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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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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 system 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 appropriate selection of R-groups in the starting organic substrates. Based on experimental observations, we propose a reaction mechanism in which benzylic C(sp^3)–H bond activation and insertion steps play pivotal roles in this nickel-catalyzed organic transformation.

Introduction

Imidazoles and 2-imidazolines are very important five-membered heterocyclic compounds in natural product, pharmaceutical, and materials science. They constitute platforms for biologically active molecules[1] 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.[5] 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 of strong dehydration or oxidizing agents.[6]

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[7] and 2-imidazolines,[8] 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 triarylimidazoles from highly available aromatic nitriles under both neat and hydrogen pressure conditions using $[(dippe)Ni(\mu\text{-}H)]_2$ (dippe = 1,2-bis-(diisopropylphosphino)ethane) as the Ni(0)-catalyst precursor (Scheme 1a).[9] To explain the formation of the imidazole ring, the formation of imines by a Ni(0)-catalyzed hydrogenation pathway was postulated (Scheme 1a, step a).[10] 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(sp^3)–H bond activation as a key step. The activation and subsequent functionalization of C–H bonds represent major challenges in homogeneous 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.[11]

We report the catalytic dehydrogenation of benzylic-type imines to produce tetra-substituted imidazole rings using the

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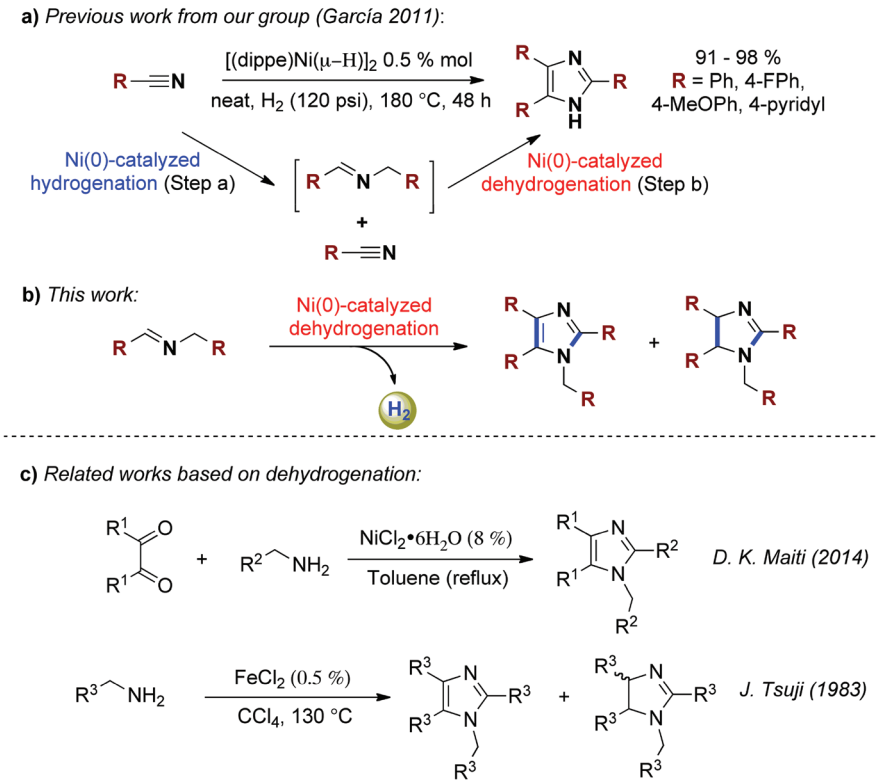


Scheme 1 Reaction design.

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 provides a method to prepare not only 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 Ni(II)-catalyzed reaction between 1,2-dicarbonyl groups and benzylamines that was very recently reported by Maiti[12] and the Fe(II)-catalyzed oxidation of benzylic-type amines that was reported by Tsuji[13] 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.[14]

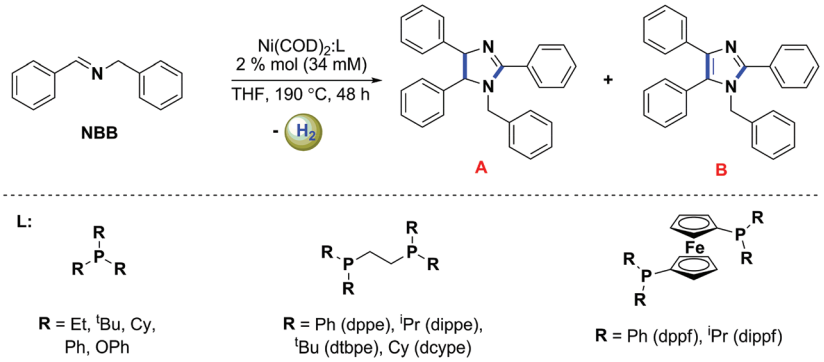
Results and discussion

In order to establish the best reaction conditions for the Ni(0)-catalytic system, we assessed the reactivity of the model substrate *N*-benzylidenebenzylamine (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 °C 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 imidazole 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 with those afforded by exclusive σ-donor ligands (Table 1, entries 1–3). Moreover, the π acceptor character seems to be a determining property, as PPh_3 and $P(OPh)_3$ have almost the same effect, although their cone angles are different.[15] This could also be seen when comparing the effect of PEt_3, P^tBu_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 dcype (Table 1, entries 7–9)

Table 1 Ligand screening[a]



Entry	Ligand	Metal : ligand ratio	NBB conv. (%)	**A** yield (%)	**B** yield (%)
1	PEt_3	1 : 2	15	5	2
2	P^tBu_3	1 : 2	25	8	5
3	PCy_3	1 : 2	20	5	3
4	PPh_3	1 : 2	37	13	7
5	$P(OPh)_3$	1 : 2	30	10	11
6	dppe	1 : 1	30	6	5
7	dippe	1 : 1	60	30	6
8	dtbpe	1 : 1	60	38	12
9	dcype	1 : 1	79	45	20
10	dppf	1 : 1	11	10	0.5
11	dippf	1 : 1	15	3	0.5
12	No-ligand added	—	43	13	8

[a] 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 ESI.

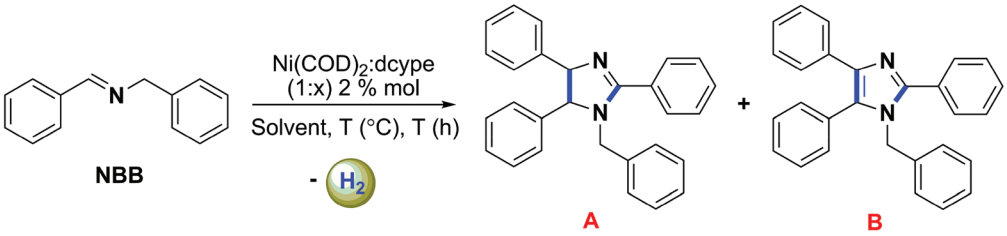
afforded higher yields of products **A** (30–45%) and **B** (6–20%), in addition to better substrate conversions (60–79%) in comparison with those produced by the analogous σ-donor/π-acceptor ligand dppe (Table 1, entry 6). Therefore, to gain insight into the role of the ethane scaffold, we investigated 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.

After establishing that the [$Ni(COD)_2$]/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 in improving activity (Table 2). We screened three different solvents with different polarities.[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 comparison with 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 °C was assessed in toluene to establish milder reactions conditions while maintaining good catalytic activity (Table 2, entries 4 and 5). At 170 °C, there is good NBB conversion (71%) and similar product yields of **A** (53%) and **B** (11%) in comparison with the reaction at 190 °C, reflecting an increase in selectivity towards the heterocyclic compounds. Importantly, upon lowering the reaction temperature to 150 °C (Table 2, entry 5), the catalytic activity of the Ni(0)/dcype system decreased. We observed not only 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 in avoiding Ni(0)-complex decomposition in toluene at 150 °C (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.[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

Table 2 Reaction optimization[a]



Entry	Metal : ligand ratio	Initial catalyst concentration (mM)	Solvent	*T* (°C)	Reaction time (h)	NBB conv. (%)	**A** yield (%)	**B** yield (%)
1	1 : 1	34	Benzonitrile	190	48	81	37	18
2	1 : 1	34	Mesitylene	190	48	78	35	18
3	1 : 1	34	Toluene	190	48	81	59	15
4	1 : 1	34	Toluene	170	48	71	53	11
5	1 : 1	34	Toluene	150	48	30	22	1
6	1 : 2	34	Toluene	150	48	50	39	6
7	1 : 4	34	Toluene	150	48	33	23	2
8[b]	1 : 2	68	Toluene	150	48	71	56	11
9	1 : 2	4.2	Toluene	150	48	0	0	0
10	No catalyst	—	Toluene	150	48	0	0	0
11	1 : 2	Neat	—	150	48	51	46	3
12	1 : 2	68	Toluene	150	72	78	63	14

[a] Chromatographic yields. Complete conversion percentage of NBB is calculated by summing **A**, **B**, and additional product **C**. Information for **C** species is reported in the ESI. [b] Mercury-drop test using the same reaction conditions resulted in no inhibition.

experiments in Table 1 and entries 1–7 in Table 2 were conducted with a 34 mM initial concentration of the [Ni(COD)]/dcype system. When increasing the concentration to 68 mM (Table 2, entry 8), a remarkable effect on the catalyst performance was 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 the 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.

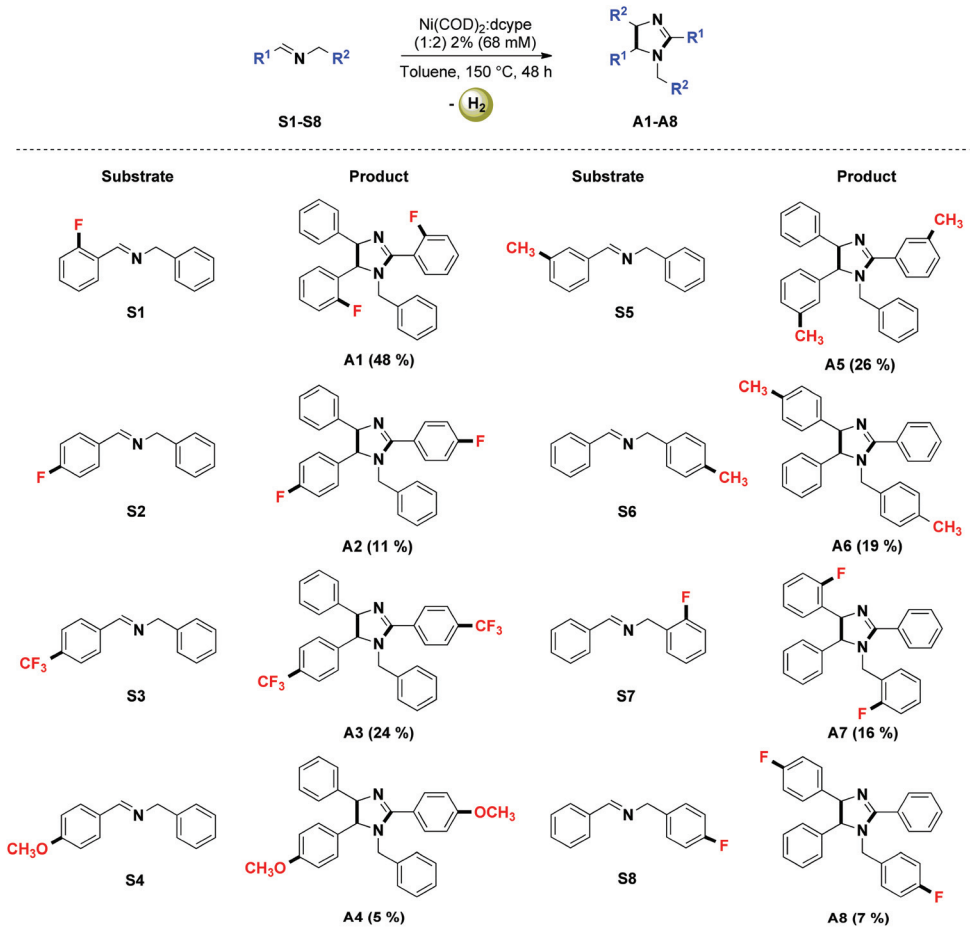
Considering these results, we established that 48 h of reaction using the reaction conditions shown in Table 2, entry 8, are the optimized reaction conditions for further studies.

Since there is a major interest, in medicinal chemistry, in the synthesis of functionalized heterocyclic molecules,[18] 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-, naftyl- and alkyl-NBB derivatives that 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, imidazole-type products were not observed in any case.[19] On the other hand, alkyl-, naftyl-, and pyridyl-NBB derivatives and bromo-, phenyl-, dimethylamino-, and hydroxyl-functionalized NBB substrates (**S9–S19**, see ESI†) did not produce 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.

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 $R^1 \neq R^2$ lead to asymmetrical 2-imidazoline products, but also it was possible to easily control the substitution pattern in these products by the appropriate 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**.

What is particularly striking is 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 their stability towards feasible side reactions such as C–F activation. This stability may arise from the steric effects associ-



Scheme 2 Reaction scope (chromatographic yield).

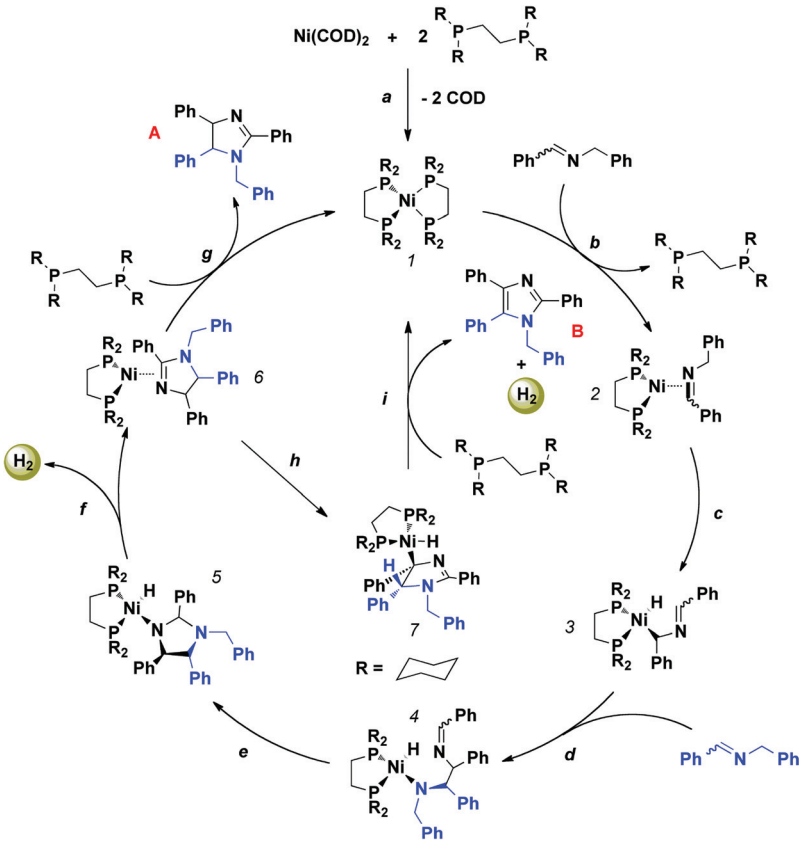
ated with the presence of the dcype ligand coordinated at the metal center during such processes.

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) the high selectivity towards 2-imidazoline product compared to the imidazole using NBB as the 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 that 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 ESI†). The low stability of [(dcype)Ni(H)(R)] (R = alkyl) intermediates would lead to either decomposition of such intermediates or undesired side reactions.

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 steps 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 this, we propose that β-hydride elimination followed by H_2 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 though β-hydride elimination, concomitant reductive elimin-



Scheme 3 Mechanistic proposal.

ation of H_2, and re-coordination of dcype to the Ni(0) center, forming the initial [(dcype)$_2$Ni] 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 with 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 from *N*-benzylidenebenzylamine, we obtained the corresponding tetra-substituted 2-imidazoline and the corresponding imidazole 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(sp^3)–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 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) was 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. PEt_3, 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^tBu_3, PCy_3, $P(OPh)_3$, 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 amounts of the ligand and the 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 place 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.

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