Pd/C-Catalyzed Reductive Formylation of Indoles and Quinolines Using Formic Acid

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Abstract: A two-step, one-pot domino reaction methodology was developed to synthesize a variety of *N*-formylindolines and *N*-formyltetrahydroquinolines from the corresponding indoles and quinolines. In the first step, the heterocyclic compounds are reduced to the corresponding dihydro or tetrahydro products by a Pd/C-catalyzed transfer hydrogenation using formic acid as a hydrogen donor. In the second step, nitrogen is formylated by formic acid to afford the final products in very good isolated yields.

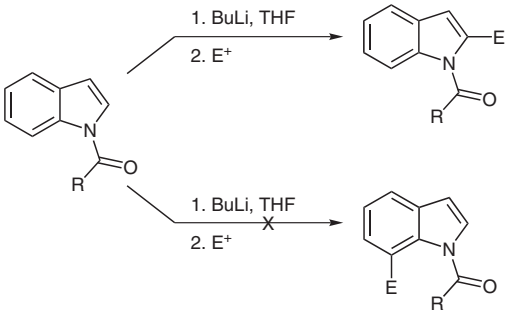
Key words: catalytic transfer hydrogenation, indoles, quinolines, formylation, domino reaction

Indolines are structural components of several pharmaceutically important and biologically active alkaloids.[1] To date, several pathways have been reported for the synthesis of indolines.[2] Most of these routes involve ring closure through amination reactions.[3] The starting materials for these amination reactions are not commercially available and their syntheses require multiple steps. There are few examples of the hydrogenation of commercially available and inexpensive indoles to their corresponding indolines.[4] The ability to easily functionalize indoles and quinolines is vital in the pharmaceutical industry due to the inherent drug-like qualities of such compounds.[5]

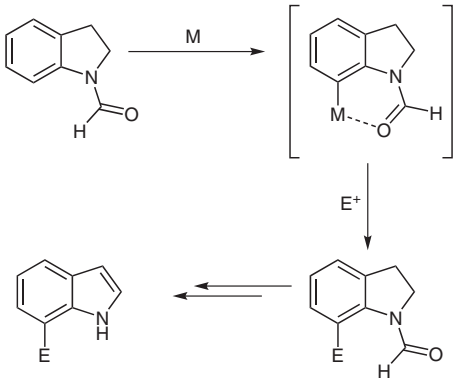
N-Formylindoline can be used as a precursor for the synthesis of 7-substituted indoles, which are otherwise difficult to synthesize. As shown in Scheme 1, the carbonyl group of *N*-acylindoles can be used as a directing group for the aromatic substitution of indoles. When nonbulky ligands are used, metalation of the more nucleophilic C-2 position is favored over the C-7 position of the indole, leading to a C-2 specific product.[6] If bulky ligands are used, the C-2 position is sterically hindered and the C-3-substituted derivative is the major product.

When the carbonyl group is used as a directing group on indolines, however, the C-7-selective product is observed as the major product.[7,8] The nitrogen can then be deprotected by hydrolysis to obtain a 7-substituted indoline which can be aromatized to obtain the corresponding C-7-substituted indole (Scheme 2).[8]

Previously, *N*-formylindolines were synthesized by the formylation of indolines, which in turn were synthesized from indoles by reduction, in separate steps.[9]



Scheme 1 Carbonyl group directed aromatic substitution of *N*-acylindoles



Scheme 2 Synthesis of 7-substituted indoles from *N*-formylindoline

Heterogeneous catalytic hydrogenation is a very efficient and powerful tool for achieving controlled reduction of various organic compounds.[10] Heterogeneous catalysts are insensitive to moisture and easy to store and handle which makes them more attractive compared to the homogeneous counterparts. They can be easily recovered by filtration and reused, and offer a possibility of using continuous-flow systems.

Herein, we describe an expedient synthesis of various *N*-formylindolines and *N*-formyltetrahydroquinolines in a two-step, one-pot fashion starting from the corresponding indoles and quinolines (Scheme 3).

Such transformations have hardly been studied despite their significant potential benefits, and the only available report was limited to indoles.[11] Our current method is efficient and requires short reaction times, and the products are obtained in high isolated yields. Furthermore, to the best of our knowledge, the reductive formylation of quin-

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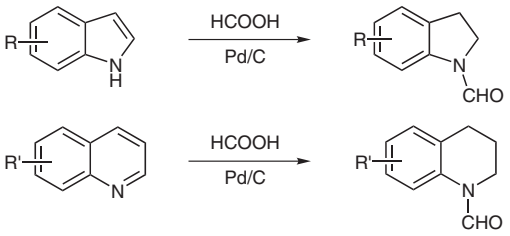


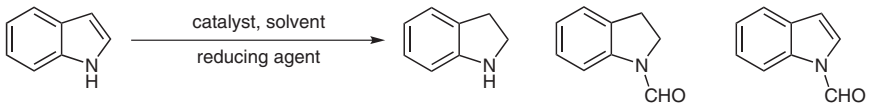
Scheme 3 Reductive formylation of indoles and quinolines using formic acid

olines has not previously been carried out in a one-pot reduction–formylation domino reaction sequence.

To optimize the conditions, the reductive formylation of indole was chosen as a model reaction (Table 1). Initially, hydrogen gas was used as a hydrogen source but the reaction afforded indoline (**1**) in traces at 40 °C after 30 minutes, independent of the catalyst used (entries 1 and 2). Therefore, transfer hydrogenation, as a versatile tool for reduction, was considered. Changing the hydrogen source to isopropyl alcohol or ammonium formate did not afford satisfactory product formation, even at 150 °C (entries 3–6). When formic acid was used as a hydrogen source in isopropyl alcohol, 23% of the desired product **2** was observed, in addition to 32% indoline (entry 7). A more acidic medium, formic acid, used both as a solvent and as a hydrogen donor gave appreciable results with a conversion of 88% and a selectivity of 82% after a reaction time of 30 minutes at 80 °C (entry 8). Further optimization of the reaction temperature and time resulted in the best conditions for the reaction; namely, a 10-minute reaction time at 100 °C with formic acid as both solvent and hydrogen donor (entry 12). Under these conditions, quantitative conversion and 100% selectivity was observed for *N*-formylindoline (indoline-1-carbaldehyde, **2**), as determined by GC-MS analysis. The use of a different metal catalyst (Pt/C) was unsuccessful, as a small amount of indoline (**1**) was observed as the only product under the same conditions (entry 13).

With the conditions optimized, attention was directed towards testing of the substrate scope of the methodology. The results are presented in Table 2. The methodology appears to be applicable to a broad range of substituted indoles and quinolines. In the case of 5-methyl, 5-methoxy and 7-methyl substitution on the indole, the corresponding *N*-formylindolines were obtained in excellent yields in short times (10 min) at 100 °C (entries 2, 3 and 5). The reaction conditions could tolerate a 5-fluoro substitution, although a higher temperature was required (entry 4). 2-Methyl and 2-ethoxycarbonyl substitution on indole also required higher temperature probably because of an inability of these compounds to adsorb on the surface of the Pd catalyst (entries 6 and 7). Ethyl indole-2-carboxylate also required a significantly longer reaction time of three hours due to the strong electron-withdrawing nature of the ester group. As anticipated, attempts to use chloro-, bro-

Table 1 Synthesis of *N*-Formylindoline (**2**) from Indole under Various Experimental Conditions



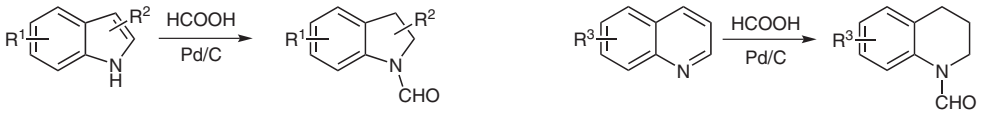
1 **2** **3**

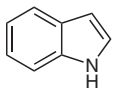
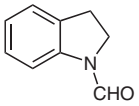
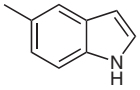
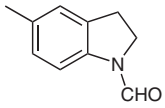
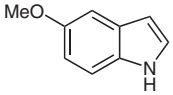
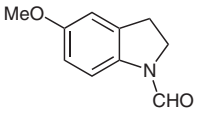
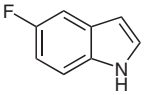
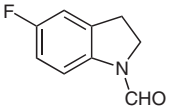
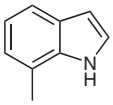
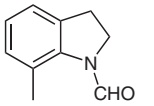
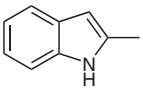
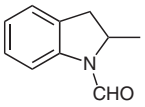
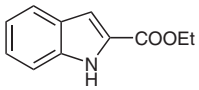
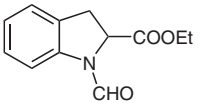
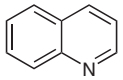
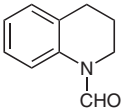
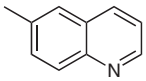
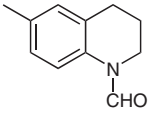
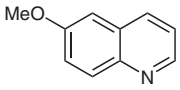
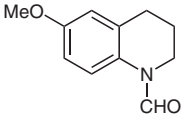
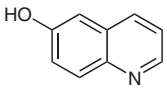
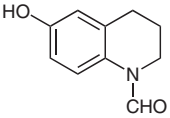
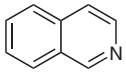
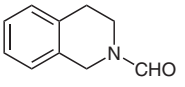
Entry	Catalyst	Solvent	Reducing agent	Temp (°C)	Time (min)	Yield[a] (%) **1/2/3**
1	Rh/alumina	*i*-PrOH	H_2	40	30	5:0:0
2	Pd/C	*i*-PrOH	H_2	40	30	3:0:0
3	Pd/C	*i*-PrOH	*i*-PrOH	80	30	0:0:0
4	Pd/C	*i*-PrOH	$HCOONH_4$	80	30	8:0:0
5	Pd/C	*i*-PrOH	$HCOONH_4$	120	60	20:0:0
6	Pd/C	DMF	$HCOONH_4$	150	30	2:0:0
7	Pd/C	*i*-PrOH	HCOOH	80	30	32:23:0
8	Pd/C	HCOOH	HCOOH	80	30	6:82:0
9	Pd/C	HCOOH	HCOOH	80	60	8:86:0
10	Pd/C	HCOOH	HCOOH	100	60	0:90:10
11	Pd/C	HCOOH, H_2O	HCOOH	100	10	6:39:0
12	Pd/C	HCOOH	HCOOH	100	10	0:100:0
13	Pt/C	HCOOH	HCOOH	100	10	23:0:0

[a] GC yields, based on residual indole.

mo- or iodoindoles resulted in dehalogenation. Next, we turned our attention towards quinolines. It was observed that quinoline itself also gave the desired product, in quantitative yield (entry 8), although after 180 minutes at 150 °C. Quinolines with electron-donating substituents on the carbocyclic ring gave the desired products in excellent yields (entries 9–11). Isoquinoline also gave the desired product in very good isolated yield (entry 12). One of the limitations of this methodology is that no substituent, whether electron donating or electron withdrawing, was tolerated on the heterocyclic ring of quinoline; the starting material was recovered from these reaction mixtures.

Table 2 Reductive Formylation of Various Substituted Indoles and Quinolines



Entry	Starting material	Temp (°C)	Time (min)	Product	Yield[a] (%)
1		100	10		>99
2		100	10		88
3		100	10		94
4		150	10		86
5		100	10		97
6		120	15		54
7		150	180		50
8		150	180		>99
9		150	180		92
10		150	180		93
11		150	180		89
12		150	180		84

[a] Isolated yields after flash chromatography.

During the NMR characterization of the products an interesting observation was made (Figure 1). The ^{1}H NMR spectrum of indoline-1-carbaldehyde (Figure 1a) showed the appearance of two formyl protons. The formyl group is able to rotate around the C–N bond and the two stable conformers, namely *endo* and *exo*, can be observed in the ^{1}H NMR spectrum.[11,12] The *exo*-conformer of indoline-1-carbaldehyde is the major conformer at room temperature and the ratio of *endo*/*exo* is 1:5. It is proposed that in the *endo*-conformer the oxygen of the formyl group forms a highly unusual hydrogen bond with the aromatic proton at the 7-position of the carbocyclic ring. Since, due to the proposed hydrogen bonding, this H-7 is in a more electronegative environment, its doublet shifts downfield (δ = 8.08 ppm). For comparison, the doublet of the same proton in the *exo*-conformer is observed at around 7.15 ppm.[13] The amount of the *endo*-conformer increased in the case of 2-methylindoline-1-carbaldehyde (Figure 1b), where the conformers were observed in the ratio (*endo*/*exo*) of 1:2.5. It is proposed that the presence of the methyl group in the adjacent 2-position of the heterocyclic ring sterically destabilizes, at least partially, the *exo*-conformer. In contrast, when a methyl group is placed at the 7-position (7-methylindoline-1-carbaldehyde, Figure 1c), it was observed that the conformational equilibrium completely shifted towards the *exo*-conformer. The rotation of the formyl group is hindered by the 7-methyl group, and the stabilizing force of the hydrogen bonding is not present. Thus, the *endo*-conformer was not observed in the ^{1}H NMR spectrum.

In summary, an efficient method for the synthesis of *N*-formylindolines and *N*-formyltetrahydroquinolines from the corresponding indoles and quinolines, respectively, has been developed. The products can be obtained in a one-pot process involving a reduction–formylation domino sequence. In the first step of the sequence, the indoles/quinolines are reduced by a Pd/C-catalyzed transfer hydrogenation using formic acid. In the second step, the resulting indolines/tetrahydroquinolines are formylated in situ to give the final products: *N*-formylindolines are obtained in short reaction times, whereas *N*-formyltetrahydroquinolines require longer reaction times and higher temperatures. The products were obtained in very good isolated yields. The use of an economic, readily available, recyclable catalyst and the two-step one-pot domino process are the attractive aspects of this methodology.

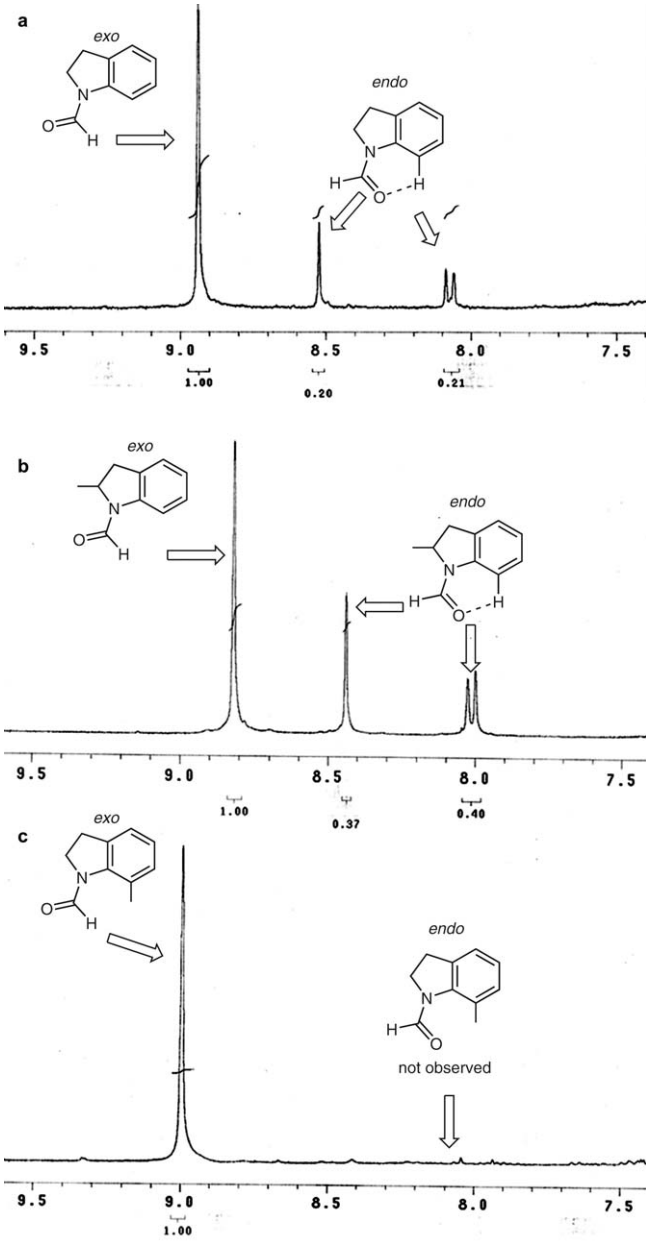


Figure 1 Partial ^{1}H NMR spectra indicating rotation of the formyl group around the N–C bond; NMR analysis of (a) indoline-1-carbaldehyde, (b) 2-methylindoline-1-carbaldehyde and (c) 7-methylindoline-1-carbaldehyde

All starting materials were purchased from Aldrich and used without further purification. $CDCl_3$ (99.8%) used as a solvent for NMR studies was an Aldrich product. Other solvents used in synthesis or purification, with minimum purity of 99.5%, were Fisher products. The mass spectrometric identification of the products was carried out by GC-MS analysis with an Agilent 6850 gas chromatograph–5973 mass spectrometer (70 eV, electron-impact ionization) using a 30-m DB-5 column (J&W Scientific). ^{1}H (300.128 MHz) and ^{13}C (75.474 MHz) NMR spectra were obtained on a Varian Gemini 2000 NMR spectrometer, using $CDCl_3$ as solvent with tetramethylsilane or the residual solvent signal as internal standard, at a temperature of 25 °C (accuracy ±1 °C) controlled by the Varian control unit. All melting points were recorded on a MEL-TEMP apparatus and are uncorrected.

N-Formylindolines and *N*-Formyltetrahydroquinolines; General Procedure

A round-bottom flask connected to an air condenser was charged with an indole or a quinoline (1 mmol), Pd/C (10% by wt, 50 mg) and formic acid (2 mL). The reaction mixture was stirred in a preheated oil bath at the desired temperature. If the formic acid evaporated over the duration of the reaction, the volume was supplemented by adding fresh formic acid to maintain the concentration of the reactant at its initial level. The progress of the reaction was monitored by GC-MS. After completion of the reaction, the mixture was allowed to cool to r.t. The catalyst was collected by filtration and washed with 80% aq MeOH (10 mL). The filtrate was quenched with sat. $NaHCO_3$ soln. The aqueous layer was extracted

with EtOAc (2 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography. NMR data for the major conformers only are provided below.

Indoline-1-carbaldehyde (Table 2, Entry 1)
Yield: 146 mg; reddish purple solid; mp 60–62 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.89 (s, 1 H), 7.15 (m, 4 H), 4.02 (t, *J* = 8.1 Hz, 2 H), 3.11 (t, *J* = 8.4 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 140.6, 131.7, 127.3, 125.8, 124.1, 109.2, 44.4, 26.8.

MS (C_9H_9NO): *m*/*z* (%) = 147 (52) [M^+], 118 (100), 91 (12), 77 (2), 65 (4).

5-Methylindoline-1-carbaldehyde (Table 2, Entry 2)
Yield: 142 mg; brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.87 (s, 1 H), 7.02 (m, 3 H), 4.03 (t, *J* = 8.7 Hz, 2 H), 3.10 (t, *J* = 8.4 Hz, 2 H), 2.31 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 133.9, 131.9, 127.9, 126.6, 116.2, 108.9, 44.6, 27.0, 20.8.

MS ($C_{10}H_{11}NO$): *m*/*z* (%) = 161 (58) [M^+], 132 (100), 117 (12), 103 (4), 77 (7), 65 (3).

5-Methoxyindoline-1-carbaldehyde (Table 2, Entry 3)
Yield: 166 mg; maroon solid; mp 68–70 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.80 (s, 1 H), 7.05 (d, *J* = 8.7 Hz, 1 H), 6.73 (m, 2 H), 4.03 (t, *J* = 9.0 Hz, 2 H), 3.77 (s, 3 H), 3.10 (t, *J* = 9.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0, 133.2, 116.9, 112.5, 111.8, 110.9, 109.6, 55.5, 44.6, 27.2.

MS ($C_{10}H_{11}NO_2$): *m*/*z* (%) = 177 (81) [M^+], 162 (5), 148 (7), 134 (100), 117 (4), 104 (5).

5-Fluoroindoline-1-carbaldehyde (Table 2, Entry 4)
Yield: 142 mg; white solid; mp 100–101 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.83 (s, 1 H), 7.07 (dd, *J* = 9.0, 4.5 Hz, 1 H), 6.89 (m, 2 H), 3.97 (t, *J* = 9.0 Hz, 2 H), 3.04 (t, *J* = 8.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2, 133.8, 133.7, 117.2, 117.1, 114.2, 113.9, 113.4, 113.1, 112.2, 111.9, 109.8, 109.6, 44.6, 27.1, 27.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –119.2.

MS (C_9H_8FNO): *m*/*z* (%) = 165 (64) [M^+], 136 (100), 109 (29), 83 (8), 57 (4).

7-Methylindoline-1-carbaldehyde (Table 2, Entry 5)
Yield: 156 mg; light brown solid; mp 92–93 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.99 (s, 1 H), 7.10 (d, *J* = 7.2 Hz, 1 H), 6.98 (m, 2 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.08 (t, *J* = 8.7 Hz, 2 H), 2.43 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2, 133.2, 130.6, 123.9, 123.3, 122.4, 117.7, 45.2, 27.6, 20.9.

MS ($C_{10}H_{11}NO$): *m*/*z* (%) = 161 (48) [M^+], 132 (100), 117 (33), 105 (10), 77 (15), 65 (8).

2-Methylindoline-1-carbaldehyde (Table 2, Entry 6)
Yield: 87 mg; brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.81 (s, 1 H), 7.10 (m, 3 H), 6.97 (t, *J* = 7.2 Hz, 1 H), 4.65 (m, 1 H), 3.29 (dd, *J* = 17.1, 9.4 Hz, 1 H), 2.58 (dd, *J* = 16.2, 2.4 Hz, 1 H), 1.27 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 130.7, 127.5, 126.2, 124.2, 116.7, 109.5, 53.1, 35.7, 20.3.

MS ($C_{10}H_{11}NO$): *m*/*z* (%) = 161 (63) [M^+], 146 (33), 132 (11), 118 (100), 91 (25).

Ethyl 1-Formylindoline-2-carboxylate (Table 2, Entry 7)
Yield: 110 mg; yellow solid; mp 92–93 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.98 (s, 1 H), 7.21 (m, 3 H), 7.06 (m, 1 H), 5.04 (ddd, *J* = 11.2, 4.2, 0.9 Hz, 1 H), 4.23 (dq, *J* = 6.9, 1.2 Hz, 2 H), 3.55 (dd, *J* = 16.5, 11.1 Hz, 1 H), 3.19 (dd, *J* = 16.5, 3.9 Hz, 1 H), 1.28 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 157.4, 140.5, 128.0, 125.8, 124.4, 116.5, 109.4, 61.7, 57.6, 32.3, 14.0.

MS ($C_{12}H_{13}NO_3$): *m*/*z* (%) = 219 (14) [M^+], 191 (5), 146 (22), 118 (100), 91 (13).

3,4-Dihydroquinoline-1(2*H*)-carbaldehyde (Table 2, Entry 8)
Yield: 160 mg; light brown solid; mp 122–124 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75 (s, 1 H), 7.12 (m, 4 H), 3.77 (t, *J* = 6.0 Hz, 2 H), 2.78 (t, *J* = 6.3 Hz, 2 H), 1.92 (quintet, *J* = 6.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 137.4, 129.2, 128.2, 126.7, 124.1, 116.6, 39.8, 26.7, 21.8.

MS ($C_{10}H_{11}NO$): *m*/*z* (%) = 161 (57) [M^+], 132 (100), 118 (23), 104 (10), 77 (20).

6-Methyl-3,4-dihydroquinoline-1(2*H*)-carbaldehyde (Table 2, Entry 9)
Yield: 161 mg; yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.75 (s, 1 H), 7.01 (m, 3 H), 3.79 (t, *J* = 6.0 Hz, 2 H), 2.77 (t, *J* = 6.3 Hz, 2 H), 2.30 (s, 3 H), 1.94 (quintet, *J* = 6.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.0, 134.1, 130.1, 128.6, 127.6, 122.1, 116.8, 40.2, 27.0, 22.3, 20.6.

MS ($C_{11}H_{13}NO$): *m*/*z* (%) = 175 (52) [M^+], 146 (100), 132 (30), 118 (12), 91 (10).

6-Methoxy-3,4-dihydroquinoline-1(2*H*)-carbaldehyde (Table 2, Entry 10)
Yield: 178 mg; yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (s, 1 H), 7.05 (d, *J* = 8.7 Hz, 1 H), 6.72 (m, 2 H), 3.78 (s, 3 H), 3.77 (t, *J* = 7.2 Hz, 2 H), 2.78 (t, *J* = 6.6 Hz, 2 H), 1.94 (quintet, *J* = 6.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 156.5, 130.2, 123.8, 118.1, 114.3, 112.3, 55.3, 40.0, 27.0, 22.2.

MS ($C_{11}H_{13}NO_2$): *m*/*z* (%) = 191 (100) [M^+], 176 (11), 162 (29), 148 (90), 130 (11).

6-Hydroxy-3,4-dihydroquinoline-1(2*H*)-carbaldehyde (Table 2, Entry 11)
Yield: 158 mg; white solid; mp 124–126 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (s, 1 H), 6.99 (d, *J* = 9.0 Hz, 1 H), 6.72 (m, 2 H), 6.42 (br s, 1 H), 3.79 (t, *J* = 6.3 Hz, 2 H), 2.76 (t, *J* = 6.3 Hz, 2 H), 1.94 (quintet, *J* = 6.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.2, 153.4, 130.8, 123.8, 118.5, 116.0, 114.0, 40.3, 27.0, 22.3.

MS ($C_{10}H_{11}NO_2$): *m*/*z* (%) = 177 (100) [M^+], 148 (89), 133 (16), 120 (10), 103 (6).

3,4-Dihydroisoquinoline-2(1*H*)-carbaldehyde (Table 2, Entry 12)

Yield: 135 mg; brown oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (s, 1 H), 7.17 (m, 4 H), 4.69 (s, 2 H), 3.65 (t, *J* = 6.0 Hz, 2 H), 2.91 (t, *J* = 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.6, 133.4, 131.6, 128.8, 127.0, 126.5, 125.7, 43.1, 42.2, 29.6.

MS ($C_{10}H_{11}NO$): *m*/*z* (%) = 161 (100) [M^+], 146 (9), 132 (25), 117 (37), 104 (56).

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References

(1) (a) Rakhit, A.; Hurley, M. E.; Tipnis, V.; Coleman, J.; Rommel, A.; Brunner, H. R. *J. Clin. Pharmacol.* **1986**, *26*, 156. (b) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev*. **1997**, *97*, 787. (c) Kim, W. G.; Kim, J. P.; Koshino, H.; Shin-Ya, K.; Seto, H.; Yoo, I. D. *Tetrahedron* **1997**, *53*, 4309. (d) Gruenfeld, N.; Stanton, J. L.; Yuan, A. M.; Ebetino, F. H.; Browne, L. J.; Gude, C.; Huebner, C. F. *J. Med. Chem.* **1983**, *26*, 1277.

(2) (a) Anas, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **2009**, *20*, 2193. (b) Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975.

(3) (a) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525. (b) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35. (c) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451. (d) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066. (e) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (f) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777.

(4) (a) Gilchrist, T. L.; Graham, K. *Tetrahedron* **1997**, *53*, 791. (b) Tan, M.; Zhang, Y. *Tetrahedron Lett.* **2009**, *50*, 4912.

(5) (a) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608. (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223.

(6) Fukuda, T.; Mine, Y.; Iwao, M. *Tetrahedron* **2001**, *57*, 975.

(7) Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T. *Chem. Pharm. Bull.* **1987**, *35*, 3146.

(8) Yamada, Y.; Arima, S.; Okada, C.; Akiba, A.; Kai, T.; Hariyaga, Y. *Chem. Pharm. Bull.* **2006**, *54*, 788.

(9) Ciske, F. L.; Barbachyn, M. R.; Genin, M. J.; Grega, K. C.; Lee, C. S.; Dolak, L. A.; Seest, E. P.; Watt, W.; Adams, W. J.; Friis, J. M.; Ford, C. W.; Zurenko, G. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4235.

(10) (a) Bartók, M.; Molnár, *Heterogeneous Catalytic Hydrogenation, In The Chemistry of Functional Groups*, Suppl. A3; Patai, S., Ed.; Wiley: Chichester, **1997**, Chap. 16, 843. (b) Smith, G. V.; Notheisz, F. *Heterogeneous Catalysis in Organic Chemistry*; Academic Press: San Diego, **1999**. (c) Kulkarni, A.; Török, B. *Curr. Org. Synth.* **2011**, *8*, 187.

(11) Kikugawa, Y.; Kashimura, M. *Synthesis* **1982**, 785.

(12) Abraham, R. J.; Byrne, J. J.; Griffiths, L.; Perez, M. *Magn. Reson. Chem.* **2006**, *44*, 491.

(13) See the spectroscopic data for more information.