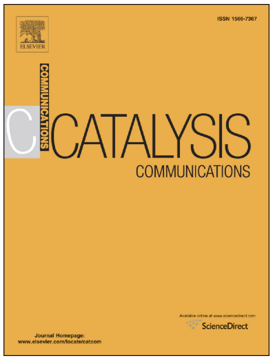

Unprecedented synthesis of symmetrical azines from alcohols and hydrazine hydrate using nickel based NNN-pincer catalyst: An experimental and computational study

Bilal Ahmad Shiekh, Damanjit Kaur, Sachin Kumar Godara

PII: S1566-7367(19)30058-5
DOI: https://doi.org/10.1016/j.catcom.2019.02.024
Reference: CATCOM 5635

To appear in: *Catalysis Communications*

Received date: 20 December 2018
Revised date: 31 January 2019
Accepted date: 22 February 2019

Please cite this article as: B.A. Shiekh, D. Kaur and S.K. Godara, Unprecedented synthesis of symmetrical azines from alcohols and hydrazine hydrate using nickel based NNN-pincer catalyst: An experimental and computational study, Catalysis Communications, https://doi.org/10.1016/j.catcom.2019.02.024

Unprecedented Synthesis of Symmetrical Azines from Alcohols and Hydrazine Hydrate using Nickel Based NNN-Pincer Catalyst: An Experimental and Computational study.

Bilal Ahmad Shiekh*, Damanjit Kaur, Sachin Kumar Godara
Department of Chemistry, UGC Sponsored Centre of Advanced Studies-I, Guru Nanak Dev University, Amritsar India-143005.
*E-mail: bilal.ahmad459@gmail.com.

Abstract

Azines are having widespread applications in both industry as well as synthetic chemistry. Thus new catalytic synthetic protocols are desirable as they are greener alternatives than traditional methods of synthesis. Thus, herein a novel earth abundant nickel based NNN-pincer catalyst Ni(BPEA)(Cl_2) is synthesized for the first time for the direct transformation of alcohols and hydrazine hydrate into symmetrical azines. This catalytic reaction is accompanied by dehydrogenative coupling of alcohols and hydrazine hydrate and is carried out in presence of a base. Theoretical calculations supported by experimental evidence have been performed for understanding the mechanistic insights of the reaction.

Keywords: Symmetrical azines; Ni-pincer catalyst; Alcohol dehydrogenation; Hydrazine hydrate; Computational study.

1. Introduction

Azines constitute a stereochemically important class of compounds with wide range of applications in nonlinear optical materials [1], liquid crystals as twisted-nematic displays [2] and in synthetic chemistry [3]. Because of their modulating behavior towards bio-receptors they serve as important scaffolds for drug designing and pharmocolgy [4]. They are also important candidates showing anti-bacterial, anti-malarial, anti-viral, anti-tumor and anti-inflammatory properties [5a]. Furthermore, azine-based receptors are used as fluorescent imaging reagents in living cells which are affected with Hg^{2+} [5b]. The aromatic substituted azines hold a great promise in dye industries as coloring agents [6]. Because of conjugation stopping ability, these compounds can be used as conjugation switches in tunable optical and mechano-optical molecular devices. Recently, azines have been used in synthesis of covalent organic frameworks (COF) which possess high sensitivity in chemosensing [7] and are used in light induced hydrogen gas generation [8].

There are various conventional approaches of symmetrical azine synthesis including direct treatment of hydrazine with carbonyl compounds [9]. In recent years, transition metal catalysts have gained attention for symmetrical azine synthesis as they are greener bond formation alternatives compared to conventional methods. Amongst these, the first transition metal catalyst was reported by Michelin in 2002 which involves decomposition of 9-diazofluorene in the presence of Pt(0) complex $[Pt(C_2H_4)(PPh_3)_2]$ [10]. Recently in 2016 Milstein reported a Ru-based pincer catalyst which catalyzes the acceptorless dehydrogenative coupling of alcohols with hydrazine hydrate [11]. More recently in 2018 while our work was under process, Goswami reported a Ni-pincer catalyst for the direct transformation of alcohols into azines [12]. First two metal-catalyzed methods of symmetrical azine synthesis involve rare and precious transition metals. Therefore, it's much desirable to synthesize cheap and earth abundant transition metal complexes for such important chemical transformations.

So in context of prolonged sustainability and cost efficiency we decided to explore the dehydrogenative coupling of alcohols with hydrazine hydrate using a more earth abundant and less costly transition metal complexes. Thus, herein we report Ni-based NNN-pincer catalyst Ni(BPEA)(Cl_2) for one-pot transformation of alcohols into azines which as per our knowledge has not been reported before (Scheme 1). It's worthy to mention here that the direct usage of hydrazine hydrate is challenging [11]. The above synthesized pincer complex is stable in both solid and in dissolved state. The mechanistic details of the reaction were investigated by carrying DFT studies without searching for alternate pathways.

2. Experimental

2.1 Catalyst Synthesis

The synthesis of the catalyst was carried out in three steps, first step involves the synthesis of N,N-bis(2-{pyrid-2-ylethyl})hydroxylamine (**BPEHA**) from vinylpyridine and hyrdoxylamine hydrochloride, the second step involves synthesis of N,N-bis(2-{pyrid-2-yl}ethyl)amine (**BPEA**) by reduction of **BPEHA** and in the final step catalyst is synthesised from BPEA using anhydrous $NiCl_2$. See the supplementary data for detailed information.

Synthesis of N,N-bis(2-{pyrid-2-ylethyl})hydroxylamine: A mixture of 2-vinylpyridine (6.571 g, 62.5 mmol) and hydroxylamine hydrochloride (2.1715 g, 31.25 mmol) was kept for 48 hours in solvent free environment [13,14]. The resulting mixture was basified with $NaHCO_3$ solution. The water layer was washed several times with $CHCl_3$ (5x25 ml) and the organic extracts collected were dried over sodium sulfate. The mixture was filtered, concentrated and then mixed with 100 ml hexane. The white coloured product separated out and was purified by recrystallization using chloroform and hexane. The product obtained was characterized by ^1H NMR and $^{13}C\{^1H\}$NMR spectroscopy. Yield 3.67 g, 42%.

Synthesis of N,N-bis(2-{pyrid-2-yl}ethyl)amine: BPEHA (2.0 g, 8.22 mmol) was reduced using Zn dust and dilute HCl in absolute ethyl alcohol with constant stirring at 313 K temperature for 10 hours [13]. Then the mixture was neutralised with dilute NaOH solution followed by washing with chloroform. After separating from water, the organic layer was dried in sodium sulfate and then filtered. The solvent was removed by rotary evaporator under reduced pressure and a pure paye yellow oil collected was characterised by ^1H and $^{13}C\{^1H\}$NMR spectroscopy. Yield 1.83 g, 92%.

Synthesis of bis(2-{pyrid-2-yl}ethyl)amine, Ni(BPEA)(Cl_2): In 100 ml schlenk flask, BPEA (1.0 g, 4.4 mmol), anhdrous $NiCl_2$ (0.57 g, 4.4 mmol) and 75 ml dry THF were mixed under nitrogen atmosphere. The reaction mixture was heated at 313 K temperature with contineous stirring for 24 hrs. All volatiles were removed leaving behind a greenish coloured complex at the bottom of the flask which was washed with 50 ml of hexane. The solution was then dried under vacuum to obtain the desired catalyst. Yield 1.41 g, 89.9%.

2.2 X-ray Diffraction Analysis: The crystal suitable for x-ray diffraction analysis was obtained in saturated solution of methanol by slow evaporation of the solvent at room temperature. The solid state representation of the structure thus obtained by x-ray diffraction technique to confirm the mode of coordination is portrayed in Figure 1. The unit cell contains four molecules with with monoclinic space group (*P* 21/*c*). The geometry of the complex resembles trigonal bipyramid in shape with two pyridine rings above and below metal-ligand plane. The Cl which lies above the Ni-ligand plane have a larger bond distance by 0.044 Å compared to the one which lies below plane. The angle between Cl19─Ni1─Cl20 is 124.6°. Furthermore, the N2 forms a stronger bond compared to N6 and N14 of two pyrimidine rings as depicted by their bond distances in the Figure. The x-ray diffraction analysis confirms the structure proposed by spectroscopic data.

3. Results and Discussions

3.1 Exploration of Catalytic Reaction: While exploring the reaction, the pincer precatalyst was found to be inactive for azine synthesis on its own under standard conditions which is due to the saturated coordination at the metal center thus making substrate binding difficult. In order to get an active catalyst, we added $NaBH_4$ and *t*-BuOK to the solution of precatalyst before adding to the reaction mixture containing excess alcohol and hydrazine hydrate which resulted in the formation of azine with the generation of H_2 and water. Encouraged with this attempt, we started searching for standard optimized reaction conditions and it was revealed that the reaction afforded best conversion (almost 75% yield, Table 1) in THF with 3 mol% catalyst loading, 5 mol% $NaBH_4$ (with respect to catalyst), 5 mol% *t*-BuOK (with respect to catalyst) and 80°C temperature for 24 hour time. However, when the catalyst loading was minimized to 1 mol% the conversion of the reactants reduced significantly to 25%. The reaction conditions needed for this catalyst are entirely different than the conditions proposed by other research groups [11,12] which suggest the use of molecular sieves. The scope of this catalytic reaction was analyzed by using various substrates ranging from aliphatic to aromatic ones in order to understand the steric effects of the substrates used (Table 1). The treatment of 1-propanol and 2-propanol with hydrazine hydrate for 24 hours yielded the corresponding azines in almost 60% (entry 1, 2). Similarly, aromatic alcohols like benzyl alcohol and 2-hydroxybenzyl alcohol afforded the aromatic azines in 68 and 73% yield, respectively (entry 3, 6) regardless of any increase in catalyst loadings or reaction timings. Likewise, α-Methylbenzyl alcohol showed similar efficiency and yielded azine in 72% (entry 4). 4-Methoxybenzyl alcohol showed the good results and gave azine with 74% yield (entry 5).

3.2 Optimization of Reaction Conditions: To optimize the reaction conditions of azine synthesis by Ni-pincer catalyst common reaction conditions such as temperature, solvent, effect of changing percentage of $NaBH_4$, K^tOBu and PNI etc. were monitored (Supplementary data). The reaction between benzyl alcohol and hydrazine hydrate was used as model reaction. In the first few attempts the effect of temperature and solvent was checked (entries 1-8) and on the basis of solvent screening results, THF gave best results (entry 3) as compared to rest of the solvents at 80° C temperature. The other solvents used were dioxane, DMF, DMSO, acetonitrile and toluene but all of them showed no significant results. The solubility of the catalyst was very low in toluene and hence gave poor results and hence we choose THF as best solvent. Changing the bases under the identical conditions didn't gave the good results either (entry 7-11). Amongst the bases used NEt_3 and Cs_2O_3 showed no activity at all. Furthermore, decreasing the temperature decreased the yield of the product dramatically (entries 9-13). Next the effect of percentage of base, $NaBH_4$ and catalyst loading were tested (entries 14-23) and it was delightful to see that a remarkable improvement in yield was observed by varying the percentage of base and $NaBH_4$ and best results were obtained for entry 22 in which the product yield was obtained in ~65% yield after 24 hours time.

3.3 Cyclic Voltammetry Studies: In order to study the mechanistic insights of the catalytic reaction of nickel complex, cyclic voltammetry of the reaction mixture (2 ml) was carried out in 0.1 M tetra-n-butyl ammonium hexafluorophosphate in THF with scan rate 100-300 mV s^{-1}. The sample studied showed a well-defined voltammogram due to the electron transfer either to metal or free ligand and is shown in the Figure 2. The voltammogram thus obtained shows two reduction potentials -1.58 V and -2.32 V, both of which are irreversible. Despite being irreversible in nature these potentials correspond to Ni(II) and Ni(I). The lower reduction potential peaks designate the ease with which an electron is added to the metal complex. In addition to these reduction potentials, there is an additional reversible reduction potential peak at -3.4 V which is probably due to the free ligand in the reaction mixture.

3.4 Computational Mechanistic Study

For understanding the mechanistic insights and characteristic features of this catalytic reaction, the Density Functional Theory (DFT) calculations were performed at wB97xD [15] level of theory (See the supplementary data for more details). As illustrated in Figure 3, the entire catalytic transformation occurs in two steps, the one in which dehydrogenation of alcohol takes place resulting in the formation of carbonyl compound and the second step involving reaction between the carbonyl compound and the hydrazine hydrate to form azine. The mechanistic insights of this two-step chemical transformation studied by DFT studies revealed that reaction proceeds through the formation of an encounter complex, **RALCT** between the active catalyst, **PNi** and alcohol, **RACL**. The formation of this encounter complex between the alcohol and the catalyst is endergonic in nature with free energy equal to 2.05 kcal mol^{-1} as portrayed in Figure 3. In the next step, the dehydrogenation of alcohol takes place in a concerted fashion by simultaneous transfer hydrogenation to the metal center and the **N** of ligand through metal-ligand cooperation. In the next step the liberation of carbonyl compound takes place through a turnover limiting transition state, **TS1** with $\Delta \boldsymbol{G}^{\#} = 27.95$ kcal mol^{-1}.The formation of **TS1** is the rate-determining step and the thermodynamic driving force for catalytic chemical transformation. The liberation of carbonyl also forms a Ni(I) oxidized state complex, **HPNi**. In the last and the final step, the carbonyl compound reacts with the hydrazine hydrate to form the desired azine. The formation of Ni(I)-**HPNi** has been confirmed by carrying out cyclic voltammetry of the reaction mixture in THF as discussed in the experimental section . The voltammogram shows two irreversible reduction potentials at -1.58 and -2.32 V which are ascribed to for Ni(II) and Ni(I), respectively. The formation of azine through dehydrogenation of alcohols was also previously suggested by other research groups [11,12].

4. Conclusions

In summary, an earth abundant, cheap and significantly valuable pincer catalyst for the first time has been reported for the convenient one-pot azine synthesis. Not only it adds to the limited stock of transition metal catalysts of azine synthesis, but it also provides an efficient strategy to synthesize the symmetrical azines. Notably, the products obtained were in good yield (75 %) with moderate usage of base. From the DFT perspective, the reaction proceeds via dehydrogenation of alcohols supported by the cyclic voltammetry which shows two irreversible reduction potentials at -1.58 V for Ni(II) and at -2.32 V for Ni(I). The reaction between the carbonyl compound formed and the hydrazine hydrate forms azines and the overall activation energy of the reaction is 27.59 kcal mol^{-1}. Further work is under process to find out the further scope of the catalyst synthesized.

Acknowledgments

This work was financially supported by UGC, Govt. of India under UGC-BSR scheme as SRF (Senior Research Fellow) vide notification number, NO.F.25-1/2013-14(BSR)/5-27/2007(BSR).

Supplementary data

Supplementary material

References

[1] V.A. Sauro, M.S. Workentin, Evaluation of the Extent of Conjugation in Symmetrical and Asymmetrical Aryl-Substituted Acetophenone Azines Using Electrochemical Methods, J. Org. Chem. 66 (2001) 831–838.

[2] R.K. Deun, T.N. Parac-Vogt, K.V. Hecke, L.V. Meervelt, K. Binnemans, D. Guillonb, B. Donnio, Liquid-Crystalline Azines Formed by the Rare-Earth Promoted Decomposition of Hydrazide ‘‘habbe’’ Ligands: Structural and Thermal Properties, J. Mater. Chem. 13 (2003) 1639–1645.

[3] R. Centore, B. Panunzi, A. Roviello, A. Sirigu, P. Villano, Synthesis, Characterisation, and Phase Behaviour of Some Azines with Potential Optical Nonlinearities of Second Order, Mol. Cryst. Liq. Cryst. 275 (1996) 107.

[4] N.V. Madhusudana, R. Shashidhar, S. Chandrasekhar, Orientational Order in Anisaldazine in the Nametic Phase, Mol. Cryst. Liq. Cryst. 13 (1971) 61.

[5] E.E. Schweizer, Z. Cao, A.L. Rheingold, M. Bruch, Reactions of Azines. 16. Preparation of 6-(Phenylmethylene)-5H-Pyrazolo[1,5-d][2,4]Benzoxazepines, 5H, 7H-Pyrazolo[1,5-d][2]Benzazepin-6-one, and Indeno[2,3-c]Pyridine-3,9-Diones, J. Org. Chem. 58 (1993) 4339.

[6] C. Sousa, C. Freire, B. de Castro, Synthesis and Characterization of Benzo-15-Crown-5 Ethers with Appended N_2O Schiff Bases, Molecules 8 (2003) 894–900.

[7] I. Picon-Ferrer, F. Hueso-Urena, N.A. Illan-Cabeza, S.B. Jimenez-Pulido, J.M. Martınez-Martos, M.J. Ramırez-Exposito, et al, Chloro-fac-Tricarbonylrhenium (I) Complexes of Asymmetric Azines Derived from 6-Acetyl-1,3,7-Trimethylpteridine-2,4(1H,3H)-dione

with Hydrazine and Aromatic Aldehydes: Preparation, Structural Characterization and Biological Activity against Several Human Tumor Cell Lines, J. Inorg. Biochem. 103 (2009) 94–100.

[8] V.B. Kurteva, S.P. Simeonov, M. Stoilova-Disheva, Symmetrical Acyclic Aryl Aldazines with Antibacterial and Antifungal Activity, Pharmacol. Pharm. 2 (2011) 1–9.

[9] J. Jayabharathi, V. Thanikachalam, A. Thangamani, M. Padmavathy, Synthesis, AM_1 Calculation, and Biological Studies of Thiopyran-4-one and their Azine Derivatives, Med. Chem. Res. 16 (2007) 266–279.

[10] J. Easmon, G. Purstinger, G. Heinisch, T. Roth, H.H. Fiebig, W. Holzer, W. Jager, M. Jenny, J. Hofmann, Synthesis, Cytotoxicity, and Antitumor Activity of Copper(II) and Iron(II) Complexes of 4N-Azabicyclo[3.2.2]nonane Thiosemicarbazones Derived from Acyl Diazines, J. Med. Chem. 44 (2001) 2164–2171.

[11] M. Suresh, A.K. Mandal, S. Saha, E. Suresh, A. Mandoli, R.D. Liddo, P.P. Parnigotto, A. Das, Azine-Based Receptor for Recognition of Hg^{2+} Ion: Crystallographic Evidence and Imaging Application in Live Cells, Org. Lett. 12 (2010) 5406–5409.

[12] M.M. Habashy, M.S. Antonious, B.A. El-sayed, M.S.A. Abdel-mottaleb, Fluorescence Properties of Some Substituted Acyclic Azines, J. Lumin. 36 (1986) 173–176.

[13] S. Dalapati, S. Jin, J. Gao, Y. Xu, A. Nagai, D. Jiang, An Azine-Linked Covalent Organic Framework, J. Am. Chem. Soc. 135 (2013) 17310−17313.

[14] V.S. Vyas, F. Haase, L. Stegbauer, G. Savasci, F. Podjaski, C. Ochsenfeld, B.V. Lotsch, A Tunable Azine Covalent Organic Framework Platform for Visible Light-Induced Hydrogen Generation, Nat. Commun. 6:8508 doi: 10.1038/ncomms9508 (2015).

[15] J. Safari, S. Gandomi-Ravandi, Highly Efficient Practical Procedure for the Synthesis of Azine Derivatives Under Solvent-Free Conditions, Synth. Commun. 41 (2011) 645–651.

[16] D.E. Applequist, H. Babad, Reactions of Diphenyldiazomethane and 2-Diazopropane with Zinc Iodide, J. Org. Chem. 27 (1962) 288–290.

[17] C.J. Abelt, J.M. Pleier, Stereoselective Azine Formation in the Decomposition of Phenyldiazomethanes, J. Am. Chem. Soc. 111 (1989) 1795–1799.

[18] S.N. Shah, N.K. Chudgar, Thermolysis of Semicarbazones to the Corresponding Azines Through Reactive N-Substituted Isocyanate Intermediates, Molecules 5 (2000) 657–664.

[19] Y.F. Wang, G.H. Lonca, S. Chiba, PhI(OAc)2-Mediated Radical Trifluoromethylation of Vinyl Azides with Me_3SiCF_3, Angew. Chem. 126 (2014) 1085–1089.

[20] M.L. Trudell, N. Fukada, J.M. Cook, Hydrazine-Mediated One-Pot Amination-Oxidation Reaction: Facile Synthesis of 4-Amino-.beta.-Carbolines and 4-Aminoisoquinolines, J. Org. Chem. 52 (1987) 4293–4296.

[21] R. Bertani, M. Biasiolo, K. Darini, R.A. Michelin, M. Mozzon, F. Visentin, L. Zanotto, Catalytic Transformations of Diazo Compounds Promoted by Platinum(0) and Dicationic Platinum(II) Complexes, J. Organomet. Chem. 642 (2002) 32–39.

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

[23] M. Chakraborty, D. Sengupta, T. Saha, S. Goswami, Ligand Redox-Controlled Tandem Synthesis of Azines from Aromatic Alcohols and Hydrazine in Air: One-Pot Synthesis of Phthalazine, J. Org. Chem. 83 (2018) 7771−7778.

[24] S.A. Leaver, M. Palaniandavar, C.A. Kilner, M.A. Halcrow, A new synthesis of bis(2-{pyrid-2-yl}ethyl)amine (L^{H}) from bis(2-{pyrid-2-yl}ethyl)hydroxylamine (L^{OH}), and the copper-dependent reduction of L^{OH} to L^{H}, Dalton Trans. (2003) 4224−4225.

[25] W.B. Christopher, A. Cetin, N.V. Barone, C.J. Ziegler, Transition Metal Coordination Chemistry of N,N-Bis(2-{pyrid-2-ylethyl})hydroxylamine, Inorg. Chem. 47 (2008) 7114−7120.

[26] J.D. Chai, M. Head-Gordon, Long-Range Corrected Hybrid Density Functionals with Damped Atom–Atom Dispersion Corrections, Phys. Chem. Chem. Phys. 10 (2008) 6615−6620.

Graphical abstract

Scheme 1. Recent Examples and our Newly Designed Ni-Pincer Catalyst for Symmetrical Azine Synthesis.

Figure 1. Cyclic voltammogram of reaction mixture in THF solution confirming the presence of Ni(II) and Ni(I) oxidation states of Ni-pincer complex in the solution (scan rate 300 mV S^{-1}).

Figure 2. X-ray structure of the complex Ni(BPEA)(Cl_2) with all H-atoms omitted for clarity (thermal ellipsoids are drawn with 50% probability). Ni1─Cl20=2.30 Å, Ni1─Cl19=2.34 Å, Ni1─N14=2.17 Å, Ni1─N2=2.10 Å, Cl19─Ni1─Cl20=124.6º, N2─Ni─Cl19=121.8º, N14─Ni1─N6=176.6º, N2─Ni1─N14=90.9º, N2─Ni1─Cl19=113.5º.

Figure 3. Proposed reaction mechanism for symmetrical azine synthesis from alcohols and hydrazine hydrate using Ni-pincer complex. All the given values are reported in kcal mol^{-1}.

Table 1. One-pot synthesis of symmetrical azines from alcohols and hydrazine hydrate using nickel catalyst.[a]

[a] Optimized Reaction Conditions: Alcohols (3 mmol), hydrazine hydrate (1.6 mmol), PNi catalyst (3 mol %), $NaBH_4$ (5 mol %) with respect to catalyst, *t*-BuOK (5 mol %) with respect to the catalyst in THF (5 ml). The reaction was heated under reflux in oil bath at 80°C for 24 hours time. [b] The yields under parenthesis are GC-MS yields while as the values outside parenthesis are isolated yields.

Highlights:

- Highly effective protocol is unveiled for the synthesis of symmetrical azines.
- The protocol uses an Nickel based NNN-pincer catalyst.
- Catalytic reaction shows best results in THF in presence of base, K^{t}OBu.
- The catalytic reaction proceeds through dehydrogenation of alcohols.
- Mechanism involves formation of both Ni(I) and Ni(II) complexes during the reaction.

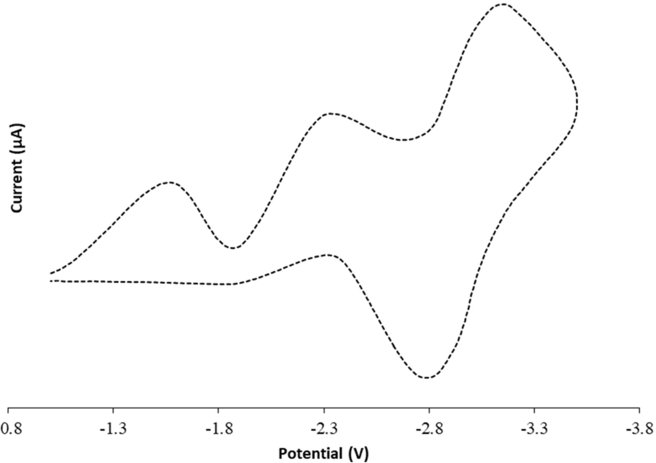

Figure 1

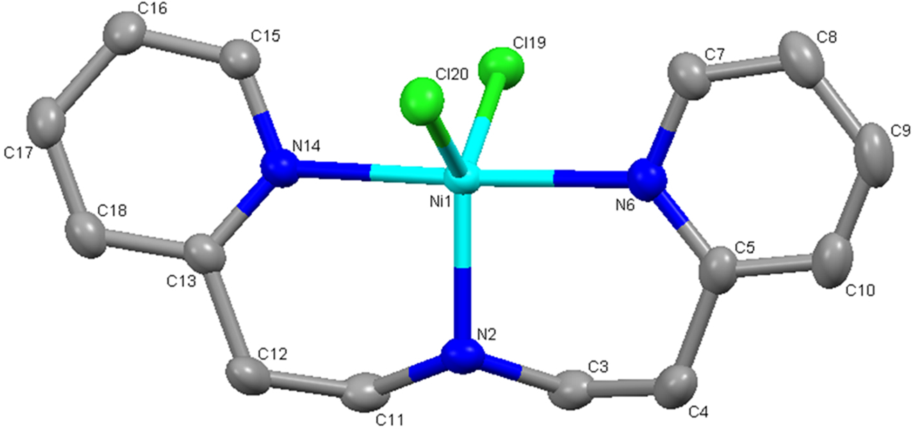
C16
C15
Cl19
Cl20
C7
C8
C9
C17
N14
Ni1
N6
C18
C5
C13
C10
N2
C12
C3
C4
C11

Figure 2

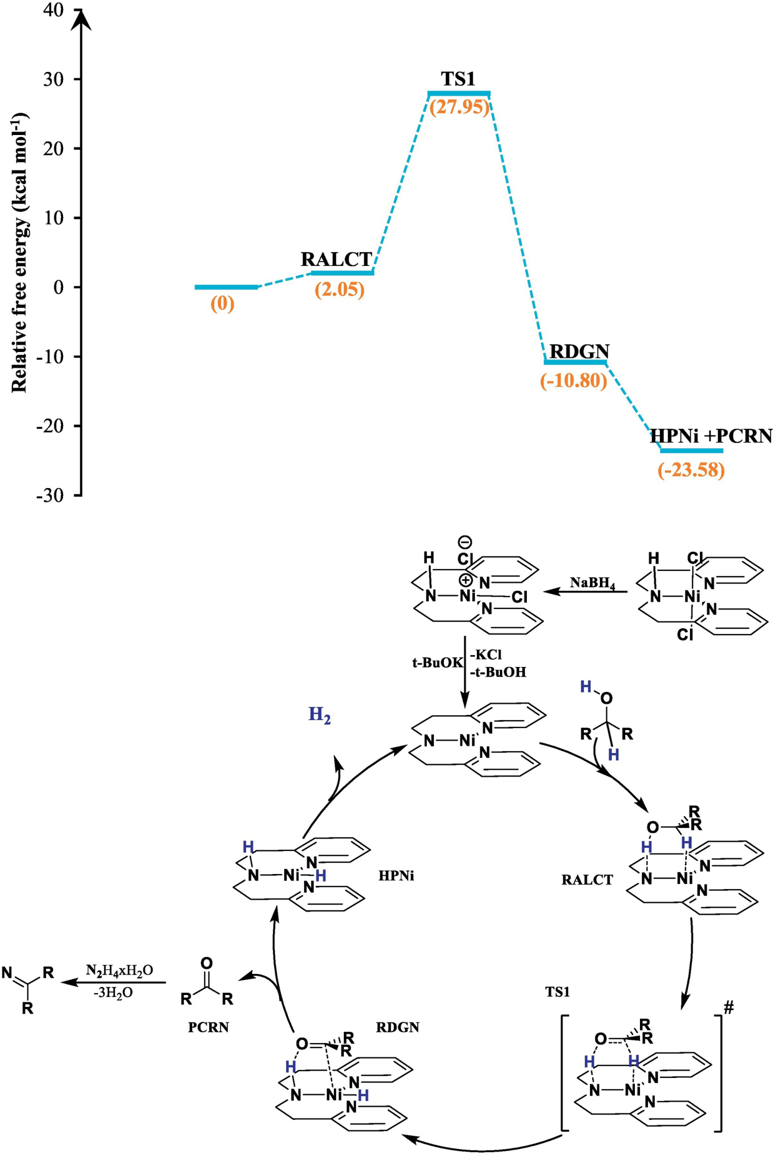
40
30
20
10
0
-10
-20
-30
Relative free energy (kcal mol-1)
(0)
RALCT
(2.05)
TS1
(27.95)
RDGN
(-10.80)
HPNi +PCRN
(-23.58)
NaBH4
t-BuOK
-KCl
-t-BuOH
H2
HPNi
RALCT
TS1
#
RDGN
PCRN
N2H4xH2O
-3H2O
H
Cl
N
Ni
R
O

Figure 3