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Ligand Redox Controlled Tandem Synthesis of Azines from Aromatic Alcohols and Hydrazine in Air: One-Pot Synthesis of Phthalazine

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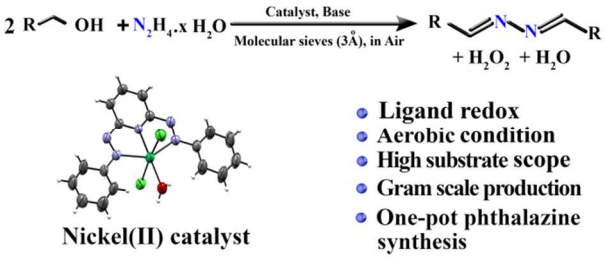


ABSTRACT:

A controlled tandem synthetic route to azines from various alcohols and hydrazine hydrate by the use of a Ni(II) complex of 2,6-bis(phenylazo)pyridine as a catalyst is reported. In marked contrast to the previous report, the reaction is operative using earth-abundant metal catalyst, milder reaction condition, and in aerobic conditions which though are desirable but unprecedented in the literature. The catalytic reaction has vast substrate scope including a single step synthesis of phthalazine from 1,2-benzenedimethanol and hydrazine hydrate via intramolecular coupling. Mechanistic investigation suggests that the coordinated ligand redox controls the reaction by the use of reversible azo (-N=N-)/ hydrazo (-NH-NH-) redox couple where the metal centre is used primarily as a template.

INTRODUCTION:

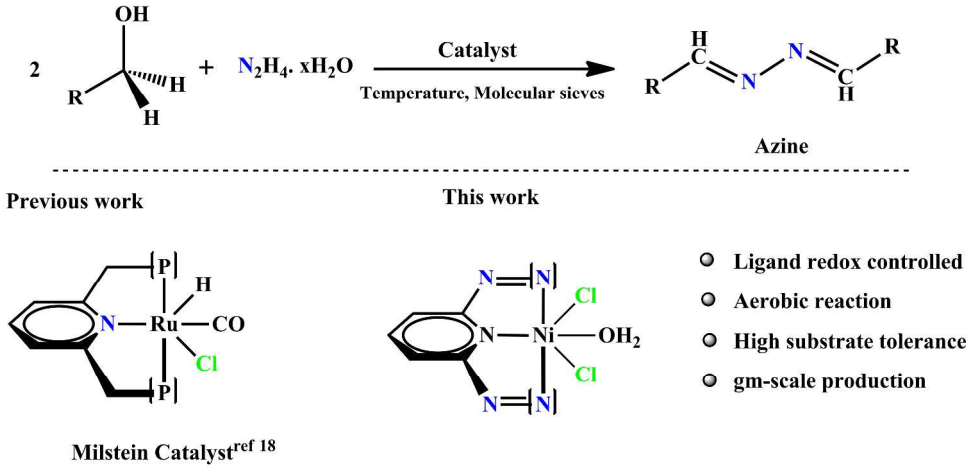
Azines (-CH=N-N=CH-) are important class of compounds having various industrial and chemical applications due to their unique structural and stereochemical properties.[1-4] This class of compounds is now used as drug developing agents in pharmacological,[5] and biological industries,[6] NLO materials,[7] organic sensors,[8,9] conductive polymers, image recording materials etc.[3] Apart from the industrial applications; azines are also widely used[10-12] to synthesise hydrazones and heterocyclic compounds. Heterocyclic azines[13-15] have been widely used as building blocks in supramolecular chemistry.

Synthesis of azines commonly[3] involves the coupling of hydrazines or hydrazones with the respective carbonyl compounds. Besides, there are alternative routes,[16] which are applicable only for some specific substrates. Industrialists, however, have been using[4,17] a multistep "peroxide process" where ketones are coupled with ammonia in the presence of a sacrificial oxidant, hydrogen peroxide. In this context, development of a single-step catalytic protocol for azine synthesis directly from alcohol and hydrazine has been challenging. Recently, Milstein et al. have reported[18] a direct synthesis of azines from alcohols and hydrazine hydrate using a ruthenium-PNP complex as a catalyst. Similar and recent work from the same group by the use of a Mn-catalyst[19] has led to the formation of hydrazones instead of azines. Notably, the afore noted azine synthesis protocol requires a long duration (>50h) and are carried out in deaerated conditions using a precious metal Ru-catalyst.

Herein, we wish to introduce a cascade synthetic route to azines in aerobic conditions, catalyzed by a nickel(II) complex of a bis(azoaromatic) ligand. A wide variety of azines were synthesized in high yields starting from the corresponding alcohols. Cascade reactions are worthy in the synthetic organic chemistry because of higher atom economy and production of reduced

chemical waste. Moreover, aerobic synthesis is not only users friendly, and is most desirable option which produces no waste or water as sole by product.

Scheme 1. Overview of the present work



RESULTS AND DISCUSSION

Herein we have explored a new reaction protocol of using ligand redox for tandem synthesis of a large variety of substituted azines by the coupling[20-25] of hydrazine hydrate and alcohols strictly in aerobic conditions. The catalyst is a Ni^{II}-complex (**1**) of a recently reported[26, 27] pincer ligand, L (L = 2,6-bis(phenylazo)pyridine) where the coordinated ligand controls the dehydrogenation reaction, and the metal centre is used primarily as a template. The catalytic reaction has a huge substrate scope, which includes aryl, polyaryl, heterocyclic moieties and operates in a relatively milder conditions (Scheme 1) than the reported[18] one. Using a similar protocol the synthesis of phthalazine from 1,2-benzenedimethanol has also been achieved in one-pot via the single step[28] intramolecular coupling reaction. The synthesis of phthalazine and its derivatives commonly involve multiple steps,[17,28] and to the best of our knowledge,[18] no catalytic method for direct synthesis of phthalazine from 1,2-benzenedimethanol is reported so far.

The complex, **1** is hexa-coordinated where a Ni^{II} ion is coordinated by a tridentate ligand L, two chloride ions and a labile water molecule (Figure 1). Recently, we have reported[26] that this complex brings about aerial alcohol dehydrogenation reaction[29] effectively in the presence of a reducing agent, zinc dust. This has prompted us to explore the one-pot coupling[30-33] reaction between hydrazine hydrate and alcohols using hydrazine hydrate both as a reducing agent and the reactant. We wish to note here that direct use of hydrazine in catalysis is challenging.[18]

To explore the ideal reaction conditions, we have selected benzylalcohol as a model substrate. To begin with, a mixture of equimolar solutions of benzylalcohol and hydrazine hydrate in the presence 2 mol% **1**, 5 mol% of potassium tert-butoxide (^{t}BuOK) and 1 g molecular sieves (3Å) in toluene was heated at 80^{o}C for 24h. The reaction resulted in the formation of 70% benzaldehyde (**3a**) along with 25% of benzaldazine (entry 1, Table 1). Under identical conditions, the reaction with the use of 2.1 equivalents of hydrazine hydrate led to the formation of benzaldazine in 82% of isolated yield (entry 2-4, Table 1). Finally, in an optimum reaction condition, a mixture of 1 mmol of benzylalcohol, 2 mol% of catalyst, 2.1 mmol of hydrazine hydrate and 5 mol% of ^{t}BuOK was heated at 80^{o}C in toluene solvent in the presence of 1 g of molecular sieves (3Å) for 24 h. The product was filtered through Whatman 41 filter paper to remove the catalyst and molecular sieves. Finally, the crude mixture was purified by preparative thin layer chromatographic technique using 1:10 ethyl acetate and hexane mixture as eluent. Table 1 collects the optimization conditions of the reaction.

Table 1. Optimizations table for the one-pot coupling of hydrazine hydrate with benzylalcohol

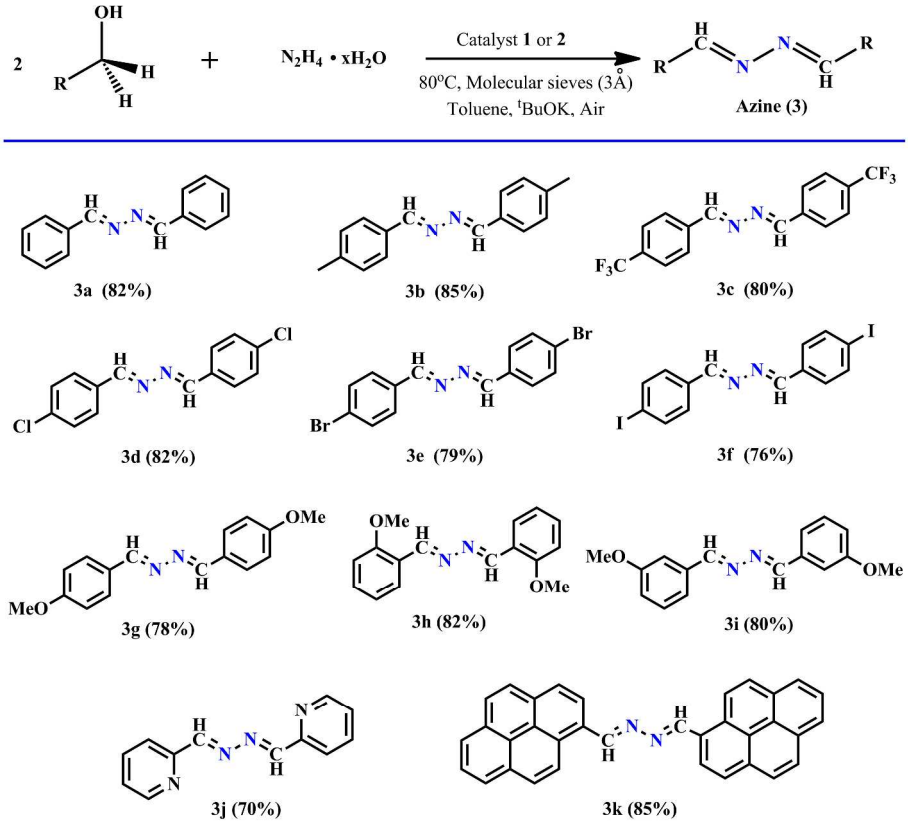
Entry	Time (h)	Temp. (^oC)	Base (mol %)	Molecular Sieves	Yield of azine (%)	Yield of Aldehyde (%)
1[a]	24	80	5	3 Å	25[c], 32[d]	60[d]
2	12	80	5	3 Å	38[c]	48[c]
3	18	80	5	3 Å	70[c]	18[c]
4	24	80	5	3 Å	82[c], 94[e]	6[e]
5	24	40	5	3 Å	12[c], 13[d]	85[d]
6	24	60	5	3 Å	46[c]	42[c]
7	24	80	Nil	3 Å	71[c]	18[c]
8	24	80	Nil	Nil	Trace	82[c]
9	24	80	5	Nil	15[c]	72[c]
10	24	80	5	4 Å	78[c]	10[c]
11	24	80	5	5 Å	76[c]	11[c]
12[b]	24	80	5	3 Å	79[c]	9[c]

Catalytic condition: Catalyst **1** (2 mol%), benzylalcohol (1 mmol), hydrazine hydrate (2.1 mmol), 5 mL toluene. The reaction mixture was placed in a preheated oil bath with a condenser under aerobic conditions. [a]Here 1 mmol hydrazine hydrate was used. [b]Here catalyst **2** was employed instead of catalyst **1**. [c]Isolated yield, [d]GCMS yield and [e]NMR yield.

Afterwards, we examined the scope of this protocol using various substituted benzylalcohols. Substrates containing both electron donating (-OMe, -Me etc.) and electron withdrawing (-halogens, -CF_3) groups work similarly in identical reaction conditions producing the desired products in high isolated yields (>75%). For example, the reaction of 4-(methyl) and 4-(methoxy) benzylalcohol with hydrazine hydrate in air afforded the corresponding azines (**3b** and **3g**) in 85% and 78% of yield respectively in 24h. The reactions also occur freely with 3-(methoxy) and 2-(methoxy benzylalcohols: the corresponding aldazines were isolated in 80% and 82%, yields. Similarly, the reaction between 4-(trifluoromethyl)benzylalcohol with hydrazine hydrate yielded 80% of the corresponding aldazines (**3c**). The reaction also proceeded smoothly for the coupling of halogen substituted benzylalcohol (**3d-f**) where 76-82% yields were

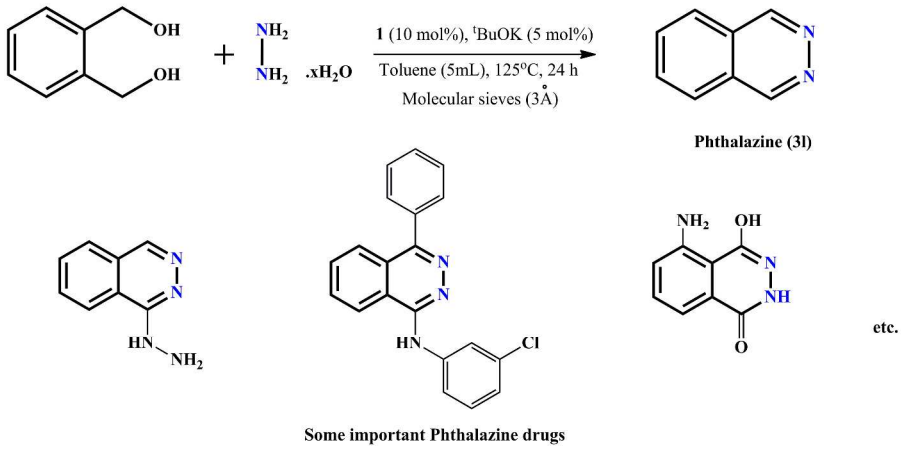
achieved. The latter compounds especially, bromo- and iodo- substituted aldazines are useful for further functionalisation. To demonstrate the high scalability of the method, a gram-scale reaction was also performed with the benzylalcohol (isolated product, **3a**), where 80% yield was achieved. The reaction protocol is not restricted only to the benzylalcohols but can be extended further for polyaryl (pyrenaldazine, **3k**) and heterocyclic (pyridinaldazine, **3j**) substitutions. Notably, the pyridinaldazines are useful building blocks for polymerisation,[34] drug industries[35] and supramolecular chemistry.[36] However; these compounds are not otherwise achievable from pyridylmethanols and hydrazine hydrate. The isolated azines along with their yields are collected in Table 2.

Table 2. $[NiCl_2L(H_2O)]$ (**1**) catalysed one-pot coupling of alcohols with hydrazine hydrate



Encouraged by the above results, we subsequently have explored the intramolecular coupling between 1,2-benzenedimethanol and hydrazine hydrate using an identical synthetic protocol. The coupling does occur between the above two substrates in one-pot producing N-heterocyclic phthalazine. The isolated yield of phthalazine (**3l**) was 52% with 10 mol% of catalytic loading and heating the reaction mixture at 125^{o}C for 24h; 18% of *ortho*-phthalaldehyde was also isolated as a byproduct. It may be noted here that phthalazines belong to a special class of nitrogen containing heterocycles, which are highly useful materials[28] in medicinal as well as material sciences (Scheme 2).

Scheme 2. Single step catalytic phthalazine formation: Tandem coupling of 1,2-benzenedimethanol with hydrazine hydrate



It is presumed that the first step of the reaction involves substitution of coordinated H_2O in the catalyst (**1**) by alcohol. To establish the substitution reaction, we stirred a methanolic solution of the complex **1** at room temperature in the presence of 3Å molecular sieves for 4h. The colour of the solution gradually became brownish green due to a substitution of H_2O by CH_3OH. A new crystalline product was isolated from the reaction mixture and its single crystal X-ray diffraction analysis has revealed that the isolated complex (**2**) is a methanol coordinated molecule with a

similar structure to that of the aqua-complex, **1**. An ORTEP representation of the isolated complex **2** is shown in Figure 1. Spectral characterizations are described in experimental section (Figure S13).

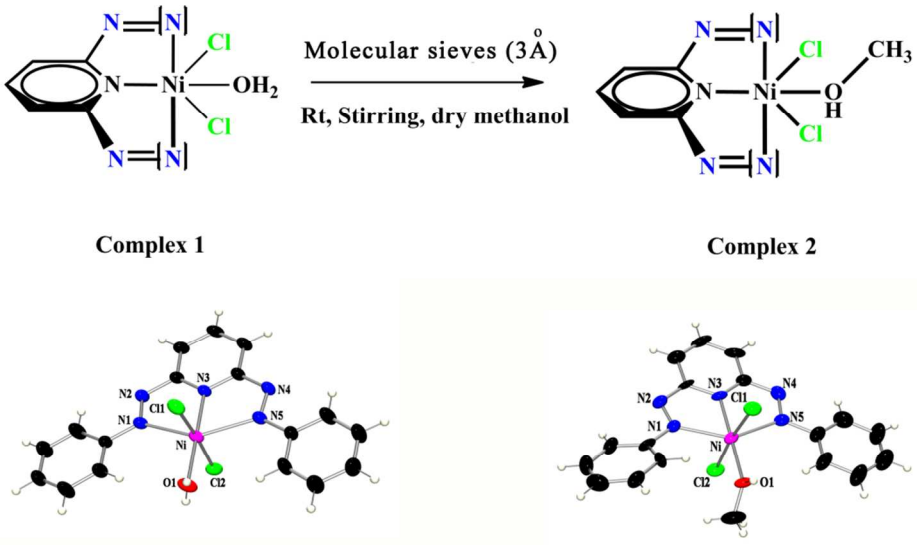


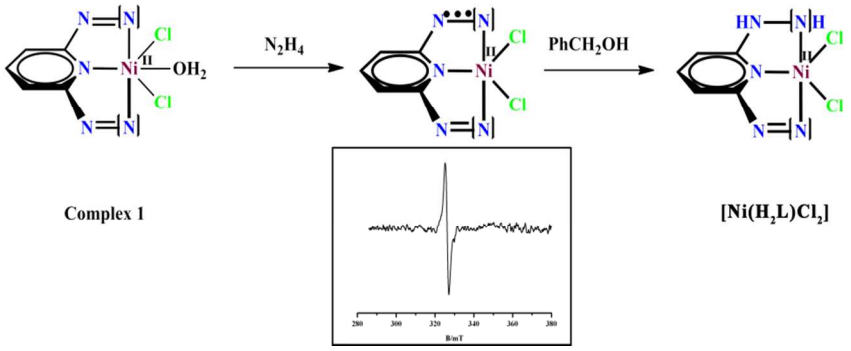
Figure 1. Isolation of complex **2** from complex **1** and their ORTEP representations with 30% probability ellipsoid. Solvent molecules were omitted for clarity.

Catalytic efficiencies of both **1** and **2** for the reference reaction are similar. For example, a reaction between benzylalcohol and hydrazine hydrate under identical reaction conditions with the use of complex **2** as catalyst yielded the product, **3a** in 79% yield (entry 12, Table 1).

To elucidate the reaction further, we have followed a stoichiometric reaction between **1** and hydrazine hydrate in benzylalcohol at room temperature. The green solution of **1** rapidly changes to greenish-blue on the addition of hydrazine hydrate and the resultant mixture showed a single line EPR spectrum signifying[26] the formation of an azo-anion radical intermediate. The colour of the mixture, on further stirring, became intense blue. The UV-visible spectral feature of the isolated blue intermediate is identical to that of the previously isolated complex, $[Ni(H_2L)Cl_2]$

(Scheme 3, Figure S14). Taken all these together we conclude that the azine formation proceeds via dehydrogenation[37] of alcohols (Scheme 4). The reactions are controlled exclusively by ligand redox and occur in the presence of air, which plays a crucial role[26] in catalyst regeneration.

Scheme 3. Single electron reduction of complex **1** in the presence of hydrazine hydrate



The catalytic reaction is also operative under base-free conditions; where 71% of the respective azine (**3a**) was isolated (entry 7, Table 1). It thus appears that there is no major participation of base in the catalytic cycle. But in the absence of molecular sieves and/or base (entries 8 and 9, Table 1) the primary product is benzaldehyde (70%), and only trace amount of azine (**3a**) was isolated from the mixture. This is as expected since it was reported previously[26] that alcohol dehydrogenation does take place freely even in the absence of a base. Thus the presence of molecular sieves in azine formation directly from alcohol and hydrazine hydrate is vital, which was also previously[18] noted by Milstein.

To have a closer look at the possible interactions between the catalyst and hydrazine hydrate in the cycle, three different reaction mixtures were subjected to spectroscopic analysis (Figure 2). Firstly, we have performed an in-situ IR study of the stoichiometric reaction mixture (A)

consisted of the equimolar amount of catalyst **1** and benzylalcohol in the presence of two equivalent of hydrazine hydrate and molecular sieves (3Å).

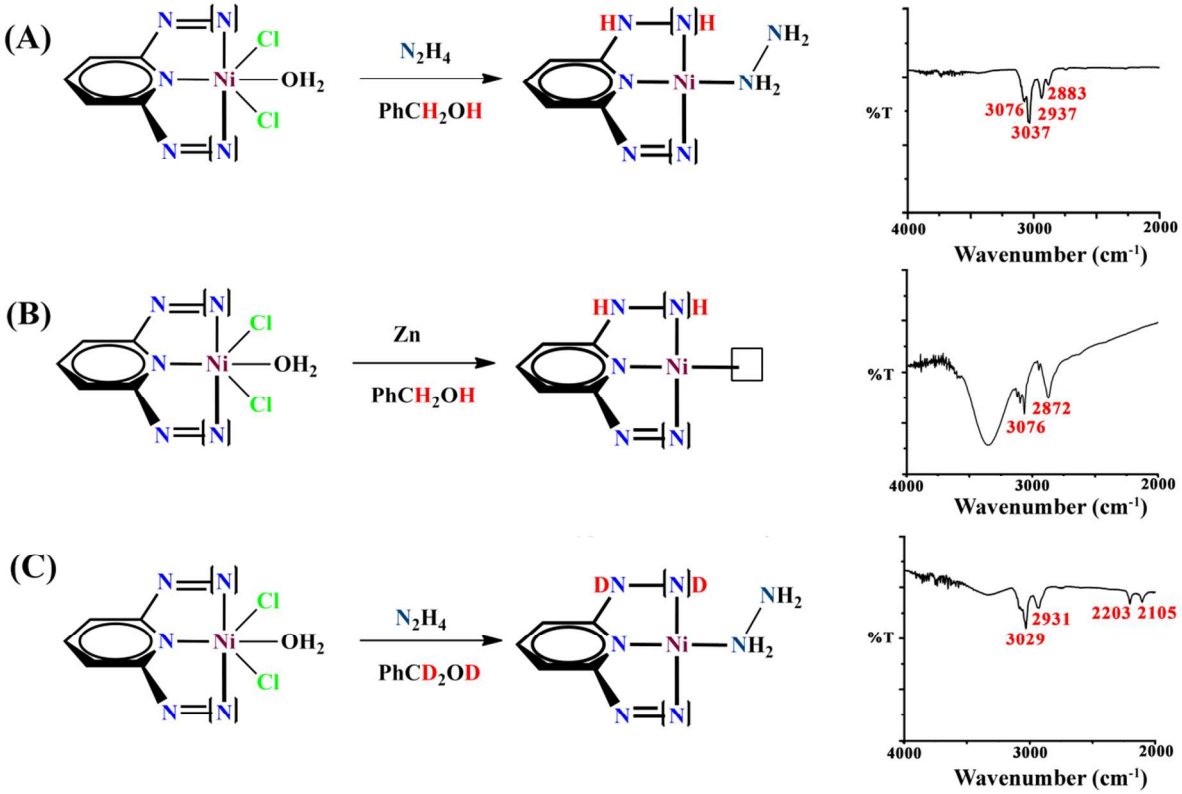
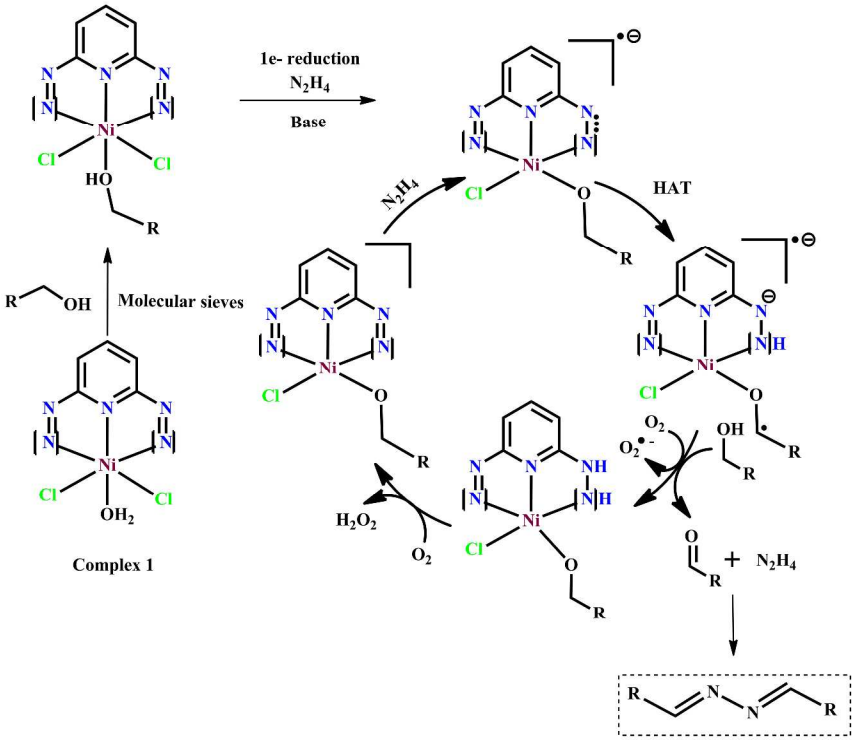


Figure 2. IR-spectral monitoring of N-H vibrational mode of hydrazine in the different reaction mixtures

Notably, two sets of doublets characterising stretching modes of N-H (hydrazine) were observed at 2883, 3076 and 2937, 3037 cm^{-1}. Presence of two types of hydrazine functions in the mixture is as anticipated: (a) hydrazine function in coordinated H_2L (formed during alcohol dehydrogenation) and (b) hydrazine as the reagent for coupling reactions. To characterize the above IR-stretching modes, we have performed IR spectral measurement on a similar reaction mixture (B) where hydrazine hydrate was replaced by zinc dust as a reducing agent. Here only one doublet stretching mode was observable at 2872 and 3076 cm^{-1} which indicates that the other

two IR-modes in mixture arose due to the attachment of hydrazine hydrate to the central nickel centre (N-H stretching mode of free hydrazine appears[38] as a singlet at 3332 cm^{-1}). Furthermore, a third reaction mixture (C), which is identical to that of (A), but contained D_8-benzylalcohol in place of H_8-benzylalcohol was then examined using hydrazine hydrate as the reactant. Here the NH stretching frequencies of coordinated hydrazines appeared at 2931 and 3029 cm^{-1} while the N-D stretching frequencies of the reduced ligand (D_2L) appeared[26] at 2105 and 2203cm^{-1} (Figure 2). Thus it may be concluded that hydrazine is activated via coordination with the catalyst (Ni^{II}-complex) to facilitate the coupling reaction. The proposed catalytic cycle is as follows.

Scheme 4. Proposed catalytic cycle



CONCLUSION:

In conclusion, we have introduced the first example of ligand redox-controlled direct synthesis of azines by one-pot coupling[39-41] of aromatic alcohols and hydrazine hydrate in air using a Ni(II)-complex of a bis-azoaromatic ligand as a catalyst. The working principle of our catalyst is entirely different[42-45] than that of commonly used catalysts. Notably, the catalytic reactions occur in aerobic conditions which have been a challenge to both academia and industry. The reaction encompasses high yield synthesis of a large variety of substrates including one-pot synthesis of industrially important phthalazine via intramolecular coupling of 1,2-benzenedimethanol and hydrazine hydrate. Our future attempts are focused on the design of redox inactive main group metal complexes of this and related azo-ligands for dehydrogenative[46-49] coupling reactions.

EXPERIMENTAL SECTION:

Materials. $[Ni(H_2O)_6]Cl_2$ was purchased from Merck, India. Alcohols were purchased from either Sigma-Aldrich or Alfa Aesar. All other reagents and chemicals were obtained from commercial sources and were used without further purifications. Solvents were dried before use.

Physical Measurements. A PerkinElmer Lambda 950 spectrophotometer was used to record UV−Vis spectra. Infrared spectra were obtained using a PerkinElmer 783 spectro-photometer. ESI mass spectra were recorded on a micromass Q-TOF mass spectrometer (serial no. YA 263). GC-MS analyses were performed using a Perkin Elmer CLARUS 680 instrument. NMR spectra were recorded on a Bruker Avance 400 MHz or 500 MHz spectrometer, and $SiMe_4$ was used as the internal standard. A PerkinElmer 240C elemental analyzer was used to collect microanalytical data (C, H, N). X-band EPR spectra were recorded with a JEOL JES-FA200

spectrometer. Room-temperature magnetic moment measurement for the complex **2** was performed with a Gouy balance (Sherwood Scientific, Cambridge, U.K).

X-ray Crystallography. Crystallographic data for the compound **2** are collected in Table S1. Suitable X-ray quality crystal of the complex **2** was obtained by the slow evaporation of a dichloromethane-methanol solution (1:10) of the complex. The data were collected on a Bruker SMART APEX-II diffractometer, equipped with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å), and were corrected for Lorentz polarisation effects. Data for **2**: a total of 10889 reflections were collected, of which 4177 were unique (R_{int} = 0.211), satisfying the I > 2σ(I) criteria and were used in subsequent analysis. The structure was solved by employing the SHELXS-2014 program package[50] and was refined by full-matrix least-squares based on F^2 (SHELXL-2014).[51] All hydrogen atoms were added in calculated positions.

Synthesis. The ligand L and the complex **1** were synthesised and purified as before.[26,52]

Synthesis of [$Ni^{II}Cl_2L(CH_3OH)$], 2. A methanolic solution of 435 mg of the complex **1** was stirred in the presence of 3Å molecular sieves for 4h. During this time the initial dark green colour of the solution turned brownish-green. The crude mass, obtained by evaporation of the solvent in vacuum, was purified by fractional crystallisation from methanol and ether solvent mixture. Finally, the precipitate was recrystallised by slow evaporation of its dichloromethane-methanol (1:10) solution. Its yield and characterisation data are as follows: Brownish-green coloured solid. Yield: 367 mg (82%). Anal. Calcd. for $C_{18}H_{19}Cl_2N_5NiO_2$: C, 46.30; H, 4.10; N, 15.00, Found C, 46.82; H, 3.91; N, 15.12%. Magnetic moment (μ(300K)) = 2.43 B.M. UV−Vis (CH_3OH): λ [nm] (ε, M^{-1} cm^{-1}) = 230 (41272), 275 (63027), 330 (44046): ν (N=N): 1404 cm^{-1}.

General procedure for catalysis. The catalytic reactions were performed following a general procedure. In a round-bottom flask containing 1 mmol substrate in dry toluene (5ml) solvent was mixed with 2-5 mol% of catalyst, 5 mol% of potassium tert-butoxide (^{t}BuOK), 2.1 mmol hydrazine hydrate in the presence of 1g of molecular sieves (3Å). The flask was equipped with a condenser, and the reaction mixture was heated at 80^{o}C with constant stirring in a preheated oil bath. The stirring was continued for 24-30 h depending upon a substrate. The resulting solution was then filtered through Whatman 41 filter paper to remove the catalyst and the molecular sieves. The filtrate was dried under reduced pressure and the organic product was extracted by solvent extraction technique using dichloromethane/water solvent mixture. The dichloromethane solution was collected, and the product was purified on a preparative Silica Gel GF 254 TLC plate using hexane as eluent.

*(1E,2E)-1,2-dibenzylidenehydrazine (**3a**).*[18] The reaction was performed with a 108 mg (1mmol) of benzylalcohol and 2 mol% of catalyst. Yellow solid (85 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45-7.46 (m, 6H), 7.83-7.85 (m, 4H), 8.66 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 128.7, 128.9, 131.3, 134.3, 162.1.

*(1E,2E)-1,2-bis(4-methylbenzylidene)hydrazine (**3b**).*[18] The reaction was performed with a 122 mg (1mmol) of 4-methylbenzylalcohol and 2 mol% of catalyst. Yellow solid (100 mg, 85% yield). ^{1}H NMR (400 MHz, CD_3CN): δ = 2.38 (s, 6H), 7.31 (d, *J* = 8Hz, 4H), 7.75 (d, *J* = 8Hz, 4H), 8.59 (s, 2H). ^{13}C NMR (125 MHz, CD_3CN): δ = 20.6, 128.3, 129.5, 133.3, 139.5, 161.3.

*(1E,2E)-1,2-bis(4-(trifluoromethyl)benzylidene)hydrazine (**3c**).*[53] The reaction was performed with a 176mg (1mmol) of 4-trifluromethyl benzylalcohol and 2 mol% of catalyst. Yellow solid (138 mg, 80% yield). ESI-MS for [**3c**+H]$^+$: calcd. for $[C_{16}H_{10}F_6N_2+H]^+$, 345.0859; found,

345.0851. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.0, 4H), 7.98 (d, *J* = 8.0, 4H), 8.68 (s, 2H) ^{13}C NMR (125 MHz, $CDCl_3$): δ = 125.9, 126.0, 129.0, 133.1, 137.4, 161.0.

*(1E,2E)-1,2-bis(4-chlorobenzylidene)hydrazine (**3d**).*[18] The reaction was performed with a 143 mg (1mmol) of 4-chloro benzylalcohol and 2 mol% of catalyst. Yellow solid (113 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.4, 4H), 7.79 (d, *J* = 8.4, 4H), 8.61 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.3, 129.9, 132.6, 137.5, 161.2.

*(1E,2E)-1,2-bis(4-bromobenzylidene)hydrazine (**3e**).*[54] The reaction was performed with a 187 mg (1mmol) of 4-bromo benzylalcohol and 2 mol% of catalyst. Yellow solid (144 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 8, 4H), 7.81 (d, *J* = 8.4, 4H), 8.65 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.9, 128.8, 130.1, 131.5, 161.1.

*(1E,2E)-1,2-bis(4-iodobenzylidene)hydrazine (**3f**).*[55] The reaction was performed with a 234 mg (1mmol) of 4-iodo benzylalcohol and 2 mol% of catalyst. Yellow solid (175 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.4, 4H), 7.72 (d, *J* = 8.8, 4H), 8.65 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 126.0, 130.1, 132.3, 133.1, 161.3.

*(1E,2E)-1,2-bis(4-methoxybenzylidene)hydrazine (**3g**).*[18] The reaction was performed with a 138 mg (1mmol) of 4-methoxy benzylalcohol and 2 mol% of catalyst. Yellow solid (104 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 6H), 7.03 (d, *J* = 8.8Hz, 4H), 7.82 (4H, *J* = 8.8, 4H), 8.62 (s, 2H).

*(1E,2E)-1,2-bis(2-methoxybenzylidene)hydrazine (**3h**).*[54] The reaction was performed with a 138 mg (1mmol) of 2-methoxy benzylalcohol and 2 mol% of catalyst. Yellow solid (110 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 3.89 (s, 6H), 6.95 (d, *J* = 8.4Hz, 2H), 7.01 (m 2H), 7.41

(m2H), 8.11 (d, *J* = 7.5Hz, 2H), 9.08 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8, 111.4, 121.0, 123.1, 127.5, 132.5, 157.6, 159.3.

*(1E,2E)-1,2-bis(3-methoxybenzylidene)hydrazine (**3i**).*[18] The reaction was performed with a 138 mg (1 mmol) of 3-methoxy benzylalcohol and 2 mol% of catalyst. Yellow solid (107 mg, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.88 (s, 6H), 7.02 (m, 2H), 7.35 (m, 4H), 7.44 (s, 2H), 8.62 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.5, 112.1, 118.1, 122.1, 129.9, 135.6, 160.1, 162.0.

*(1E,2E)-1,2-bis(pyridin-2-ylmethylene)hydrazine (**3j**).*[3] The reaction was performed with a 109 mg (1mmol) of 2-pyridine methanol and 5 mol% of catalyst. Yellow solid (73 mg, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ =7.29-7.32 (m, 2H), 7.74 (t, *J*=7.5 2H), 8.08 (d, *J*=8, 2H), 8.63 (s, 2H), 8.67 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 122.5, 125.1, 136.6, 150.0, 152.9, 162.1.

*(1E,2E)-1,2-bis(pyren-1-ylmethylene)hydrazine (**3k**).*[56] The reaction was performed with a 232 mg (1mmol) of 1-pyrene methanol and 5 mol% of catalyst. Yellow solid (194 mg, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ =8.09-8.31 (m, 14H), 8.49 (m, 2H), 9.05 (d, 2H), 9.56 (s, 2H).

*Phthalazine (**3l**).*[28] The reaction was performed with a 138 mg (1mmol) of 1,2-benzenedimethanol and 10 mol% of catalyst. Brownish yellow solid (68 mg, 52% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.94-7.97 (m, 4H), 9.54 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 126.4, 126.7, 132.8, 151.2 .

Controlled reactions:

a. Reaction between complex 1 and hydrazine hydrate and H_8-benzylalcohol. In a round-bottom flask, 1 mmol H_8-benzylalcohol in dry toluene (5ml) solvent was mixed with 1mmol of catalyst, 2 mmol hydrazine hydrate, and 1g of molecular sieves (3Å). The flask was attached to a schelnk line, and the reaction mixture was stirred at 320K under argon atmosphere. The stirring was continued for 4h, and the solution was subjected to IR spectral analysis.

b. Reaction between complex 1 and zinc and H_8-benzylalcohol. In a round-bottom flask, 1 mmol H_8-benzylalcohol in dry toluene (5ml) solvent was mixed with 1mmol of catalyst, 1 mmol of zinc dust, and 1g of molecular sieves (3Å). The flask was attached to a schelnk line, and the reaction mixture was stirred at 320K under argon atmosphere. The stirring was continued for 4h, and the solution was subjected to IR spectral analysis.

c. Reaction between complex 1 and hydrazine hydrate and D_8-benzylalcohol. In a round-bottom flask, 1 mmol D_8-benzylalcohol in dry toluene (5ml) solvent was mixed with 1mmol of catalyst, 2 mmol hydrazine hydrate, and 1g of molecular sieves (3Å). The flask was attached to a schelnk line and the reaction mixture was stirred at 320K under argon atmosphere. The stirring was continued for 4h and the solution was subjected to IR spectral analysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

CCDC number 1819227 contains the crystallographic data of the complex **2.**

Crystallographic details of complex **2** and copies of NMR spectra of the products are collected as supporting information (PDF).

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Huisgen, R.: Cycloadditions - definition, classification, and characterization. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 321-8.

(2) Kuriyama, Y.; Nagata, N.; Yoshida, K.: Continuous manufacture of ketazine as an intermediate for hydrazine hydrate. Mitsubishi Gas Chemical Company, Inc., Japan. US Patent

US5986134A, 1997. Abstact. A process for continuously and stably synthesizing a ketazine from hydrogen peroxide, ammonia and methyl ethyl ketone in the presence of a solution containing a catalyst. The process comprises removing sec-butyl alcohol by distillation from methyl ethyl ketone, which is reused by circulation. Also a process for preparing a hydrazine hydrate which comprises hydrolyzing the ketazine. By circulating unreacted ketone, accumulation of impurities in the circulated ketone can be prevented to obtain a high yield of the ketazine and the hydrazine hydrate, for a long period of time.

(3) Safari, J.; Gandomi-Ravandi, S.: Structure, synthesis and application of azines: a historical perspective. *RSC Adv.* **2014**, *4*, 46224-46249.

(4) Schirmann, J. P.; Tellier, P.; Mathais, H.; Weiss, F.: Azines. Ugine Kuhlmann . 1973; pp 19. Abstract: Method azine mixture for preparing the formula: (I) and hydrazone of formula: (II) wherein R1, R2, R3 and R4, identical or different, represent either a hydrogen atom or a linear alkyl radical having from 1 to 12 carbon atoms, a branched alkyl or cycloalkyl having from 3 to 12 carbon atoms, or a hydrocarbon radical having from 6 to 12 carbon atoms and comprising an aromatic ring, naphthalene or pyridine, one of R3 or R4 of formulas (II) and (III) may represent a hydrogen atom . The method comprises reacting hydrogen peroxide with a mixture of ammonia and a primary or secondary amine. (III) in the presence of a carbonyl compound (IV) (IV) and a catalyst selected from the group consisting of selenium, selenium dioxide, alkali or alkaline earth metal selenite, selenium trioxide, selenic acid and alkali and alkaline earth selenates. Azines (I) and hydra zones (II), the joint production is the first object of the present invention, are useful synthetic agents, which may include hydrolyzed according to known methods, to obtain the corresponding hydrazines or salts thereof with release of the carbonyl compound which can be recycled.

(5) Khodair, A. I.; Bertrand, P.: A new approach to the synthesis of substituted 4-imidazolidinones as potential antiviral and antitumor agents. *Tetrahedron* **1998**, *54*, 4859-4872.

(6) Veena, K.; Ramaiah, M.; Shashikaladevi, K.; Avinash, T. S.; Vaidya, V. P.: Synthesis and antimicrobial activity of asymmetrical azines derived from naphtho[2,1-b]furan. *J. Chem. Pharm. Res.* **2011**, *3*, 130-135.

(7) Bell, T. W.; Papoulis, A. T.: Ion-selective hydrazone-azine tautomerization of a fourteen-membered macrocyclic ligand. *Angew. Chem.* **1992**, *104*, 792-4 (See also Angew. Chem., Int. Ed. Engl., 1992, 31, 749-51).

(8) Chen, G. S.; Wilbur, J. K.; Barnes, C. L.; Glaser, R.: Stereochemistry and stereoelectronics of azines. 5. Push-pull substitution versus intrinsic or packing related N-N gauche preferences in azines. Synthesis, crystal structures and packing of asymmetrical acetophenone azines. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2311-17.

(9) Glaser, R.; Chen, G. S.; Anthamatten, M.; Barnes, C. L.: Comparative analysis of crystal structures of E,E-configured para-substituted acetophenone azines with halogen, oxygen, nitrogen and carbon functional groups. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1449-58.

(10) Goodall, G. W.; Hayes, W.: Advances in cycloaddition polymerizations. *Chem. Soc. Rev.* **2006**, *35*, 280-312.

(11) Wagner-Jauregg, T.: Reactions of azines and imines (azomethines, Schiff bases) with dienophiles. *Synthesis* **1976**, *6*, 349-73.

(12) Xiong, Y.; Yao, S.; Driess, M.: Unusual [3+1] Cycloaddition of a Stable Silylene with a 2,3-Diazabuta-1,3-diene versus [4+1] Cycloaddition toward a Buta-1,3-diene. *Organometallics* **2010**, *29*, 987-990.

(13) Alahakoon, S. B.; Thompson, C. M.; Nguyen, A. X.; Occhialini, G.; McCandless, G. T.; Smaldone, R. A.: An azine-linked hexaphenylbenzene based covalent organic framework. *Chem. Commun.* **2016**, *52*, 2843-2845.

(14) Dalapati, S.; Jin, S.; Gao, J.; Xu, Y.; Nagai, A.; Jiang, D.: An Azine-Linked Covalent Organic Framework. *J. Am. Chem. Soc.* **2013**, *135*, 17310-17313.

(15) Li, Z.; Feng, X.; Zou, Y.; Zhang, Y.; Xia, H.; Liu, X.; Mu, Y.: A 2D azine-linked covalent organic framework for gas storage applications. *Chem. Commun.* **2014**, *50*, 13825-13828.

(16) Hopkins, J. M.; Bowdridge, M.; Robertson, K. N.; Cameron, T. S.; Jenkins, H. A.; Clyburne, J. A. C.: Generation of Azines by the Reaction of a Nucleophilic Carbene with Diazoalkanes: A Synthetic and Crystallographic Study. *J. Org. Chem.* **2001**, *66*, 5713-5716.

(17) Schirmann, J.-P.; Bourdauducq, P.: Hydrazine. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA, 2000.

(18) Bauer, J. O.; Leitus, G.; Ben-David, Y.; Milstein, D.: Direct Synthesis of Symmetrical Azines from Alcohols and Hydrazine Catalyzed by a Ruthenium Pincer Complex: Effect of Hydrogen Bonding. *ACS Catal.* **2016**, *6*, 8415-8419.

(19) Das, U. K.; Ben-David, Y.; Diskin-Posner, Y.; Milstein, D.: N-Substituted Hydrazones by Manganese-Catalyzed Coupling of Alcohols with Hydrazine: Borrowing Hydrogen and Acceptorless Dehydrogenation in One System. *Angew. Chem., Int. Ed.* **2018**, *57*, 2179-2182.

(20) Hanson, S. K.; Wu, R.; Silks, L. A.: Mild and Selective Vanadium-Catalyzed Oxidation of Benzylic, Allylic, and Propargylic Alcohols Using Air. *Org. Lett.* **2011**, *13*, 1908-1911.

(21) Crabtree, R. H.: Homogeneous Transition Metal Catalysis of Acceptorless Dehydrogenative Alcohol Oxidation: Applications in Hydrogen Storage and to Heterocycle Synthesis. *Chem. Rev.* **2017**, *117*, 9228-9246.

(22) Lane, E. M.; Uttley, K. B.; Hazari, N.; Bernskoetter, W.: Iron-catalyzed amide formation from the dehydrogenative coupling of alcohols and secondary amines. *Organometallics* **2017**, *36*, 2020-2025.

(23) Daw, P.; Ben-David, Y.; Milstein, D.: Direct Synthesis of Benzimidazoles by Dehydrogenative Coupling of Aromatic Diamines and Alcohols Catalyzed by Cobalt. *ACS Catal.* **2017**, *7*, 7456-7460.

(24) Gunanathan, C.; Milstein, D.: Bond Activation and Catalysis by Ruthenium Pincer Complexes. *Chem. Rev.* **2014**, *114*, 12024-12087.

(25) Khalafi-Nezhad, A.; Panahi, F.: Ruthenium-Catalyzed Synthesis of Benzoxazoles Using Acceptorless Dehydrogenative Coupling Reaction of Primary Alcohols with 2-Aminophenol under Heterogeneous Conditions. *ACS Catal.* **2014**, *4*, 1686-1692.

(26) Sengupta, D.; Bhattacharjee, R.; Pramanick, R.; Rath, S. P.; Saha Chowdhury, N.; Datta, A.; Goswami, S.: Exclusively Ligand-Mediated Catalytic Dehydrogenation of Alcohols. *Inorg. Chem.* **2016**, *55*, 9602-9610.

(27) Sengupta, D.; Ghosh, P.; Chatterjee, T.; Datta, H.; Paul, N. D.; Goswami, S.: Ligand-Centered Redox in Nickel(II) Complexes of 2-(Arylazo)pyridine and Isolation of 2-Pyridyl-Substituted Triaryl Hydrazines via Catalytic N-Arylation of Azo-Function. *Inorg. Chem.* **2014**, *53*, 12002-12013.

(28) Kessler, S. N.; Wegner, H. A.: One-Pot Synthesis of Phthalazines and Pyridazino-aromatics: A Novel Strategy for Substituted Naphthalenes. *Org. Lett.* **2012**, *14*, 3268-3271.

(29) Weiss, C. J.; Das, P.; Miller, D. L.; Helm, M. L.; Appel, A. M.: Catalytic Oxidation of Alcohol via Nickel Phosphine Complexes with Pendant Amines. *ACS Catalysis* **2014**, *4*, 2951-2958.

(30) Maji, M.; Chakrabarti, K.; Paul, B.; Roy, B. C.; Kundu, S.: Ruthenium(II)-NNN-Pincer-Complex-Catalyzed Reactions Between Various Alcohols and Amines for Sustainable C-N and C-C Bond Formation. *Adv. Synth. Catal.* **2018**, *360*, 722-729.

(31) Musa, S.; Ackermann, L.; Gelman, D.: Dehydrogenative cross-coupling of primary and secondary alcohols. *Adv. Synth. Catal.* **2013**, *355*, 3077-3080.

(32) Mukherjee, A.; Nerush, A.; Leitus, G.; Shimon, L. J. W.; Ben David, Y.; Espinosa Jalapa, N. A.; Milstein, D.: Manganese-Catalyzed Environmentally Benign Dehydrogenative Coupling of Alcohols and Amines to Form Aldimines and H2: A Catalytic and Mechanistic Study. *J. Am. Chem. Soc.* **2016**, *138*, 4298-4301.

(33) Li, F.; Sun, C.; Wang, N.: Catalytic acceptorless dehydrogenative coupling of arylhydrazines and alcohols for the synthesis of arylhydrazones. *J. Org. Chem.* **2014**, *79*, 8031-9.

(34) Maier, G.; Nuyken, O.; Losert, K.: Polymers by [3 + 2] cycloaddition. 6. Polyureas with novel structure elements. *Macromol. Chem. Phys.* **1994**, *195*, 2057-72.

(35) Allan, F. J.; Allan, G. G.: Pyridinaldazines. *J. Org. Chem.* **1958**, *23*, 639-40.

(36) de Almeida, L. R.; Carvalho, P. S.; Napolitano, H. B.; Oliveira, S. S.; Camargo, A. J.; Figueredo, A. S.; de Aquino, G. L. B.; Carvalho-Silva, V. H.: Contribution of Directional Dihydrogen Interactions in the Supramolecular Assembly of Single Crystals: Quantum Chemical and Structural Investigation of C17H17N3O2 Azine. *Cryst. Growth Des.* **2017**, *17*, 5145-5153.

(37) Sordakis, K.; Tang, C.; Vogt, L. K.; Junge, H.; Dyson, P. J.; Beller, M.; Laurenczy, G.: Homogeneous Catalysis for Sustainable Hydrogen Storage in Formic Acid and Alcohols. *Chem. Rev.* **2018**, *118*, 372-433.

(38) Sacconi, L.; Sabatini, A.: The infrared spectra of metal(II)-hydrazine complexes. *J. Inorg. Nucl. Chem.* **1963**, *25*, 1389-93.

(39) Chen, Z.; Lu, B.; Ding, Z.; Gao, K.; Yoshikai, N.: α-Palladation of Imines as Entry to Dehydrogenative Heck Reaction: Aerobic Oxidative Cyclization of N-Allylimines to Pyrroles. *Org. Lett.* **2013**, *15*, 1966-1969.

(40) Srimani, D.; Balaraman, E.; Gnanaprakasam, B.; Ben-David, Y.; Milstein, D.: Ruthenium pincer-catalyzed cross-dehydrogenative coupling of primary alcohols with secondary alcohols under neutral conditions. *Adv. Synth. Catal.* **2012**, *354*, 2403-2406, S2403/1-S2403/21.

(41) Taddei, M.; Mura, M. G.; Rajamaeki, S.; De Luca, L.; Porcheddu, A.: Palladium-Catalysed Dehydrogenative Generation of Imines from Amines. A Nature-Inspired Route to Indoles via Cross-Couplings of Amines with Arylhydrazines. *Adv. Synth. Catal.* **2013**, *355*, 3002-3013.

(42) Gunanathan, C.; Milstein, D.: Applications of acceptorless dehydrogenation and related transformations in chemical synthesis. *Science* **2013**, *341*, 1229712.

(43) Garg, J. A.; Chakraborty, S.; Ben-David, Y.; Milstein, D.: Unprecedented iron-catalyzed selective hydrogenation of activated amides to amines and alcohols. *Chem. Commun.* **2016**, *52*, 5285-5288.

(44) Elangovan, S.; Neumann, J.; Sortais, J.-B.; Junge, K.; Darcel, C.; Beller, M.: Efficient and selective N-alkylation of amines with alcohols catalyzed by manganese pincer complexes. *Nat. Commun.* **2016**, *7*, 12641pp.

(45) Mellmann, D.; Sponholz, P.; Junge, H.; Beller, M.: Formic acid as a hydrogen storage material - development of homogeneous catalysts for selective hydrogen release. *Chem. Soc. Rev.* **2016**, *45*, 3954-3988.

(46) Fujita, K.-i.; Yoshida, T.; Imori, Y.; Yamaguchi, R.: Dehydrogenative Oxidation of Primary and Secondary Alcohols Catalyzed by a Cp*Ir Complex Having a Functional C,N-Chelate Ligand. *Org. Lett.* **2011**, *13*, 2278-2281.

(47) Tseng, K.-N. T.; Kampf, J. W.; Szymczak, N. K.: Mechanism of N,N,N-amide ruthenium(II) hydride mediated acceptorless alcohol dehydrogenation: Inner-sphere β-H elimination versus outer-sphere bifunctional metal-ligand cooperativity. *ACS Catal.* **2015**, *5*, 5468-5485.

(48) Espinosa-Jalapa, N. A.; Kumar, A.; Leitus, G.; Diskin-Posner, Y.; Milstein, D.: Synthesis of Cyclic Imides by Acceptorless Dehydrogenative Coupling of Diols and Amines Catalyzed by a Manganese Pincer Complex. *J. Am. Chem. Soc.* **2017**, *139*, 11722-11725.

(49) Llabres-Campaner, P. J.; Ballesteros-Garrido, R.; Ballesteros, R.; Abarca, B.: Straight Access to Indoles from Anilines and Ethylene Glycol by Heterogeneous Acceptorless Dehydrogenative Condensation. *J. Org. Chem.* **2018**, *83*, 521-526.

(50) Sheldrick, G. M.: SHELXL 97. Program for the refinement of crystal structures; University of Göttingen; Göttingen, Germany, 1997., 1997.

(51) Sheldrick, G. M.: Crystal structure refinement with SHELXL. *Acta Crystallogr., Sect. C: Struct. Chem.* **2015**, *71*, 3-8.

(52) Ghosh, P.; Samanta, S.; Roy, S. K.; Demeshko, S.; Meyer, F.; Goswami, S.: Introducing a New Azoaromatic Pincer Ligand. Isolation and Characterization of Redox Events in Its Ferrous Complexes. *Inorg. Chem.* **2014**, *53*, 4678-4686.

(53) Kallitsakis, M.; Loukopoulos, E.; Abdul-Sada, A.; Tizzard, G. J.; Coles, S. J.; Kostakis, G. E.; Lykakis, I. N.: A Copper-Benzotriazole-Based Coordination Polymer Catalyzes the Efficient One-Pot Synthesis of (N'-Substituted)-hydrazo-4-aryl-1,4-dihydropyridines from Azines. *Adv. Synth. Catal.* **2017**, *359*, 138-145.

(54) Lee, B.; Lee, K. H.; Cho, J.; Nam, W.; Hur, N. H.: Synthesis of Azines in Solid State: Reactivity of Solid Hydrazine with Aldehydes and Ketones. *Org. Lett.* **2011**, *13*, 6386-6389.

(55) Nenajdenko, V. G.; Shastin, A. V.; Korotchenko, V. N.; Varseev, G. N.; Balenkova, E. S.: A novel approach to β-chloro-β-fluorostyrenes. *Eur. J. Org. Chem.* **2003**, 302-308.

(56) Martínez, R.; Espinosa, A.; Tárraga, A.; Molina, P.: New Hg2+ and Cu2+ Selective Chromo- and Fluoroionophore Based on a Bichromophoric Azine. *Org. Lett.* **2005**, *7*, 5869-5872.