounds to form N–C bond-forming products, such as alkyl and arylamines, imines, and amides.[1] However, studies on versatile, substituted primary anilines at the aromatic ring are not so numerous. For example, the substituents introduced into anilines were isopropyl groups, aromatic groups,[2] and alkyne groups[3] at the *o*-positions, which were used as building units of specific metal ligands for sterically demanding metal catalysts.

We thought of a bifunctional molecule, which was inspired from the tagged molecules in organic synthesis[4] and was designed in order to expand the variation of the aniline reactions. That is, the molecule having a catalyst group at the neighbouring position of the reactant group, $-NH_2$, as shown in Figure 1. Catalysts close to the reactant group could perform specific reactions to yield other products than those generally expected in the standard reactions of common anilines. In this study, we applied this concept to a series of anilines first having tertiary or secondary amines at the *o*-positions, in which the *o*-amine could act as a base in the nucleophilic reactions of anilines.

[a] Department of Chemistry, Faculty of Science, Fukuoka University,
Nanakuma, Jonan-ku, Fukuoka 814-0180, Japan
Fax: +81-92-871-6631
E-mail: kmatsuba@fukuoka-u.ac.jp
[b] Analysis Center, Advanced Institute for Materials Chemistry and Engineering, Kyushu University,
Kasuga, Fukuoka, Japan

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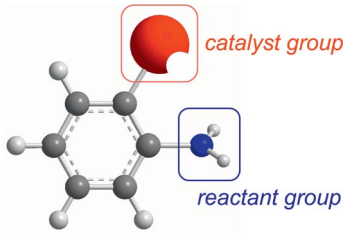
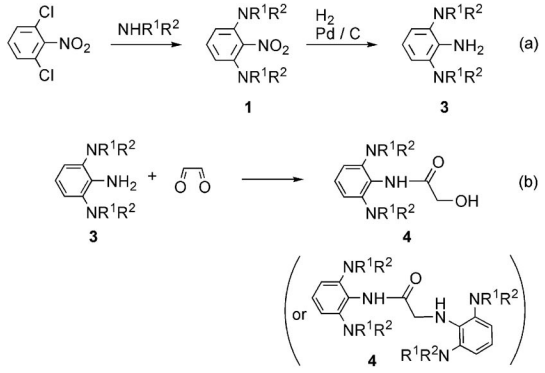


Figure 1. A designed model for a bifunctional molecule.

A series of *o*-monoamine-substituted anilines have already been reported.[5] However, although some primary anilines having amines at the 2- and 6-positions have been synthesized until now,[6] difficulties in the synthesis are unknown to prepare various new 2,6-diaminoanilines. This prompted us to prepare several new 2,6-substituted anilines having secondary or primary amino substituents. After several attempts, we found an efficient synthetic route to the anilines via double amination of 2,6-dihalonitrobenzene[7] and subsequent reduction to achieve the preparation of 2,6-diaminoanilines [Scheme 1 (a)]. Furthermore, we found that reactions of the anilines with glyoxal formed not diimine but α-hydroxy-acetamides as a result of the Cannizzaro reaction, which was induced by successful assistance the *o*-amine substituents [Scheme 1 (b)].

The Cannizzaro reaction is a hydride transfer from aldehyde,[8] which is added by a nucleophile, to another carbonyl carbon under a basic or acidic condition to form a carboxylic acid derivative and alcohol in an intermolecular version[9] or α-hydroxy-carboxylic acid derivatives in an intramolecular version.[10–12] Several studies on intramolecular Cannizzaro reactions have been reported, such as reac-



Scheme 1. Synthetic route for (a) 2,6-diaminoaniline and (b) α-hydroxy amide.

tions of glyoxal derivatives with alkoxy[10] and amide anions[11] under basic conditions, and alcohol in the presence of Lewis acids.[12]

The products, α-hydroxy amide derivatives, are commonly known as the significant core structure for anticonvulsion drugs[13] and fundamental components included in other pharmaceutical compounds[14] and agrochemicals,[15] and also significant synthetic precursors of biologically active substances.[16] Thus, several synthetic routes to α-hydroxy amides have been developed.[17] This is the first intramolecular Cannizzaro reaction of glyoxal with amine in the absence of strong bases and Lewis acids to form α-hydroxy amide derivatives, showing the specific reactivity of novel *o*-amine-substituted anilines.

Results and Discussion

Synthesis of 2,6-Diaminoanilines

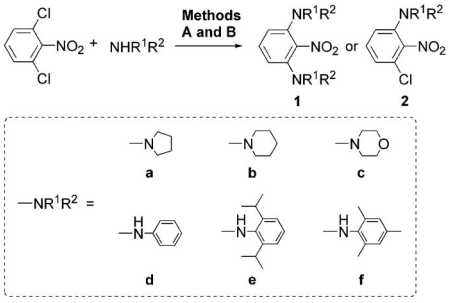
We explored two synthetic routes for the novel 2,6-amine-substituted aniline: one is that 2,6-dibromoaniline is acetylated by acetyl chloride, bromides at the 2,6-positions are substituted with amines by a palladium catalyst, and then the acetyl unit is deprotected to form the desired product; the other is that 2,6-dihalonitrobenzene is substituted with amines at the 2,6-positions and subsequently, the nitro group is reduced. As a result, while (2,6-dibromophenyl)-acetamide, which was obtained from 2,6-dibromoaniline and acetyl chloride in 69% yield, could not react with amines, 2,6-dihalonitrobenzene was successfully substituted with cyclic amines to form 2,6-diaminonitrobenzene in high yields and subsequent reduction formed 2,6-diaminoaniline in excellent yields. The conditions of the amination processes are shown below as Methods A and B:

Method A: Amine (3.0 equiv.), $Pd(OAc)_2$, BINAP, Cs_2CO_3 (2.8 equiv.), and toluene were added and the mixture was heated at 100 °C.

Method B: Amine (30.0 equiv.) was added and the mixture was refluxed without adding solvents.

In Method A, halogen atoms in 2,6-dihalonitrobenzene were substituted with amine in the presence of a palladium catalyst [$Pd(OAc)_2$ (2 mol-%) and BINAP (4 mol-%)] and a base (Cs_2CO_3) in toluene, whereas these halogens were also substituted by nucleophilic substitution of electron-poor haloarene with amine as shown in Method B. In the synthesis of pyrrolidine-substituted amine, substitution of 2,6-dibromo-1-nitrobenzene via Method A was completed in 36 h using the Pd compound (2 mol-%) and the ligand (4 mol-%), whereas its chloride analog was substituted in 96 h using the Pd catalyst (5 mol-%) and the ligand (7.5 mol-%), to form **1** in high yields in both cases. When these reactions were quenched after 12 h, the substitution conversions from 2,6-dichloro-1-nitrobenzene in Methods A and B were 30 and 32%, respectively, indicating that Method B is better than Method A for obtaining 2,6-diamino-1-nitrobenzene (**1**). So, we prepared some 2,6-amine-substituted nitrobenzene derivatives with secondary amines almost quantitatively from 2,6-dichloro-1-nitrobenzene via Method B (Table 1, entries 1–3), but primary anilines did not react with 2,6-dichloro-1-nitrobenzene in Method B. Diamination of 2,6-dichloronitrobenzene with anilines was achieved via Method A using palladium acetate and an *N*-heterocyclic carbene ligand, bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr). **1d**, **1e**, and **1f** were formed after isolation by silica gel column chromatography (entries 4–6) in 72, 74, and 56% yield, respectively, higher than those using BINAP. The palladium-catalyzed substitution also formed monoamine-substituted products **2** in 48 h in low yields, 6–17%. The nitrobenzene derivatives **1a**–**1d** were fully identified by means of ^1H and ^{13}C NMR and IR spectroscopy and elemental analysis.

Table 1. Amination of 2,6-dichloro-1-nitrobenzene.



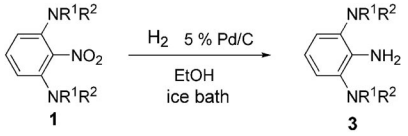
Entry	Method	–NR^1R^2	Time [h]	% Yield[a]	
				1	**2**
1	B	**a**	120	97	0
2	B	**b**	216	99	0
3	B	**c**	72	85	0
4	A′ [b]	**d**	48	72	14
5	A′ [b]	**e**	48	74	6
6	A″ [c]	**f**	48	57	17

[a] The products were isolated by silica gel column chromatography. [b] Method A′: $Pd(OAc)_2$ (3.0 mol-%) and IPr (4.5 mol-%) were used. [c] Method A″: $Pd(OAc)_2$ (4.0 mol-%) and IPr (8.0 mol-%) were used.

Subsequently, the products, 2,6-diamino-1-nitrobenzene (**1**), were reduced by hydrogen in the presence of Pd/C (Pd content: 5%) in ethanol to form 2,6-diaminoaniline (**3**). The reduction of **1a**–**1c** having the cyclic amino substituents

proceeded quantitatively to yield a series of 2,6-diaminoanilines **3a**–**3c** in excellent yields (Table 2, entries 1–3). In the reduction of **1d** having anilines at the 2,6-positions, an aniline derivative **3d** was generated quantitatively (entry 4), but anilines having bulky substituents, such as 2,6-bis(2,6-diisopropylanilino)nitrobenzene (**3e**) and 2,6-bis(2,4,6-trimethylanilino)nitrobenzene (**3f**), could hardly be reduced (entries 5–6).

Table 2. Reduction of 2,6-diamino-1-nitrobenzene (**1**).



Entry	–NR^1R^2	mol-% Pd/C	Time [h]	% Yield[a]
1	**a**	5	12	88
2	**b**	2.5	14	98
3	**c**	5	5	94
4	**d**	10	5	89
5	**e**	50	12	4 (30)[b]
6	**f**	50	12	– (70)[b]

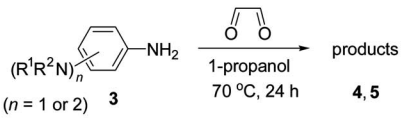
[a] The products were isolated by silica gel column chromatography. [b] Isolated yields of starting material **1**.

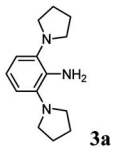
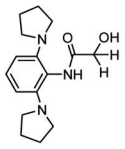
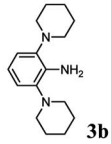
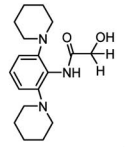
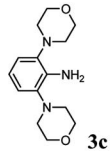
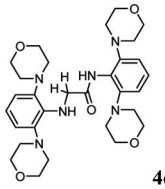
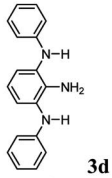
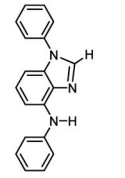
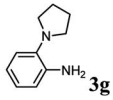
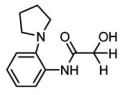
The aniline derivatives **3a**–**3e** were also fully characterized. The IR resonances due to the NH_2 stretching vibration of the primary anilines **3a**–**3e** appear at 3300–3450 cm^{-1}. The existence of the primary amino groups was revealed by the observation of the ^1H resonances at δ = 4.02, 4.26, and 4.27 in the spectra for **3a**, **3b**, and **3c** and at δ = 3.90 and 3.73 ppm for **3d** and **3e** due to the amino protons. In the ^1H and ^{13}C NMR spectra for **3a**–**3c** similar characteristic sets of high-field signals from δ_H = 6.68 to 6.92 and δ_C = 112–141 ppm appear due to the amine-substituted aromatic groups.

Reactions of 2,6-Diaminoanilines with Glyoxal

The new series of aniline derivatives **3a**–**3d** was treated with glyoxal. We found that no imines were formed, instead the new α-hydroxy amides **4a** and **4b** were generated from **3a** and **3b** (Table 3, entries 1–2). Interestingly, from **3c**, the α-amino carboxamide **4c** was obtained (entry 3). The yields depend on the amount of glyoxal: when the amount of glyoxal was increased, the yield of the products also increased within 24 h. Generation of **4b** was almost quantitatively, whereas the starting materials were also obtained in the reaction of **3a** and **3c**, probably because of the lower reactivity of **3a** and **3c** than that of **3b**. From the crystal structures of the products and some experiments as shown below, we conclude that a Cannizzaro reaction proceeds to form **4a**–**4c**. Aniline-substituted aniline **3d** also reacts with glyoxal to form the imidazole **5** as shown in Table 3, entry 4.

Table 3. Reactions of glyoxal with 2,6-diamino- or 2-aminoanilines **3** (the products were isolated by silica gel column chromatography).

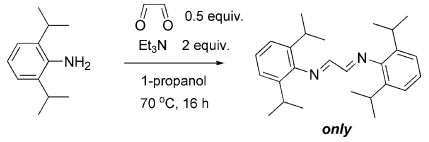


Entry	Substrate	Product	Glyoxal (equiv.)	% Yield
1	 **3a**	 **4a**	0.5	41
			1.0	53
2	 **3b**	 **4b**	0.5	55
			1.0	66
3	 **3c**	 **4c**	0.5	8
			1.0	16
4	 **3d**	 **5**	0.5	55
			1.0	43
5	 **3g**	 **4g**	2.0	15

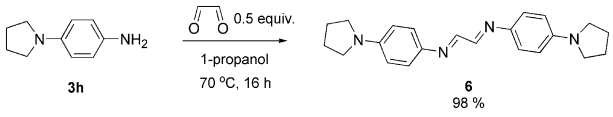
The influence of the number of amine substituents in the aniline on the Cannizzaro reaction was also studied. Interestingly, as shown in entry 5 of Table 3, *o*-pyrrolidinylaniline **3g** also reacts with glyoxal to form α-hydroxy amide **4g** in low yield (15%), but does not form imine derivatives. Compound **4g** was characterized by NMR and IR spectroscopy and elemental analysis. IR signals due to the carbonyl CO stretching band and NH and OH stretching broad bands were detected at 1670 cm^{-1} and around 3300 cm^{-1}, respectively.

Several studies on nucleophilic substitution of glyoxal with 2,6-substituted anilines to form only diimines have been reported previously.[2–3] So, we attribute these abnormal reactions to some specific reactivity of the *o*-amine-substituted anilines as mentioned in the Introduction of this article. We were interested to see which rôle tertiary alkylamines like **3a**–**c** and **3g** could play in the Cannizzaro reaction. Triethylamine was added to the reaction mixture of glyoxal with a 2,6-dialkylaniline, e.g. 2,6-diisopropylaniline. In the presence of triethylamine (2 equiv. to aniline), the reaction of glyoxal with the aniline yields diimine compound in high yield as shown in Scheme 2, no α-hydroxy

amide is formed.[18] We also investigated the effect of the substitution position of the amino substituents. When a 4-aminoaniline, for instance 4-pyrrolidinylaniline **3h**, was added to glyoxal, a normal diimine **6** was obtained in 98% yield and no formation of α-hydroxy amide was detected (Scheme 3), suggesting that the presence of basic amines in the neighbourhood of the nucleophilic nitrogen in **3a**–**c** and **3g** is essential for the Cannizzaro reaction. We tested reac tions of 1,2-diones, such as phenylglyoxal and 1,2-propanedione, with the anilines **3** but, in all cases, we obtained starting materials mostly and, unfortunately, hydroxy amides and imines were not obtained, probably due to steric factors and/or low basicity of *o*-amines in the anilines.



Scheme 2. The reaction of glyoxal with 2,6-diisopropylaniline in the presence of triethylamine.



Scheme 3. The reaction of glyoxal with 4-pyrrolidinylaniline **3h**.

X-ray Crystal Structures of 4a, 4c, 4g, and 5

Finally, the crystal structures of products **4a**, **4c**, **4g**, and **5** obtained from anilines **3** with glyoxal, α-hydroxy amide, α-amino amide, and imidazole derivatives were determined by single-crystal X-ray diffraction studies.[19] The structures of these compounds are depicted in Figure 2. Table 4 lists the representative bond lengths and angles of these compounds. The C2–O2 bond lengths of α-hydroxy amides **4a** and **4g** are 1.409(2) and 1.417(2) Å, respectively, and thus do not correspond to a double bond [cf. C1–O1 bond lengths were 1.233(2) and 1.229(2) Å] but a single C–O bond length; consequently, an alcohol was generated in these reactions. Also, the C2–N4 bond lengths in **4c** are 1.436(3) Å, suggesting that a C–N single bond was formed as a result of hydride rearrangement. On the other hand, it was found that the reaction of 2,6-dianilinoaniline **3d** with glyoxal did not yield α-hydroxy amide or diimine but the imidazole derivative **5**, as shown in part (d) of Figure 2.

Mechanistic Considerations

The above results demonstrated that the presence of tertiary amines close to the NH_2 moiety of aniline in **3** clearly affects the reactivity of **3** with glyoxal so as not to yield diimines, interestingly. As discussed in the literature on Cannizzaro reactions,[9] we investigated whether hydride transfer occurred or not in the formation of the amide compounds **4**. When [D_4]methanol was used as a solvent in the reaction of **3b** with glyoxal, the ^1H and ^2H NMR spectroscopic analysis of the isolated α-hydroxy amide **4b** revealed that deuterium was not incorporated (< 10%), at least not within 1 h at 60 °C (Scheme 4).[20] This shows that no proton exchange between hydrogen atoms derived from glyoxal and the solvent occurs. So the process does not proceed through an ene-diol intermediate, which is proposed in the Lobry de Bruyn-Alberda van Ekenstein reaction.[21]

Although an intermolecular hydride-transfer mechanism cannot be ruled out, this process might be disfavoured, because, at present, we cannot find factors inhibiting the intramolecular hydride transfer. The proposed intramolecular reaction mechanism is depicted in Scheme 5. In the tetrahedral intermediate having a hydroxy group, a basic lone pair of the nitrogen of *o*-substituted amines may easily interact with this hydroxy group and abstract a proton to induce hydride transfer from the tetrahederal carbon to the adjacent carbonyl carbon to form a zwitter-ionic amide. In other words, the hydride transfer in the Cannizzaro reaction may be assisted by the neighbouring basic amine. Such assistance of amines in the hydride rearrangement has never been reported before to the best of our knowledge.

Table 4. Representative bond lengths [Å] and angles [°] of **4a**, **4c**, **4g**, and **5**.

4a		**4c**		**4g**		**5**	
Bond lengths							
N1–C1	1.336(2)	N1–C1	1.364(3)	N1–C1	1.339(2)	N1–C1	1.310(2)
N1–C3	1.432(2)	N1–C3	1.433(3)	N1–C3	1.415(2)	N1–C2	1.394(2)
C1–O1	1.233(2)	C1–O1	1.225(3)	C1–O1	1.229(2)	N2–C3	1.393(2)
C1–C2	1.519(2)	C1–C2	1.517(3)	C1–C2	1.517(2)	N2–C8	1.393(2)
C2–O2	1.409(2)	C2–N4	1.436(3)	C2–O2	1.417(2)	N3–C1	1.376(2)
						N3–C14	1.422(2)
Bong angles							
C1–N1–C3	125.10(14)	C1–N1–C3	123.59(19)	C1–N1–C3	127.93(14)	N1–C1–N3	114.22(16)
N1–C1–O1	124.82(15)	N1–C1–O1	121.4(2)	N1–C1–O1	126.01(15)	N1–C2–C3	127.93(16)
N1–C1–C2	115.85(14)	N1–C1–C2	116.66(17)	N1–C1–C2	114.78(14)	C1–N1–C2	103.93(15)
O1–C1–C2	119.33(15)	O1–C1–C2	121.63(19)	O1–C1–C2	119.21(15)	C1–N3–C7	106.04(14)
C1–C2–O2	114.16(14)	C1–C2–N4	108.69(17)	C1–C2–O2	112.38(14)	C3–N2–C8	127.93(16)
		C2–N4–C17	125.93(18)				

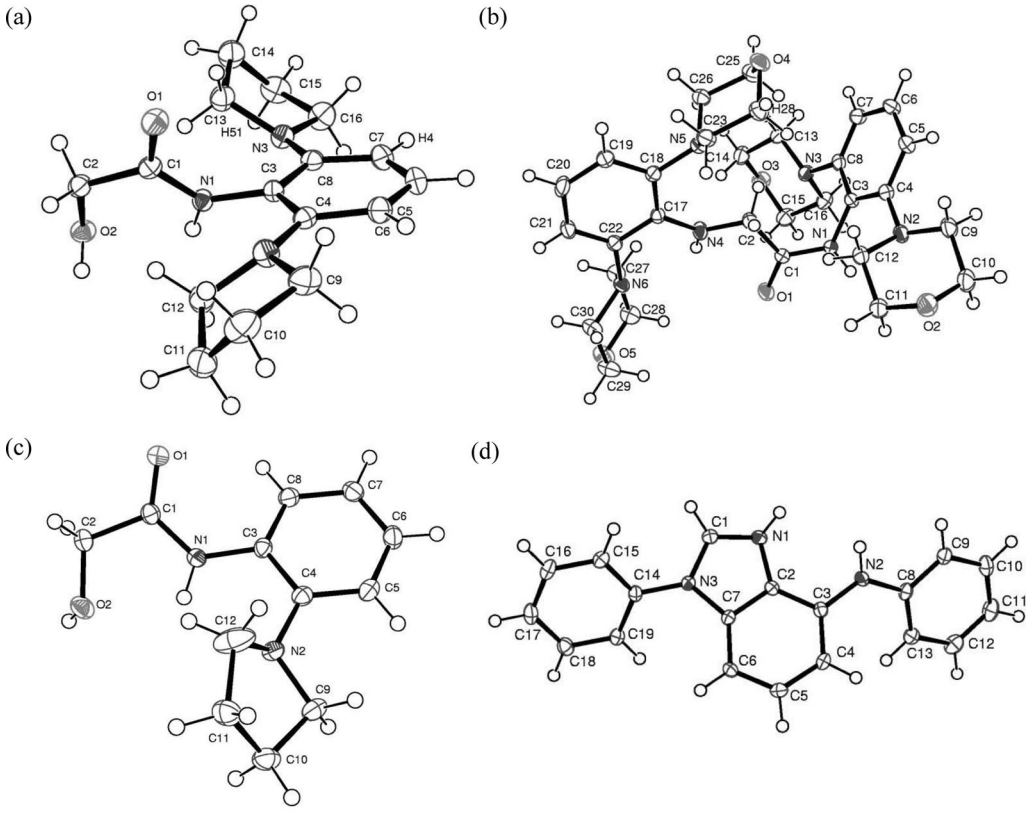
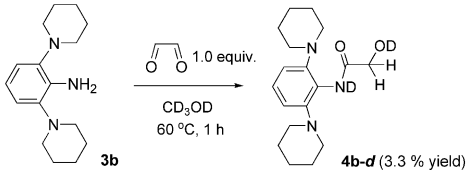
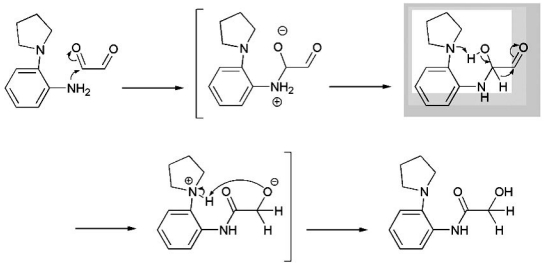


Figure 2. Crystal structures of (a) **4a**, (b) **4c**, (c) **4g**, and (d) **5** (50% probability thermal ellipsoids).

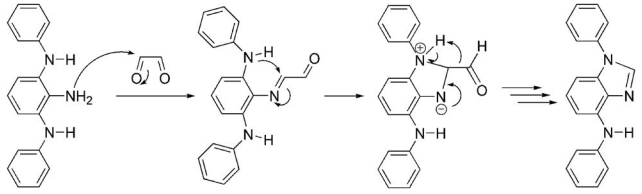


Scheme 4. The reaction of glyoxal with 2,6-dipyrrolidinylaniline in the presence of [D_4]methanol.



Scheme 5. Proposed mechanism for *o*-amine-assisted intramolecular Cannizzaro reaction.

Although decarboxylation of α-keto carboxylic acid derivatives with *o*-phenylenediamine to form benzimidazole compounds is known,[22] such benzimidazole derivatives have not been formed by the condensation using α-keto carbonyl compounds like glyoxal. The proposed mechanism for the formation of **5** is shown in Scheme 6. After the electrophilic imine is attacked by the *o*-substituted amine, deformylation might proceed to form **5**.



Scheme 6. Proposed mechanism for the formation of **5**.

The relationship between the products, α-hydroxy amide and α-amino amide, with the basicity of *o*-substituted amines like pyrrolidine, piperidine, and morpholine may also support the above mechanism. The reactions of glyoxal with the strongly basic amines **3a** and **3b** containing pyrrolidine (pK_b = 2.9) and piperidine (pK_b = 2.8) form the α-hydroxy amides **4a** and **4b**, whereas less basic amines like morpholine (pK_b = 5.6) in **3c** provid the α-amino amide **4c**, which may be generated via imine formation at one of two carbonyl groups in glyoxal. A tetrahedral intermediate formed by the addition of a second aniline molecule possibly induces the formation of **4c** by intramolecular Cannizzaro reaction, as a result of the increased acidity of the hydroxy proton to form.

The reaction true mechanism for the formation of compound **5** may be more complex, and several plausible reaction mechanisms can be proposed. We assume that the first imine formation and then intramolecular nucleophilic at-

tack of the secondary *o*-amines to the imine carbon might proceed to form an imidazole compound, accompanied by elimination of the other carbonyl group.

Conclusions

A series of new anilines containing cyclic amine or aniline moieties at the 2- and/or 6-positions was synthesized by a convenient procedure. Nucleophilic substitution or palladium-catalyzed amination of 2,6-dihalonitrobenzene with a cyclic or aromatic amine results in the formation of 2,6-diaminonitrobenzene **1** in high yields. Subsequent reduction of **1** with Pd/C and hydrogen affords the anilines **3** in excellent yields. These anilines have a special reactivity towards glyoxal to form α-hydroxy amide, α-amino amide, and imidazole derivatives, the structures of which were determined by spectroscopic methods and X-ray crystallography. The reactions yielding amide compounds are the first examples of intramolecular Cannizzaro reactions with anilines where no addition of Lewis acids or strong bases is needed. Obviously the reaction is significantly assisted by the basic *o*-substituted amines. Other 1,2-dicarbonyl compounds do not react with these anilines. We are now going to expand the above bifunctional system to develop various new organic reactions.

Experimental Section

General: Catalytic reactions were conducted under inert gas atmosphere using standard Schlenk techniques and a glove box (MBraun UniLab). Toluene as a solvent for catalytic reactions was distilled from benzophenone ketyl and stored under nitrogen. Other reagents were used as purchased. Column chromatography of organic products was carried out using silica gel [Kanto Kagaku, silica gel 60 N (spherical, neutral)]. The ^{1}H NMR spectra were taken with a VARIAN Mercury Y plus 400 MHz spectrometer at room temperature. Chemical shifts (δ) were recorded in ppm from the signal assigned as [D]chloroform, which was passed through a column with neutral alumina before use. IR spectra were recorded with a Perkin–Elmer Spectrum One spectrometer equipped with a universal diamond ATR (wavenumbers given in cm^{-1}). Elemental analyses were carried out with a YANACO CHN Corder MT-5, AUTO-SAMPLER. Antipyrine was used as the standard sample. Mass spectra (EHMS) were recorded with a JEOL JMS-GCmateII.

Preparation of 2,6-Diaminonitrobenzenes 1a–c and Monoaminonitrobenzenes 1g and 1h: In a typical example, 2,6-dipyrrolidinyl-1-nitrobenzene (**1a**) was prepared as follows. To a 200 mL round-bottom flask were added 2,6-dichloronitrobenzene (3.84 g, 20.0 mmol) and pyrrolidine (51.0 mL, 600 mmol). The mixture was refluxed (at 118 °C) for 120 h. After the reaction, pyrrolidine was evaporated under reduced pressure to yield a red solid, which was then dissolved in CH_2Cl_2 (50 mL) and washed with water. Removal of the solvent afforded an orange solid (yield 5.05 g, 97%).

1a: $C_{14}H_{19}N_3O_2$ (261.32): calcd. C 64.35, H 7.33, N 16.08; found C 64.20, H 7.26, N 15.81. ^{1}H NMR ($CDCl_3$): δ = 7.09 (t, J = 8.3 Hz, 1 H), 6.34 (d, J = 8.3 Hz, 2 H), 3.23–3.20 (m, 8 H), 1.92–1.89 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 143.49, 131.38, 130.20, 106.18, 49.54, 25.40 ppm. IR (neat): $\tilde{\nu}$ = 1510 (N=O) cm^{-1}.

1b: Yellow solid, yield 5.75 g, 99.5%. $C_{16}H_{23}N_3O_2$ (289.4): calcd. C 66.41, H 8.01, N 14.52; found C 66.39, H 7.98, N 14.25. ^{1}H NMR ($CDCl_3$): δ = 7.30 (t, J = 8.1 Hz, 1 H), 6.92 (d, J = 8.1 Hz, 2 H), 2.91–2.88 (m, 8 H), 1.66–1.61 (m, 8 H), 1.53–1.47 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 146.74, 145.74, 130.44, 117.30, 54.38, 26.35, 24.08 ppm. IR (neat): $\tilde{\nu}$ = 1537 (N=O) cm^{-1}.

1c: Pale-yellow solid, yield 4.97 g, 84.5%. $C_{14}H_{19}N_3O_4$ (293.32): calcd. C 57.33, H 6.53, N 14.33; found C 57.28, H 6.39, N 14.28. ^{1}H NMR ($CDCl_3$): δ = 7.40 (t, J = 8.1 Hz, 1 H), 7.03 (d, J = 8.2 Hz, 2 H), 3.77 (t, J = 4.5 Hz, 8 H), 2.97 (m, J = 4.6 Hz, 8 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 146.11, 145.16, 131.01, 118.24, 67.15, 53.15 ppm. IR (neat): $\tilde{\nu}$ = 1531 (N=O), 1110 (C–O) cm^{-1}.

The synthetic method of **1g** and **1h** was similar to that for **1a**–**1c**. In these cases, the reaction mixtures were stirred refluxed (at 108 °C) for 2 h to yield **1g** as an orange solid (yield 7.54 g, 98%) and **1h** as a yellow solid (yield 1.89 g, 98%).

1g: ^{1}H NMR ($CDCl_3$): δ = 7.74 (dd, J = 8.2, 1.6 Hz, 1 H), 7.36 (dt, J = 8.7, 1.7 Hz, 1 H), 6.90 (dd, J = 8.6, 1.0 Hz, 1 H), 6.71 (dt, J = 8.2, 1.1 Hz, 1 H), 3.23–3.20 (m, 4 H), 2.00–1.97 (m, 4 H) ppm.

1h: ^{1}H NMR ($CDCl_3$): δ = 8.12 (dd, J = 9.3, 1.9 Hz, 2 H), 6.47 (dd, J = 9.2, 1.0 Hz, 2 H), 3.40 (t, J = 6.5 Hz, 4 H), 2.09–2.06 (m, 4 H) ppm.

Preparation of 2,6-Dianilinonitrobenzenes 1d–1f: In a typical example, to a 100 mL Schlenk flask were added 2,6-dichloro nitrobenzene (3.00 g, 15.6 mmol), IPr (273 mg, 0.702 mmol), $Pd(OAc)_2$ (105 mg, 0.468 mmol), Cs_2CO_3 (14.2 g, 43.7 mmol), aniline (4.3 mL, 46.8 mmol), and toluene (32 mL), and the mixture was stirred at 100 °C for 48 h. After the resulting suspension was cooled to room temperature, the precipitate in the reaction mixture was removed by filtration and washing with CH_2Cl_2. After the solvent was evaporated, the residual black solid was dissolved in CH_2Cl_2 and crystallized. The crystals were washed with cold methanol to yield **1d** as black crystals (yield 3.24 g, 68%). As the filtered solution contained **1d** and aniline, the solvent was evapolated and, subsequently, aniline was removed by heating the mixture at 100 °C to give a black solid. The solid mixture was separated by silica gel column chromatography to yield disubstituted compound **1d** (black solid, yield 235 mg, 4.9%) and monosubstituted compound **2d** (red oil, yield 554 mg, 14%).

1d: $C_{18}H_{15}N_3O_2$ (305.34): calcd. C 70.81, H 4.95, N 13.76; found C 70.64, H 5.16, N 13.79. ^{1}H NMR ($CDCl_3$): δ = 9.60 (br., 2 H), 7.39 (t, J = 6.8 Hz, 4 H), 7.27 (d, J = 6.45 Hz, 4 H), 7.19 (t, J = 7.4 Hz, 2 H), 7.03 (t, J = 8.4 Hz, 1 H), 6.49 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 144.85, 139.56, 135.29, 129.55, 125.08, 124.68, 124.20, 103.82 ppm. IR (neat): $\tilde{\nu}$ = 3368 (N–H), 1570 (N=O) cm^{-1}.

The disubstituted compound **1e** was crystallized from hexane to yield purple crystals (total yield 5.45 g, 74%).

1e: $C_{30}H_{39}N_3O_2$ (473.66): calcd. C 76.07, H 8.30, N 8.87; found C 76.04, H 8.17, N 8.76. ^{1}H NMR ($CDCl_3$): δ = 9.75 (br., 2 H), 7.35 (t, J = 7.7 Hz, 2 H), 7.25 (d, J = 8.4 Hz, 4 H), 6.79 (t, J = 8.3 Hz, 1 H), 5.48 (d, J = 8.4 Hz, 2 H), 3.11 (sept, J = 6.9 Hz, 4 H), 1.20 (d, J = 6.8 Hz, 12 H), 1.15 (d, J = 6.9 Hz, 12 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 148.35, 147.08, 136.32, 133.42, 128.27, 124.03, 121.47, 101.04, 28.39, 24.66, 23.04 ppm. IR (neat): $\tilde{\nu}$ = 3372 (N–H), 1573 (N=O) cm^{-1}.

1f: Purple solid, yield 3.43 g, 57%. $C_{24}H_{27}N_3O_2$ (389.50): calcd. C 74.01, H 6.99, N 10.79; found C 74.00, H 6.96, N 10.82. ^{1}H NMR ($CDCl_3$): δ = 9.62 (br., 2 H), 6.96 (s, 4 H), 6.82 (t, J = 8.3 Hz, 1 H), 5.50 (d, J = 8.3 Hz, 2 H), 2.32 (s, 6 H), 2.18 (s, 12 H) ppm. ^{13}C

NMR ($CDCl_3$): δ = 147.13, 136.85, 136.56, 136.17, 133.56, 129.27, 121.91, 100.37, 20.96, 18.15 ppm. IR (neat): $\tilde{\nu}$ = 3347 (N–H), 1571 (N=O) cm^{-1}.

Preparation of Diaminoanilines 3a–e and Monoaminoanilines 3g and 3h: In a typical example, 2,6-dipyrrolidinylaniline **3a** was obtained as follows. To a 1 L round-bottom flask were added 2,6-dipyrrolidinyl-1-nitrobenzene **1a** (4.54 g, 17.4 mmol), EtOH (350 mL), 5% Pd/C (1.85 g, 0.87 mmol). The flask was evacuated and filled with hydrogen gas (1 atm). The mixture was stirred at 5 °C for 5–14 h. Filtration of the resulting suspension and removal of the solvent gave a pale-yellow solid (3.67 g), which was dissolved in ethanol (20 mL) in a 500 mL Erlenmeyer flask by heating. After the solution was cooled to –30 °C, ice-cold water (80 mL) was slowly added. The precipitate was filtered and dried to yield **3a** as a white solid (yield 3.55 g, 88%).

3a: $C_{14}H_{21}N_3$ (231.34): calcd. C 72.69, H 9.15, N 18.16; found C 72.56, H 9.03, N 10.82. ^1H NMR ($CDCl_3$): δ = 6.75–6.68 (m, 3 H), 4.02 (br., 2 H), 3.09–3.06 (m, 8 H), 1.93–1.90 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 137.94, 135.85, 117.51, 112.49, 50.76, 24.09 ppm. IR (neat): $\tilde{\nu}$ = 3406, 3319 (N–H) cm^{-1}.

3b: White solid, yield 3.04 g, 98%. $C_{16}H_{25}N_3$ (259.39): calcd. C 74.09, H 9.71, N 16.20; found C 74.35, H 9.65, N 16.00. ^1H NMR ($CDCl_3$): δ = 6.77–6.69 (m, 3 H), 4.26 (br., 2 H), 2.86 (br., 8 H), 1.73–1.68 (m, 8 H), 1.57 (br., 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 140.74, 136.39, 117.38, 114.33, 52.57, 26.92, 24.43 ppm. IR (neat): $\tilde{\nu}$ = 3419, 3406, 3324 (N–H) cm^{-1}.

3c: White solid, yield 3.76 g, 94%. $C_{14}H_{21}N_3O_2$ (263.3): calcd. C 63.85, H 8.04, N 15.96; found C 63.69, H 8.00, N 16.03. ^1H NMR ($CDCl_3$): δ = 6.82–6.74 (m, 3 H), 4.27 (br., 2 H), 3.86 (t, J = 4.5 Hz, 8 H), 2.94 (t, J = 4.6 Hz, 8 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 139.11, 136.19, 117.68, 114.77, 67.48, 51.27 ppm. IR (neat): $\tilde{\nu}$ = 3423, 3319 (N–H), 1111 (C–O) cm^{-1}.[23]

3d: Pale-purple solid, yield 2.56 g, 89%. $C_{18}H_{17}N_3$ (275.4): calcd. C 78.52, H 6.22, N 15.26; found C 78.55, H 6.40, N 15.16. ^1H NMR ($CDCl_3$): δ = 7.23 (t, J = 7.8 Hz, 4 H), 7.00 (d, J = 8.0 Hz, 2 H), 6.84 (t, J = 7.4 Hz, 2 H), 6.78 (d, J = 8.0 Hz, 4 H), 6.73 (t, J = 8.0 Hz, 1 H), 5.25 (br., 2 H), 3.90 (br., 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 145.18, 137.66, 129.51, 129.33, 120.85, 119.49, 118.52, 115.38 ppm. IR (neat): $\tilde{\nu}$ = 3428, 3397, 3334 (N–H) cm^{-1}.

3e: Purple solid, which was separated by column chromatography, yield 16.7 mg, 3.5%. EHMS Calcd for $C_{30}H_{41}N_3$: (M^+) 443.3301. Found: 443.3333. ^1H NMR ($CDCl_3$): δ = 7.22–7.20 (m, 6 H), 6.43 (t, J = 8.0 Hz, 1 H), 5.87 (d, J = 8.0 Hz, 2 H), 4.88 (br., 2 H), 3.73 (br., 2 H), 3.14 (sept, J = 6.8 Hz, 4 H), 1.21 (br., 12 H), 1.11 (br., 12 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 144.88, 137.53, 137.37, 125.57, 124.78, 123.66, 120.14, 109.38, 27.98, 24.64, 23.15 ppm. IR (neat): $\tilde{\nu}$ = 3372, 3302 (N–H) cm^{-1}.

The synthetic method for **3g**[5] and **3h**[24] was similar to that for **3a**–**3d**.

The Reactions of Glyoxal with 2,6-Diaminoanilines 3a–c and 2-Aminoaniline 3g: In a typical example, the reaction of glyoxal with 2,6-dipyrrolidinylaniline **3a** was as follows. To a 20 mL Schlenk tube were added 2,6-dipyrrolidinylaniline (0.2 g, 0.865 mmol), 1-propanol (0.78 mL), and a 40% glyoxal solution (99.2 μL, 0.865 mmol) under an argon atomsphere. After the tube was sealed, the mixture was stirred at 70 °C for 24 h. The volatile compounds were removed under reduced pressure to obtain a brown solid. The residual solid was separated by silica gel column chromatography using ethyl acetate as an eluent to yield **4a** as a pale yellow solid (yield 133.5 mg, 53%).

4a: $C_{16}H_{23}N_3O_2$ (289.4): calcd. C 66.41, H 8.01, N 14.52; found C 66.57, H 7.90, N 14.12. ^1H NMR ($CDCl_3$): δ = 7.08 (t, J = 8.2 Hz, 1 H), 6.87 (br., 1 H) 6.36 (br., 2 H) 3.71 (br., 2 H), 3.24 (br., 8 H), 3.07 (br., 1 H), 1.90 (br., 8 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 174.92, 149.25, 129.21, 110.97, 106.45, 59.60, 50.88, 25.52 ppm. IR (neat): $\tilde{\nu}$ = 3218 (N–H, O–H), 1673 (C=O) cm^{-1}.

The product **4b** was obtained only by washing the residual solid after evaporation with diethyl ether (pale-yellow solid, yield 210.2 mg, 66%): $C_{18}H_{27}N_3O_2$ (317.43): calcd. C 68.11, H 8.57, N 13.24; found C 67.83, H 8.58, N 13.35. ^1H NMR ($CDCl_3$): δ = 7.17 (t, J = 8.1 Hz, 1 H), 6.80 (d, J = 8.1 Hz, 2 H), 4.25 (d, J = 4.9 Hz, 2 H), 3.03 (br., 1 H), 2.81 (t, J = 5.2 Hz, 8 H), 1.69–1.63 (m, 8 H), 1.57–1.51 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.37, 150.34, 127.77, 124.29, 115.06, 61.43, 52.94, 26.51, 24.23 ppm. IR (neat): $\tilde{\nu}$ = 3320, 3264 (N–H, O–H), 1660 (C=O) cm^{-1}.

4c: Pale-yellow solid, yield 26.4 mg, 16%. $C_{30}H_{42}N_6O_5$ (566.3): calcd. C 63.58, H 7.47, N 14.83; found C 63.13, H 7.21, N 14.49. ^1H NMR ($CDCl_3$): δ = 7.24 (t, J = 7.9 Hz, 2 H), 6.86 (d, J = 8.0 Hz, 4 H), 6.83 (br., 2 H), 4.38 (br., 2 H), 3.74 (br., 8 H), 3.61 (br., 8 H), 2.90 (br., 8 H), 2.79 (br., 8 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 172.71, 149.49, 142.77, 136.57, 128.33, 125.94, 121.06, 115.97, 115.83, 67.21, 67.14, 51.90, 51.48, 47.39 ppm. IR (neat): $\tilde{\nu}$ = 3258 (N–H, O–H), 1681 (C=O), 1108, 1100 (C–O) cm^{-1}.

4g: Brown solid, yield 64.8 mg, 15%. This material was pure enough for further use; purification by recrystallization from methanol yielded pale-yellow crystals. $C_{12}H_{16}N_2O_2$ (220.3): calcd. C 65.43, H 7.32, N 12.72; found C 64.72, H 7.03, N 12.02. ^1H NMR ($CDCl_3$): δ = 9.13 (br., 1 H), 8.15 (dd, J = 7.4, 1.3 Hz, 1 H), 7.11–7.00 (m, 3 H), 4.22 (br., 2 H), 3.04–3.03 (m, 4 H), 1.94–1.91 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.67, 140.91, 131.03, 124.70, 123.29, 120.92, 118.80, 62.71, 51.90, 24.45 ppm. IR (neat): $\tilde{\nu}$ = 3391, 3348 (N–H, O–H), 1662 (C=O) cm^{-1}.

5: Pale-yellow solid, yield 156.8 mg, 55%. $C_{19}H_{15}N_3$ (285.3): calcd. C 79.98, H 5.30, N 14.73; found C 79.74, H 5.48, N 14.73. ^1H NMR ($CDCl_3$): δ = 8.03 (br., 1 H), 7.60–7.53 (m, 4 H), 7.49–7.45 (m, 1 H), 7.35–7.34 (m, 4 H), 7.21–7.20 (m, 2 H), 7.00 (br., 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 141.98, 140.11, 136.53, 135.88, 134.31, 133.87, 129.98, 129.29, 127.96, 124.65, 123.99, 121.68, 119.16, 104.94, 101.52 ppm.

The Reaction of Glyoxal with 4-Pyrrolidinylaniline 3h: To a 20 mL Schlenk tube were added 4-pyrrolidinylaniline (0.1622 g, 1.0 mmol), 1-propanol (0.9 mL), and a 40% glyoxal solution (57.3 μL, 0.5 mmol). The mixture was stirred at 70 °C for 24 h. The reaction mixture was filtered and washed with cold methanol to yield **6** as a brown solid (yield 158.1 mg, 91%). $C_{22}H_{26}N_4$ (346.5): calcd. C 76.27, H 7.56, N 16.17; found C 76.02, H 7.55, N 16.07. ^1H NMR ($CDCl_3$): δ = 8.47 (s, 2 H), 7.36 (d, J = 8.9 Hz, 4 H), 6.58 (d, J = 8.9 Hz, 4 H), 3.36–3.32 (m, 8 H), 2.04–2.01 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 154.24, 147.91, 138.24, 123.46, 111.88, 47.68, 25.52 ppm. IR (neat): $\tilde{\nu}$ = 1598 (C=N) cm^{-1}.

X-ray Crystallography: Single crystals of α-hydroxy amide, α-amino amide, and imidazole derivatives **4a**, **4c**, **4g**, and **5** suitable for X-ray diffraction studies were grown in the methanol/diethyl ether, dichloromethane/hexane, methanol, and toluene/hexane solutions, respectively. All data were collected on a Rigaku Saturn CCD diffractometer at 123 K using mirror-focused graphite-monochromated Mo-K_α radiation (λ = 0.71070 Å). The structures were solved by direct methods and refined by full-matrix least-squares fitting based on F^2 using the PC version of the program SHELXL 97-2.[25] All H atoms were located at ideal positions and were included in the refinement, but were restricted to ride on the atom to which they were bonded.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for the new organic compounds and additional X-ray measurement data.

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[1] a) N. V. Sidgwick, I. T. Millar, H. D. Springall, *The Organic Chemistry of Nitrogen*, 3rd ed, Clarendon Press, Oxford, **1966**; b) G. Sauvé, V. S. Rao, in *Comprehensive Organic Functional Group Transformations* (Eds.: A. R. Katritzky, O. Meth-Cohn, C. W. Rees), Pergamon, Oxford, **1995**, vol. 2, pp. 752–817; c) J. L. Chiara, in *Comprehensive Organic Functional Group Transformations II* (Eds.: A. R. Katritzky, R. J. K. Taylor), Pergamon, Oxford, **2005**, vol. 2, p. 731–852.

[2] a) D. Meinhard, M. Wegner, G. Kipiani, A. Hearley, P. Reuter, S. Fischer, O. Marti, B. Rieger, *J. Am. Chem. Soc.* **2007**, *129*, 9182–9191; b) J. Gavenonis, T. D. Tilley, *Organometallics* **2004**, *23*, 31–43; c) I. Göttker-Schnetmann, P. Wehrmann, C. Röhr, S. Mecking, *Organometallics* **2007**, *26*, 2348–2362.

[3] Y.-K. Lim, X. Jiang, J. C. Bollinger, D. Lee, *J. Mater. Chem.* **2007**, *17*, 1969–1980.

[4] a) J. Yoshida, K. Itami, *Chem. Rev.* **2002**, *102*, 3693–3716; b) K. Itami, T. Nokami, Y. Ishimura, K. Mitsudo, T. Kamei, J. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 11577–11585; c) K. Itami, K. Mitsudo, J. Yoshida, *Angew. Chem. Int. Ed.* **2001**, *40*, 2337–2339.

[5] M. D. Nair, R. Adams, *J. Am. Chem. Soc.* **1961**, *83*, 3518–3521.

[6] B. K. Trivedi, A. Holmes, T. L. Stoeber, C. J. Blankley, W. H. Roark, J. A. Picard, M. K. Shaw, A. D. Essenburg, R. L. Stanfield, B. R. Krause, *J. Med. Chem.* **1993**, *36*, 3300–3307, and some patents described about such anilines.

[7] J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1144–1157.

[8] a) J. March, *Advanced Organic Chemistry*, 4th ed., John Wiley & Sons, New York, **1992**, p. 1233–1235; b) S. Cannizzaro, *Justus Liebigs Ann. Chem.* **1853**, *88*, 129–130; c) T. A. Geissman, *Org. React.* **1944**, *11*, 94–113; d) C. G. Swain, A. L. Powell, W. A. Sheppard, C. R. Morgan, *J. Am. Chem. Soc.* **1979**, *101*, 3576–3583; e) S. K. Chung, *J. Chem. Soc., Chem. Commun.* **1982**, 480–481; f) E. C. Ashby, D. T. Coleman III, M. P. Gamasa, *Tetrahedron Lett.* **1983**, *24*, 851–854.

[9] Recent examples a) D. Basavaiah, D. S. Sharada, A. Veerendhar, *Tetrahedron Lett.* **2006**, *47*, 5771–5774; b) K. Yoshizawa, S. Toyota, F. Toda, *Tetrahedron Lett.* **2001**, *42*, 7983–7985; c) A. Sharifi, M. M. Mojtahedi, M. R. Saidi, *Tetrahedron Lett.* **1999**, *40*, 1179–1180.

[10] a) K. Bowden, A. M. Butt, M. Streater, *J. Chem. Soc. Perkin Trans. 2* **1992**, 567–571; b) R. S. McDonald, C. E. Sibley, *Can. J. Chem.* **1981**, *59*, 1061–1067; c) Y. Vida, E. Perez-Inestrosa, R. Suau, *Tetrahedron Lett.* **2005**, *46*, 1575–1577.

[11] K. Ishihara, T. Yano, *Org. Lett.* **2004**, *6*, 1983–1986.

[12] A. E. Russell, S. P. Miller, J. P. Morken, *J. Org. Chem.* **2000**, *65*, 8381–8383.

[13] S. L. Shapiro, I. M. Rose, L. Freedman, *J. Am. Chem. Soc.* **1959**, *81*, 6322–6329.

[14] a) T. Punniyamurthy, J. Iqbal, *Tetrahedron Lett.* **1997**, *38*, 4463–4466; b) K. X. Chen, F. G. Njoroge, J. Pichardo, A. Prongay, N. Butkiewicz, N. Yao, V. Madison, V. Girijavallabhan, *J. Med. Chem.* **2006**, *49*, 567–574.

[15] M. Hladik, J. J. Hsiao, A. Lynnroberts, *Environ. Sci. Technol.* **2005**, *39*, 6561–6574.

[16] a) J. W. Jaroszewski, E. S. Olafsdottir, P. Wellendorph, J. Christensen, H. Franzyk, B. Somanadhan, B. A. Budnik, L. B. Jørgensen, V. Clausen, *Phytochemistry* **2002**, *59*, 501–511; b) N. R. Candeias, P. M. P. Gois, C. A. M. Afonso, *J. Org. Chem.* **2006**, *71*, 5489–5497; c) N. Kambe, T. Inoue, N. Sonoda, *Org. Synth.* **1995**, *72*, 154–162; d) N. R. Candeias, P. M. P. Gois, C. A. M. Afonso, *J. Org. Chem.* **2006**, *71*, 5489–5497.

[17] a) J. M. Concellón, E. Bardales, *Org. Lett.* **2003**, *5*, 4783–4785; b) T. Kurz, K. Widyan, *Tetrahedron* **2005**, *61*, 7247–7251; c) S. E. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2003**, *125*, 7825–7827; d) Q. Xia, B. Ganem, *Org. Lett.* **2002**, *4*, 1631–1634; e) M. Adamczyk, J. Grote, S. Rege, *Tetrahedron: Asymmetry* **1997**, *8*, 2509–2512.

[18] a) A. J. Arduengo III, R. Krafczyk, R. Schmutzler, *Tetrahedron* **1999**, *55*, 14523-l4534; b) J. Huang, S. P. Nolan, *J. Am. Chem. Soc.* **1999**, *121*, 9889–9890; c) M. B. Abrams, B. L. Scott, R. T. Baker, *Organometallics* **2000**, *19*, 4944–4956.

[19] CCDC-717675 (for **4a**), -717676 (for **4c**), -717677 (for **4g**), -717678 (for **5**) contain the supplementary crystallographic data (excluding structure factors) 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.

[20] Finally, the deuterium content of the α-hydrogen in **4b** was 30% after 16 h at 70 °C, probably due to enolization by the basic amines.

[21] Lobry de Bruyn-Alberda van Ekenstein reaction; see review article: J. C. Speck, *Adv. Carbohydr. Chem.* **1958**, *13*, 63–103.

[22] a) F. Szydlo, B. Andrioletti, E. Rose, C. Duhayon, *Tetrahedron Lett.* **2008**, *49*, 3749–3751; b) R. Duval, G. Lewin, R. Hocquemiller, *Bioorg. Med. Chem.* **2003**, *11*, 3439–3446.

[23] R. Varala, E. Ramu, M. M. Alam, S. R. Adapa, *Synlett* **2004**, *10*, 47–1750.

[24] Syntheses of compounds **1c** and **3c** are described in a patent, no detailed characterizations are given: J. R. Brian, G. R. David, F. Gillian (Knoll Aktiengesellschaft, Germany), WO96/17612, **1996**. CAS numbers: 179900-23-3 (**1c**), 179900-24-4 (**3c**).

[25] G. M. Sheldrick, *SHELXL-97, A program for crystal structure refinement*, release 97-2, University of Göttingen, **1997**.

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