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Synthesis of tetra-substituted imidazoles and 2-imidazolines by Ni(0)-catalyzed dehydrogenation of benzylic-type imines

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Abstract
Ni(0)-catalyzed dehydrogenation of benzylic-type imines was performed to yield asymmetrical tetra-substituted imidazoles and 2-imidazolines. This was achieved with a single operational step while maintaining good selectivity and atom economy. The catalytic systems shows low to moderate tolerance for fluoro-, trifluoromethyl-, methyl-, and methoxy-substituted benzylic-type imines. In addition, the substitution pattern at the N-heterocyclic products was easily controlled by the proper selection of R-groups in the starting organic substrates. Based on experimental observations, we propose a reaction mechanism in which benzylic C(sp³)-H bond activation and insertion steps play pivotal roles in this nickel-catalyzed organic transformation.

Keywords: nickel, imidazole, imidazoline, catalysis.

Introduction
Imidazoles and 2-imidazolines are very important five-membered heterocyclic compounds in natural products, pharmaceutical, and materials sciences. They constitute platforms for biologically active molecules¹ and advanced materials.² In addition, they have broad applications as ligands in coordination chemistry,³ and their imidazolium salts are widely used as N-heterocyclic carbene precursors.⁴ Moreover, these imidazolium-type species are currently being investigated as ionic
liquids in the search for environmentally friendly solvents for novel organic transformations. Typically, polysubstituted imidazoles and 2-imidazolines are prepared from multicomponent condensation reactions between carbonyl compounds and nitrogen sources such as ammonia, ammonium salts, and amines, providing a plethora of synthetic methodologies towards these valuable organic compounds. Nevertheless, such procedures usually involve harsh reaction conditions, for instance, high temperatures and the use strong dehydration or oxidizing agents.

In recent years, transition-metal-catalyzed organic transformations based on Zr, Rh, Pd, Ag, Cu, Yb, and La-complexes have emerged as powerful tools for obtaining both polysubstituted imidazoles and 2-imidazolines, enabling novel synthetic procedures that normally require a single operational step and simple organic building blocks as starting materials. In the search for complementary synthetic methodologies involving more abundant and cheaper transition metal catalysts, our group reported a Ni(0)-catalyzed synthesis of triaryl-imidazols from highly available aromatic nitriles under both neat and hydrogen pressure conditions using [(dippe)Ni(µ-H)]₂ (dippe = 1,2-bis(diisopropylphosphino)ethane) as the Ni(0)-catalyst precursor (Scheme 1a). To explain the formation of the imidazol ring, the formation of imines by a Ni(0)-catalyzed hydrogenation pathway was postulated (Scheme 1a, step a). These imines would then react with nitriles to form the organic product through a Ni(0)-catalyzed dehydrogenation process (Scheme 1a, step b).

As a continuation of our interest in the synthesis of five-membered N-heterocyclic species, we envisioned the formation of tetra-substituted products by replacing the nitrile building block by a second equivalent of imine during the Ni(0)-catalyzed dehydrogenation step (Scheme 1b). This would lead to new atom-economical processes towards highly functionalized imidazoles, in which readily available starting materials are used with C(sp³)-H bond activation as a key step. The activation and subsequent functionalization of C-H bonds represent major challenges in homogenous catalysis in the search for sustainable catalytic organic transformations. However, the application of these methodologies usually requires stoichiometric amounts of bases and external oxidants such as Cu or Ag salts along with quinone-derivates.
We report the catalytic dehydrogenation of benzylic-type imines to produce tetra-substituted imidazol rings using commercially available [Ni(COD)$_2$] (COD = 1,5-cyclooctadiene) complex and organophosphorous ligands as a catalytic system, without the use of additives. In addition, we show that this system not only provides a method to prepare functionalized imidazoles, but also their partially saturated analogs 2-imidazolines as a result of incomplete catalytic dehydrogenation (Scheme 1b). This process becomes part of the very recently reported Ni(II)-catalyzed reaction between 1,2-dicarbonyl groups and benzylamines by Maiti, and the Fe(II)-catalyzed oxidation of benzylic-type amines by Tsuji to afford tetra-substituted five-membered heterocyclic compounds (Scheme 1c). Such reactions also involve dehydrogenation pathways of imines, but the current reaction offers the use of both catalytic amounts of Ni-complexes and a lack of toxic reaction media such as CCl$_4$.

**Scheme 1.** Reaction design.
Results and discussion

In order to establish the best reaction conditions for the Ni(0)-catalytic system, we assessed the reactivity of the model substrate N-benzylidenbezylation (NBB) with catalytic amounts (2 % mol) of [Ni(COD)_2] in the presence of either mono- or diphosphines with different steric and electronic properties using an initial catalyst concentration of 34 mM. The metal-to-ligand ratios shown in Table 1 were used. We investigated the effect of these ligands in THF at 190 ºC for 48 h.

As shown in Table 1, the use of either mono- or diphosphines in combination with [Ni(COD)_2] produced the expected tetra-substituted imidazol 1-Benzyl-2,4,5-triphenyl-imidazole B in addition to the corresponding partially saturated heterocycle 1-Benzyl-2,4,5-triphenyl-4,5-dihydro-imidazole A, which arises from the incomplete catalytic dehydrogenation of NBB. Notably, phosphine ligands have important effects on the catalytic system in terms of both substrate conversion and selectivity, and interesting trends emerge. In the case of monophosphines, σ-donor/π-acceptor ligands such as PPh_3 and P(OPh)_3 (Table 1, entries 4 and 5) produce higher yields of A (10-13 %) and B (7-11 %), along with moderate NBB conversions (30-37 %) in comparison to those afforded by exclusive σ-donor ligands (Table 1, entries 1-3). Moreover, the π acceptor character seems to be a determinant property, as PPh_3 and P(OPh)_3 have almost the same effect, although their cone angles are different. This could also be seen when comparing the effect of PEt_3, P^Bu_3, and PCy_3 ligands (Table 1, entries 1-3). Another interesting feature is the sole use of [Ni(COD)_2] (Table 1, entry 12), which gave almost the same catalytic activity as the [Ni(COD)_2]/π-acceptor ligand system. Since COD ligands are easily replaced from the Ni(0) coordination sphere, we believe that NBB probably behaves as both ligand and substrate in this system, and it seems to have good π acceptor properties due to the presence of a low-energy π* C-N orbital.

Notably, opposite electronic effects were observed in the case of diphosphines. The use of ethane-bridged σ-donor ligands such as dippe, dtbpe, and dctype (Table 1, entries 7-9) afforded higher yields of products A (30-45 %) and B (6-20 %), in addition to better substrate conversions (60-79 %) in comparison to those produced by the analogous σ-donor/π-acceptor ligand dppe
Therefore, to gain insight into the role of the ethane scaffold, we investigated the effect of ferrocenyl-bridged phosphines featured with isopropyl and phenyl groups on the phosphorous atoms (Table 1, entries 10 and 11). Both ligands have similar effects on the Ni(0)-center and led to low NBB conversions and product yields. This indicates that the ethane bridge in the ligands is a key feature for good catalytic activity.

Table 1. Ligand screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Metal:ligand ratio</th>
<th>NBB Conv. (%)</th>
<th>A Yield (%)</th>
<th>B Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PEt₃</td>
<td>2</td>
<td>15</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>P'Bu₃</td>
<td>2</td>
<td>25</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>PCy₃</td>
<td>2</td>
<td>20</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>PPh₃</td>
<td>2</td>
<td>37</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>P(OPh)₃</td>
<td>2</td>
<td>30</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>dppe</td>
<td>1</td>
<td>30</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>dippe</td>
<td>1</td>
<td>60</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>dtbpe</td>
<td>1</td>
<td>60</td>
<td>38</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>dcype</td>
<td>1</td>
<td>79</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>dppf</td>
<td>1</td>
<td>11</td>
<td>10</td>
<td>0.5</td>
</tr>
<tr>
<td>11</td>
<td>dippf</td>
<td>1</td>
<td>15</td>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>12</td>
<td>No-ligand added</td>
<td>-</td>
<td>43</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>

*Chromatographic yield. Complete conversion percentage of NBB is calculated by summing A, B and additional product C. Information for species C is included in the SI.
Once establishing that the [Ni(COD)\textsubscript{2}]/dcype system provides the best catalytic performance (Table 1, entry 9), we investigated different ligand-to-metal ratios and the effect of solvents, reaction temperatures, and initial catalyst concentrations to improve activity (Table 2). We screened three different solvents with different polarities.\textsuperscript{16} Surprisingly, despite the remarkable polarity difference between benzonitrile and mesitylene (Table 2, entries 1 and 2), they gave similar results in terms of both NBB conversion (78-81 %) and product yields of A (35-37 %) and B (18 %). Nevertheless, the catalytic activity in these solvents was low in compassion to that in THF (Table 1, entry 9). Despite having almost the same polarity as mesitylene, toluene (Table 2, entry 3) gave better results: 81 % NBB conversion, 15 % yield of B, and a notable 59 % yield of A. Thus, we selected the last solvent to continue our studies.

The impact of performing the reaction at temperatures lower than 190 ºC was assessed in toluene to establish milder reactions conditions while maintaining good catalytic activity (Table 2, entries 4 and 5). At 170 ºC, there is good NBB conversion (71 %) and similar product yields of A (53 %) and B (11 %) in comparison to the reaction at 190 ºC, reflecting an increase in selectivity towards the heterocyclic compounds. Importantly, upon lowering the reaction temperature to 150 ºC (Table 2, entry 5), the catalytic activity of the Ni(0)/dcype system decreased. We not only observed poor NBB conversion (30 %), but also rather low yields of A (22 %) and B (1 %). In addition, even under these milder reaction conditions, we observed minute amounts of black metal deposits, presumably from Ni(0)-catalyst decomposition. Considering this, we assessed the effect of different metal-to-ligand ratios to avoid Ni(0)-complex decomposition in toluene at 150 ºC (Table 2, entries 5-7). There is an important effect on the catalyst performance when increasing the metal-to-ligand ratio from 1:1 to 1:2 (Table 2, entries 5 and 6), and black Ni(0) deposits were not detected in such experiments.\textsuperscript{17} In addition, better NBB conversion and A and B yields were obtained. Interestingly, using a 1:4 metal-to-ligand ratio had almost the same result as the 1:1 ratio (Table 2, entries 5 and 7). This could be attributed to competition between dcype and NBB for coordination sites in the Ni(0)-catalyst.
In order to increase the catalyst performance, we examined the effect of its initial concentration on the reaction. The experiments in Table 1 and entries 1-7 in Table 2 were conducted with a 34 mM initial concentration of the \([\text{Ni(COD)}]_{x}/\text{dcype}\) system. When increasing the concentration to 68 mM (Table 2, entry 8), a remarkable effect on the catalyst performance was observed.
observed. Both good NBB conversion and A yield were obtained (71% and 56 %, respectively), but the imidazole B yield remained rather low (11 %) despite this improvement. The impact of the initial catalyst concentration turns out to be very important. For instance, with an initial concentration of 4.2 mM, there is no reaction at all (Table 2, entry 9), which is the same result as running the experiment without Ni(0)-catalyst (Table 2, entry 10). Further efforts were made to increase the catalyst performance. We did an experiment using neat (no solvent) reaction conditions (Table 2, entry 11) and longer reaction time (Table 2, entry 12) under the conditions shown in Table 2, entry 8. Unfortunately, none of these changes increased the reaction yields.

Considering these results, we establish that 48 h of reaction using the reaction condition shown in Table 2, entry 8 are the optimized reaction conditions for further studies.

Since there is a major interest in medicinal chemistry in the synthesis of functionalized heterocyclic molecules, we decided to use the optimized reactions conditions to examine the reaction scope of this process with a variety of dimethylamino-, methoxy-, hydroxyl-, methyl-, phenyl-, bromo-, fluoro-, and trifluoromethyl-functionalized NBB substrates in addition to pyridyl-, naphthyl- and alkyl-NBB derivatives were studied.

As shown in Scheme 2, low to moderate reaction yields of the corresponding tetra-substituted 2-imidazoline-type products A1-A8 were obtained in the case of methoxy- (5 %), fluoro- (7-48 %), trifluoromethyl- (24 %), and methyl-NBB (19-26 %) substrates (S1-S8). However, imidazol-type products were not observed in any case. On the other hand, alkyl-, naphthyl-, and pyridyl-NBB derivatives, and bromo-, phenyl-, dimethylamino-, and hydroxyl-functionalized NBB substrates (S9-S19, see SI), did not produced the corresponding heterocyclic products. In the particular case of alkyl-NBB derivatives, substrate conversion was not observed. This indicated that benzylic motifs at the imines play a central role in the reactivity towards dehydrogenation pathways.
Scheme 2. Reaction scope*

The results in Scheme 2 point out the remarkable features of the developed catalytic system. Since there are two different functionalization sites at the imine scaffold (R_1 and R_2), not only did the use of substrates where R_1 ≠ R_2 lead to asymmetrical 2-imidazoline products, but also, it was possible to easily control the substitution pattern in these products by the proper selection of R-groups. For instance, the use of 2-fluorophenyl as R_1 in S1 gives the 2-imidazoline A1 functionalized with these groups at the 2- and 5-positions. On the other hand, if 2-fluorophenyl is
used instead as R\(^2\) (S7), this yields A7 as the product, with 2-fluorophenyl at the N-CH\(_2\)- and 4-positions. These changes in the substitution pattern could also be seen upon comparing products A2 and A8.

It is particularly striking the influence that fluorine atoms at different positions in the aromatic motifs in R\(^1\) and R\(^2\) (S1 and S2, S7 and S8) have on the formation of the corresponding 2-imidazolines. We speculate that 2-fluoro functionalized substrates generally give higher product yields due to its stability towards feasible side reaction such as C-F activation. This stability may arise from the steric effects associated to the presence of dcype ligand coordinated at the metal center during such processes.

A mechanistic proposal for the Ni(0)-catalyzed process is depicted in Scheme 3. We include the following considerations for this proposal: (i) the use of a strong σ-donor ligand (dcype), (ii) the high catalyst concentration required, and (iii) high selectivity towards 2-imidazoline product compared to the imidazol using NBB as substrate.

Since COD ligands are easily replaced from Ni(0)-centers by phosphines, we postulate the formation of the catalytic active species [(dcype)\(_2\)Ni] by reaction of Ni(COD)\(_2\) with two equivalents of dcype in Step a. From there, a ligand substitution reaction by NBB takes place to form the 16-electron π-complex 2 (Step b).\(^{20}\) This Ni(0)-species undergoes benzylic C-H bond activation through oxidative addition to afford Ni(II)-intermediate 3 (Step c).\(^{21}\) As this kind of oxidative addition process is promoted by electron-rich metal centers, we believe it certainly accounts for the use of strong σ-donor ligands such as dcype.\(^{22}\) However, considering the ligand screening in Table 1, we also believe that dcype not only increases the electron density at the Ni-metal center, but also plays a pivotal role in stabilizing Ni(II)-intermediates throughout the catalytic cycle through both steric effects and the ethane backbone. In addition, the formation of intermediate 3 accounts for the lack of reactivity of alkyl-NBB derivatives (See SI). The low stability of [(dcype)Ni(H)(R)] (R = alkyl) intermediates would lead to either decomposition of such intermediates or undesired side reactions.
Scheme 3. Mechanistic proposal

Once intermediate 3 has been formed in Step c, there is an insertion reaction by a second equivalent of NBB into the Ni(II)-C bond affording a new C-C bond in species 4 (Step d). The high catalyst concentration needed for this transformation accounts for a possible bimolecular nature of such step also showing the rather poor nucleophilic character of Ni-C bonds. Then, the five-membered heterocyclic ring is assembled in intermediate 5 by an intramolecular insertion pathway in Step e. From there, we propose that β-hydride elimination followed by H₂ reductive elimination and re-coordination of the produced 2-imidazoline species affords the Ni(0)-intermediate 6 (Step f). Product A is then finally released in Step g by a ligand substitution reaction with dcype closing the catalytic cycle.
In order to explain the formation of the complete unsaturated product B, we propose that intermediate 6 undergoes C-H bond activation at the imidazoline framework yielding intermediate 7 (Step h). Then, 7 releases product B in Step i through β-hydride elimination, concomitant reductive elimination of H₂, and re-coordination of dcype to the Ni(0) center, forming the initial [(dcype)₂Ni] complex. Since the B yield was always low starting from NBB, we believe that imidazoline C-H bond activation in Step h is a very slow step in comparison to the release of product A (Step g), perhaps due to steric hindrance at the oxidative addition intermediate 7 between the cyclohexyl units of dcype and the imidazoline heterocycle.

Conclusions

We have shown the additive-free Ni(0)-catalyzed dehydrogenation of benzylic-type imines to yield five-membered heterocyclic compounds. Starting out from N-benzylidenbenzylamine, we obtained the corresponding tetra-substituted 2-imidazoline and the corresponding imidazol in good and moderate yields, respectively. On the other hand, using fluoro-, trifluoromethyl-, methoxy-, and methyl-substituted NBB imines, we observed the sole formation of the asymmetric 2-imidazoline products in low to moderate yields. We have also shown the feasibility of controlling the substitution pattern in these products by carefully selecting the substituents at the starting imine.

We proposed a mechanistic pathway for this transformation based on simple experimental observations. Benzylic C(sp³)-H bond activation of the substrate through oxidative addition and bimolecular insertions into the Ni-C bond formed seemed to be the slow steps. Since both C-H bond activation and functionalization are topical issues, we believe that the current contribution sheds some light on the design of operationally simple and novel methodologies using abundant metal catalysts towards important organic molecules.

Experimental

General Considerations
Unless otherwise noted, all experiments were carried out using standard Schlenk techniques in a double-vacuum argon manifold or in a glovebox (MBraun Unilab) under high-purity argon (Praxair 99.998) with controlled concentrations of water and oxygen (<1 ppm). Catalytic experiments were carried out in Schlenk tubes. All purchased liquid reagents were of reagent grade and degassed before use. All solvents were dried and deoxygenated by standard procedures. NBB and S1-S10 substrates were prepared by reported methods. [Ni(COD)₂] (COD = 1,5-cyclooctadiene) were purchased from Strem and stored in the glovebox for further use. dippe (1,2-bis(diisopropylphosphino)ethane) was prepared from 1,2-bis(dichloro)ethane (Aldrich) and a solution of isopropylmagnesium chloride (2.0 M, Aldrich) in THF. PEt₃, dppe (1,2-bis(diphenylphosphino)ethane), dippf (1,1′-bis(diisopropylphosphino)ferrocene), and dppf (1,1′-bis(diphenylphosphino)ferrocene) were purchased from Aldrich and used without further purification. P^Bu₃, PCy₃, P(OPh)₃, dtbpe (1,2-bis(ditertbutylphosphino)ethane), and dcype (1,2-bis(dicyclohexylphosphino)ethane) were purchased from Strem Chemicals and stored in the glovebox for further use. GC-MS determinations were performed using an Agilent 5975C system equipped with a 30-m DB-5MS capillary (0.32-mm i.d.) column.

**General procedure.**

In a typical experiment [Ni(COD)₂] (2.8 mg, 0.010 mmol), NBB (0.1 g, 0.512 mmol) and the corresponding amount of ligand and solvent were placed in a Schlenk tube. The tube was then closed and taken out from the glovebox. Using an oil bath, the tube was heated to the required temperature for 48 h. After this time, the reaction mixture was cooled down to room temperature, exposed to air, and analyzed by GC-MS.

**Reaction Scope**

In a typical experiment, [Ni(COD)₂] (2.8 mg, 0.010 mmol), dcype (8.6 mg, 0.020 mmol), 0.512 mmol of a given substrate, and 0.15 ml of toluene were placed in a Schlenk tube. The tube was then closed and taken out of the glovebox. Using an oil bath, the tube was heated to 150 °C for 48 h.
After this time, the reaction mixture was cooled down to room temperature, exposed to air, and analyzed by GC-MS.

Acknowledgments

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Supplementary Material Available

Figures with selected GC-MS data and additional dehydrogenation experiments. This material is available free of charge via the Internet.

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(10) Imines have been selectively obtained in similar catalytic process by our group, see: P. ZerecerowSilva, I. Jimenez-Solar, M. G. Crestani, A. Arévalo, R. Barrios-Francisco and J. J. García, *Applied Catalysis A: General*, 2009, **363**, 230.


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