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Cobalt-catalyzed selective conversion of diallylanilines and arylimines to quinolines

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Abstract

Dicobaltoctacarbonyl has been found to be an effective catalyst for the conversion of diallylanilines to quinolines. Arylimines are also found to undergo heteroannulation in the presence of diallylaniline as allyl fragment donor to give quinolines. Imines can also be allylated to give quinoline derivatives. Initial studies of the scope and mechanism of the reaction are presented.

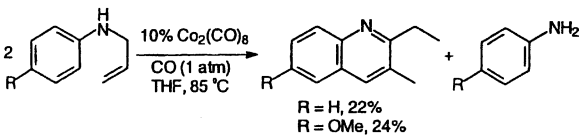
Keywords: Quinolines; Cobalt; C–N cleavage; Catalysis; Heterocycles

1. Introduction

Transition metal-catalyzed heteroannulation provides a useful and convenient tool for the construction of *N*-heterocycles [1]. Quinolines and their derivatives form an important class of *N*-heterocycles in that they display attractive applications as pharmaceuticals (e.g. antimalarial drugs) as well as being general synthetic building blocks due to their chemical and biological relevance [2,3]. Many catalytic processes based on palladium [4–6], rhodium [7–9], ruthenium [10–14] and iron [15] have been developed towards the synthesis of quinoline skeletons. Despite the advances in methodology towards the construction of quinoline derivatives, the development of new catalytic routes towards their synthesis remains an active area of research (for recent examples, see [16]). We report here a novel cobalt-catalyzed selective conversion of diallylanilines to quinolines and the cross-coupling of arylimines with diallylanilines to generate quinolines.

2. Results and discussion

N-allylaniline, when heated in presence of 10 mol% $Co_2(CO)_8$ and 1 atm of CO at 85 °C, leads to the selective formation of 2-ethyl-3-methylquinoline (Eq. (1)):



(1)

Aniline and propene are also observed in the reaction. The presence of carbon monoxide is necessary to stabilize $Co_2(CO)_8$ under the reaction conditions. In its absence, reduced yields of products are obtained.

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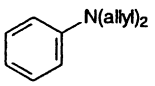
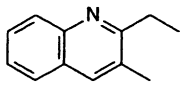
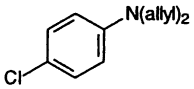
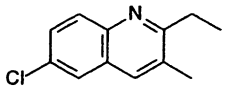
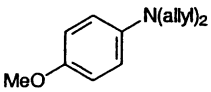
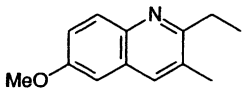
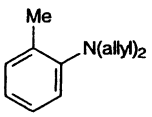
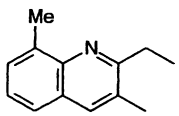
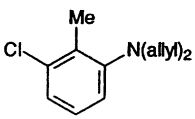
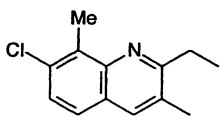
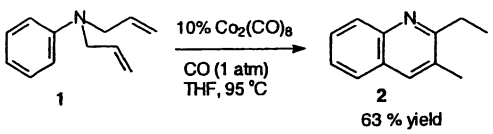
Table 1
Isolated yields for the conversion of diallylanilines to quinolines[a]

Entry	Diallylaniline	Product	Temperature (°C)	Isolated yield (%)
1			95	63
2			105	56
3			95	68
4			95	56
5			105	42

[a] Isolated yields at 100% conversion using 10% $Co_2(CO)_8$ in THF solvent under 1 atm CO. Typical reaction time is 36–48 h.

Use of 4-methoxyallylaniline led to the corresponding 6-substituted quinoline in 24% isolated yield. Although the reaction is selective for quinoline formation, half of the starting material acts as a sacrificial reagent in the reaction, rendering the maximum yield possible only 50%. A more atom economical approach is achieved by the use of readily available diallylanilines. Diallylaniline forms the same product with higher yields and the same selectivity under the same conditions (Eq. (2)):[1]



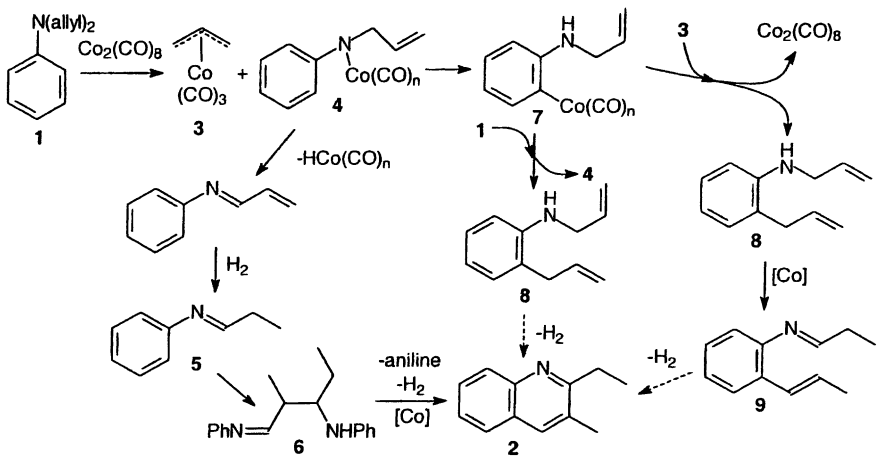
(2)

The reaction is easily extended to other diallylanilines to generate quinolines in good yields, as shown in Table 1. Diallylanilines are easily and quantitatively prepared by refluxing the aniline with allylbromide in the presence of potassium carbonate.

The reaction is unique in that it forms quinolines selectively and in good yields. The 2-ethyl-3-methyl substitution pattern is common to products derived from both mono- and diallylanilines.[2] A speculative reaction scheme showing several possible pathways and intermediates is outlined in Scheme 1. The reaction most likely proceeds by an initial cleavage of the allylic C–N bond by $Co_2(CO)_8$ to generate intermediates **3** and **4**. With certain substrates, palladium and ruthenium complexes have been shown in the past to cleave allylic C–N bonds [17,18]. In addition, allylcobalttricarbonyl, **3**, can be detected and isolated at intermediate times during the reaction, strongly suggesting an initial breaking of the allylic C–N bond. For experiments with diallylaniline, monoallylaniline and allylcobalttricarbonyl are the only intermediates observed in the system by NMR spectroscopy. The formation of monoallylaniline can be explained by the reaction of the proposed intermediate **4** with $HCo(CO)_4$ or H_2. The formation of imine **5** can be explained by beta-elimination in **4** to give an enimine followed by olefin hydrogenation with $HCo(CO)_4$ or the H_2 that is produced in the reaction. Imine **5** can

[1] Addition of a molecule of hydrogen to the right-hand side balances Eqs. (1) and (2).

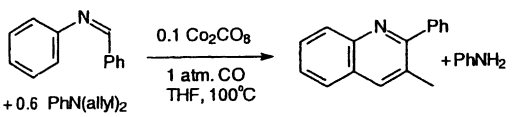
[2] Similar 2-ethyl-3-methyl substitution pattern has been reported in literature for quinoline synthesis catalyzed by ruthenium and rhodium (see Refs. [9–13]).



Scheme 1. Possible pathways for the catalytic conversion of **1** to **2** with $Co_2(CO)_8$.

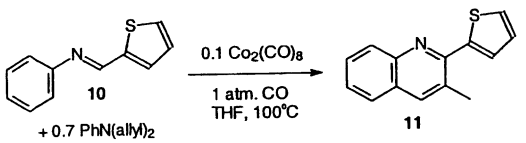
then form quinoline via the Schiff-base dimer **6**, as seen earlier with ruthenium [12]. In a second pathway, an orthometallated intermediate as in **7** is proposed which might either react with allylcobalttricarbonyl or the starting diallylaniline to generate an intermediate of type **8**. $HCo(CO)_4$ has been shown in the literature to effect double bond isomerizations and hence it is reasonable to propose isomerization of **8** to **9** under the reaction conditions [19].Compound **9** is poised for cyclization to generate **2** with elimination of hydrogen.

Although a thorough mechanistic understanding is lacking at this stage, imines such as **5** are likely intermediates in the system. To test this hypothesis, the cross-coupling of the imine derived from aniline and benzaldehyde with diallylaniline was studied (Eq. (3)):



(3)

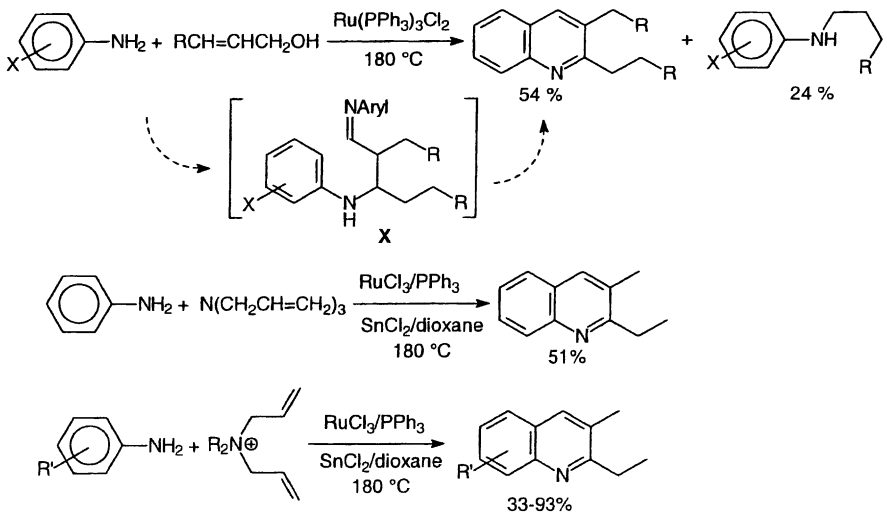
As anticipated, the cross-coupled quinoline product was isolated in 47% yield (59% by NMR). The imine also underwent competitive reduction to form the secondary amine, accounting for the balance of the reaction. No Schiff-base dimer is observed, but a small amount (<5%) of quinoline derived from diallylaniline can be seen in the reaction. In another experiment, the cross-coupling of the imine **10** with diallylaniline was studied and the cross-coupled product **11** was isolated in 47% yield (Eq. (4)):



(4)

Again competitive reduction of the imine to form the secondary amine is observed. Nevertheless, this observation widely expands the scope of this cobalt-catalyzed reaction since it facilitates the introduction of various substituents at the 2-position of the quinoline skeleton.

As mentioned earlier, other transition metal-based systems have been used to form quinoline derivatives, with the formation of the 2-methyl-3-ethyl derivative being commonly observed. Several of these proceed from aniline (or a nitroarene that is reduced in situ) plus an allyl source such as an allyl alcohol [10,12,13], triallylamine [11] or allylammonium salts [14] (Scheme 2). While details of the mechanism(s) of these reactions were not elucidated, the intermediacy of imine intermediates and a Schiff-base dimer were implied. In the present system, attempts to use triallylamine as an allyl source in the reactions of imines with $Co_2(CO)_8$ met with failure. Reaction of the Schiff-base dimer **X** (R = Me) with $Co_2(CO)_8$ under CO, however, led to the formation of aniline and



Scheme 2. Other organometallic routes to quinolines.

2-propyl-3-ethylquinoline just as in the earlier studies with ruthenium [12]. This observation suggests that a similar mechanism is responsible for quinoline formation in the present system, at least with imines, but the yields of quinolines of >50% obtained from diallylanilines cannot be accommodated by this pathway alone. Also a mechanism involving only an imine dimer pathway cannot explain the formation of the cross-coupling products reported in Eqs. (3) and (4). Further mechanistic studies will be required, with the role of (allyl)$Co(CO)_3$ to be determined.

In summary, a simple, mild and efficient synthesis of quinolines from diallylanilines is reported. The raw materials are cheap and the catalyst is readily available. The reaction is easily extended to imines where a cross-coupling reaction with diallylaniline generates quinoline derivatives. Studies are now underway to elucidate the mechanism of these reactions as well as to widen their scope, utility and yield.

3. Experimental

3.1. Materials and methods

Most manipulations were performed under a N_2 atmosphere either on a high-vacuum line using modified Schlenk techniques or in a Vacuum Atmospheres Corporation glove box. All diallylanilines were synthesized from the corresponding aniline by reaction with allylbromide and sodium carbonate in methanol. The diallylanilines were purified by distillation over potassium hydroxide prior to use. Cobalt octacarbonyl was purchased from Strem and used as-received. CO was purchased from Air Products. THF and THF-d_8 were distilled over sodium/benzophenone prior to use. The Schiff-base dimer **X** (R = Me) was synthesized as previously published [20].

All ^1H and ^{13}C NMR spectra were recorded either on a Bruker AMX400 spectrometer or an AVANCE400 spectrometer. All ^1H chemical shifts are reported in ppm (δ) relative to tetramethylsilane and referenced using chemical shifts of residual solvent references (THF-d_8, 1.73 or C_6D_6, 7.15). GC–MS was conducted on a 5890 Series II Gas Chromatograph fitted with an HP 5970 Series Mass Selective Device. All isolated quinolines gave satisfactory NMR and mass spectral data.

3.2. General procedure for the synthesis of quinolines from diallylaniline

For the quinolines recorded in Table 1, a general procedure using diallylaniline is as follows. In a 50 ml round-bottomed (RB) flask equipped with a Teflon seal, 100 mg of diallylaniline (0.58 mmol) and 19.8 mg

of $Co_2(CO)_8$ (0.1 equiv., 0.058 mmol) are added to 5 ml of dry THF in a glove box. The flask is then connected to a Schlenk line and any dissolved nitrogen is removed by freeze-pump-thaw degassing the solution three times. Carbon monoxide is then introduced at 1 atm and the reaction mixture is heated at 95 °C in an oil bath for 48 h with stirring. The solution is then concentrated to ∼1 ml and chromatographed using 10% ethylacetate in hexane. Isolated yield of 2-ethyl-3-methylquinoline: 62.8 mg.

3.3. Cross-coupling of N-phenylbenzaldehyde imine with diallylaniline

In a 50 ml RB flask equipped with a Teflon seal, 50 mg of *N*-phenylbenzaldehyde imine (0.28 mmol), 28.7 mg of diallylaniline (0.6 equiv., 0.17 mmol) and 9.6 mg of $Co_2(CO)_8$ (0.1 equiv., 0.028 mmol) are taken in 5 ml of dry THF in a glove box. The flask is then connected to a Schlenk line, the solution is freeze pump thawed three times to remove any dissolved nitrogen and then carbon monoxide is introduced at 1 atm. This solution is heated in an oil bath at 100 °C with stirring for 48 h. The reaction mixture is then concentrated to ∼1 ml and the quinoline product is isolated by preparative TLC using 10% ethylacetate in hexane as eluent. Isolated yield of 3-methyl-2-phenylquinoline: 28.4 mg (47% yield based on the imine).

3.4. ^1H and ^{13}C NMR data and mass spectral data for the quinolines

2-Ethyl-3-methylquinoline: ^{1}H NMR: δ 7.97 (d, 1H, J = 8.4 Hz) 7.89 (s, 1H), 7.74 (d, 1H, J = 8.0 Hz) 7.59 (t, 1H, J = 8.0 Hz), 7.43 (t, 1H, J = 8.4 Hz), 2.98 (q, 2H, J = 7.6 Hz), 2.48 (s, 3H), 1.42 (t, 3H, J = 7.6 Hz) ppm. ^{13}C NMR: δ 162.09, 146.84, 134.67, 129.25, 128.72, 127.54, 127.31, 126.39, 125.08, 28.56, 18.01 and 11.28 ppm. MS: *m*/*e* 171, 170 (b.p.), 143, 115, 89, 63.

6-Chloro-2-ethyl-3-methylquinoline: ^{1}H NMR: δ 7.99 (d, 1H, J = 8.8 Hz), 7.38 (d, 1H, J = 2.4 Hz), 7.25 (dd, 1H, J = 8.8 and 2.4 Hz), 7.00 (s, 1H), 2.64 (q, 2H, J = 7.6 Hz), 1.87 (s, 3H), 1.37 (t, 3H, J = 7.6 Hz) ppm. ^{13}C NMR: δ 163.08, 145.71, 134.21, 131.29, 131.18, 130.55, 129.14, 128.32, 125.75, 29.20, 18.79 and 12.06 ppm. MS: *m*/*e* 205, 204 (b.p.), 177, 154, 140, 115, 89, 63.

2-Ethyl-6-methoxy-3-methylquinoline: ^{1}H NMR: δ 7.84 (d, 1H, J = 9.2 Hz), 7.79 (s, 1H), 7.23 (dd, 1H, J = 9.2 and 2.8 Hz), 7.09 (d, 1H, J = 2.8 Hz), 3.89 (s, 3H), 2.92 (q, 2H, J = 7.2 Hz), 2.45 (s, 3H), 1.39 (t, 3H) ppm. ^{13}C NMR: δ 159.31, 157.22, 142.80, 133.79, 130.01, 129.32, 128.12, 120.01, 104.10, 54.54, 28.28, 18.05 and 11.38 ppm. MS: *m*/*e* 201, 200 (b.p.), 186, 173, 157, 143, 130, 115, 102, 77, 63.

2-Ethyl-3,8-dimethylquinoline: ^{1}H NMR: δ 7.99 (s, 1H), 7.71 (d, 1H, J = 8.0 Hz), 7.58 (d, 1H, J = 6.8 Hz), 7.46 (dd, 1H, J = 8.0 and 6.8 Hz), 3.13 (q, 2H, J = 7.2 Hz), 2.93 (s, 3H), 2.61 (s, 3H), 1.59 (t, 3H, J = 7.2 Hz) ppm. ^{13}C NMR: δ 166.61, 151.40, 142.20, 140.92, 134.80, 133.68, 133.02, 130.78, 130.35, 34.53, 23.77, 22.88 and 17.15 ppm. MS: *m*/*e* 185, 184 (b.p.), 157, 142, 128, 115, 90, 77, 63.

7-Chloro-2-ethyl-3,8-dimethylquinoline: ^{1}H NMR: δ 7.83 (s, 1H), 7.53 (d, 1H, J = 8.4 Hz), 7.40 (d, 1H, J = 8.4 Hz), 2.96 (q, 2H, J = 7.6 Hz), 2.85 (s, 3H), 2.43 (s, 3H), 1.41 (t, 3H, J = 7.6 Hz) ppm. ^{13}C NMR: δ 167.83, 151.60, 141.00, 139.72, 138.75, 135.21, 132.19, 131.58, 131.03, 34.54, 23.64, 19.31 and 16.95 ppm. MS: *m*/*e* 219, 218, 204, 191, 168, 127, 102, 79.

3-Methyl-2-phenylquinoline: ^{1}H NMR: δ 8.08 (s, 1H), 7.99 (d, 1H, J = 8.4 Hz), 7.80 (d, 1H, J = 7.6 Hz), 7.63 (m, 3H), 7.47 (m, 4H), 2.50 (s, 3H) ppm. ^{13}C NMR: δ 156.68, 152.79, 147.11, 142.10, 135.12, 134.86, 134.71, 134.01, 133.51, 133.46, 133.43, 132.36, 131.83 and 25.69 ppm. MS: *m*/*e* 219, 218 (b.p.), 108, 89, 77, 63.

3-Methyl-2-(2-thiophenyl)quinoline: ^{1}H NMR: δ 8.06 (s, 1H), 7.97 (d, 1H, J = 8.4 Hz), 7.76 (d, 1H, J = 8.0 Hz), 7.71 (d, 1H, J = 3.6 Hz), 7.62 (t, 1H, J = 8.0 Hz), 7.54 (d, 1H, J = 4.8 Hz), 7.47 (t, 1H, J = 8.0 Hz), 7.14 (dd, 1H, J = 4.8 and 3.6 Hz), 2.76 (s, 3H) ppm. ^{13}C NMR: δ 157.95, 152.38, 143.13, 134.56, 134.36, 134.06, 133.76, 133.29, 133.08, 133.03, 132.28, 131.74, 118.32 and 26.92 ppm. MS: *m*/*e* 225, 224 (b.p.), 198, 180, 167, 140, 115, 89, 63.

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