ACS Catalysis

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Synthesis of Amidines and Benzoxazoles from Activated Nitriles with Ni(0) Catalysts

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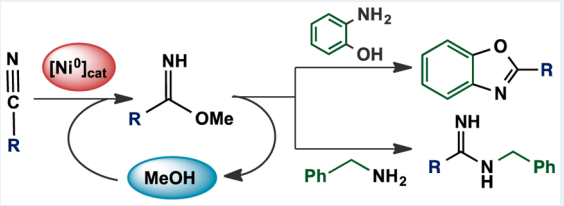
Supporting Information

ABSTRACT: Amidines and 2-substituted benzoxazoles were synthesized from N-heterocyclic nitriles under mild conditions (50 °C, 48 h, two steps) in an atom-economical process that involves addition of methanol, the solvent, to a nitrile moiety to yield a methyl imidate and the subsequent extrusion of solvent in the presence of amines to afford the title compounds. Methyl imidate formation was achieved by developing a new catalytic pathway using $[(dippe)Ni(H)]_2$ (dippe = 1,2-bis(diisopropylphosphino)ethane), $[Ni(cod)_2]$/dppe, or $[Ni(cod)_2]/P(OPh)_3$ (cod = 1,5-cyclooctadiene, dppe = 1,2-bis(diphenylphosphino)ethane, $P(OPh)_3$ = triphenyl phosphite) as the catalyst precursor. Regarding the ligands, for a given substrate, namely 4-cyanopyridine, the best performance for the Ni(0)-catalyzed system was found for the σ-donor bidentate dippe, whereas the monodentate π acceptor $P(OPh)_3$ was less efficient. In relation to the substrates, for a given Ni−dippe system, steric hindrance and, more importantly, substrate electron-withdrawing character control imidate formation and thus the yield of amidines and benzoxazoles.



KEYWORDS: *N-heteroarylcarbonitrile, methanol, nickel, catalysis, methyl imidate, amidine, benzoxazole*

INTRODUCTION

Amidines and benzoxazoles are compounds of general interest found in the structure of natural substances and active ingredients of a variety of drugs.[1] The amidino group is also important in the synthesis of N-heterocyclic compounds, including benzoxazole cores.[2,3] Direct synthesis of amidines from nitriles and primary amines can be accomplished when starting from electron-withdrawing substituted nitriles.[4] Otherwise, stoichiometric amounts of Lewis acids are required. For instance, aluminum and zinc chlorides have been successfully used at high temperatures, and amidine synthesis mediated by copper(I) chloride, La(III) ions, and alkylchloroaluminum amides has been achieved in good yields.[5]

There are examples involving the stoichiometric use of complexes bearing transition-metal centers, typically in high oxidation states, such that reaction with amines is considered as a nucleophilic addition to a coordinated nitrile type process.[6] Amidines from nonactivated alkyl and aryl nitriles can be prepared via a Pinner-type reaction between either anhydrous ethanol or methanol and an acid-insensitive nitrile, since an excess of hydrogen chloride is needed.[7] The afforded imidate hydrochlorides are then allowed to react with primary amines or *o*-aminophenols to yield the corresponding amidines and benzoxazoles, respectively.

In general, amidine synthesis methods suffer from disadvantages such as strongly acidic conditions, high temperatures, or the use of stoichiometric amounts of additives to avoid harsh conditions. Nevertheless, there are examples of the use of catalytic amounts of cationic Ni(II) POCOP pincer-type complexes which have been shown to be useful in the direct addition of amines to nitriles, thus yielding amidines under mild conditions from both cinnamonitrile and 4-cyanostyrene, and morpholine.[8] Another example of the catalytic activity of cationic Ni(II) pincer-type complexes in this transformations is the addition of piperidine to acetonitrile, also under mild conditions.[9] In these two reports the best yields were 34%, 25%, and 68% for the three systems described, respectively, so that the development of alternative methodologies is not undesirable.

With regard to the amidino group two-step synthesis via imidate formation, the main difficulties are related to the synthesis of such an intermediate. Some processes in which imidate formation has been involved include the use of stoichiometric amounts of both trimethylsilane triflate and water in the synthesis of esters from nitriles and aliphatic alcohols.[10] In the case of N-heterocyclic nitriles, only methyl isonicotinimidate and methyl picolinimidate have been successfully prepared from methanol in a zeolite-mediated system in the case of 4-cyanopyridine and in a cerium-oxide-mediated reaction under harsh conditions for 2-cyanopyridine. Nitrile hydration was also observed in the case of 4-cyanopyridine.[11]

Regarding the use of transition-metal centers in the addition of alcohols to nitriles, stoichiometric studies have been reported using high-valent platinum-group metals.[12] For Ni(II) complexes, it is known that phosphines and pyridines readily substitute N-coordinated nitriles, whereas alcohols react with the nitriles in a nucleophilic addition followed by a proton

Received: February 17, 2015
Revised: April 27, 2015
Published: May 4, 2015

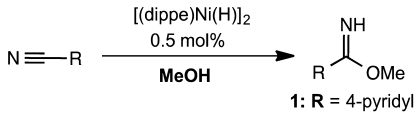
DOI: 10.1021/acscatal.5b00348
ACS Catal. 2015, 5, 3470−3477

transference type process to afford coordinated imidates.[13] The addition of methanol to 2-cyanopyridine coordinated to Ni(II) affords chelated species that are bonded through nitrogen atoms from both pyridine and imidate moieties.[14] Among the scarce catalytic examples of alcohol addition to nitriles, Ru(II) has been used in the synthesis of esters from aliphatic nitriles and alcohols in the presence of water.[15] Catalyzed Ir(III) addition of methanol to benzonitrile has also been reported.[16] To the best of our knowledge there are no reported examples involving the catalytic use of low-valent nickel complexes in the addition of alcohols to aliphatic, aromatic, or heteroaromatic nitriles.

The complex $[(dippe)Ni(\mu\text{-}H)]_2$ (dippe = 1,2-bis-(diisopropylphosphino)ethane) is known to react with both aliphatic and aromatic organonitriles to yield species of the type $[(dippe)Ni(\eta^2\text{-}C,N\text{-}CNR)]$ (R = alkyl, aryl, N-heteroaryl).[17] Such compounds have been shown to be useful in the catalytic hydrogenation of both nitriles and imines, when C═N moieties act as ligands, and in the catalyzed dehydrogenation of benzylic-type imines.[18] These processes have allowed the formation of both amines and imines and also imidazole cores. Another useful transformation known for the low-valent Ni species is the catalytic hydration of aromatic mono- and dinitriles and of 2-, 3-, and 4-cyanopyridines.[19] Inspired by this latter process, we report a new methodology to obtain methyl imidates from bifunctional N-heterocyclic carbonitriles and methanol. These species reacted with benzylamine and *o*-aminophenol under mild conditions to afford amidines and 2-substituted benzoxazoles. Methyl imidate synthesis was achieved through a catalytic pathway using low-valent nickel complexes.

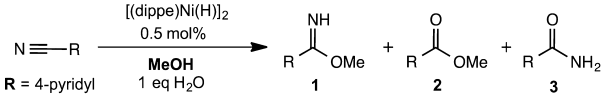
RESULTS AND DISCUSSION

The addition of methanol to N-heterocyclic carbonitriles was carried out first in alcoholic media with 4-cyanopyridine (4Cypy) as the model substrate and using 0.5 mol % of precatalyst $[(dippe)Ni(\mu\text{-}H)]_2$ (eq 1).



(1)

At a given reaction time of 48 h, the temperature was gradually decreased from 180 to 70 °C with no significant increase in conversion (48−51%), but an increase was observed when the reaction temperature was decreased to 50 °C and to room temperature (87−89% of **1**) (for details see Table S1 in the Supporting Information). At 140 °C, a stoichiometric amount of water was added, yielding a mixture of corresponding methyl isonicotinate (**2**), which comes from **1**,[20] and isonicotinamide (**3**) formed directly by nitrile hydration (eq 2).[21] This result is consistent with previous reports on the production of esters from alcohols, nitriles, and water and on nitrile hydration (vide supra).



(2)

Following the target methyl imidate production, the catalytic anhydrous system became selective to **1** below 120 °C.[22] At 70 °C, a control experiment without $[(dippe)Ni(\mu\text{-}H)]_2$ yielded none of the products mentioned. Additionally, in another control experiment carried out at 140 °C, the corresponding methyl imidate was detected but only in 7% yield (for more details, see the Supporting Information), thus suggesting the need for a catalyst to achieve this transformation at low temperature and with high yield.

From the experiments described above, two regions of temperature dependence can be identified: namely 70 °C and above and 50 °C and below. To shed more light on this, a $^{31}P\{^1H\}$ NMR study was performed using stoichiometric amounts of reagents in THF-d_8 (Figure 1). The spectra show two doublets at 67.4 and 79.4 ppm ($^2J_{P-P}$ = 64 Hz) assigned to the complex $[(dippe)Ni(\eta^2\text{-}N,C\text{-}4Cypy)]$ (**4**) that appear first at room temperature. Additionally, there are two doublets at 73.0 and 83.0 ppm ($^2J_{P-P}$ = 24 Hz) that correspond to the complex [(dippe)Ni(CN)(4-pyridyl)] (**5**). Complex **5** stems from **4** when the temperature is increased beyond 50 °C,[23] so that from 80 to 100 °C only signals for species **5**, $[(dippe)_2Ni]$, and $[(dippe)Ni(CN)_2]$ can be observed. These last two complexes come from **5**, which disproportionates to $[(dippe)Ni(CN)_2]$ and $[(dippe)Ni(4\text{-pyridyl})_2]$. Due to its low solubility, the $[(dippe)Ni(CN)_2]$ complex separates from the reaction mixture. A signal for $[(dippe)Ni(4\text{-pyridyl})_2]$ was not seen during these experiments; nevertheless the homocoupling product 4,4′-dipyridine was detected when analyzing the reaction crude by CG-MS (see Figure S6 in the Supporting Information). In situ formation of $[(dippe)Ni(4\text{-pyridyl})_2]$ and its reductive elimination are also consistent with formation of the species $[(dippe)_2Ni_2]$ (Scheme S1 in the Supporting Information). Further heating of the reaction mixture at 100 °C results in decomposition of the system, as evidenced by the formation of a black solid. On the basis of these observations species **4** is proposed to be that acting as a catalyst.

In order to assess the reactivity of **4** toward methanol at 50 °C, a novel series of experiments was carried out in THF-d_8, now with the addition of 1 equiv of anhydrous and deoxygenated methanol to a stoichiometric mixture of dimer $[(dippe)Ni(H)]_2$ and 4Cypy (Figure 2). Signals for **4** and **5** in $^{31}P\{^1H\}$ NMR spectra are the same as those previously assigned (vide supra). When a stoichiometric amount of methanol is added, there is a difference in the relative intensity of the signals of **4** and **5**. Signals for **4** are relatively more intense in comparison with those appearing in the corresponding spectrum at 50 °C (Figure 1) with no stoichiometric MeOH added. Also of note is the presence of a new singlet at 72.6 ppm, along with the evolution of signals for **5**, $[(dippe)_2Ni_2]$, and $[(dippe)Ni(CN)_2]$, thus being consistent with a signal for $[(dippe)Ni(4\text{-pyridyl})_2]$ so that this Ni(II) species is rather stable to detection at 50 °C but not at a higher temperature (vide supra).

From this series, two additional signals labeled as **6** in Figure 2 are observed at 84.9 ppm (d, $^2J_{P-P}$ = 27 Hz) and at 74.8 ppm (d, $^2J_{P-P}$ = 27 Hz). Coupling constants are characteristic for a Ni(II) complex. At first sight one might suspect a hydride complex resulting from an oxidative addition reaction of methanol to a low-valent Ni species, but given that no signals for hydride were observed in ^1H NMR spectra (see Figure S7 in the Supporting Information), these signals are proposed to originate from a Ni(II) complex whose structure appears labeled as **6** in Scheme 1.[24] Formation of the latter Ni(II) species is competitive with the C−C bond activation of nitrile, thus preventing decomposition. Subsequent release of the

DOI: 10.1021/acscatal.5b00348
ACS Catal. 2015, 5, 3470−3477

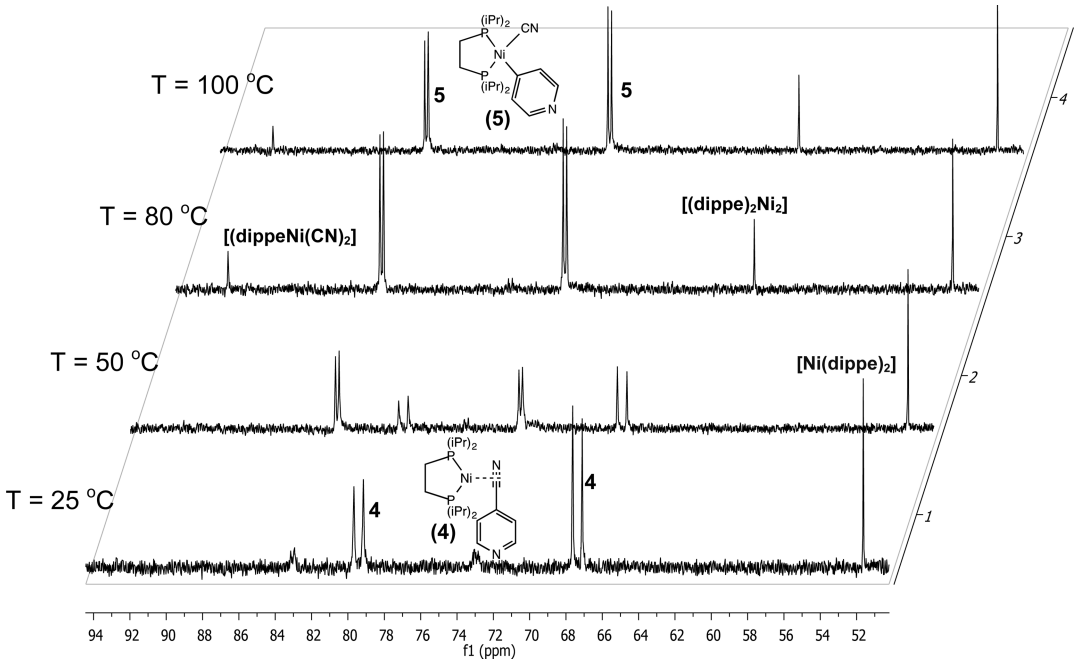


Figure 1. $^{31}P\{^{1}H\}$ NMR (THF-d_8, 121.3 MHz) monitoring of the reaction between $[(dippe)Ni(H)]_2$ and 4Cypy for 4 h at each indicated temperature.

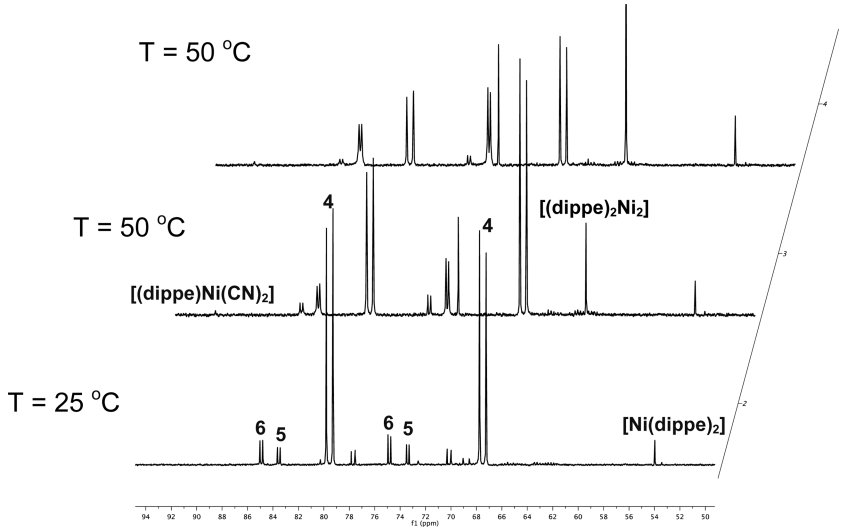
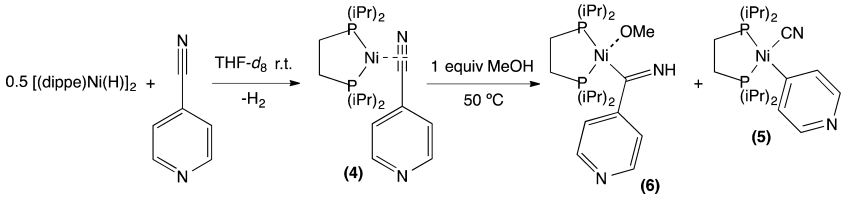


Figure 2. $^{31}P\{^{1}H\}$ NMR (THF-d_8, 121.3 MHz) monitoring of the reaction of $[(dippe)Ni(H)]_2$, 4Cypy, and MeOH for 3 h at each indicated temperature.

Scheme 1. Reactivity of 4 with a Stoichiometric Amount of MeOH in THF-d_8



methyl imino ester **1** from **6** is then consistent with the formation of such a target product along with an increase in the $[(dippe)_2Ni_2]$ signal.[25]

With the aim of finding out how a significant increase in methanol concentration would modify the reactivity, a 1/20 THF-d_8/CD_3OD mixture was used (for $^{31}P\{^{1}H\}$ NMR and ^{1}H spectra see Figures S8 and S9 in the Supporting Information). In such a medium, starting at room temperature, a stoichiometric mixture of $[(dippe)Ni(H)]_2$ and 4Cypy reacted partially to yield **4**, as evidenced by signals corresponding to free 4Cypy in ^{1}H NMR spectra. In $^{31}P\{^{1}H\}$ NMR, signals for **4** are observed from the beginning of the reaction and they

DOI: 10.1021/acscatal.5b00348
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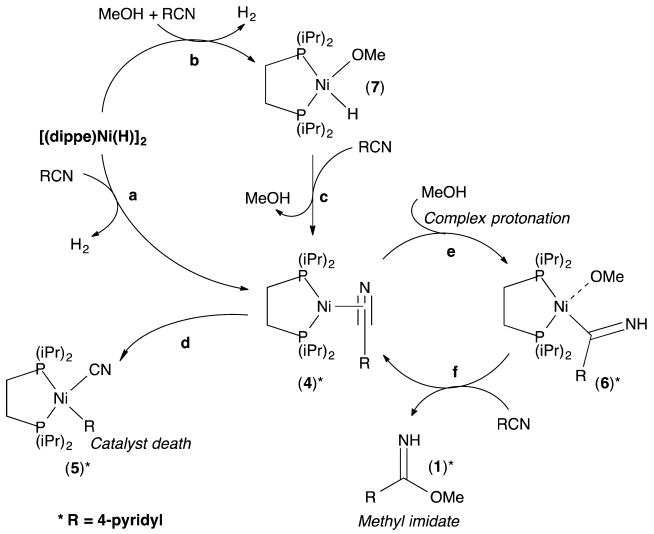
persist during the entire time of heating (i.e. 9 h at 50 °C). Nevertheless, despite the fact that the chemical shift values (81.3 ppm (d, $^2J_{P-P}$ = 53 Hz), 69.4 ppm (d, $^2J_{P-P}$ = 53 Hz)) are practically the same as those for experiments in THF (vide supra), coupling constants (i.e., 53 Hz) are decreased by 10 Hz. This offers evidence of an additional interaction between complex **4** and methanol as solvent. In this sense, very similar observations have been reported for a closely related Ni(0) complex bearing a side-on-coordinated nitrile. In such a case, chemical shift values remained the same after adduct formation with an acid, namely BPh_3; however, a decrease of about 10 Hz was observed for the $^2J_{P-P}$ value.[26] This said, in the current system it is not unreasonable to propose an acid−base type reaction between complex **4**, acting as a base, and methanol, acting as a proton donor (see Scheme 1).

In addition in this series, a pair of multiplets in $^{31}P\{^1H\}$ NMR were observed at 72.9 ppm and at 70.5 ppm. From these signals a coupling constant is distinguished to have a value of 35 Hz, which is consistent with a $^2J_{P-P}$ value for a Ni(II) complex. In this case, an additional fine structure pattern would be expected for phosphorus−deuterium coupling, thus accounting for a complex of the type [(dippe)Ni(D)(CD_3)] (**7**; D = ^2H). This oxidative addition product from a reaction mixture containing methanol, monovalent Ni dimer, and 4-Cypy explains the presence of free 4Cypy. Additionally, upon warming at 50 °C, signals corresponding to **7** decrease in intensity along with an increase of two signals at 84.4 ppm (d, $^2J_{P-P}$ = 25 Hz) and at 74.1 ppm (d, $^2J_{P-P}$ = 25 Hz) assigned to complex **5**. Further heating (i.e., 9 h at 50 °C) leads to complete disappearance of complex **7**, thus leaving **4**, which would stem from **7** after reductive elimination of methanol; **5** and deuterated **6** (86.7 ppm (bs) and 75.4 ppm (bs)) now appear.

The results presented so far are summarized in Scheme 2. The mechanistic proposal starts with the reaction between

Scheme 2. Mechanistic Proposal



[(dippe)Ni(H)]$_2$ and 4Cypy (pathway a) to yield **4** with the simultaneous formation of **7** (pathway b), which after reductive elimination of methanol and further reaction with free 4Cypy yields complex **4** as well (pathway c). Active species **4** can be oxidized by C−C activation (pathway d) to yield **5**. Back-reaction from **5** to regenerate **4** is known not to happen;[23] thus, formation of **5** is the pathway leading to catalyst death. On the other hand, **4** can also react with methanol (pathway e) via protonation of the nitrogen atom on the side-on-coordinated nitrile, as such an atom is expected to be electron rich to a higher extent than carbon. Once the side-on complex is protonated in the presence of methanol, two pathways are possible: namely, methoxide coordination and subsequent reductive elimination or nucleophilic abstraction of the carbon-bonded imino moiety carried out by anionic alkoxide. In the end, both alternatives lead to the formation of the corresponding methyl imidate[27] and, in the presence of excess nitrile in catalysis, to the regeneration of the active species **4** (pathway f).

To test this proposal and gain information about the influence of ancillary ligands in catalysis, dppe (1,2-bis-(diphenylphosphino)ethane) and triphenyl phosphite (P-(OPh)$_3$) were allowed to react along with the precatalyst [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene) as an alternative Ni(0) source. Using this methodology, a series of Ni-catalyzed reactions were carried out with 4Cypy and 2Cypy in methanol at the two temperature values for which change in conversion was observed. Key results for this experiments are summarized in Table 1.[28]

For 4Cypy at 70 °C, a dependence on the electronic acceptor character of the P ligand was observed, as the yield increased on an increase in π acceptance (Table 1, entries 1, 2 and 4). At 50 °C the opposite was seen, the very same ligand being less efficient (entries 11−13). These results suggest that protonation could determine the rate at this temperature.

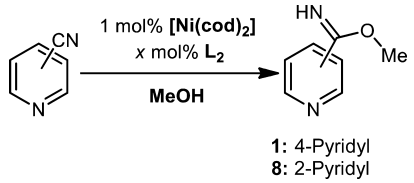
Considering this, at 70 °C, better performance is achieved with π-acceptor ligands because they prevent C−C activation, and thus catalyst decomposition, by lowering the electron density at the metal center. This is in turn detrimental to protonation; however, as long as the Ni(0) species is prevented from decomposition, both the reaction time (48 h) and temperature are long and high enough to achieve such a process and complete the reaction to an extent which is, nevertheless, minor in comparison with the best yield obtained with the σ-donor ligand at 50 °C (Table 1, entries 4 and 11). Following this, at the lower temperature the low-valent Ni−dippe system is rather stable in MeOH; thus, deactivation by C−C activation is no longer an important side reaction. This way the σ-donor ligand favors protonation because electron density on the Ni center is increased, thus increasing the extent of back-bonding and therefore the basicity of the coordinated nitrile. At this point a difference in the extent of π acceptance of dppe in comparison to P(OPh)$_3$ should be adverted, as dppe also shows good performance at 50 °C. As an additional informative experiment, ethanol was assessed under the conditions shown in Table 1, entry 12, to yield only 5% of corresponding ethyl imidate.

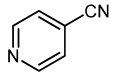
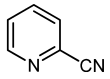
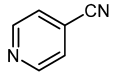
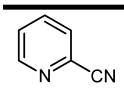
In the case of 2Cypy, excellent conversion was achieved at 70 and 50 °C when using bidentate phosphino ligands (Table 1, entries 6, 7, 14, and 15), but this was not the case for the monodentate phosphite ligand at higher temperature. To understand this, the ratio nickel/phosphite was modified to compare both 4Cypy and 2Cypy. The conversion of 4Cypy was rather sensitive to changes in the stoichiometry of the ligand (entries 3−5), while reaction with 2Cypy seemed to be unaffected (entries 8−10), probably due to favorable formation of chelated species.[14]

Using 0.5 mol % of the precatalyst [(dippe)Ni(H)]$_2$, a series of N-heterocyclic carbonitriles and benzonitriles was used to

DOI: 10.1021/acscatal.5b00348
ACS Catal. 2015, 5, 3470−3477

Table 1. Ligand Assessment on a Ni-Catalyzed System[c]



Entry	T /°C	Cypy	Ligand	Ni:Ligand	%Yield[a]
1	70		dippe[b]	1:1	**51**
2			dppe	1:1	**58**
3			$P(OPh)_3$	1:1	**66**
4				1:2	**80**
5				1:4	**56**
6			dippe[b]	1:1	**99**
7			dppe	1:1	**99**
8			$P(OPh)_3$	1:1	**86**
9				1:2	**83**
10				1:4	**78**
11	50		dippe[b]	1:1	**89**
12			dppe	1:1	**91**
13			$P(OPh)_3$	1:2	**73**
14			dippe[b]	1:1	**99**
15			dppe	1:1	**99**

[a]Chromatographic yield (GC/MS). [b]0.5 mol % $[(dippe)Ni(H)]_2$ was used; these results are shown for comparative purposes. [c]Conditions: $[Ni(cod)_2]$/*n*Cypy 1/100, *n*Cypy/MeOH 1/100, under an inert atmosphere, 48 h.

determine the reaction scope (Table 2) for 24 h at 50 °C (see Table S2 in the Supporting Information for further details on the time of the reaction). For a given series of both pyridines and benzonitriles, the reaction yield depends primarily on the extent of activation given by the electron-withdrawing features of the substrate (entries 1−3 and 7−9). This is in accordance with what is expected for a system in which protonation of an electron-rich side-on-coordinated nitrile is the followed pathway (see Scheme 2), as the extent of back-bonding increases when the electron deficiency of the substituents on the ligand is increased. The same dependence was expected for quinoline and isoquinoline derivatives (entries 4−6), but in this case steric hindrance could account for a decrease in the higher expected yields, considering that obtained for the analogue 2Cypy. An additional explanation for this is the known fluxionality exhibited by the benzo-fused N-heterocycles, as in the case of 2-cyanoquinoline, whose coordination modes toward the [(dippe)Ni] moiety include not only the nitrile but also the C−C unsaturated bonds of the cycle.[29]

Products obtained from the addition of methanol to N-heterocyclic substituted carbonitriles were used to prepare a series of amidines and 2-substituted benzoxazoles. Scheme 3 illustrates a two-step methodology for such a purpose, the first step being Ni-catalyzed formation of a methylimidate by the addition of methanol to a nitrile moiety and the second step being the extrusion of methanol promoted by the addition of an amino group to the methylimidate to finally yield the corresponding amidines or benzoxazoles along with the evolution of ammonia in the latter case.

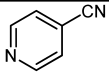
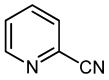
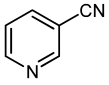
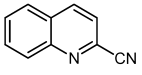
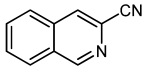
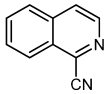
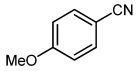
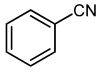
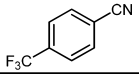
Benzylamine and *o*-aminophenol were chosen for a model study with 4Cypy following the two sequential steps illustrated in Scheme 4, in which also the best conditions and yields found for each system are shown. For benzylamine, control experiments without methanol yielded no products, thus evidencing the need for the alcohol, and in attempts to synthesize amidine in one operational step, the yields were only 39% and 57% for reaction times of 24 and 48 h, respectively. Attempts to lower the second-step temperature from 50 to 30 °C resulted in 10% yield. An additional experiment using cyclohexylamine under the best conditions for amidine production (Scheme 4, left side) yielded 71% product, suggesting a reaction dependence on the steric hindrance of substituents on the amino moiety.

For *o*-aminophenol, a control experiment without Ni precatalyst yielded 5% product. In an experiment under the conditions shown in Scheme 4 (right side), the release of ammonia was confirmed by bubbling the gas produced into a $CuSO_4{\cdot}5H_2O$-saturated aqueous solution.

The key results of the reaction scope for N-heterocyclic nitriles are summarized in Table 3. From this series, amidine

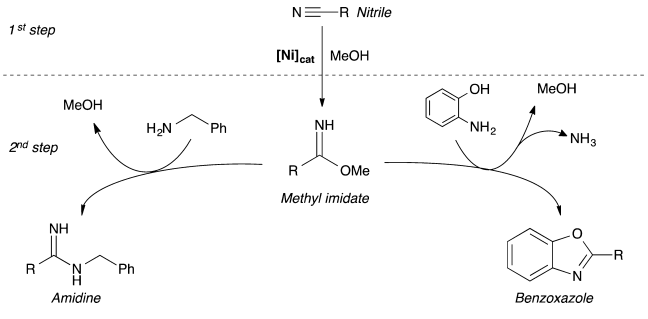
DOI: 10.1021/acscatal.5b00348
ACS Catal. 2015, 5, 3470−3477

Table 2. Reaction Scope[b]

Entry	R-CN	%Yield[a]
1		91
2		95
3		70
4		60
5		80
6		n.d.
7		5
8		14
9		54

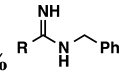
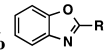
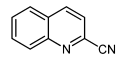
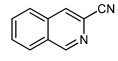
[a]Chromatographic yield (GC/MS). [b]Conditions: $[(dippe)Ni(H)]_2$/RCN 1/200, under an inert atmosphere, 24 h, 50 °C.

Scheme 3. Two-Step Synthesis of Amidines and Benzoxazoles from Nitriles



formation was achieved in high yields for 4- and 2Cypy, which best react toward methanol addition (entries 1 and 2). The

Table 3. Amidine and Benzoxazole Formation Scope[a]

Entry	RCN	% 	% 
1		88	75
2		95	92
3		57	66
4		28	56
5		n.d.	53

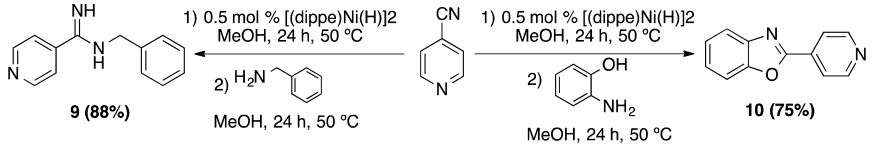
[a]Conditions: (first step) $[(dippe)Ni(H)]_2$/RCN 1/200, RCN/MeOH 1/100, 24 h, 50 °C, under inert atmosphere; (second step) addition of $PhCH_2NH_2$ or *o*-NH_2PhOH, 24 h, 50 °C, uncontrolled atmosphere. Chromatographic yields (GC/MS) are given.

yield for 3Cypy is once again conditioned primarily by the lesser extent of electron-withdrawing character of 3Cypy in comparison with the other two pyridine-nitriles, and in the case of benzofused substrates, the reactivity is lowered due to their additional coordination modes, which have already been mentioned. Additionally, as dependence on steric hindrance on the amino moiety has been observed for this reaction, it is not unreasonable to state something similar for quinoline derivatives (entries 3−5). Following the same ideas, the yield for benzoxazole formation could be almost directly related to the initial reactivity toward methanol addition. In this reaction the release of ammonia along with aromatization is an additional driving force not happening in the sole formation of amidines, so that once nitrile has been activated, the second step proceeds readily to yield the target products. These considerations help to explain the difference in reactivity of quinoline derivatives, which different from the case for amidine formation do react in the cyclization process.

CONCLUSIONS

The addition of methanol to aromatic nitriles catalyzed by zerovalent Ni species was studied. With this catalytic system, methyl imidates were obtained under mild conditions in an atom-economical process. Mechanistic insights for alcohol addition were provided on the basis of NMR studies of stoichiometric mixtures of $[(dippe)Ni(H)]_2$ and the model substrate 4Cypy. It was found that such an addition occurs by initial protonation of in situ formed side-on complex and a subsequent reaction with methoxide, the conjugate base, to

Scheme 4. Model Reactions with Benzylamine and *o*-Aminophenol



DOI: 10.1021/acscatal.5b00348
ACS Catal. 2015, 5, 3470−3477

yield the target compound. In catalysis, electron-deficient substrates along with bidentate phosphines favored both alcohol addition and protonation at 50 °C for 24 h to yield the corresponding methyl imidates. Methyl imidate mediated synthesis of amidines and 2-substituted benzoxazoles was carried out following a two-step methodology at 50 °C for 48 h from N-heterocyclic nitriles in alcoholic media in the presence of Ni(0) species. In addition to the electronic features of the substrate, steric hindrance plays an important role in both the first alcohol addition and subsequent amidine formation. The benzoxazole yield is primarily dependent on substrate electronic features. Further studies are under way to extend the scope of this methodology to the synthesis of other related organic systems.

EXPERIMENTAL SECTION

General Considerations. The synthesis of $[(dippe)Ni(H)]_2$ was performed under an argon atmosphere (Praxair, 99.998%) in an MBraun glovebox (<1 ppm of H_2O and O_2) and an inert-gas/vacuum double manifold. The synthesis was done using standard Schlenk techniques according to a reported procedure.[30] Deuterated solvents for NMR experiments were purchased from Cambridge Isotope Laboratories and stored over 3 Å molecular sieves in a glovebox for at least 24 h before use. Regular THF and methanol (J. T. Baker, reagent grade) were dried and distilled from sodium/benzophenone and magnesium/iodine, respectively.

The following substrates were purchased from Aldrich: 4-pyridinecarbonitrile, 2-pyridinecarbonitrile, 3-pyridinecarbonitrile, 2-quinolinecarbonitrile, 3-isoquinolinecarbonitrile, benzonitrile, 4-methoxybenzonitrile, 4-trifluoromethylbenzonitrile, benzylamine, cyclohexylamine, and *o*-aminophenol. These were used without any additional purification, but they were dried under vacuum and stored in a glovebox for at least 24 h before use. All other reagent-grade chemicals, filter aids, and chromatographic materials were used as received. Catalysis experiments were performed either in a 75 mL stainless steel vessel Parr reactor or in 50 mL Schlenk flasks, all of which were charged inside a glovebox.

In each catalysis experiment, the respective Ni(0) catalysts were prepared in situ. The total amount of nitrile used was calculated on the basis of either 0.5 mol % of the Ni(I) catalyst precursor or 1 mol % of the species $[Ni(COD)_2]$, from which the amount of the corresponding P ligand was also calculated. The amount of amines was calculated on the basis of the starting nitrile.

NMR spectra of the complexes and products were recorded at room temperature on a 300 MHz Varian Unity spectrometer. ^1H and $^{13}C\{^1H\}$ NMR spectra of **8**−**10** were obtained using crude solutions dissolved in $CDCl_3$ or DMSO-d_6. ^1H and $^{31}P\{^1H\}$ NMR spectra of mixtures of complexes **4**−**7** were obtained using a THF-d_8 solution of the nickel compounds prepared in situ. The sample was handled under argon using a thin-walled 0.38 mm WILMAD NMR tube equipped with a J. Young valve. ^1H and $^{13}C\{^1H\}$ chemical shifts (δ/ppm) are reported relative to either the residual proton or deuterated carbon resonances of the solvent, respectively. $^{31}P\{^1H\}$ NMR spectra were recorded relative to external 85% H_3PO_4. Crude reaction mixtures were analyzed by GC/MS (Agilent 7890A/5975C, DB-5 ms capillary column, 30 m length, 0.32 mm i.d., 99.999% helium).

Addition of Methanol to 4Cypy in the Presence of $[(dippe)Ni(H)]_2$ at Different Temperatures. In a glovebox, stainless reactor vessels ($T \geq 120$ °C) or Schlenk flasks ($T < 120$ °C) were charged in different runs with $[(dippe)Ni(H)]_2$ (0.0109 or 0.0036 mmol) in 1 or 0.4 mL of THF, respectively, along with 4Cypy (2.176 or 0.725 mmol) and methanol (9 mL for the reactor and 2.8 mL for the flasks). The mixtures were heated at temperatures indicated in Table 1 in an appropriate oil bath under an inert atmosphere for 48 h. On exposure to air, the pale yellow crude products were analyzed by GC/MS. Before analysis, the crude products from the mixtures at temperatures higher than 70 °C were filtered through a Celite plug.

Addition of Methanol to 4Cypy and 2Cypy in the Presence of a Mixture of $[Ni(COD)_2]$ with P Ligands. Synthesis of 8. In a glovebox, Schlenk flasks were charged in different runs with $[Ni(COD)_2]$ (0.0072 mmol) in 0.2 mL of THF, dppe (0.0072 mmol) or $P(OPh_3)$ (0.0072, 0.0145, or 0.0217 mmol) in 0.2 mL of THF, 4Cypy or 2Cypy (0.73 mmol), and methanol (2.8 mL, 69.2 mmol). The mixtures were heated at 50 or 70 °C in a silicon oil bath under an inert atmosphere for 48 h. On exposure to air, the pale yellow crude products were analyzed by GC/MS. ^1H NMR ($CDCl_3$, 300 MHz) δ/ppm for **8**: 3.89 (s 3H), 7.24 (m 1H), 7.71−7.66 (m 2H), 8.52 (m 1H), 9.06 (bs NH). $^{13}C\{^1H\}$ NMR, δ/ppm: 54.1 (CH_3), 121.2, 125.5, 137.4, 149.4 (CH), 147.7, 167 (C). MS (EI) *m*/*z*: 137 (M + 1, 20), 136 (M, 88), 135 (100).

Scope of the Addition of Methanol to N-Heterocyclic Carbonitriles. In a glovebox, Schlenk flasks were charged in different runs with $[(dippe)Ni(H)]_2$ (0.0036 mmol) in 0.4 mL of THF, the corresponding nitrile (0.725 mmol), and methanol (2.8 mL). The mixtures were heated at 50 °C in a silicon oil bath under an inert atmosphere for 24 h. On exposure to air, the pale yellow crude products were analyzed by GC/MS.

Model Synthesis of Amidines and Benzoxazoles. Formation of 9 and 10. In a glovebox, Schlenk flasks were charged in two different runs with $[(dippe)Ni(H)]_2$ (0.0036 mmol) in 0.4 mL of THF, 4Cypy (0.725 mmol), and methanol (2.8 mL, 69.2 mmol). The mixtures were heated at 50 °C in a silicon oil bath under an inert atmosphere for 24 h. On exposure to air, the pale yellow crude products were analyzed by GC/MS (91% and 84% yields of **1**). Then, benzylamine (0.725 mmol) or *o*-aminophenol (0.725 mmol) was added to the crude mixtures, which were heated again at 50 °C for 24 h. The final samples were analyzed by GC/MS (97% and 89% yields of **9** and **10**, respectively). Product **9** was chromatographed on a silica gel column (eluent THF/hexanes). Data for **9** are as follows. ^1H NMR (300 MHz, $CDCl_3$) δ/ppm: 4.65 (s, 2H), 6.09 (bs, 2H), 7.48−7.61 (m, 5H), 7.70−7.72 (m, 2H), 8.73−8.75 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ/ppm: 47.5 (CH_2), 120.7, 126.9, 127.4, 128.4, 149.8 (CH), 138.7, 144.4, 159.2 (C). MS (EI) *m*/*z*: 212 (M + 1, 15), 211 (M, 57), 210 (100). Data for **10** are as follows. ^1H NMR (300 MHz, DMSO-d_6) δ/ppm: 7.39−7.50 (m, 2H), 7.74−7.78 (m, 1H), 7.81−7.84 (m, 1H), 8.06−8.08 (m, 2H), 8.81−8.82 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6) δ/ppm: 111.0, 120.2, 120.6, 125.0, 126.2, 150.6 (CH), 133.5, 141.1, 150.2, 160.0 (C). MS (EI) *m*/*z*: 197 (M + 1, 14), 196 (M, 100), 195 (15).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00348.

DOI: 10.1021/acscatal.5b00348
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GC traces of typical experiments, detailed tables of time and temperature variation for the model substrate, mass spectra of the products reported, ^{1}H and $^{31}P\{^{1}H\}$ NMR spectra corresponding to stoichiometric studies, and schemes depicting the reactivity observed on the basis of NMR experiments (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank PAPIIT-DGAPA-UNAM (IN-210613) and CONACYT (0178265) for their financial support. We also thank Dr. Alma Arévalo for her technical assistance.

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(20) Ester formation is proposed to occur via hydrolysis of the intermediate imino ester coming from addition of alcohol to the nitrile moiety. See ref 15.

(21) The study began at 180 °C, since hydration of 4Cypy had been studied at this temperature in a previous work. From 100 °C and over 120 °C, water is known to react with pyridinecarbonitriles to yield amides and carboxylic acids, the selectivity being controlled by temperature. See ref 19d.

(22) Above 120 °C low amounts of subproducts **2** and **3** were observed in this series. Detailed information appears in Table S1 in the Supporting Information.

(23) Species **4** and **5** have been previously assigned, as well as $[Ni(dippe)_2]$, $[(dippe)_2Ni_2]$, and $[(dippe)Ni(CN)_2]$, whose signals in $^{31}P\{^{1}H\}$ NMR appear in Figure 1 at 54, 62 and 91 ppm, respectively. See: (a) García, J. J.; Brunkan, N. M.; Jones, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 9547−9555. (b) García, J. J.; Arévalo, A.; Brunkan, N. M.; Jones, W. D. *Organometallics* **2004**, *23*, 3997−4002.

(24) In Scheme 2, intermediate **6** is depicted with a dashed bond, as this could be the neutral species [(dippe)Ni(OMe)(C(NH)pyridyl)] or the ionic species [(dippe)Ni(C(NH)pyridyl)](OMe).

(25) If **6** is a neutral complex, reductive elimination would take place. Otherwise, if **6** is a cationic species whose counterion is a methoxide anion, formation of the corresponding C−O bond would then be accounted for by a nucleophilic abstraction of the −C(NH)pyridyl moiety.

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(27) Our group has reported a mechanistic proposal in which a reductive elimination from an intermediate of the type [(dippe)Ni(OMe)(C(O)R)] was invoked to yield the corresponding methyl esters along with a low-valent Ni species. See: (a) González-Sebastián, L.; Flores-Alamo, M.; García, J. *Organometallics* **2012**, *31*, 8200−8207. For further discussion on this eliminations see, for instance: (b) Matsunaga, P. T.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 2077−2078. (c) Matsunaga, P. T.; Mavropoulos, J. C.; Hillhouse, G. L. *Polyhedron* **1995**, *14*, 175−185 In the current case it is not unreasonable to propose a reductive elimination from [(dippe)Ni(C(NH)pyridyl)(OMe)] since this can be seen as an analogous system in terms of a Ni-complex bearing both a methoxy-ligand and a $C(sp^2)$-atom bonded to a heteroatom. .

(28) A second nitrile was chosen because of electronic features similar to those of 4Cypy.

(29) A study of reactivity between 2-cyanoquinoline and $[(dippe)Ni(H)]_2$ has been reported. See ref 23a.

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ACS Catal. 2015, 5, 3470−3477