

Aromatic Cyanoalkylation through Double C–H Activation Mediated by Ni(III)

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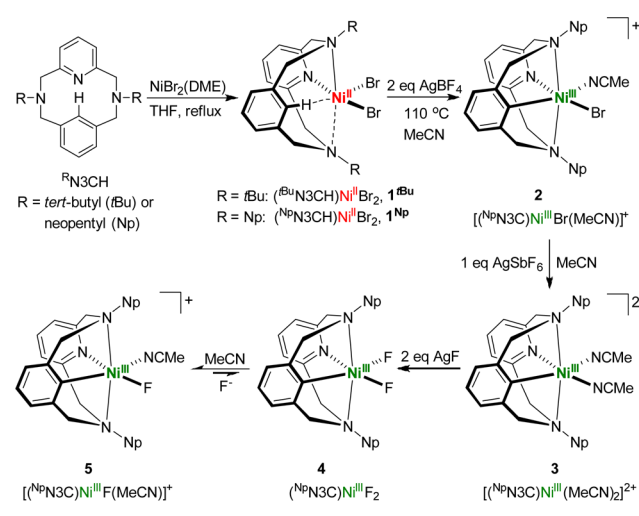
S Supporting Information

ABSTRACT: Herein we report an atom- and step-economic aromatic cyanoalkylation reaction that employs nitriles as building blocks and proceeds through C_{sp}²–H and C_{sp}³–H bond activation steps mediated by Ni^{III}. In addition to cyanomethylation with MeCN, regioselective α -cyanoalkylation was observed with various nitrile substrates to generate secondary and tertiary nitriles. Importantly, to the best of our knowledge these are the first examples of C–H bond activation reactions occurring at a Ni^{III} center, which may exhibit different reactivity and selectivity profiles than those corresponding to analogous Ni^{II} centers. These studies provide guiding principles to design catalytic C–H activation and functionalization reactions involving high-valent Ni species.

The direct functionalization of C–H bonds of unactivated substrates such as alkanes and arenes is of great importance to chemical synthesis and industrial applications.¹ Among the many transition metal catalysts employed in organic chemistry, the low toxicity and low cost of Ni-based catalysts have drawn great attention,² and Ni^{II}-catalyzed C_{sp}²–H³ and C_{sp}³–H⁴ bond activation and functionalization reactions have been developed in the past decade. In addition, C_{sp}³–H bonds α to reactive functional groups can be activated by Ni^{II} complexes in the presence of strong bases.⁵ However, there are no examples of C_{sp}²–H or C_{sp}³–H activation/functionalization reactions mediated by high-valent Ni^{III} or Ni^{IV} species. Moreover, only a very limited number of direct aromatic cyanoalkylation reactions using common nitriles have been reported⁶ and none of them can be performed at rt under mild conditions.

Recently, our group has employed the tetradentate ligand *N,N'*-di-*tert*-butyl-2,11-diaza[3.3](2,6)-pyridinophane (*t*Bu₄N4)⁷ and its C-donor derivative *t*Bu₄N3C[–] to stabilize Ni^{III} complexes that exhibit C–C and C–O bond formation reactivity.⁸ Among others,^{9a} Zargarian et al. have reported that modification of the side arms of “ECE” pincer system (where E is an L type donor and C is the *ipso*-carbon of the phenyl ring) can dramatically impact the properties of the corresponding Ni^{II} complexes,⁹ and thus we decided to develop ligand derivatives such as ^{Np}N3C[–] by substituting the *tert*-butyl groups (*t*Bu) with less sterically hindered neopentyl (Np) groups as the two amine N-substituents (Scheme 1). Gratifyingly, the investigated systems undergo both C_{sp}²–H and C_{sp}³–H bond activation at a Ni^{III} center, followed by rapid C–C bond formation to generate the cyanoalkylation product under mild conditions. This Ni^{III}-

Scheme 1. C_{sp}²–H Activation and Synthesis of Ni^{II} and Ni^{III} Complexes 1–4



mediated process is both atom- and step-economic. As pointed out by the Nobel laureate Prof. E. Negishi, “many more *d*-block transition metal-catalyzed green organic synthetic methods will be and will have to be discovered and developed for a sustainable 21st century and beyond”,¹⁰ we report herein the first example of C–C bond formation through a double C_{sp}²–H and C_{sp}³–H bond activation mediated by Ni^{III}. Overall, these studies could provide guidance for the development of catalytic C–H activation and functionalization reactions mediated by high-valent Ni species.

Complexes (*t*Bu₄N3CH)Ni^{II}Br₂, **1^{tBu}**, and (^{Np}N3CH)Ni^{II}Br₂, **1^{Np}**, were synthesized in 70% and 63% yields, respectively, by reacting ^{Np}N3CH and *t*Bu₄N3CH with NiBr₂(DME). Although no C_{sp}²–H bond activation is observed in their solid state structures (Figure 1), **1^{tBu}** and **1^{Np}** exhibit interesting metal–arene interactions. While the Ni1–C1 and Ni1–H1 distances and the Ni1–H1–C1 angle (2.789 Å, 2.437 Å, and 101.7°) indicate an agostic interaction in **1^{tBu}**, the analogous metrical parameters (2.479 Å, 2.261 Å, and 91.7°, respectively) suggest an appreciable agostic interaction in **1^{Np}**,¹¹ as well as a stronger Ni1–C1 interaction in **1^{Np}** suggestive of the possibility of C–H bond activation reactivity.¹² Also, since C–H bond activation was shown to occur at Pd^{IV} centers,¹³ we anticipated that high-valent Ni centers should also be able to facilitate a similar process.

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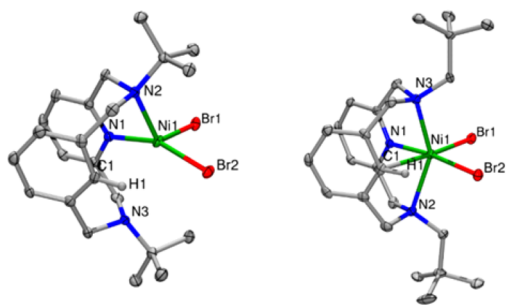


Figure 1. ORTEP (50% probability thermal ellipsoids) of 1^{tBu} (left) and 1^{NP} (right). Selected bond distances (Å) and angles (deg $^\circ$), 1^{tBu} : Ni1–C1, 2.789(3); Ni1–N1, 1.995(2); Ni1–N2, 2.141(2); Ni1–N3, 3.075(3); Ni1–Br1, 2.432(1); Ni1–Br2, 2.395(1); Ni1–H1, 2.437(1); Ni1–H1–C1, 101.7(2); 1^{NP} : Ni1–C1, 2.479(3); Ni1–N1, 1.984(3); Ni1–N2, 2.363(3); Ni1–N3, 2.255(3); Ni1–Br1, 2.462(1); Ni1–Br2, 2.456(1); Ni1–H1, 2.261(1); Ni1–H1–C1, 91.7(1).

Indeed, addition of 2 equiv of AgBF_4 to 1^{NP} at 110 $^\circ\text{C}$ in MeCN leads to $\text{C}_{\text{sp}^2}\text{--H}$ bond activation to generate $[(^{\text{NP}}\text{N3C})\text{Ni}^{\text{III}}\text{Br}(\text{MeCN})]^+$, **2**, in 20% yield. The solid state structure of **2** reveals the $^{\text{NP}}\text{N3C}^-$ ligand bonds to the Ni^{III} center along with one bromide and one MeCN to form a distorted octahedral geometry (Figure 2, left). Complex **2** is paramagnetic and exhibits an

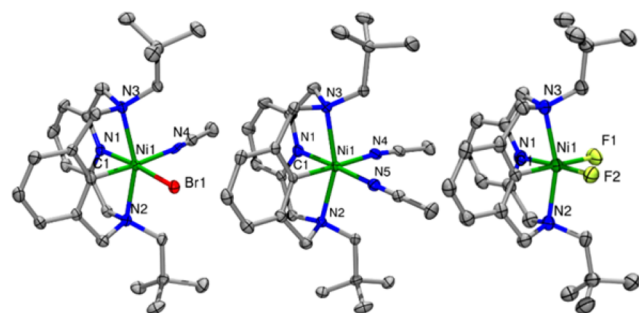


Figure 2. ORTEP (50% probability thermal ellipsoids) of the cations of **2** (left) and **3** (middle), and neutral complex of **4** (right). Selected bond distances (Å), **2**: Ni1–C1, 1.911(3); Ni1–N1, 1.938(3); Ni1–N2, 2.239(3); Ni1–N3, 2.238(3); Ni1–N4, 2.061(2); Ni1–Br1, 2.373(1); **3**: Ni1–C1, 1.900(2); Ni1–N1, 1.901(2); Ni1–N2, 2.196(2); Ni1–N3, 2.213(2); Ni1–N4, 1.993(2); Ni1–N5, 1.959(2); **4**: Ni1–C1, 1.886(4); Ni1–N1, 1.904(4); Ni1–N2, 2.185(4); Ni1–N3, 2.162(3); Ni1–F1, 1.916(2); Ni1–F2, 1.932(3).

effective magnetic moment μ_{eff} of 1.74 μ_{B} at 298 K, corresponding to one unpaired electron. The EPR spectrum of **2** (77 K, PrCN glass) reveals a rhombic signal with a g_{ave} value of 2.132, along with superhyperfine coupling to the two axial N donors ($I = 1$) in the g_z direction and superhyperfine coupling to the Br atom ($I = 3/2$) in the g_x and g_y directions (Figure 3, left). Overall, the observed structural and EPR parameters for **2** suggest the presence of a Ni^{III} d^7 center with a d_{z^2} ground state.

Additional studies were performed to investigate the observed $\text{C}_{\text{sp}^2}\text{--H}$ bond activation. First, no $\text{C}_{\text{sp}^2}\text{--H}$ bond activation was observed for 1^{NP} in the presence of various bases, Ni salt sources, or milder oxidants (Table S1), suggesting that the observed reactivity is occurring at the Ni^{III} stage. Second, while no $\text{C}_{\text{sp}^2}\text{--H}$ bond activation occurred when 1^{NP} was treated with 2 equiv of TlPF_6 , treatment of 1^{NP} with both 2 equiv of TlPF_6 and 1 equiv of NOBF_4 at 110 $^\circ\text{C}$ in MeCN generates the $\text{C}_{\text{sp}^2}\text{--H}$ bond activation Ni^{III} product in 20% yield, similar to that obtained in the presence of AgBF_4 (Table S1), further supporting our

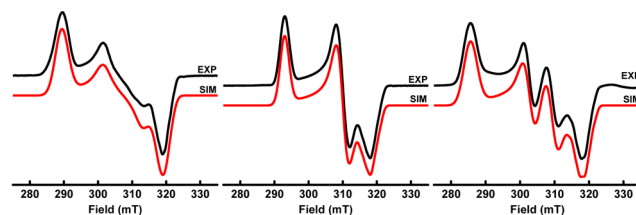
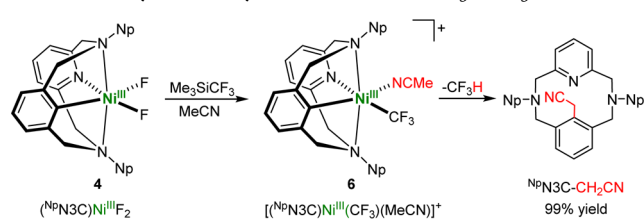


Figure 3. Experimental (PrCN glass, 77 K) and simulated EPR spectra of **2** (left), **3** (middle), and **4** (right). Parameters used for simulations: **2**, $g_x = 2.244$; $g_y = 2.115$ ($A_{\text{Br}} = 29.0$ G); $g_z = 2.037$ ($A_{2\text{N}} = 12.0$ G, $A_{\text{Br}} = 6.0$ G); **3**, $g_x = 2.217$; $g_y = 2.095$; $g_z = 2.041$ ($A_{2\text{N}} = 14.0$ G); **4**, $g_x = 2.274$; $g_y = 2.124$ ($A_{\text{F}} = 65.0$ G); $g_z = 2.043$ ($A_{2\text{N}} = 13.5$ G, $A_{\text{F}} = 17.5$ G).

hypothesis that a Ni^{III} species is responsible for C–H activation. Finally, no C–H activation was observed when 1^{tBu} was reacted with 2 equiv of AgBF_4 under the same conditions (Table S1), likely due to the inability of the sterically hindered $^{\text{tBu}}\text{N3C}^-$ ligand to support a $\text{Ni}\cdots\text{C--H}$ interaction that promotes C–H activation upon oxidation to Ni^{III} (although the slightly different electronic properties of the N-alkyl substituents may also play a role). These studies provide evidence for an oxidatively induced $\text{C}_{\text{sp}^2}\text{--H}$ bond activation at the Ni^{III} center of 1^{NP} , in which the less steric neopentyl substituents enable an agostic interaction between the Ni center and C–H bond to be activated.

To further probe the reactivity of Ni^{III} centers, the green air-stable Ni^{III} complex $[(^{\text{NP}}\text{N3C})\text{Ni}^{\text{III}}(\text{MeCN})_2](\text{SbF}_6)(\text{PF}_6)$, **3**, was prepared by reacting complex **2** with 1 equiv of AgSbF_6 (Scheme 1). The X-ray structure of **3** reveals the Ni^{III} center has two *cis* coordination sites available for exogenous ligands (Figure 2, middle). Indeed, when **3** was reacted with 2.2 equiv of AgF in THF, a bluish-green air-stable complex $(^{\text{NP}}\text{N3C})\text{Ni}^{\text{III}}\text{F}_2$, **4**, was obtained and structurally characterized (Figure 2, right). Importantly, **4** is the first isolated high-valent organometallic Ni–F complex, although such species have recently been proposed as intermediates in oxidatively induced C–F bond formation.¹⁴ Both **3** and **4** are paramagnetic and exhibit effective magnetic moments μ_{eff} of 1.71 and 1.77 μ_{B} at 298 K, corresponding to one unpaired electron. Their EPR spectra (77 K, PrCN glass) reveal rhombic signals with g_{ave} values of 2.118 for **3** and 2.147 for **4**, along with superhyperfine coupling to the two axial N donors ($I = 1$) observed in the g_z direction. When comparing the EPR spectra of **2** and **3**, the removal of the Br^- ligand ($I = 3/2$) leads to the loss of the additional superhyperfine coupling in the g_x and g_y directions (Figure 3). Interestingly, the EPR spectrum of **4** was best simulated using superhyperfine coupling in the g_x and g_z directions to only one F^- ion ($I = 1/2$). This is further supported by the slightly different EPR spectra obtained when **3** was reacted with either 1 equiv or 5 equiv of AgF in MeCN (Figure S1), suggesting that **4** exists predominantly as the monofluoride species **5** in solution. In addition, the ^{19}F NMR spectrum of **4** reveals a broad peak at -35.8 ppm, indicating a rapid exchange between the dissociated fluoride and the fluoride bonded to the Ni^{III} center.

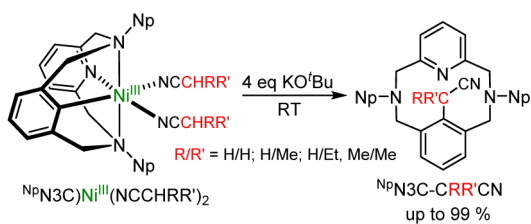
Initial reactivity studies using **4** focused on C–F and C– CF_3 bond formation reactions, given the recently proposed involvement of high-valent Ni species in such transformations.^{14,15} We first attempted to synthesize $[(^{\text{NP}}\text{N3C})\text{Ni}^{\text{III}}(\text{CF}_3)(\text{MeCN})]^+$, **6**, by reacting **4** with Me_3SiCF_3 .¹⁶ However, when **4** is reacted with 2 equiv of Me_3SiCF_3 in MeCN, the cyanomethylation product $^{\text{NP}}\text{N3CCCH}_2\text{CN}$ is generated quantitatively (Scheme 2). Alternatively, when **4** is reacted with 2 equiv of Me_3SiCF_3 at -35 $^\circ\text{C}$ in THF, the *in situ* generation of

Scheme 2. Cyanomethylation of **4** with Me₃SiCF₃

$[(^{\text{Np}}\text{N3C})\text{Ni}^{\text{III}}(\text{CF}_3)]^+$ is observed by ESI-MS (m/z 505.2211, calcd for $[(^{\text{Np}}\text{N3C})\text{Ni}^{\text{III}}(\text{CF}_3)]^+$: 505.2209) and EPR ($g_{\text{ave}} = 2.154$, Figure S3). Addition of MeCN (15% v/v in THF) to freshly made $[(^{\text{Np}}\text{N3C})\text{Ni}^{\text{III}}(\text{CF}_3)]^+$ generates the cyanomethylation product $^{\text{Np}}\text{N3CCH}_2\text{CN}$, as observed by ESI-MS (m/z 419.3171, calcd for $[(^{\text{Np}}\text{N3CCH}_2\text{CNH}]^+$, $\text{C}_{27}\text{H}_{39}\text{N}_4$: 419.3170), suggesting that the C–H bond activation of MeCN and subsequent C–C bond formation is mediated by **6**.

Since cyanomethylation is a powerful organic transformation and current cyanomethylation reactions usually require multiple steps and harsh reaction conditions,¹⁷ we further investigated this one-step cyanomethylation reaction occurring rapidly at rt. When **4** is reacted with 2 equiv of Me₃SiCF₃ in CD₃CN, $^{\text{Np}}\text{N3CCD}_2\text{CN}$ was also generated quantitatively within minutes at rt, while CF₃D (–78.2 ppm) was detected by ¹⁹F NMR, indicating that CF₃[–] likely serves as the base. Moreover, an intermolecular kinetic isotope effect $k_{\text{H}}/k_{\text{D}} = 1.9 \pm 0.1$ at rt was measured when **4** was reacted with 2 equiv of Me₃SiCF₃ in CD₃CN/MeCN (1:1), suggesting that the C–H bond activation is favored over C–D bond activation. In the absence of Me₃SiCF₃, no reaction between **4** and MeCN is observed, further supporting that **6** is the reactive species in this case.

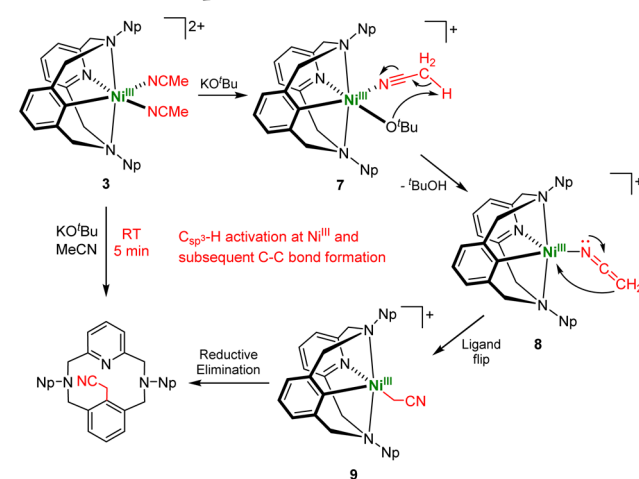
As CF₃[–] is proposed to serve as the base, we used a common base such as KO^tBu; indeed, the cyanomethylation proceeded quantitatively for both MeCN and CD₃CN (Scheme 3, entries 1–2). Besides MeCN and CD₃CN, cyanoalkylation of nitriles such as EtCN and *n*PrCN (Scheme 3, entries 3–4) can also occur at rt to generate the secondary nitrile products $^{\text{Np}}\text{N3CCHMeCN}$ and $^{\text{Np}}\text{N3CCHEtCN}$, in 84% and 79% yields, respectively. Based on the NMR spectra, this cyanoalkylation is regioselective for the α position of the nitrile substrate. Excitingly, cyanoalkylation

Scheme 3. Cyanoalkylation of **4** with Various Nitriles

Entry	Nitrile ^a	Time	Product	Yield (%) ^d
1	MeCN	5 min	$^{\text{Np}}\text{N3CCH}_2\text{CN}$	99 ^b
2	CD ₃ CN	5 min	$^{\text{Np}}\text{N3CCD}_2\text{CN}$	99 ^b
3	EtCN	5 min	$^{\text{Np}}\text{N3CCHMeCN}$	84 ^c
4	<i>n</i> PrCN	5 min	$^{\text{Np}}\text{N3CCHEtCN}$	79 ^c
5	<i>i</i> PrCN	10 min	$^{\text{Np}}\text{N3CCMe}_2\text{CN}$	33 ^c

^aThe nitrile acts also as the reaction solvent. ^bYield based on isolated product. ^cYield based on NMR integration. ^dThe remaining yield corresponds to protonated ligand $^{\text{Np}}\text{N3CH}$ side product.

with Me₂CHCN can also be performed to generate the tertiary nitrile $^{\text{Np}}\text{N3CCMe}_2\text{CN}$ in 33% yield (Scheme 3, entry 5), an uncommon example of C–C bond formation involving a tertiary alkyl group.¹⁸ The trend of decreasing yield of cyanoalkylation products from primary to secondary to tertiary nitriles suggests that most likely a ligand rearrangement occurs following C_{sp}³–H bond activation (Scheme 4), as observed previously. Finally, the

Scheme 4. Possible Mechanism of C_{sp}³–H Bond Activation of MeCN and Subsequent C–C Bond Formation

use of 1 equiv of MeCN in THF generates the cyanomethylation product $^{\text{Np}}\text{N3CCH}_2\text{CN}$ in 59% yield, supporting the possibility of using various nitrile substrates that are not also the solvent of the reaction.

In order to probe the mechanism of this C_{sp}³–H bond activation and subsequent C–C bond formation, the reaction between **3** and KO^tBu was monitored by EPR. The simulation of the resulting EPR spectrum strongly suggests the formation of $(^{\text{Np}}\text{N3C})\text{Ni}^{\text{III}}(\text{O}^t\text{Bu})_2$, by analogy to our previously reported Ni^{III}-bisalkoxide complexes (Figure S6).⁸ When MeCN (15% v/v in THF) was added to the above reaction, the EPR signal quickly disappeared and the cyanomethylation product $^{\text{Np}}\text{N3CCH}_2\text{CN}$ was produced quantitatively. Based on these experimental results, a reaction mechanism is proposed, as shown in Scheme 4 for the MeCN substrate. While addition of excess KO^tBu to **3** generates $(^{\text{Np}}\text{N3C})\text{Ni}^{\text{III}}(\text{O}^t\text{Bu})_2$, it is expected that in the presence of MeCN an asymmetric complex $[(^{\text{Np}}\text{N3C})\text{Ni}^{\text{III}}(\text{O}^t\text{Bu})(\text{MeCN})]^+$, **7**, is the predominant species.⁸ The latter intermediate is proposed to promote the C_{sp}³–H bond activation of MeCN assisted by ^tBuO[–] to form **8**, $[(^{\text{Np}}\text{N3C})\text{Ni}^{\text{III}}(\text{N}=\text{C}=\text{CH}_2)]^+$. Rearrangement of the [–]N=C=CH₂ ligand would generate $[(^{\text{Np}}\text{N3C})\text{Ni}^{\text{III}}(\text{CH}_2=\text{C}=\text{N})]^+$, **9**, which contains a new Ni–C bond, followed by reductive elimination from this 5-coordinate species to generate the cyanomethylation product $^{\text{Np}}\text{N3CCH}_2\text{CN}$.¹⁹ Notably, a similar N=C=CH₂[–] ligand flip was recently reported for a Ni^{II} system and proposed to be thermodynamically favored based on theoretical calculations.^{5a} While ^tBuO[–] may be a strong enough base in MeCN to deprotonate the solvent,²⁰ the observed quantitative cyanomethylation reaction is most likely promoted by the Ni^{III} center that plays an important role in activating the nitrile for α -C–H bond activation.^{5a} Finally, performing the cyanoalkylation reaction in the presence of radical traps PBN and DMPO did not reveal the formation of radical species, arguing against a radical mechanism.^{16b,15c}

The above reactivity studies show that the oxidatively induced C_{sp^2} -H bond activation as well as the C_{sp^3} -H bond activation reaction and the subsequent C-C bond formation can be performed using the same ($^{Np}N3CH$)Ni system, suggesting that these transformations could be performed in a one-pot transformation. Indeed, when $^{Np}N3CH$ is reacted with $NiBr_2(DME)$ and 2 equiv of $AgBF_4$ at 110 °C for 12 h in 1:1 THF/MeCN, followed by addition of 4 equiv KO^tBu , the cyanomethylation product $^{Np}N3CCH_2CN$ was generated in 22% yield. The product yield is likely limited by the oxidatively induced C_{sp^2} -H bond activation step, since the reaction of $^{Np}N3CBr$ with $Ni(COD)_2$ in MeCN, followed by addition of 2 equiv of $AgBF_4$ and 4 equiv of KO^tBu , afforded $^{Np}N3CCH_2CN$ in 86% yield. Overall, while the oxidatively induced C_{sp^2} -H bond activation step needs to be optimized, these results suggest that an oxidative aromatic cyanoalkylation reaction involving a double C-H activation mediated by Ni^{III} could be potentially developed into a catalytic transformation.

In conclusion, we have shown that by employing the less bulky $^{Np}N3C^-$ ligand, the corresponding ($^{Np}N3CH$) $Ni^{II}Br_2$ complex can undergo oxidatively induced C_{sp^2} -H bond activation at a Ni^{III} center. In addition, isolated ($^{Np}N3C$) Ni^{III} complexes were shown to perform C_{sp^3} -H bond activation of various primary, secondary, and tertiary nitriles in the presence of a base, followed by rapid cyanoalkylation at room temperature. To the best of our knowledge, these are the first examples of C-H bond activation reactions occurring at a Ni^{III} center. Finally, since the C_{sp^2} -H/ C_{sp^3} -H bond activations and subsequent C-C bond formation can be performed in one pot, this suggests the possibility of designing an atom- and step-economic catalytic oxidative coupling of arenes and nitriles involving high-valent Ni species. Current efforts are focused on expanding the substrate scope of C-H bond activation and functionalization and rendering this transformation catalytic.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02405.

Synthetic details, spectroscopic characterization, reactivity studies, and X-ray data (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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