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Synthesis of 3-Substituted Quinolines via Transition-Metal-Catalyzed Reductive Cyclization of *o*-Nitro Baylis−Hillman Acetates

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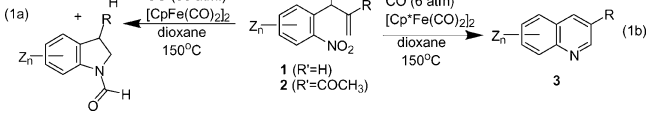
Abstract: Reductive cyclization of *o*-nitro-substituted Baylis−Hillman acetates by carbon monoxide, catalyzed by $[Cp^*Fe(CO)_2]_2$, gives moderate to good yields of 3-substituted quinolines.

Quinolines are important heterocyclic compounds that are used for a variety of applications from pharmaceuticals to materials.[1] While numerous quinoline syntheses have been developed,[2] many suffer from limitations (harsh conditions, poor availability of starting materials, limited regioselectivity) that preclude their general application. These factors have spurred the development of new synthetic methods for these important compounds.[3]

A recent focus of the research in our laboratory has been the discovery and development of transition-metal-promoted amination reactions of hydrocarbons.[4] After uncovering the intermolecular $[CpFe(CO)_2]_2$ (Fp_2)-catalyzed allylic amination of olefins by nitrobenzene and CO,[4f] we have examined the application of this protocol to the intramolecular reaction of *o*-nitroarenes bearing pendant unsaturation as an entry to important nitrogen heterocycles.[5]

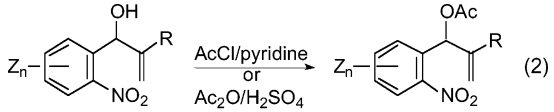
The Baylis−Hillman reaction is a powerful carbon−carbon bond-forming reaction between a carbonyl compound and an electrophilic olefin.[6] The products of these reactions, the so-called Baylis−Hillman adducts (BH adducts), are polyfunctional allylic alcohols. Several groups have targeted BH adducts as precursors to nitrogen heterocycles to give quinolines,[7] dihydroquinolines,[8] 2-quinolones,[9] 4-quinolones,[10] and quinoline *N*-oxides.[11] These reactions, however, often give mixtures of products,[9c] require substrates that are not easily prepared,[7a] or lack generality.[7b,c,8]

Recently we reported the Fp_2-catalyzed cyclization of *o*-nitro-substituted BH adducts **1** which produced, quite surprisingly, indoles and *N*-formylindolines, albeit in low yield (eq 1a).[12]



Bassaviah et al. found that the reduction of *o*-nitro-substituted Baylis−Hillman acetates (BH acetates) by Fe/AcOH gives 2-quinolones.[9b] Given the markedly different outcome of the cyclization of BH adducts with the $[CpFe(CO)_2]_2$/CO reductive system compared to that of other methods, we chose to investigate the reductive behavior of the corresponding BH acetates.

The BH adducts **1a**−**f** were efficiently acetylated by treatment with either AcCl/pyridine or Ac_2O/H_2SO_4[13] to give the BH acetates **2a**−**f** in 71−99% yield (eq 2).



The initial reaction of acetate **2a** (Z_n = H, R=CO_2Me) employing Fp_2 as a catalyst under 55 atm of CO in dioxane (150 °C, 21 h) afforded a 21% isolated yield of

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TABLE 1. Optimization of the Conversion of Acetate 2a to Quinoline 3a

entry	amt of **2a**[a] (mmol)	catalyst[b]/ concn (mol %)	CO pressure (atm)	time (h)	yield of **3a**[c] (%)	conversn[d] (%)
1	1.16	Fp_2/25	56	21	21	ND
2	1.0	Fp_2/100	56	21	26	>99
3	0.11	Fp_2/35	56	23	21	46
				45	69	>99
4	0.11	$[Cp^*Ru(CO)_2]_2$/35	56	46	83	>99
5	0.11	$[(C_5H_3)_2(SiMe_2)_2\}Ru_2(CO)_4$/35	56	46	37	>99
6	0.11	$(Cp)_2Fe_2(CO)_2$(dppe)/20	20	44	24	>99
7	0.11	Fp^*_2/5	56	42	80	>99
8	0.11	Fp^*_2/10	20	42	79	>99
9	0.11	Fp^*_2/10	6	42	73	>99
10	0.11	Fp_2/20	6	70	28	
11	0.11	$[Cp^*Ru(CO)_2]_2$/20	6	70	41	
12	0.72	Fp^*_2/10	6	42	67	>99

[a] 0.02 M in dioxane, T = 150 °C. [b] $Fp_2 = [CpFe(CO)_2]_2$; $Fp^*_2 = [Cp^*Fe(CO)_2]_2$. [c] Entries 1 and 12 are isolated yields; entries 2−11 are GC yields using naphthalene as an internal standard. [d] The percent conversion of **2a** was determined by GC with naphthalene as an internal standard.

the quinoline **3a** as the major product (eq 1b, Table 1, entry 1). It is worth noting that none of the previously encountered indole or *N*-formylindoline was detected (NMR/GC−MS of crude reaction mixtures).

The reaction was then optimized with respect to substrate concentration, catalyst, catalyst loading, and CO pressure (Table 1, entries 2−11). Initial success with the Fp_2 complex prompted us to study other group 8 metal carbonyl dimers as potential catalysts for this reaction. Commercially available $[Cp^*Fe(CO)_2]_2$ (Fp^*_2) was found to be a superior catalyst, giving good yields at low catalyst loading (entry 7) and at lower CO pressure (entries 9 and 12). The conditions in entries 9 and 12 were chosen as the most convenient since the lower pressure enables the reactions to be safely carried out in common thick-walled glass vessels.[14]

After the initial optimization with substrate **2a**, the BH acetates **2b**−**f** were cyclized employing similar conditions, the results of which are presented in Table 2. The reaction is effective for substrates bearing either electron-donating (entries 1 and 3) or electron-withdrawing groups (entry 2), though the former react more slowly. The carbomethoxy and cyano groups are both tolerated well (entry 5). The benzo[*h*]quinoline **3e** was also accessible (entry 4). In addition to quinolines **3b**−**f** some minor products (inseparable) were also isolated. GC−MS analysis revealed two main byproducts 2 and 4 mass units higher than the quinoline with fragmentation patterns similar to those of the quinolines, suggestive of the corresponding dihydro- and tetrahydroquinolines.

The most established route to 3-carboalkoxyquinolines requires the preparation of 4-quinolone derivatives through a Gould−Jacobs reaction, followed by chlorination, and then catalytic reduction with H_2/Ni or Pd catalysts.[15] More recent reports have employed sulfonamides derived from BH adducts that undergo intramolecular aromatic substitution via the pendant amino group.[7] The nitro BH acetates required for our route are easily prepared in high yield, and the reaction's tolerance for electronically diverse substituents on the aromatic ring promises to make this a general and preferred route to these quinolines.

The mechanistic pathway for the Fp^*_2-catalyzed reductive cyclization to quinolines is presently uncertain. Our prior probes of the corresponding intermolecular allylic aminations have excluded free nitrosoarene and nitrene intermediates[4f] and suggested a role for coordinated organonitrogen species.[4e] Furthermore, the contrasting 2-quinolone products formed in reactions of BH acetates **2** with conventional metal reductants (presumably via hydroxylamine or amine addition to the carboxylate group)[9b] appear to exclude these intermediates as well in the iron-promoted reactions. Besides Fp*-catalyzed reduction of the nitro group, a coordinated organonitrogen and/or olefin(allyl) species may thus be involved in the cyclization (and subsequent reduction) step(s). The marked difference in reaction products derived from the BH alcohols (indoles, *N*-formylindolines) as compared to the BH acetates (quinolines) is also striking. We suggested that the formation of indole and *N*-formylindoline in the former occurred via a retroaldol reaction of a cyclized β-hydroxy ester intermediate.[12] The suppressed decarbonylation pathway found with the BH acetates may reflect the inhibited retroaldol reaction of the corresponding β-acetoxy ester intermediates. Efforts are currently under way to further elucidate the mechanistic details and to expand the scope of these novel metal-catalyzed reductive cyclizations.

Experimental Section

General Methods. Compounds **2a**,[13] $[Cp^*Ru(CO)_2]_2$,[16] $[(C_5H_3)_2(SiMe_2)_2]Ru_2(CO)_4$,[17] $Cp_2Fe_2(CO)_2$(dppe),[18] and $[Cp^*Fe(CO)_2]_2$[19] were prepared according to literature procedures and gave

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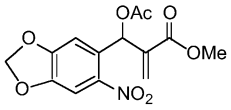
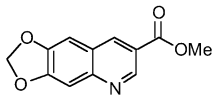
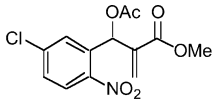
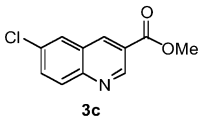
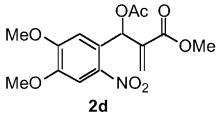
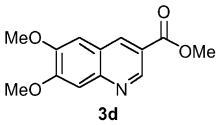
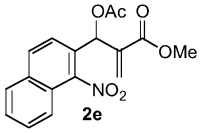
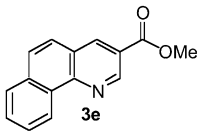
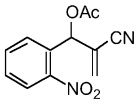
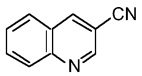
TABLE 2. Quinolines Synthesized by [Cp*Fe(CO)$_2$]$_2$-Catalyzed Cyclization of BH Acetates

Entry	BH-acetate	Time (hr)	Product	Yield (%)[a]
1	 **2b**	81	 **3b**	65
2	 **2c**	52	 **3c**	48
3	 **2d**	89	 **3d**	60
4	 **2e**	40	 **3e**	47
5	 **2f**	39	 **3f**	65

[a] Isolated yield after chromatography/recrystallization.

satisfactory spectroscopic data. ^{1}H NMR spectra were obtained at 300 MHz and ^{13}C NMR spectra at 75.45 MHz. Flash chromatography was carried out using silica gel with the indicated eluants.

Preparation of Baylis−Hillman Acetates 2b−f. The following procedure is representative of the preparation of **2b−f**.

The Baylis−Hillman adduct **1b** (500 mg, 1.78 mmol) was dissolved in CH_2Cl_2 (15 mL) and cooled with an ice bath. Pyridine (0.29 mL, 3.56 mmol) was added followed by acetyl chloride (0.26 mL, 3.56 mmol) and the mixture stirred for 1 h. The reaction mixture was then taken up with ether and washed with 2 M HCl (2 × 20 mL), saturated $NaHCO_3$ (2 × 20 mL), and H_2O (1 × 10 mL). The organic layer was dried with $MgSO_4$ and concentrated to give the acetates generally as white solids, which were obtained in pure form by recrystallization from toluene or by silica gel chromatography with 1:1 hexane/ether.

Data for methyl 2-[acetyloxymethyl(6-nitro-1,3-benzodioxol-5-yl)]acrylate (2b): 94% yield; mp 123−125 °C; IR (KBr) 1753, 1714, 1521, 1220, 1035 cm^{-1}; ^{1}H NMR (CD_3CN) δ 2.07 (s, 3 H), 3.72 (s, 3 H), 5.58 (d, J = 1.2 Hz, 1 H), 6.14 (d, J = 0.9 Hz, 1 H), 6.15 (d, J = 0.9 Hz, 1 H), 7.04 (s, 1 H), 7.12 (d, J = 1.2 Hz, 1 H), 7.55 (s, 1 H); ^{13}C NMR (CD_3CN) δ 21.2, 52.9, 69.5, 104.9, 106.2, 108.1, 123.1, 128.5, 130.6, 139.5, 153.5, 166.0, 170.2; MS (ESI) m/z 346.1 (M + Na, 63). Anal. Calcd for $C_{14}H_{13}NO_8$: C, 52.02; H, 4.05; N, 4.33. Found: C, 51.92; H, 4.07; N, 4.30.

Data for methyl 2-[acetyloxymethyl(5-chloro-2-nitrophenyl)]acrylate (2c): 99% yield; mp 103−104 °C; IR (KBr) 1753, 1706, 1521, 1204, 1027 cm^{-1}; ^{1}H NMR (d_6-acetone) δ 2.14 (s, 3H), 3.74 (s, 3 H), 3.74 (s, 3 H), 5.74 (d, J = 1.2 Hz, 1 H), 6.43 (d, J = 0.3 Hz, 1 H), 7.21 (d, J = 0.3 Hz, 1 H), 7.67−7.71 (m, 2 H), 8.12 (td, J = 9.0 Hz, J = 1.5 Hz, 1H); ^{13}C NMR (75.45 MHz; d_6-acetone) δ 20.6, 52.5, 68.7, 127.5, 128.5, 129.4, 130.3, 135.7, 138.8, 140.0, 165.2, 169.4; MS (ESI) m/z 336 (M + Na, 100). Anal. Calcd for $C_{13}H_{12}NO_6Cl$: C, 49.78; H, 3.86; N, 4.47. Found: C, 49.85; H, 3.89; N, 4.46.

Data for methyl 2-[acetyloxymethyl(4,5-dimethoxy-2-nitrophenyl)]acrylate (2d): 96% yield; mp 145−147 °C; IR (KBr) 1753, 1719, 1523 cm^{-1}; ^{1}H NMR (d_6-acetone) δ 2.10 (s, 3 H), 3.75 (s, 3 H), 3.95 (s, 3 H), 3.96 (s, 3 H), 5.58 (d, J = 1.2 Hz, 1 H), 6.35 (s, 1 H), 7.10 (s, 1H), 7.27 (d, J = 1.2 Hz, 1 H), 7.68 (s, 1 H); ^{13}C NMR (75.45 MHz; d_6-acetone) δ 21.0, 52.7, 56.8, 56.9, 69.6, 109.1, 110.9, 128.4, 128.6, 140.1, 149.7, 154.7, 165.9, 169.7; HRMS (ESI) m/z calcd for $C_{15}H_{17}NO_8Na$ (M + Na) 362.0852, found 362.0816.

Data for methyl 2-[acetyloxymethyl(1-nitro-2-naphthyl)]acrylate (2e): 93% yield; mp 105−107 °C; IR (KBr) 1753, 1707, 1529 cm^{-1}; ^{1}H NMR (d_6-acetone) δ 2.12 (s, 3 H), 3.72 (s, 3 H), 5.89 (d, J = 1.5 Hz, 1 H); 6.50 (d, J = 0.9 Hz, 1 H); 6.90 (s, 1 H), 7.68 (d, J = 9.0 Hz, 1 H), 7.71−7.81 (m, 3 H), 8.13 (m, 1 H), 8.23 (d, J = 9.0 Hz, 1 H); ^{13}C NMR (75.45 MHz; d_6-acetone) δ 21.4, 53.3, 70.3, 123.1, 125.6, 126.1, 128.6, 129.4, 129.7, 129.9, 130.8, 132.9, 135.3, 139.6, 166.1, 170.1; HRMS (ESI) m/z calcd for $C_{17}H_{15}NO_6Na$ (M + Na) 352.0797, found 352.0558.

Data for 2-[acetyloxymethyl(2-nitrophenyl)acrylonitrile (2f): 71% yield; yellow oil; R_f = 0.25; IR (KBr) 2228, 1750, 1528 cm^{-1}; ^{1}H NMR (d_6-acetone) δ 2.18 (s, 3 H), 6.24 (d, J = 0.9 Hz, 1 H), 6.36 (s, 1 H), 6.98 (s, 1 H), 7.65−7.72 (m, 1 H), 7.82−7.89 (m, 2 H), 8.11 (d, J = 7.8 Hz); ^{13}C NMR (75.45 MHz; d_6-acetone) δ 20.5, 70.2, 116.6, 121.5, 125.5, 129.1, 130.7, 131,8, 134.7, 135.3, 148.5, 169.2; HRMS (ESI) m/z calcd for $C_{12}H_{10}N_2O_4Na$ (M + Na) 269.0538, found 269.0490.

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Preparation of 3-Substituted Quinolines by Iron-Catalyzed Reductive Cyclization. Methylquinoline-3-carboxylate (3a). In a glass-lined, stainless steel Parr reactor or a thick-walled glass vessel (e.g., Fisher−Porter bottle[14]) the acetate **3a** (200 mg, 0.72 mmol) was combined with $[Cp^*Fe(CO)_2]_2$ (35 mg, 0.070 mmol) and dioxane (70 mL). The vessel was flushed three times with CO (*fume hood!*), charged to 100 psi (6 atm; ca. 15 equiv) with CO, and heated to 150 °C with an oil bath for 41 h. After cooling, the vessel was vented (*fume hood!*), and the ruby-colored solution was concentrated on a rotary evaporator. The solid red-brown residue was chromatographed on SiO_2 with Et_2O/hexanes (2:3) to give 134 mg (67%) of a white solid, which was the quinoline **3a**, R_f = 0.35 (1:1, Et_2O/hexanes), spectroscopically identical to that reported previously:[20] mp 68−71 °C; lit.[21] mp 70−74 °C. A portion of the catalyst $[Cp^*Fe(CO)_2]_2$ was also recovered (13 mg, 0.030 mmol).

Data for methyl [1,3]dioxolo[4,5-g]quinoline-7-carboxylate (3b): 80 h reaction time; chromatography with $CHCl_3$/MeOH (30:1; R_f = 0.44); 65% yield; white needles; mp 210−213 °C; IR (KBr) 1709, 1470, 1203 cm^{-1}; ^1H NMR (300 MHz; d_6-acetone) δ 3.95 (s, 3 H), 6.27 (s, 1 H), 7.36 (s, 1 H), 7.42 (s, 1 H), 8.71 (d, J = 2.1 Hz, 1 H), 9.12 (d, J = 2.1 Hz, 1 H); ^{13}C NMR (75.45 MHz; d_6-acetone) δ 53.3, 104.3, 105.2, 106.9, 138.1, 149.1, 167.1; MS (EI) m/z 231 (M^+, 100), 200 (95), 172 (65), 142 (15), 114 (20). Anal. Calcd for $C_{12}H_9NO_4$: C, 62.33; H, 3.92; N, 6.05. Found: C, 62.42; H, 3.94; N, 6.08.

Data for methyl 6-chloroquinoline-3-carboxylate (3c): 24.5 h reaction; chromatography with $CHCl_3$/MeOH (30:1; R_f = 0.78); 48% yield; mp 174−176 °C; IR (KBr) 3066, 2950, 1722, 1491, 1436, 1336, 1267, 1097, 819 cm^{-1}; ^1H NMR (d_6-acetone) δ 4.00 (s, 3 H), 7.89 (dd, J = 9.0 Hz, J = 2.4 Hz, 1 H), 8.12 (d, J = 9.0 Hz, 1 H), 8.24 (d, J = 2.1 Hz, 1 H), 8.93 (d, J = 1.5 Hz, 1 H), 9.35 (d, J = 2.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 52.7, 132.7, 127.5, 130.9, 132.7, 133.3, 137.7, 148.0, 150.0, 165.3; MS (EI) m/z 221 (M^+, 100), 190 (95), 162 (70), 127 (27), 99 (16), 74 (5); HRMS (ESI) m/z calcd for $C_{11}H_8ClNO_2Na$ (M + Na) 244.0141, found 244.0092.

Data for methyl 6,7-dimethoxyquinoline-3-carboxylate (3d): 89 h reaction; chromatography with $CHCl_3$/MeOH (30:1; R_f = 0.44); 60% yield; mp 161−163 °C; IR (KBr) 1722, 1618, 1599, 1505, 1432 cm^{-1}; ^1H NMR (300 MHz; d_6-acetone) δ 3.95 (s, 3 H), 4.0 (s, 3 H), 4.04 (s, 3 H), 7.43 (s, 1 H), 7.45 (s, 1 H), 8.70 (s, 1 H), 9.14 (s, 1 H); ^{13}C NMR (75.45 MHz; d_6-acetone) δ 51.9, 55.7, 55.8, 106.5, 107.9, 121.3, 122.7, 136.1, 147.5, 147.8, 150.9, 154.9, 165.9; HRMS (ESI) m/z calcd for $C_{13}H_{14}NO_4$ (M + H) 248.0923, found 248.0795 (100); calcd for $C_{13}H_{13}NO_4Na$ (M + Na) 270.0742, found 270.0569 (44).

Data for methyl benzo[h]quinoline-3-carboxylate (3e): 40 h reaction; chromatography with Et_2O/hexanes (3:7; R_f = 0.32); 47% yield; mp 125−127 °C; IR (KBr) 3066, 2949, 1706, 1610, 1323, 1267, 1214 cm^{-1}; ^1H NMR (d_6-acetone) δ 4.01 (s, 3 H), 7.76−7.86 (m, 2 H), 7.93−8.1 (m, 3 H), 8.90 (d, J = 2.1 Hz, 1 H), 9.26−9.34 (m, 1 H), 9.45 (d, J = 2.1 Hz, 1 H); ^{13}C NMR (d_6-acetone) δ 53.5, 125.4, 126.4, 126.8, 127.3, 128.9, 129.6, 130.1, 130.9, 132.4, 136.2, 138.0, 150.0, 150.1, 166.8; MS (EI) m/z 237 (M^+, 100), 206 (60), 178 (65), 151 (25). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.20; H, 4.75; N, 5.95.

Data for quinoline-3-carbonitrile (3f): 39 h; chromatography with Et_2O/hexanes (4:7; R_f = 0.32); 65% yield; mp 104−106 °C; lit.[21] mp 107−108 °C; IR (KBr) 2228, 1619, 1489 cm^{-1}; ^1H NMR (d_6-acetone) δ 7.77 (t, J = 7.5 Hz, 1 H), 7.97 (t, J = 7.5 Hz, 8.08−8.15 (m, 2 H), 8.90 (d, J = 1.5 Hz, 1 H), 9.10 (d, J = 1.5 Hz, 1 H); ^{13}C NMR (d_6-acetone) δ 107.2, 117.7, 126.9, 129.0, 129.3, 130.1, 133.3, 142.5, 149.3, 150.5; MS (EI) m/z 154 (M^+, 100), 127 (20), 100 (5).

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Supporting Information Available: Experimental procedures for the preparation of compounds **1a**−**f** and their characterizational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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