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Palladium-catalyzed unstrained C(sp^3)-N bond activation: the synthesis of *N*,*N*-dimethylacetamide by carbonylation of trimethylamine

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This work describes a highly efficient unstrained C(sp^3)-N bond activation approach for synthesis of *N*,*N*-dimethylacetamide (DMAc) via catalytic carbonylation of trimethylamine using a $PdCl_2$/bipy (bipy = 2,2′-bipyridine)/Me_4NI catalyst system. A low Pd catalyst dosage (1.0 mol%) is sufficient for high selectivity (98.1%) and yield (90.8%), with a turnover number (TON) of 90.0 mmol of DMAc obtained per mmol of $PdCl_2$ employed under mild reaction conditions. The influence of reaction parameters such as catalyst precursor dosage, ligand type and promoter on activity is investigated. This work also discusses in detail the halide promoter's role in the reaction, and provides a plausible mechanism based on the intermediates methyl iodide and acetyl iodide. Analyses indicate that the carbonylation of trimethylamine may proceed through an active intermediate acetyl iodide formed by carbonylation of methyl iodide generated from the decomposition of the promoter Me_4NI under reaction conditions. The formation of acetyl iodide favors the cleaving efficiency of the inert unstrained C(sp^3)-N bond of trimethylamine. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: C(sp^3)-N activation; carbonylation; homogeneous catalysis; *N*,*N*-dimethylacetamide; palladium

Introduction

The C-N bond is one of the most abundant and nonreactive bonds in organic molecules. The catalytic activation of a C-N bond is of considerable importance in synthetic organic chemistry, particularly for synthesizing N-containing compounds. Generally, C-N bonds are activated by conversion to diazonium salts,[1] ammonium salts[2] or aza-heterocycles.[3] However, these existing methodologies are still plagued with some problems such as the explosive and unstable nature of the substrate, and the quantity of waste produced. Therefore, there is still a need to develop new methods to cleave C-N bonds. In this paper, we provide an example of catalytic activation of an unstrained C(sp^3)-N bond using a Pd complex catalyst based on our experience with palladium-catalyzed carbonylation reactions.[4]

The carbonylation of amine is a significant topic of interest as the fine chemicals and pharmaceutical sectors view the process as an atom-efficient method. As such, the method has experienced impressive improvements in recent years.[5] However, most researchers have focused on the aminocarbonylation of primary or secondary amines,[5b,6] or on specialized types of carbonylation such as ring expansion–carbonylation reactions of strained tertiary amines like aziridines,[7] azetidines[8] or pyrrolidines.[9] To the best of our knowledge, carbonylation of unstrained tertiary amines such as Me_3N or Et_3N, which are typically used as a base in aminocarbonylation reactions, has rarely been reported.[10] The lack of research in this topic is likely attributable to the inertness of the unstrained C(sp^3)-N bonds of tertiary amines compared to the C-H bonds of primary and secondary amines, which exhibit lower oxidative addition reactivity toward transition-metal complex catalysts.

In this work, we study the direct carbonylation of Me_3N with a $PdCl_2$/bipy/Me_4NI catalytic system for synthesis of *N*,*N*-dimethylacetamide (DMAc) (Scheme 1). DMAc is a polar aprotic solvent which is widely employed as a reaction medium in the production of many fine chemicals and pharmaceuticals. In recent years, DMAc was discovered to be a privileged solvent for non-water-soluble polysaccharides[11a] and the solvent's excellent solubility for these polymers enables the synthesis of the renewable platform chemical 5-hydroxymethylfurfural from untreated lignocellulosic biomass.[11b,c] Traditionally, industrial synthesis of DMAc relies on a reaction of acetic acid or acetic derivatives. However, this transformation suffers from low atom efficiency as well as the inherent drawback of producing waste products along with DMAc.

So far, only a very few patent applications have described the preparation of DMAc through carbonylation of Me_3N. Results reported in the literature to date are far from satisfactory, as the result of obvious disadvantages such as involving the catalyst $Co_2(CO)_8$, which is very difficult to prepare, handle and reuse.[12]

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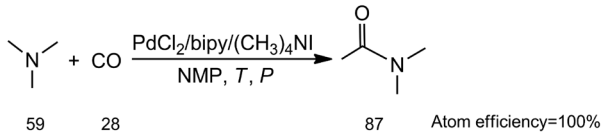


Scheme 1. Catalytic carbonylation of Me_3N to DMAc.

Other catalyst options use expensive noble metals such as Rh[13a] or Rh/Ir.[13b] Also Roose.[14] has reported that a $PdCl_2/Me_4NI$ system could catalyze carbonylation of Me_3N into DMAc at 240°C and initial CO of 6.5 MPa. The goals of this work are to improve Pd catalyst performance and impede the formation of Pd black by tuning various ligands and promoters, to unravel the role of promoters as well as the mechanism of how the unstrained C(sp^3)-N bonds of Me_3N are activated in the reaction.

Experimental

$PdCl_2$, $RuCl_3.xH_2O$, KI, NaOH, soda lime, PPh_3, bipy (2,2′-bipyridine), phen(1,10-phenanthroline), 5-NO_2-phen, 5-NH_2-phen, isoquinoline, 1-Me-isoquinoline, quinoline, 2,2′-bis(2-oxazoline), Me_4NI, Me_4NBr, Me_4NCl, Et_4NI, *n*BuNI, methyl iodide and trimethylamine hydrochlorate were purchased from Chinese National Medicines Corporation Ltd and used as received. Solvents such as *N*-methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylformamide (DMF) and toluene were distilled prior to use. The 4 Å molecular sieves were calcined at 350°C for 3 h before use.

Analyses of the products by gas chromatography were performed in an Agilent GC 1790 apparatus equipped with an HP-5 (30 m × 0.32 mm × 0.25 μm) capillary column and a flame ionization detector (FID). GC-MS analyses were performed in an Agilent 6890/5973 GC-MS apparatus equipped with a split/splitless injection system and FID. The capillary column was an Agilent HP-5MS (30 m × 0.25 mm × 0.25 μm). Helium (1.0 ml min^{-1}) was used as the carrier gas. FT-IR spectra in KBr pellets were recorded with a Bruker Equinox 55 FTIR spectrophotometer in the range of 4000–400 cm^{-1}. ^1H NMR spectra were obtained on a Bruker AV 400 spectrometer in DMSO-d_6 using tetramethylsilane (TMS) as internal standard.

Catalyst Preparation

$[RuCl_2(PPh_3)_3]$ was prepared according to the literature[15] and identified by melting point and FT-IR. m.p. 132–134°C (lit.132–134°C); IR (KBr): $\tilde{\nu}$ = 3048 (m), 1479 (m), 1435 (s), 1087 (s), 743 (s), 693 cm^{-1} (s). $[PdCl_2(bipy)]$ was synthesized according to the literature[16] and identified by FT-IR and ^1H NMR. IR (KBr): $\tilde{\nu}$ = 1481 (s), 1435 (s), 1097 (m), 747 (s), 692 cm^{-1} (s). ^1H NMR (400 MHz, DMSO-d_6, 25°C, TMS): δ = 9.143 ppm (d, J = 4.8 Hz, 2H; CH_2), 8.580 ppm (d, J = 7.6 Hz, 2H; CH_2), 8.359 ppm (dt, J_a = 1.2 Hz, J_b = 7.6 Hz, 2H; CH_2), 7.814 ppm (dq, J_a = 1.2 Hz, J_b = 5.6 Hz, 2H; CH_2).

Preparation of Me_3N/NMP Solution

As Me_3N is very volatile at room temperature, we used an Me_3N/NMP solution prepared in our lab as a reaction substrate solution by the reaction of trimethylamine hydrochlorate with an aqueous solution of sodium hydroxide and then introduced Me_3N gas to dissolve into the NMP solvent before going through two drying towers loaded with soda lime and 4Å molecular sieves respectively. The Me_3N/NMP solution was collected in a receiving flask immersed in an ice-salt bath and stored in a refrigerator for use. By weighing the masses of NMP solution before and after dissolving Me_3N, the concentration of Me_3N in NMP solvent expressed as mass percentage was calculated.

Typical Procedure for the Carbonylation Reaction

The catalytic carbonylation was carried out in a stainless steel autoclave (250 ml) according to the general procedure in the literature.[14] In a typical experiment, $PdCl_2$ (35.5 mg, 0.2 mmol), bipy (31.2 mg, 0.2 mmol), Me_4NI (0.9 g, 4.5 mmol) and NMP solvent (10 ml) were consecutively charged into the reactor. After flushing the autoclave three times using CO, Me_3N/NMP solution (7.8 wt%, 15 ml) and NMP solvent (5 ml) were successively added to the autoclave using a syringe. The autoclave was pressurized to 3.0 MPa with CO at room temperature and then the reaction was carried out at 200°C for several hours. After the reaction, the reactor was cooled to room temperature and depressurized carefully. The reaction mixture was centrifuged at 2500 rpm for 5 min and the clear supernatant, to which was added *n*-butyl alcohol as an internal standard, was analyzed by gas chromatography. In order to make the mass balance on N-containing compounds, the amounts of substrate, products and byproducts were analyzed in both the gas and liquid phase after reaction. In all experiments, mass balances were about 100 ± 5%.

Analysis of Me_4NI

The analyses of iodide ions and quaternary ammonium cations were made after reaction. By the gravimetric method, the determination of I^- ions in the liquid mixture was based on its quantitative reaction with Ag^+ ions to afford AgI. An aqueous solution of $AgNO_3$ (60 ml, 0.08 M) was added dropwise into part of the liquid product (34.9 g) after reaction, which was acidified by nitric acid to pH 3. Both Cl^- ions from $PdCl_2$ and I^- ions quantitatively precipitated, due to the small solubility product constants of AgCl and AgI. The precipitate was isolated by filtration, dried and weighed. The amount of I^- ions calculated from the stoichiometry reaction equaled 95% of I^- ions of Me_4NI added initially. Qualitative analysis of quaternary ammonium cations was made according to its quantitative reaction with sodium tetraphenylboron.[17] Part of the liquid product (30.0 g) was added dropwise to an aqueous solution of sodium tetraphenylboron (20 ml, 0.30 M) and a white solid $[Me_4N]^+[B(Ph)_4]^-$ quickly precipitated. Adding water (50 ml) to the mixture facilitated more solids to separate out, because we found that $[Me_4N]^+[B(Ph)_4]^-$ could partly dissolve in NMP solvent but was completely insoluble in water. The precipitated solid was filtered, washed thoroughly with water and dried. It was identified by FT-IR and the IR spectrum was in accordance with that of the product of pure Me_4NI with sodium tetraphenylboron. IR (KBr): $\tilde{\nu}$ = 3052 (s), 2995 (s), 1469 (s), 1427 (m), 744 (s), 710 cm^{-1} (s). The amount of Me_4N^+ ions calculated from the stoichiometry reaction in the mixture of products was 91% of Me_4N^+ ions of Me_4NI added initially.

Results and Discussion

Effect of Catalyst Precursors and Dosages

Table 1 lists results of the reaction using different catalytic precursors. The activity of the two Ru compounds is very poor, although the selectivity of DMAc is excellent (Table 1,

Table 1. Effect of catalyst precursors and dosages[a]

Entry	Catalyst	Cat. dosage (mol%)	Time (h)	Sel.[b] (%)	Yield (%)	TON[c]
1	$RuCl_3{\cdot}xH_2O$	2.0	8	98.0	10.0	4.5
2	$RuCl_2(PPh_3)_3$	2.0	8	98.3	12.0	5.4
3	$PdCl_2$	2.0	8	97.8	69.6	31.6
4	$PdCl_2$(bipy)	2.0	8	97.8	83.2	34.9
5[d]	$PdCl_2$/bipy	2.0	8	97.8	85.0	35.7
6[d]	$PdCl_2$/bipy	1.0	8	99.1	87.0	86.2
7[d]	$PdCl_2$/bipy	0.5	10	98.5	32.3	66.0

[a]Reaction conditions: Me_4NI (4.5 mmol), *w*(Me_3N/NMP) (7–8%), Me_3N/NMP (15 ml), NMP (15 ml), 200°C, CO (3.0 MPa, r.t.), stirring speed (700 rpm).
[b]Sel. $= \frac{n_{DMAc}}{n_{DMAc}+n_{DMF}+n_{NMA}} \times 100\%$.
[c]TON (mmol DMAc $mmol^{-1}$ $PdCl_2$).
[d]$PdCl_2$/bipy (1:1 molar ratio).

entries 1 and 2). GC-MS analysis confirms that the two byproducts are *N*,*N*-dimethylformamide (DMF) and *N*-methylacetamide (NMA) (see below), which might be generated by the carbonylation of demethylated Me_3N.

Over the last four decades, organic transformations catalyzed by Pd complexes have become one of the most active research fields in organometallic catalysis.[18] Therefore, we chose to adopt the simple palladium salt $PdCl_2$ for this study. There is a considerable improvement in the transformation of Me_3N when using $PdCl_2$ as the catalyst compared with that of Ru-based systems. The Pd-based system produces a 69.6% yield of DMAc, accompanied by a turnover number (TON) of 31.6 mmol DMAc/mmol $PdCl_2$ (Table 1, entry 3). However, note that decomposition of the catalyst – i.e. the reduction of Pd^{II} to Pd^0 by CO – occurs when using $PdCl_2$ as the catalyst, and a Pd black deposit forms on the bottom of the autoclave after the reaction. Therefore, we introduced a 2,2′-bipyridine (bipy) ligand to the catalytic system to try to inhibit Pd black formation. The simple ligand results in an obvious increase of activity, with an 85.0% yield of DMAc accompanied by a TON of 35.7 mmol DMAc $mmol^{-1}$ $PdCl_2$ (Table 1, entry 5). Our hypothesis is that a Pd complex with the bipy ligand forms *in situ* and becomes the active catalyst. The ligand helps prevent Pd^0 from depositing as bulk palladium black and improves catalytic activity through coordination with the palladium center. The catalytic complex formed *in situ* displays a higher catalytic activity than the preformed complex (Table 1, entry 4). Encouraged by the high reactivity of this $PdCl_2$/bipy system, we tried lower catalyst dosages. A reaction performed on 1.0 mol% Pd results in an 87.0% yield of DMAc accompanied by a 99.1% selectivity with a TON of 86.2 mmol DMAc/mmol $PdCl_2$ (Table 1, entry 6). Further reducing the dosage of the palladium catalyst dramatically deteriorates the reaction rate down to a 32.3% yield of DMAc, even after a prolonged reaction time (Table 1, entry 7).

Effect of Ligands

N-containing ligands are widely used in Pd-catalyzed carbonylation reactions under severe conditions,[19] as they can enhance the activity and stability of the Pd catalyst via coordination with the palladium and prevent aggregation of Pd black. Therefore, we screened a number of different N-containing ligands along with PPh_3 for this study (Table 2).

Table 2. Effect of ligands on activity[a]

Entry	Ligand	Ligand: Pd (molar ratio)	Sel.[b] (%)	Yield (%)	TON[c]
1	PPh_3[d]	1:2	77.8	37.8	15.9
2	bipy	1:1	97.8	85.0	35.7
3	bipy	2:1	99.7	36.0	15.6
4	phen	1:1	99.7	35.8	16.2
5	5-NO_2-phen	1:1	99.6	22.6	10.4
6	5-NH_2-phen	1:1	99.3	39.7	18.1
7	quinoline	2:1	98.4	43.7	20.1
8	isoquinoline	2:1	98.1	83.0	35.4
9	1-Me-isoquinoline	2:1	99.3	83.8	35.7
10	2, 2′-bis(2-oxazoline)	1:1	98.7	76.1	33.3

[a]Reaction conditions: Pd (2.0 mol%), Me_4NI/Pd (10:1 molar ratio), *w*(Me_3N/NMP) (7–8%), Me_3N/NMP (15 ml), NMP (15 ml), 200°C, CO (3.0 MPa, r.t.), 8 h, stirring speed (700 rpm).
[b]Sel. $= \frac{n_{DMAc}}{n_{DMAc}+n_{DMF}+n_{NMA}} \times 100\%$.
[c]TON (mmol DMAc/mmol $PdCl_2$).
[d]*N*, *N*-dimethylbenzamide and benzene were found in liquid product and characterized by GC-MS. MS (70 eV, EI): *m/z* (%): (1) *N*, *N*-dimethylbenzamide: 148.0 (68) [M^+], 105.0 (100) [$C_6H_5CO^+$], 77.0 (60) [$C_6H_5^+$], 51.0 (16) [$C_4H_3^+$]; (2) Benzene: 78.0 (100) [M^+], 52.0 (16) [$C_4H_3^+$], 39.0 (8) [$C_3H_2^+$].

We found that catalytic systems of mono- and bidentate N-containing ligands (Table 2, entries 2–10) are more active than that of the PPh_3 ligand (Table 2, entry 1). The selectivity towards DMAc remains high for all systems using N-containing ligands, with DMAc selectivity ranging between 97.8% and 99.7%, compared with only 77.8% for the PPh_3 system. This is likely due to thermal dissociation of PPh_3 at elevated temperatures (~200°C),[20] which can lead to decomposition and inactivation of the Pd complex. GC-MS (see below) analysis shows that benzene and *N*,*N*-dimethylbenzamide were in the liquid product which might be generated by carbonylation of the decomposed PPh_3 with Me_3N.

Among the N-containing ligands examined, the combination of $PdCl_2$/bipy showed the highest catalytic activity, obtaining a maximal DMAc yield of 85.0% (Table 2, entry 2). When the dosage of $PdCl_2$ is kept at 2.0 mol%, the yield of DMAc decreased sharply, with the molar ratio of bipy/$PdCl_2$ increasing from 1 to 2 (Table 2, entry 3). This result suggests that when bipy concentration is too high compared to $PdCl_2$ concentration, the ligand takes up all of the coordination vacancy of Pd^{II}, which results in no vacancies being available for the substrate to be coordinated. Interestingly, more electron-rich ligands such as 1,10-phenanthroline (phen) and its derivates, give a lower yield compared to bipy (Table 2, entries 4–6). The decreasing trend of the catalytic activity in the sequence of 5-NH_2-phen, phen and 5-NO_2-phen may be related to the σ-donor ability of the ligands in the same decreasing order. Furthermore, quinoline, a versatile heterocyclic N-donor ligand in Pd-catalyzed carbonylation reactions,[21] has a 43.7% yield of DMAc (Table 2, entry 7), whereas isoquinoline and 1-Me-isoquinoline work quite well in the system, with yields of 83.0% and 83.8% of DMAc, respectively (Table 2, entries 8 and 9). The electron-donating methyl group increases the electronic density of the aromatic isoquinoline moiety, thus, causing a slight increase in DMAc yield. On the other hand, a wide range of applications successfully employ oxazolines consisting of a five-membered ring of N-containing ligands, particularly for asymmetric catalysis.[22] Using 2,2′-bis(2-oxazoline) as the ligand in our system produces a good yield of 76.1% and selectivity of 98.7% (Table 2, entry 10). Based on the results of these experiments, we decided to use bipy as the ligand for further optimization.

Effect of Promoters

The effect of different promoters on the performance of the catalysts is summarized in Table 3. We found that the reactions studied herein could only obtain trace amounts of DMAc in the absence of a promoter, and almost the entire palladium complex turned into Pd black (Table 3, entry 1). However, by introducing KI into the $PdCl_2$/bipy system, the reaction achieves a 17.8% yield and 93.6% selectivity for DMAc (Table 3, entry 2). When we switched to CH_3I as the promoter, DMAc yield significantly increases to 62.0%, while DMAc selectivity declines to 75.1% because Me_3N converts to Me_4NI through an *in situ* reaction with CH_3I (Table 3, entry 3). Based on this result, we added 1.0 mol% Me_4NI directly into the system. This produces a 7.1% yield and 93.4% selectivity for DMAc (Table 3, entry 4). Increasing the molar ratio of Me_4NI/$PdCl_2$ from 1 to 30 significantly increases DMAc yield, as well as providing consistently excellent selectivity for DMAc (Table 3, entries 4–8), and a maximal DMAc yield of 90.8% with a TON of 90.0 mmol DMAc/mmol $PdCl_2$. Notably, the use of quaternary ammonium salts as a promoter is of crucial importance in this carbonylation reaction. For this reason, we applied other iodine-containing quaternary ammonium salts such as Et_4NI and nBu$_4$NI in combination with the $PdCl_2$/bipy catalytic system, and very different results were obtained. Catalytic activity is poor with Et_4NI or nBu$_4$NI as the promoter, with yields of DMAc of 17.2% and 28.2%, respectively (Table 3, entries 9 and 10). For comparison, we also used Me_4NBr and Me_4NCl as co-catalysts in the reaction. Conventionally introducing Me_4NBr instead of Me_4NI as the promoter results in a 82.7% yield and excellent selectivity of DMAc (98.8%), while the promoter activity of Me_4NCl is quite poor (Table 3, entries 11 and 12).

Table 3. Effect of promoters on activity[a]

Entry	Promoter	Promoter:Pd (molar ratio)	Sel. (%)	Yield (%)	TON[b]
1	—	—	77.7	1.4	1.3
2[c]	KI	10	93.6	17.8	8.6
3[c]	CH_3I	10	75.1[d]	62.0	28.4
4	Me_4NI	1	93.4	7.1	6.6
5	Me_4NI	5	98.1	35.7	33.1
6	Me_4NI	10	98.7	66.2	61.5
7	Me_4NI	22.5	99.1	87.0	86.2
8	Me_4NI	30	98.1	90.8	90.0
9	Et_4NI	22.5	96.1	17.2	18.0
10	nBu$_4$NI	22.5	95.3	28.2	29.2
11	Me_4NBr	22.5	98.8	82.7	79.0
12	Me_4NCl	22.5	98.0	10.0	9.8

[a]Reaction conditions: Pd (1.0 mol%), $PdCl_2$/bipy (1:1 molar ratio), w(Me_3N/NMP) (7–8%), Me_3N/NMP (15 ml), NMP (15 ml), 200°C, CO (3.0 MPa, r.t.), 8 h, stirring speed (700 rpm).

[b]TON (mmol DMAc/mmol $PdCl_2$).

[c]Pd: 2.0 mol%.

[d]Sel. $= \frac{n_{DMAc}}{n_{DMAc}+n_{DMF}+n_{NMA}+n_{Me_4NI}} \times 100\%$

The Role of Me_4NI

Promoters are important for enhancing the activity and stability of catalysts. For example, adding iodide ions result in pronounced promotion in an amazing variety of Pd-catalyzed C-C coupling reactions and CH_3OH carbonylation reactions.[23] Some researchers have investigated the beneficial influence of iodine-containing promoters in the carbonylation of Me_3N. One report in the literature achieved 72% conversion of Me_3N and 56% yield of DMAc when using $RhCl_3$ as a catalyst in the presence of MeI as a promoter, but obtained only a small amount of DMAc without MeI.[13a] To the best of our knowledge, the details surrounding halide promoters – in particular how halides promote the catalytic cleaving of the C-N bond of tertiary amines in a carbonylation reaction – have been rarely described. The only available example constitutes the work of Kobayashi and Tanaka,[24] who observed that the cleaving of the C-N bond of triethylamine in the presence of PhI and CO using palladium complex catalysts gave a 73.9% yield of *N*,*N*-diethylbenzamide and ethyl iodide (Scheme 2). The group pointed out that an organic halide was essential for cleaving the C-N bond of tertiary amines. In the absence of organic halides, tertiary amines were not carbonylated by the same palladium catalyst, even at prolonged reaction time and under more severe conditions. It is a pity that the group did not further explore how an organic halide activates the C-N bond of tertiary amines in the carbonylation reaction.

Encouraged by the fact that Me_4NI was an effective promoter in our carbonylation reaction, we decided to examine the role of halide promoters. Taking into account the effect of promoters on the activity (see Table 3), we thought that Me_4NI plays two kinds of role. First, the introduced Me_4NI strongly interacts with Pd nanoparticles to prevent Pd black precipitation at high reaction temperatures. It is well known that the chemical reduction of transition metal salts in the presence of a surfactant such as a tetraalkylammonium salt leads to the formation of nanostructured $R_4N^+X^-$-stabilized metal clusters. In these systems, a monomolecular layer of ammonium salt surrounds each cluster, acting as a stabilizer to prevent undesirable metal aggregation.[25a] Clearly, an important role of Me_4NI is to provide electrostatic stabilization of the palladium nanoparticles through the formation of a double electric layer.[25b] On the other hand, Me_4NI may provide MeI in a decomposition reaction (equation (1)),[26] which activates the inert C-N bond of the amine.

$$(CH_3)_4NI \xrightarrow[T]{\text{base}} CH_3I + Me_3N \qquad (1)$$

We speculate that the C-N bond of Me_3N is activated by the reaction of Me_3N and acetyl iodide, which may be generated by the carbonylation of MeI catalyzed by the Pd catalyst. Laboratories and industry extensively use palladium-catalyzed carbonylation of methanol to produce acetic acid.[27a] It has been widely accepted that the presence of iodide is necessary in order to convert methanol into methyl iodide prior to carbonylation; thus the actual substrate for the carbonylation of methanol is methyl iodide.[27b,c] By the same consideration, it is likely that the Pd complex first catalyzes the MeI in our system to yield acetyl iodide, a more reactive intermediate (equation (2)).

$$CH_3I + CO \xrightarrow{\text{cat.}} CH_3COI \qquad (2)$$

Khai and Arcelli[28a] observed that acid anhydrides are highly active in promoting the dealkylation of tertiary amines in the presence of transition metal chlorides such as $FeCl_2$, $RuCl_3$ and $PdCl_2$, obtaining good yields of *N*,*N*-dialkylamides (Scheme 3). Moreover, Voronkov *et al.*[28b] reported that reactions of tertiary amines with acyl iodides were accompanied by cleaving of the C-N bond and the formation of corresponding *N*,*N*-di(hydrocarbyl) carboxamide and alkyl iodide (Scheme 4). The reaction between acyl iodides and tertiary amines can occur under mild conditions and even at room temperature in the absence of a catalyst.[28c]

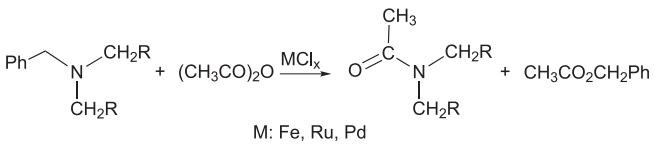
Therefore, we believe that the acetyl iodide reacts with Me_3N to afford DMAc while simultaneously producing MeI (equation (3)). Kobayashi and Tanaka have claimed that organic halides are indispensable for the carbonylation of tertiary amines to yield amides.[24] We also agree with this opinion, and we are more inclined to believe that the carbonylation of amines may proceed through an active intermediate acetyl iodide formed by carbonylation of MeI and the formation of acetyl iodide favors the cleaving efficiency of the inert C-N bond of Me_3N.

$$CH_3COI + (CH_3)_3N \longrightarrow CH_3CON(CH_3)_2 + CH_3I \qquad (3)$$

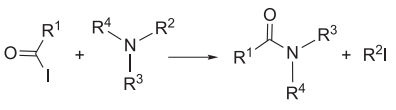
We attempted to capture MeI in the products but failed to do so. This failure can be explained by the fact that MeI is well known to convert into Me_4NI immediately in the presence of Me_3N (equation (4)), and the activation energy of the formation salt reaction is less than 10 kcal mol^{-1} at 298 K.[29] Therefore, we believe that MeI exists as an intermediate in the catalytic circle. After the reaction, we endeavored to measure the amount of I^- and Me_4N^+ in the liquid products, and found that 95% of I^- ions and 91% of Me_4N^+ ions initially added remained in the mixture.

$$CH_3I + (CH_3)_3N \longrightarrow (CH_3)_4NI \qquad (4)$$

The above discussion is in good agreement with the experimental results (see Table 3). Both Me_4NI and MeI efficiently promote the carbonylation of Me_3N, with the system exhibiting a faster reaction rate as more Me_4NI is added. A further possibility is that sufficient Me_4NI creates a fine protective layer around



Scheme 3. Reactions of acid anhydrides with tertiary amines reported by Khai.



Scheme 4. Reactions of acyl iodides with tertiary amines reported by Voronkov.

$$PhI + CO + Et_3N \xrightarrow{[(Ph_3P)_2PhPdI]} PhCONEt_2 + EtI$$

Scheme 2. Cleavage of $C(sp^3)$-N bond of Et_3N in the presence of PhI.

the palladium nanoparticles, thereby preserving the Pd catalyst's good performance under the reaction conditions.

We performed a GC-MS analysis of the liquid product with the aim of unraveling the role of Me_4NI in the reaction, and the results are given in Fig. 1. In addition to Me_3N (1.287 min), DMF (1.903 min), DMAc (2.279 min), NMA (3.006 min), NMP (4.054 min) and bipy (6.396 min), HOAc (2.459 min) also appears in the reaction mixture, which might be generated from the carbonylation of MeI.

Why do other quaternary ammonium salts such as Et_4NI or nBu$_4$NI not work in the carbonylation reaction? The different decomposition modes between Me_4NI and Et_4NI or nBu$_4$NI in a basic condition may explain this result. With Me_4NI, the active OH^- causes a reverse Menschutkin decomposition to give MeI, while for Et_4NI or nBu$_4$NI the active OH^- results in a Hofmann decomposition to give tertiary amine, olefin and water (equations (5) and (6)).[30] In other words, decomposition of Et_4NI or nBu$_4$NI does not generate a halohydrocarbon and hence cannot consequently activate the C-N bond of the tertiary amine through reaction of the amines with the acetyl iodides formed by carbonylation of the halohydrocarbon.

$$(CH_3CH_2)_4NI + OH^- \longrightarrow (CH_3CH_2)_3N + CH_2{=}\,CH_2 + H_2O + I^- \quad (5)$$

$$(CH_3CH_2CH_2CH_2)_4NI + OH^- \longrightarrow (CH_3CH_2CH_2CH_2)_3N + CH_3CH_2CH_2{=}\,CH_2 + H_2O + I^- \quad (6)$$

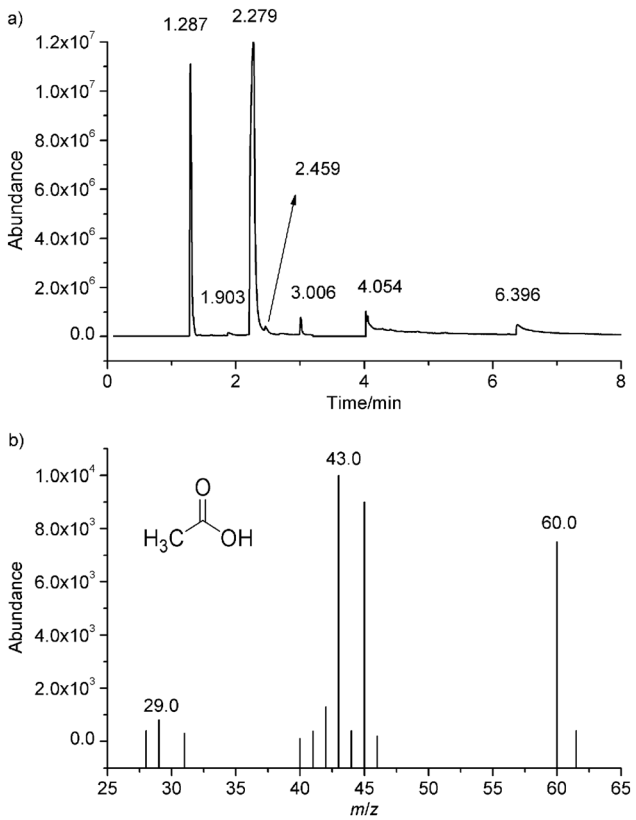


Figure 1. GC-MS data of reaction mixture obtained after carbonylation of Me_3N catalyzed by $PdCl_2$/Bipy/Me_4NI: (a) GC chromatogram; (b) MS of HOAc (70 eV, electron ionization): m/z (%): 60.0 (75) [M^+], 43.0 (100) [CH_3CO^+], 29.0 (8) [CO^+].

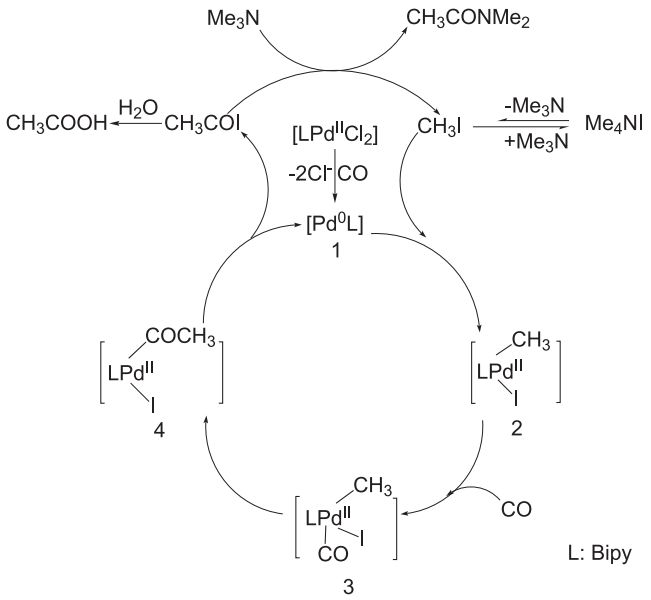


Figure 2. Proposed mechanism for carbonylation of Me_3N by Pd complex.

Proposed Mechanism

Taking into account what we know about the Pd-catalyzed carbonylation reaction mechanism, and based on the above results and discussion, we hypothesize a plausible mechanism for the carbonylation of Me_3N to DMAc in Fig. 2.

The catalytic cycle starts with the formation of the coordinatively unsaturated [Pd^0L] (L = Bipy) species **1** by reducing [$LPd^{II}Cl_2$] with CO. Next, the oxidative addition of the MeI which is generated by the decomposition of Me_4NI under the reaction conditions to **1** results in a [LPd^{II}MeI] species **2**. Meanwhile the reaction of Me_3N and MeI regenerates the Me_4NI in the system. An intermediate [$LCOPd^{II}$MeI] species **3** then forms through coordination of **2** with CO, which is transformed into an acetylpalladium iodide species **4** via migratory insertion of a coordinated CO ligand. Reductive elimination of **4** eventually leads to acetyl iodide and **1**. Acetyl iodide is converted along with Me_3N to give the final DMAc together with MeI and the presence of trace water leads to the formation of acetic acid.

Conclusion

We have developed an efficient method for the carbonylation of Me_3N to produce DMAc, catalyzed by $PdCl_2$/bipy/Me_4NI in NMP solvent. Owing to considerable differences in the chemical properties of DMAc and NMP, it is very easy to separate DMAc from the mixture of products. The catalytic system had excellent selectivity and yield of DMAc when the reaction was carried out under relatively mild conditions and with a low dosage of palladium catalyst (1.0 mol%). The role of both the ligands and promoters in the catalytic system were discussed in detail, and we proposed a plausible mechanism based on methyl iodide and acetyl iodide as intermediates in the reaction. We believe that the carbonylation of tertiary amines with a C(sp^3)-N bond may proceed through an active intermediate acetyl iodide formed by carbonylation of MeI, which is generated from decomposition of the Me_4NI promoter under reaction conditions. The formation of acetyl iodide favors the cleaving efficiency of the inert unstrained C-N bond of Me_3N.

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