Solvent-Free Preparation of *N*,*N*′-Dialkylbenzenediamines

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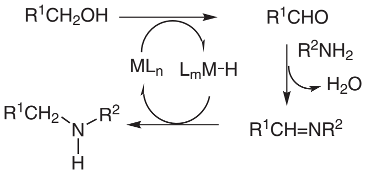
Abstract: A diiridium complex, stabilized by a bis(N-heterocyclic carbene) ligand, was found to be an effective precatalyst for the N,N′-dialkylation of *o*-, *m*-, and *p*-benzenediamine in excellent yields. Benzyl and primary aliphatic alcohols were used as alkylating reagents. Furthermore, the reactions were carried out without using any organic solvent, offering an environmentally benign process.

Key words: alkylation, amination, iridium, catalysis, carbene complex

N,*N*′-Dialkylbenzenediamines are useful chemicals for many aspects such as their application as synthetic intermediates, pharmaceuticals, chelating agents, and additives for antioxidant and dispersant viscosity modifiers.[1–3] Many synthetic approaches leading to the desired amines are known and the direct N-alkylation of amines ought to be the most useful methodology.[1,4] Transition-metal-catalyzed amination of alcohols with amines has proven to be an efficient method for the preparation of N-substituted amines.[5] The first step in this approach involves the dehydrogenation of the alcohol to give the corresponding aldehyde, accompanied by the generation of metal hydride (Scheme 1). Subsequently, the carbonyl compound reacts with an amine to form an imine, which is reduced to the corresponding amine by the pregenerated hydride. Indeed, numerous monoamine derivatives have been prepared by this approach; however, the selective N,N′-dialkylation of diamine compounds has been a challenge until the recent development of the iridium-catalyzed amination of alcohols using benzenediamines.[6]



Scheme 1 Pathway of the N-alkylation of amines with alcohols

N-Heterocyclic carbenes (NHCs) have become an important class of ligands for transition metal complex catalysis. It is known that the introduction of an NHC ligand to the metal center enhances its catalytic activity compared to the transition metal–phosphine counterpart.[7] In recent work, we have prepared a diiridium–bis(NHC) complex **1** (Figure 1) and established its catalytic activity for the dialkylation of amines.[8] Here, we explore the general applicability of this diiridium complex catalyzed N,N′-dialkylation of benzenediamines.

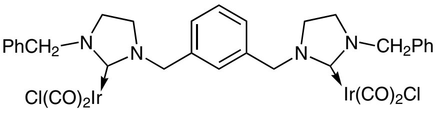


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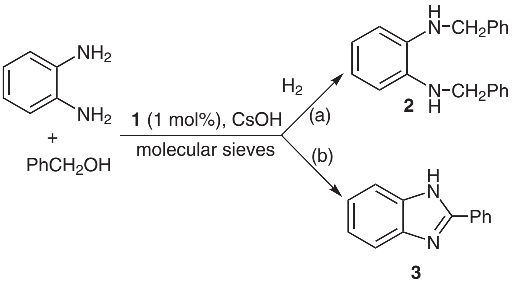
Figure 1

As a starting point, we selected the reaction of *o*-benzenediamine with benzyl alcohol as a model to examine the effectiveness of this reaction (Scheme 2). In order to meet an environmentally benign process, we carried out the reactions without using any organic solvent. Thus, a mixture of *o*-benzenediamine (0.5 mmol), benzyl alcohol (3 mmol), complex **1** (3 μmol), base (0.15 mmol), and molecular sieves (0.3 g) was heated at 120 °C for 24 hours. Instead of the desired dialkylation product **2**, 2-phenyl-1*H*-benzimidazole (**3**) was obtained as the exclusive product from this reaction. Apparently, intramolecular attack of the amino group toward the imine functionality occurs prior to the reduction of imine (Scheme 2, path b). With this disappointing result, we further modified the conditions to avoid the production of **3**. It has been disclosed that the reduction of imines in transition-metal-catalyzed amination can be facilitated in the presence of a hydrogen atmosphere.[9] Indeed, running the reaction of *o*-benzenediamine with benzyl alcohol under an atmospheric pressure of hydrogen readily afforded the desired dialkylation product **2** in 90% isolated yield (Scheme 2, path a).



Scheme 2 Alkylation of *o*-benzenediamine with benzyl alcohol

To obtain information on the catalytic system, we also examined this dialkylation with the use of various other irid-

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ium complexes as the catalyst for comparison (Table 1), given that iridium complexes are frequently used as precatalysts for C–N bond formation. Based on the 100% conversion and product analysis, all of the tested iridium complexes have excellent activity for the oxidation of benzyl alcohol into benzaldehyde; however, we found that the catalytic systems based on mononuclear iridium complexes associated with various ligands gave benzimidazole **3** as the major product, not dialkylation product **2**, even though the reactions were carried out under hydrogen atmosphere (Table 1). From this screening, it clearly shows that complex **1** is the most promising catalyst for the N,N′-dialkylation of benzenediamines with alcohols. Presumably, the cooperative effect between the two metal centers in complex **1** plays an important role in facilitating the reduction of imine, an effect which is absent in a mononuclear system.

Table 1 N,N′-Dialkylation of *o*-Benzenediamine Catalyzed by Various Iridium Complexes[a]

Entry	Iridium catalyst	Conv.[b] (%)	Yield[c] (%)	
			3	**2**
1	complex **1**	100	–	90
2	$Ir(IBn)(CO)_2Cl$[d]	100	78	–
3	$[Ir(cod)_2Cl]_2$	100	80	–
4	$[Ir(cod)_2Cl]_2/Ph_3P$	98	50	47
5	$[Ir(cod)_2Cl]_2$/dppp[e]	100	70	20
6	$IrCl_3/Me_2N(CH_2)_2NMe_2$	97	38	50

[a] Reaction conditions: diamine (0.5 mmol), alcohol (3 mmol), iridium complex (3 μmol), $CsOH·H_2O$ (0.15 mmol), molecular sieves (0.3 g), 120 °C, 48 h, under H_2 atmosphere.
[b] Based on the consumption of diamine.
[c] NMR yields.
[d] IBn = 1,3-dibenzylimidazol-2-ylidene.
[e] dppp = $Ph_2P(CH_2)_3PPh_2$.

With this promising result, the scope and generality of the N,N′-dialkylation reaction was investigated (Table 2). As expected, all of the reactions proceeded smoothly and some functional groups were tolerated, including methyl, methoxy, bromo, and trifluoromethyl groups, but not the nitro group. Thus, reaction of *o*-benzenediamine with various benzyl alcohols afforded the corresponding *N*,*N*′-dibenzyl-*o*-benzenediamines in good to excellent yields (Table 2, entries 1–4). The yield decreased slightly with the use of the *ortho*-substituted benzyl alcohol presumably due to steric hindrance (Table 2, entry 5).

Next, we explored the isomeric benzenediamines. Dialkylations of *m*- and *p*-benzenediamine with various alcohols, including aliphatic alcohols, proceeded smoothly to yield the corresponding amines in good yields (Table 2, entries 6–11). It should be noted that these reactions can be carried out under nitrogen atmosphere, i.e. the hydrogen atmosphere is not required. Furthermore, aliphatic alcohols such as 1-octanol and ethyl alcohol can also be employed as the alkylating agent. Thus, reaction of *m*- and *p*-benzenediamine with 1-octanol yielded *N*,*N*′-dioctyl-*m*-benzenediamine and -*p*-benzenediamine in 85% and 90% yield, respectively (Table 2, entries 7 and 11). In contrast, the nitro-substituted benzyl alcohol is not suitable as the alkylating agent, as the reaction gave a mixture of unidentified products (Table 2, entry 12). Presumably, partial reduction of the nitro group resulted in complication of the reaction.

In summary, we have described an efficient diiridium catalytic process for the dialkylation of benzenediamines with various alcohols. This catalytic system offers several advantages for the preparation of such benzenediamines, such as low loading of catalyst, no required organic solvent, high selectivity, and high yields, which make it a useful and attractive methodology for organic synthesis. In this study, we have established that the dimetallic catalyst affects the catalytic selectivity dramatically, presumably due to a synergistic effect. Detailed mechanistic studies and further applications are currently under investigation.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300 or Avance 400 spectrometer. Chemical shifts are given in parts per million relative to TMS. HRMS data were recorded by using ESI-TOF (Waters Micromass LCT Premier XE) and FABMS (JEOL JMS-700) techniques. Chemicals and solvents were of analytical grade and were used as received, unless otherwise stated. Complex **1** was prepared according to the method previously reported.[8]

Iridium-Catalyzed N,N′-Dialkylation of Benzenediamines; General Procedure

A mixture of the benzenediamine (54 mg, 0.5 mmol), an alcohol (3 mmol), iridium complex **1** (3 mg, 3 μmol), $CsOH·H_2O$ (25.2 mg, 0.15 mmol), and 4 Å molecular sieves (0.3 g) in a reaction tube was flushed with nitrogen gas. The reaction mixture was heated at 120 °C for 48 h under hydrogen atmosphere. After the reaction completion, H_2O (5 mL) and EtOAc (3 × 5 mL) were added. The organic extract was separated, dried ($MgSO_4$), and concentrated. The desired product was purified by chromatography (CH_2Cl_2–EtOAc, 30:1 to 10:1). The structures of the products were confirmed from their spectroscopic (^1H and ^{13}C NMR, and MS) data, which were similar to those reported in the literature. Spectroscopic data of new compounds are summarized below.

N,*N*′-Bis(*p*-bromobenzyl)-*o*-benzenediamine[10]

Yield: 0.168 g (75%); yellow solid; mp 120–122 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.28 (s, 4 H, -ArCH_2N-), 6.66–6.68 (m, 2 H), 6.81–6.83 (m, 2 H), 7.26 (d, *J* = 6.4 Hz, 4 H), 7.47 (d, *J* = 6.4 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 136.6, 131.5, 129.2, 120.8, 119.6, 112.2, 48.2.

HRMS–FAB: *m/z* $[M]^+$ calcd for $C_{20}H_{18}N_2Br_2$: 443.9837; found: 443.9830.

N,*N*′-Bis[*p*-(trifluoromethyl)benzyl]-*o*-benzenediamine

Yield: 0.149 g (70%); yellow solid; mp 118–120 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.41 (s, 4 H, -ArCH_2N-), 6.64–6.67 (m, 2 H), 6.78–6.80 (m, 2 H), 7.49 (d, *J* = 8.0 Hz, 4 H), 7.59 (d, *J* = 8.0 Hz, 4 H).

Table 2 N,N′-Dialkylation of Benzenediamines with Various Alcohols[a]

Entry	Diamine	Alcohol	Product	Yield[c] (%)
1[b]	o-$C_6H_4(NH_2)_2$	BnOH	o-$C_6H_4(NHBn)_2$	90
2[b]		p-$MeOC_6H_4CH_2OH$	o-$C_6H_4(NHCH_2C_6H_4$-p-$OMe)_2$	90
3[b]		p-$BrC_6H_4CH_2OH$	o-$C_6H_4(NHCH_2C_6H_4$-p-$Br)_2$	75
4[b]		p-$F_3CC_6H_4CH_2OH$	o-$C_6H_4(NHCH_2C_6H_4$-p-$CF_3)_2$	70
5[b]		o-$MeC_6H_4CH_2OH$	o-$C_6H_4(NHCH_2C_6H_4$-o-$Me)_2$	61
6	m-$C_6H_4(NH_2)_2$	BnOH	m-$C_6H_4(NHBn)_2$	85
7		$Me(CH_2)_7OH$	m-$C_6H_4[NH(CH_2)_7Me]_2$	85
8		EtOH[d]	m-$C_6H_4(NHEt)_2$	72
9	p-$C_6H_4(NH_2)_2$	BnOH	p-$C_6H_4(NHBn)_2$	78
10		p-$F_3CC_6H_4CH_2OH$	p-$C_6H_4(NHCH_2C_6H_4$-p-$CF_3)_2$	63
11		$Me(CH_2)_7OH$	p-$C_6H_4[NH(CH_2)_7Me]_2$	90
12		p-$O_2NC_6H_4CH_2OH$	unidentified mixture	–

[a] Reaction conditions: diamine (0.5 mmol), alcohol (3 mmol), iridium complex **1** (3 μmol), $CsOH·H_2O$ (0.15 mmol), molecular sieves (0.3 g), 120 °C, 48 h.

[b] Under H_2 atmosphere.

[c] Isolated yields.

[d] Reaction was carried out in a sealed reactor.

^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.3, 136.6, 129.6, 129.3$ ($J_{C–F}$ = 3.8 Hz), 127.7, 125.4, 119.8, 112.3, 48.3.

ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{22}H_{19}N_2F_6$: 425.1447; found: 425.1455.

N,N′-Bis(*o*-methylbenzyl)-*o*-benzenediamine

Yield: 0.094 g (61%); yellow solid; mp 110–112 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (s, 6 H, $-CH_3$), 4.29 (s, 4 H, $-ArCH_2N-$), 6.77–6.79 (m, 2 H), 6.86–6.88 (m, 2 H), 7.19–7.23 (m, 6 H), 7.32 (d, J = 6.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.8, 136.6, 136.1, 129.9, 128.1, 127.0, 125.7, 119.0, 111.5, 47.0, 19.3.

ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{22}H_{25}N_2$: 317.2012; found: 317.2017.

N,N′-Dioctyl-*m*-benzenediamine[11]

Yield: 0.141 g (85%); white solid; mp 59–60 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 6 H, $-CH_3$), 1.27–1.37 (m, 20 H, $-CH_2-$), 1.55–1.62 (m, 4 H, $-CH_2-$), 3.06 (t, J = 6.8 Hz, 4 H, $-CH_2-$), 3.49 (br, 2 H, -NH-), 5.85 (s, 1 H, Ar-H), 6.00 (dd, J = 8.0 Hz, 2.0 Hz, 2 H, Ar-H), 6.94 (t, J = 8.0 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2, 129.5, 102.4, 96.8, 44.3, 32.2, 30.0, 29.8, 29.6, 27.6, 23.1, 14.6.

ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{22}H_{41}N_2$: 333.3264; found: 333.3249.

N,N′-Diethyl-*m*-benzenediamine[12]

Yield: 0.059 g (72%); purple solid; mp 45–47 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.2 Hz, 6 H, $-CH_3$), 3.13 (t, J = 7.2 Hz, 4 H, $-CH_2N-$), 5.88 (s, 1 H, Ar-H), 6.00 (d, J = 7.6 Hz, 2 H, Ar-H), 6.96 (t, J = 7.6 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4, 129.7, 102.7, 96.9, 38.6, 15.1.

ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{10}H_{17}N_2$: 165.1386; found: 165.1390.

N,N′-Dibenzyl-*p*-benzenediamine[6a]

Yield: 0.112 g (78%); yellow solid; mp 107–109 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.43 (br, 1 H, -NH-), 4.25 (s, 4 H, $-ArCH_2N-$), 6.57 (s, 4 H, Ar-H), 7.25–7.28 (m, 2 H, Ar-H), 7.31–7.38 (m, 8 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 139.4, 128.1, 127.2, 126.6, 114.3, 49.6.

ESI-HRMS: m/z $[M + H]^+$ calcd for $C_{20}H_{21}N_2$: 289.1699; found: 289.1679.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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