N-Heterocyclic Carbene Complexes of Nickel(II) from Caffeine and Theophylline: Sustainable Alternative to Imidazol-2-ylidenes

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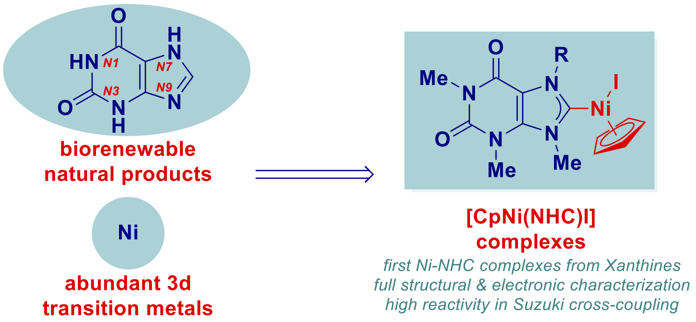
Supporting Information



ABSTRACT: Xanthines, such as caffeine and theophylline, are abundant natural products that are often present in foods. Leveraging renewable and benign resources for ligand design in organometallic chemistry and catalysis is one of the major missions of green and sustainable chemistry. In this Special Issue on *Sustainable Organometallic Chemistry*, we report the first nickel–N-heterocyclic carbene complexes derived from Xanthines. Well-defined, air- and moisture-stable, half-sandwich, cyclopentadienyl [CpNi(NHC)I] nickel–NHC complexes are prepared from the natural products caffeine and theophylline. The model complex has been characterized by x-ray crystallography. The evaluation of steric, electron-donating and π-accepting properties is presented. High activity in the model Suzuki–Miyaura cross-coupling is demonstrated. The data show that nickel–N-heterocyclic carbenes derived from both Earth abundant 3d transition metal and renewable natural products represent a sustainable alternative to the classical imidazol-2-ylidenes.

Introduction

N-Heterocyclic carbenes (NHCs) represent a tremendously important class of ligands in organometallic chemistry and catalysis. [1–3] Over the last 25 years, since the first isolation by Arduengo in 1991[4] and the first use in catalysis by Herrmann in 1995,[5] different classes of NHC ligands have been extensively investigated.[6] Principally, NHC ligands have found broad application in catalysis[7] using transition metals owing to the electronic[8] and steric[9] properties that can support various metals at different oxidation states.[10] In this context, leveraging renewable and benign resources for ligand design in organometallic chemistry and catalysis is one of the major missions of green and sustainable chemistry.[11] Likewise, the use of nickel as an Earth abundant 3d transition metal has recently garnered significant attention in catalysis owing to low price of Ni as well as a potential problem with long-term supply of Pd, which is particularly important from an industrial standpoint.[12–14]

Xanthines, such as caffeine and theophylline (Figure 1), are abundant natural products that are often found in foods.[15] The presence of an imidazole ring renders Xanthines potential precursors to N-heterocyclic carbenes.[16] Xanthines as precursors to N-heterocyclic carbenes have been well-explored for medicinal chemistry applications.[17–21] Seminal studies by Youngs and coworkers established the potential of Ag(I)–NHC complexes derived from caffeine as antimicrobial agents active against resistant respiratory pathogens.[17] Willans and co-workers demonstrated antiproliferative activity against cancer cell lines of Ag(I)–NHC complexes derived from Xanthines.[18]

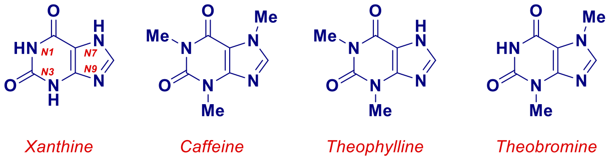


Figure 1. Xanthine natural products.

Furthermore, Casini and co-workers developed Au(I)–NHC complexes derived from caffeine with selective antiproliferative effects against human ovarian cancer cell lines.[19] Antiproliferative and cytotoxic activity of Pd(II)–NHC and Pt(II)–NHC complexes derived from Xanthines have been reported.[20,21]

In contrast, however, the development of Xanthines as NHC ligands for transition-metal-catalysis remains unexplored. At present, there are only few examples reported, including Pd, Ir, Rh and Cu catalysis.[22–25] To our knowledge, despite the explosive growth of Ni–NHCs,[14,26] there are no examples of Ni–N-heterocyclic carbene complexes derived from Xanthines.

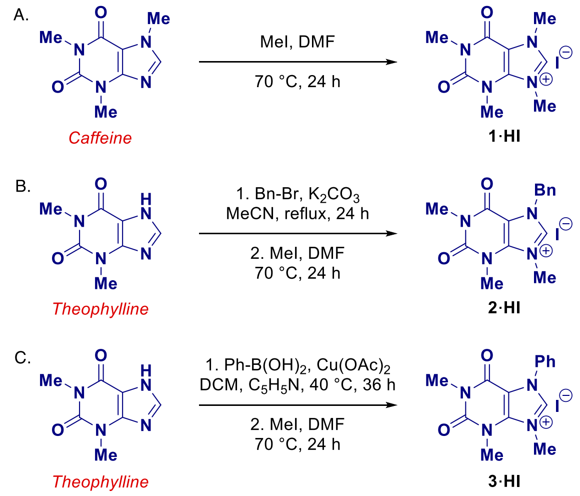
As continuation of our interest in NHC ligand development[27] and sustainable chemistry,[28] in this Special Issue on *Sustainable Organometallic Chemistry*, we report the first nickel–N-heterocyclic carbene complexes derived from Xanthines. Our data show that nickel–N-heterocyclic carbenes derived from both Earth abundant 3d transition metal and renewable natural products represent a sustainable alternative to the classical imidazol-2-ylidenes.

Results and Discussion

Imidazolium salts of **1–3** with different steric and electronic properties at the N7 position of the Xanthine scaffold were selected as NHC precursors for the study (Scheme 1). Salts of **1–3** were prepared from caffeine by methylation at the N9 position (**1·HI**) and from theophylline by a sequence involving N7-benzylation/N9-methylation (**2·HI**) or N7-arylation/N9-methylation (**3·HI**) (Scheme 1).[19] At present, synthetic methods do not permit for an easy access to N-*ortho*-sterically-hindered NHCs in xanthine scaffold. DMF is not required as a solvent and these reactions can also be conducted in the absence of the solvent. Well-defined half-sandwich cyclopentadienyl [CpNi(NHC)I] complexes (**4–6**) were prepared by the reaction of imidazolium salts with $NiCp_2$ in THF at 80 °C (Scheme 2).[26] All complexes were found to be air- and moisture-stable.

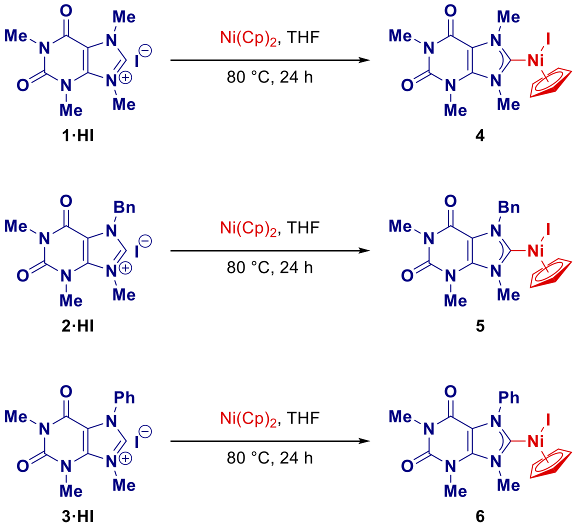
The model complex **4** (N7-Me) was characterized by X-ray crystallography (Figure 2). The single crystals were obtained by slow evaporation of dichloromethane. The X-ray crystallographic analysis of complex [CpNi(**1**)I] **4** revealed the trigonal planar geometry comprised of carbene **1**, iodide and Cp(η^5) ligands (Figure 2A-B). The Ni–C and Ni–Cp bond lengths of 1.883(9) Å and 1.748 Å are in the range for standard cyclopentadienyl Ni(II)–NHC type complexes (e.g., [CpNi(**IPr**)Cl], Ni–C, 1.875 Å; Ni–Cp, 1.800 Å; [CpNi(**IMes**)Cl], Ni–C, 1.873, 1.877 Å; Ni–Cp, 1.770, 1.764 Å).[26] The Ni–I bond length of 2.508(2) Å in **4** can be compared with the Ni–Cl bond length of standard [CpNi(**NHC**)Cl] complexes ([CpNi(**IPr**)Cl], 2.188 Å; [CpNi(**IMes**)Cl], 2.198, 2.202 Å), while the C–Ni–I bond angle of 96.9° in complex **4** is in same range as for [CpNi(**IPr**)Cl] (93.9°) and [CpNi(**IMes**)Cl] (96.8°).[26]

Scheme 1. Synthesis of Imidazolium Salts 1–3[a]



[a] Conditions: (A) Caffeine (1.0 equiv), MeI (8.6 equiv), DMF (3.0 M), 70 °C, 24 h, 81%. (B) (i) Theophylline (1.0 equiv), Bn-Br (5.0 equiv), K_2CO_3 (1.1 equiv), reflux, 24 h; (ii) 7-Benzyltheophylline (1.0 equiv), MeI (8.6 equiv), DMF (3.0 M), 70 °C, 24 h, 74%. (C) (i) Theophylline (1.0 equiv), $Ph\text{-}B(OH)_2$ (0.60 equiv), $Cu(OAc)_2$ (11.0 mol%), pyridine (5.0 equiv), CH_2Cl_2 (0.20 M), 40 °C, 36 h; (ii) 7-Phenyltheophylline (1.0 equiv), MeI (8.6 equiv), DMF (3.0 M), 70 °C, 24 h, 48%.

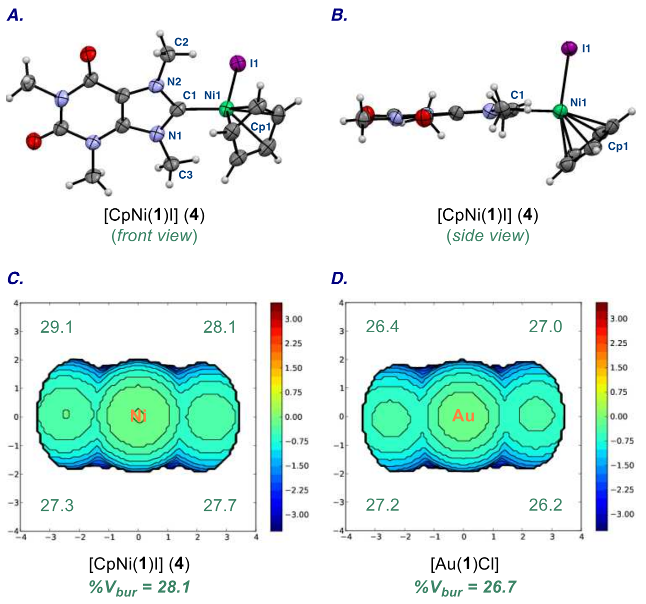
Scheme 2. Synthesis of Ni(II)–NHC Complexes 4–6[a]



[a] Conditions: **NHC·HI** (1.0 equiv), $Ni(Cp)_2$ (2.0 equiv), THF (0.10 M), 80 °C, 15 h, **4**: 61%; **5**: 65%; **6**: 69%.

The bond angles of **4** (C1–Ni1–Cp1, 131.3°; I1–Ni1–Cp1, 131.7°) are consistent with trigonal planer geometry.

To evaluate the steric impact of Xanthine-derived NHC ligand, the percent buried volume (%V_{bur}) of [CpNi(**1**)I] (**4**) was calculated using method by Cavallo (Figure 2C).[9] The %V_{bur} of (**4**) is 28.1% with quadrant distribution og 27.3% (SW), 29.1% (NW), 28.1% (NE), 27.7% (SE) for each quadrant, which could be compared with the %V_{bur} of 26.7% for the linear [Au(**1**)Cl] complex with 27.2% (SW), 26.4% (NW), 27.0% (NE), 26.2% (SE) for each quadrant reported by Casini (Figure 2D).[19] The graphical representation of steric maps is shown in Figures 2C-D.



[CpNi(**1**)I] (**4**)
(*front view*)

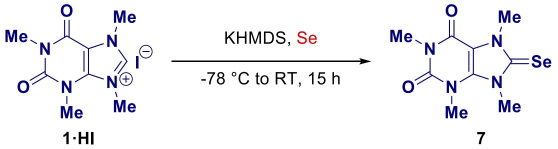
[CpNi(**1**)I] (**4**)
(*side view*)

[CpNi(**1**)I] (**4**)
%V_{bur} = 28.1

[Au(**1**)Cl]
%V_{bur} = 26.7

Figure 2. (A-B) X-ray crystal structure of complex [CpNi(**1**)I] (**4**) (50% ellipsoids), (A) front view; (B) side view. Selected bond lengths [Å], bond angle [°] and dihedral angles [°] (**4**): Ni1–C1, 1.883(9); Ni1–I1, 2.508(2); Ni1–Cp1, 1.749; C1–N1, 1.380(1); C1–N2, 1.360(1); C3–N1, 1.450(1); C2–N2, 1.450(1); C1–Ni1–I1, 96.90(3); C1–Ni1–Cp1, 131.28; I1–Ni1–Cp1, 131.70; Ni1–C1–N1, 128.10(7); Ni1–C1–N2, 125.20(7); C1–N1–C3, 122.10(8); C1–N2–C2, 124.80(8); Ni1–C1–N1–C3, 3.0(1); Ni1–C1–N2–C2, 9.0(1). (C-D) Topographical steric map of (C) [CpNi(**1**)I] (**4**) and (D) [Au(**1**)Cl],[19] showing %V*bur* per quadrant. **4**: CCDC 2141640.

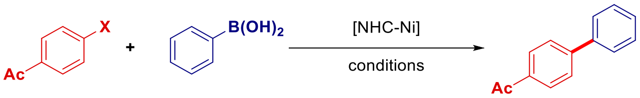
Scheme 3. Synthesis of Selenium Adduct 7[a]



[a]Conditions: **1·HI** (1.0 equiv), Se (2.0 equiv), KHMDS (1.2 equiv), THF (0.10 M), -78 °C, then 23 °C, 15 h, 52%.

We have also prepared the selenium adduct [Se(**NHC**)] (**7**) by adding the free carbene generated in situ using KHMDS to excess of selenium (Scheme 3). This permits to evaluate π-backbonding from the ^{77}Se NMR spectra.[29] The δ_{Se} value of 79.9 ppm for [Se(**NHC**)] (**7**) ($CDCl_3$) can be compared with the model imidazol-2-ylideneIPr (δ_{Se} = 90 ppm). It should be noted that ^{77}Se NMR spectroscopy is affected by anisotropic effects and the results can only be compared within the same type of NHCs. We also note that the Tolman electronic parameter (TEP)[8,30] of [Rh(**1**)(CO)$_2$Cl] has been reported;[16b] the value of 2055.8 cm^{-1} as a combined measure of the electronic properties can be compared with the model imidazol-2-ylideneIPr (TEP of 2051.5 cm^{-1}).[8,30] Note that TEP is obtained by correlation of the known data for Rh and Ni complexes.[30a] Furthermore, one-bond CH coupling ($^1J_{CH}$) constant obtained from ^{13}C satellites of the ^{1}H NMR spectrum of (**1**) is 226.95 Hz, providing a good indication of σ-donating properties of this ligand (cf. IPr, $^1J_{CH}$ = 223.70 Hz).[31]

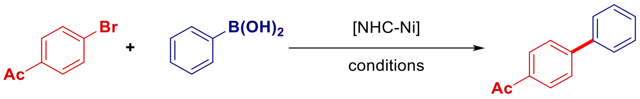
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	R-X	solvent	base	T (°C)	yield (%)[b]
1	**4**	4-Ac-C_6H_4-Br	toluene	K_3PO_4	90	76
2	**4**	4-Ac-C_6H_4-Br	toluene	K_2CO_3	90	35
3	**4**	4-Ac-C_6H_4-Br	toluene	KO*t*-Bu	90	13
4	**4**	4-Ac-C_6H_4-Br	EtOH	K_2CO_3	90	54
5	**4**	4-Ac-C_6H_4-Br	THF	K_2CO_3	90	57
6[c]	**4**	4-Ac-C_6H_4-Br	toluene	K_3PO_4	90	67
7	**4**	4-Ac-C_6H_4-Br	toluene	K_3PO_4	120	79
8[d]	**4**	4-Ac-C_6H_4-Br	toluene	K_3PO_4	120	30
9[e]	**4**	4-Ac-C_6H_4-Br	toluene	K_3PO_3	120	94
10[e]	**4**	4-Ac-C_6H_4-Cl	toluene	K_3PO_4	120	29

[a]Conditions: 4-Ac-C_6H_4-X (1.0 equiv), Ph-B$(OH)_2$ (2.0 equiv), catalyst (3 mol%), base (2.6 equiv), solvent (0.25 M), T, 12 h. [b]GC/^{1}H NMR yields. [c]base (4.0 equiv). [d]toluene (0.5o M). [e]toluene (0.10 M).

Table 2. Evaluation of Catalysts 4–6[a]



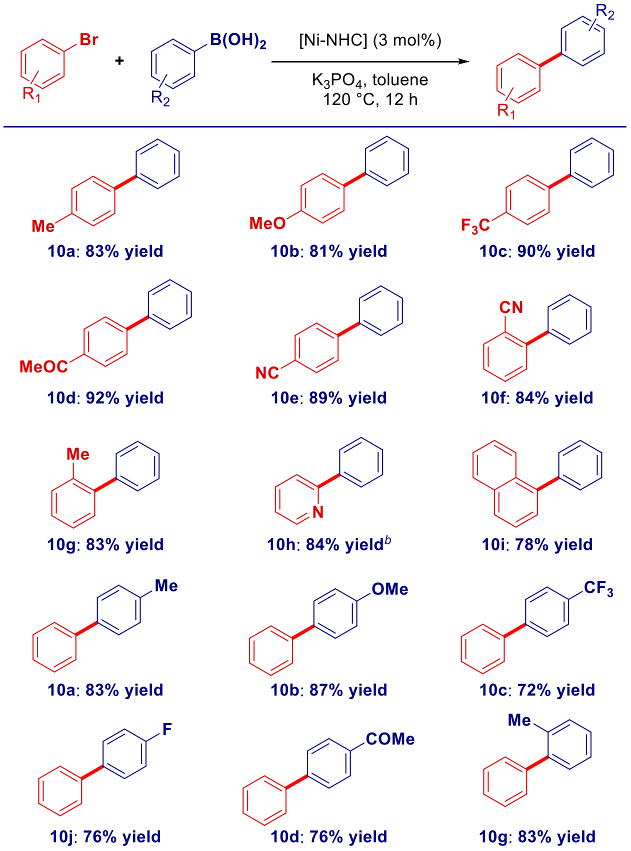
entry	catalyst	R-X	solvent	base	T (°C)	yield (%)[b]
1	**4**	4-Ac-C_6H_4-Br	toluene	K_3PO_4	120	94
2	**5**	4-Ac-C_6H_4-Br	toluene	K_3PO_4	120	91
3	**6**	4-Ac-C_6H_4-Br	toluene	K_3PO_4	120	81

[a]Conditions: 4-Ac-C_6H_4-Br (1.0 equiv), Ph-B$(OH)_2$ (2.0 equiv), catalyst (3 mol%), K_3PO_4(2.6 equiv), toluene (0.10 M), 120°C, 12 h. [b]GC/^{1}H NMR yields.

With access to [CpNi(NHC)I] complexes (**4–6**), we next investigated the catalytic activity in Suzuki–Miyaura cross-coupling. Selected optimization results are presented in Table 1. Our optimization was carried out using the model substrate combination for Suzuki–Miyaura cross-couplings using half-sandwich Ni–NHC cyclopentadienyl complexes.[26c,14] As shown in Table 1, [CpNi(NHC)I] (**4**) successfully promoted the Suzuki cross-coupling of 4-Ac-C_6H_4-Br with Ph-B$(OH)_2$ under model conditions in the presence of K_3PO_4 (2.6 equiv) in toluene at 90 °C in 76% yield (Table 1, entry 1). Examination of different bases revealed that K_3PO_4 is preferred over K_2CO_3 (Table 1, entry 2) and KO-*t*Bu (Table 1, entry 3). Likewise, other solvent/base combinations that have been used for Ni–NHC-catalyzed Suzuki cross-couplings,[32] such as EtOH/K_2CO_3 (Table 1, entry 4) and THF/K_2CO_3 (Table 1, entry 5), proved less effective. Interestingly, increasing the amount of base was detrimental to the reaction (Table 1, entry 6). In contrast, increasing the reaction temperature resulted in a further increase in yield (Table 1, entry 7). Finally, we found that changes in the reaction concentration have a significant impact on the reaction efficiency (Table 1, entries 8). The optimized system involves [CpNi(NHC)I] (3 mol%), K_3PO_4 (2.6 equiv), toluene (0.10 M), 120 °C (entry 9). Note that [CpNi(NHC)I] (**4**) gave 82% yield after 15 min. To compare the reactivity with [CpNi(IPr)Cl], we have independently prepared [CpNi(IPr)Cl] and tested this complex under the same reaction conditions. This imidazol-2-ylidene complex [CpNi(IPr)Cl] gave 81% yield (15 min), indicating comparable reactivity of (**4**) to the most reactive NHC–Ni systems.[14b,c] We note that 2 equivalents of arylboronic acid are required for the reaction. In general, Ni catalysis is still less reactive than Pd catalysis in Suzuki-type couplings. We also note that under the optimized conditions, the use of Ar-Cl, 4-Ac-C_6H_4-Cl is less effective, resulting in a modest yield of cross-coupling (Table 1, entry 10) (vide infra). Both methods gave consistent results using [CpNi(NHC)I] (**4**) as the catalyst.

Furthermore, comparison between [CpNi(NHC)I] complexes (**4–6**) (Table 2) revealed that N7-Me complex **4** is most reactive, followed by N7-Bn complex **5**, while N7-Ph complex **6** showed comparatively lower reactivity, which is consistent with less sterically-demanding complexes as more effective in [Ni–NHC] promoted Suzuki cross-coupling reactions.[33]

Scheme 4. Substrate Scope of Ni-NHC-Catalyzed Suzuki–Miyaura Cross-Coupling[a]

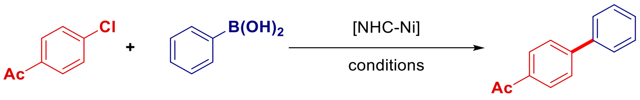


[a]Conditions: [Ni-NHC] **4** (3 mol%), Ar-Br (1.0 equiv), Ar'-$B(OH)_2$ (2.0 equiv), K_3PO_4 (2.6 equiv), toluene (0.10 M), 120 °C, 12 h. [b]Using Ar-Cl as substrate. See SI for details.

With the optimal conditions in hand, the scope of the Suzuki–Miyaura cross-coupling using complex **4** was investigated (Scheme 4). As shown, the half-sandwich, cyclopentadienyl complex (**4**) is effective in promoting the Suzuki cross-coupling of a range of aryl bromides, including electron-neutral (**10a**), challenging electron-rich (**10b**) as well as electron-deficient (**10c–10f**) substrates. Importantly, sensitive electrophilic functional groups, such as ketone (**10d**) and cyano (**10e–10f**) are readily tolerated under these mild base conditions. Importantly, challenging ortho-sterically-hindered substrates can also be used under these conditions (**10g**). It is notable that catalyst (**4**) tolerates both electron-rich and sterically-hindered aryl bromides, which are comparatively difficult substrates for related half-sandwich, cyclopentadienyl [Ni–NHC] complexes.[14,26] Furthermore, heterocyclic aryl halides are compatible as exemplified by the cross-coupling of 2-Cl-pyridine (**10h**). In this case, it is possible to use aryl chloride because of the conjugation with the electron-deficient heterocycle. Finally, polycyclic hydrocarbons, such as sterically-hindered 1-napthyl, also are compatible with this cross-coupling (**10i**).

Next, the scope of boronic acids was briefly investigated using electronically-unbiased bromobenzene (Scheme 4).

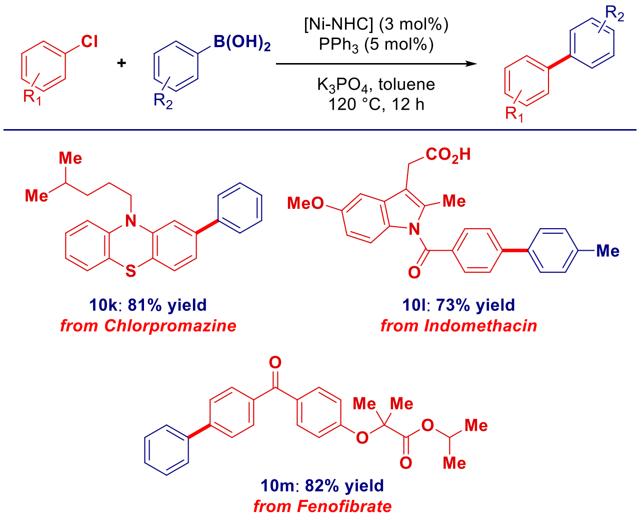
Table 3. Cross-Coupling of Aryl Chlorides Catalyzed by a Mixed Ni–NHC/Phosphine System.[a]



entry	catalyst	R-X	PPh_3 (mol%)	solvent	base	T (°C)	yield (%)[b]
1	**4**	4-Ac-C_6H_4-Cl	-	toluene	K_3PO_4	120	29
2	**4**	4-Ac-C_6H_4-Cl	5	toluene	K_3PO_4	120	98

[a]Conditions: 4-Ac-C_6H_4-Cl (1.0 equiv), Ph-$B(OH)_2$ (2.0 equiv), catalyst (3 mol%), PPh_3 (0-5 mol%), K_3PO_4 (2.6 equiv), toluene (0.10 M), 120 °C, 12 h. [b]GC/^{1}H NMR yields.

Scheme 5. Late-Stage Modification by Ni-NHC/PPh_3-Catalyzed Suzuki–Miyaura Cross-Coupling[a]



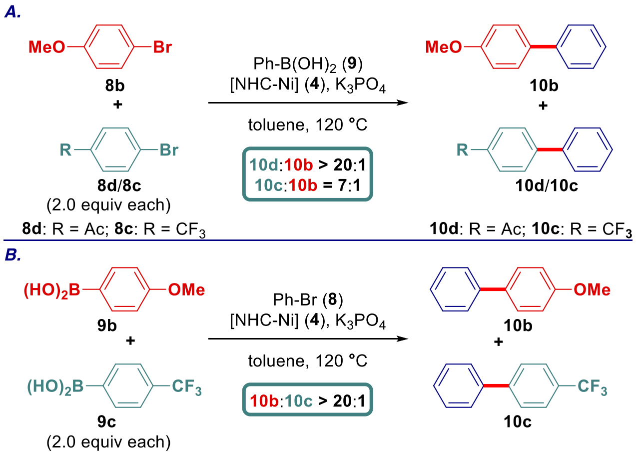
[a]Conditions: [Ni-NHC] **4** (3 mol%), PPh_3 (5 mol%), Ar-Cl (1.0 equiv), Ar'-$B(OH)_2$ (2.0 equiv), K_3PO_4 (2.6 equiv), toluene (0.10 M), 120 °C, 12 h. See SI for details.

As shown, electron-neutral (**10a**), electron-rich (**10b**), electron-deficient (**10c**, **10j**, **10d**) arylboronic acids are competent substrates for the reaction. Furthermore, we were pleased to find that sterically-hindered boronic acids also well-tolerated (**10g**). Importantly, these boronic acids delivered the cross-coupling products in high yields irrespective of electronic and steric properties of the boronic acid, which compares favorably with related half-sandwich, cyclopentadienyl [Ni–NHC] complexes based on imidazol-2-ylidenes.[14,26]

At this point, we became intrigued by the recent reports on using catalytic amounts of phosphanes to increase the reactivity of Ni–NHC complexes in the Suzuki–Miyaura cross-coupling of aryl chlorides.[34] These systems are proposed to operate through mixed NHC/PR_3 coordination to nickel(II), resulting in stable and catalytically-active precursors. Gratifyingly, we found that addition of catalytic PPh_3 (5 mol%) to the present system resulted in a significant enhancement of the reactivity in cross-coupling of aryl chlorides (Table 3).

Pleasingly, this Ni–NHC/PR_3 system is highly efficient and could be applied to the direct late-state derivatization of pharmaceuticals (Scheme 5).[35] The cross-coupling of *chloropromazine* (antipsychotic), *indomethacin* (anti-inflammatory) and *fenofibrate* (antihypercholesterolemic) delivered biaryl products in high yields. While our focus was on aryl bromides because these reactions do not require phosphine additives, the cross-couplings in Scheme 5 highlight the potential of nickel catalysis in medicinal chemistry research. Studies on the development of related Ni–NHC/phosphine catalysts are ongoing in our laboratory.

Scheme 6. Competition Experiments[a]



[a]Conditions: (A) Ar-Br (2.0 equiv each)/Ph-B(OH)$_2$ (1.0 equiv). (B) Ar-B(OH)$_2$ (2.0 equiv each)/Ph-Br (1.0 equiv), [Ni-NHC] **4** (3 mol%), K_3PO_4 (2.6 equiv), toluene (0.10 M), 120 °C, 12 h.

Next, we conducted intermolecular competition experiments to gain preliminary insight into the reaction selectivity (Scheme 6). Competition experiments revealed that electron-deficient aryl bromides are significantly more reactive than electron-rich counterparts (Ac:MeO > 95:5) (Scheme 6A). Furthermore, electron-rich boronic acids are inherently more reactive than electron-deficient boronic acids (MeO:CF_3> 95:5) (Scheme 6B). Note that ketones can coordinate to Ni(0) complexes, which may affect the selectivity. Thus, we conducted competition experiments using the 4-CF_3 analogue (CF_3:MeO = 7:1) (Scheme 6A), which is in agreement with the reaction strongly favoring electron-deficient substrates. The electronic effect is supported by the scope studies (**10b** vs. **10c-d**, Scheme 4). This data is consistent with oxidative addition and transmetallation as kinetically relevant steps in the cross-coupling.[14,26]

To further characterize the effect of Xanthine scaffold on electronic properties of carbenes, HOMO and LUMO energy levels of NHCs derived from **1–3** were determined at the B3LYP 6-311++g(d,p) level (Table 4, Figures 3-4 and SI). For comparison, orbital energy levels of reference imidazol-2-ylidenes **IMe**, **^{Me}IMe** and **^{Cl}IMe** were determined. It is now well accepted that computation of HOMO and LUMO energy levels provides the most accurate evaluation of nucleophilicity and electrophilicity of N-heterocyclic carbenes with the proviso that the comparison must be available at the same level of theory.[30,10] Higher HOMO corresponds to more σ-donating, while lower LUMO to more π-accepting NHC ligands. In select cases, π-donation should also be considered.

The HOMO-1 of carbenes **1–3** (in-plane σ-orbital, N7-Me, N7-Bn and N7-Ph, in the Xanthine scaffold, respectively) of -6.48 eV, -6.50 eV and -6.52 eV can be compared with HOMO of **IMe** (-5.89 eV), **^{Me}IMe** (-5.66 eV), and **^{Cl}IMe** (-6.38 eV). In the case of carbenes **1–3**, the HOMO is π-donor orbital (-6.34 eV, -6.35 eV and -6.29 eV, respectively), which can be compared with the corresponding π-donor orbitals (HOMO-1) of **IMe**, **^{Me}Me** and **^{Cl}Me** of -6.37 eV, -5.81 eV and -6.41 eV. Furthermore, the LUMO of carbenes **1–3** (π-acceptance) of -1.14 eV, -1.18 eV and -1.28 eV can be compared with **IMe**, **^{Me}Me** and **^{Cl}Me** of 0.40 eV, 0.49 eVand 0.20 eV (LUMO+4, LUMO+3, LUMO+4 due to required symmetry, respectively). It should be noted that in xanthine-8-ylidenes π-acceptor is asymmetrical with respect to metal-carbene axis due to the presence of the fused tetrahydropyrimidine-2,4-dione. For comparison, the values for a model N-Aryl imidazol-2-ylidene, IPr, are HOMO: -6.01 eV, LUMO: -0.48 eV. Thus, electronically, carbenes **1–3** can be described as moderately strongly σ-donating and strongly π-accepting NHC ligands. To our knowledge, this study provides the first

Table 4. HOMO and LUMO Energy Levels (eV) of Xanthine Derived NHCsCalculated at the B3LYP 6-311++g(d,p) Level[a]

entry	NHC	HOMO [eV]	LUMO [eV]
1	**1**	-6.48[b]	-1.14
2	**2**	-6.50[b]	-1.18
3	**3**	-6.52[b]	-1.28
4	**IMe**	-5.89	0.40[c]
5	**^{Me}IMe**	-5.66	0.49[c]
6	**^{Cl}IMe**	-6.38	0.20[c]
7	**IPr**	-6.01	-0.48

[a]See SI for details. [b]HOMO-1, in-plane σ-orbital. HOMO: π-donor orbital, **1**: -6.34 eV, **2**: -6.35 eV, **3**: -6.29 eV. [c]LUMO+4, LUMO+3, LUMO+4 due to required symmetry.

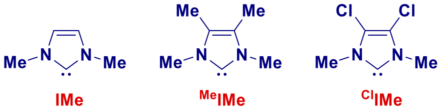


Figure 3. Structures of reference imidazol-2-ylidenes.

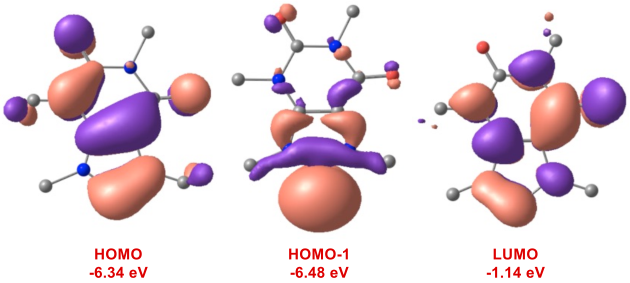
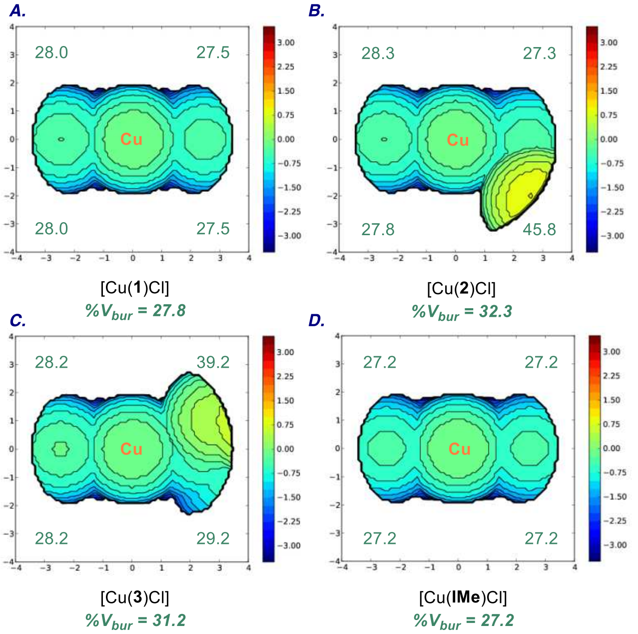


Figure 4. HOMO (π-donating orbital), HOMO-1 (σ-donating orbital) and LUMO (π-accepting orbital) of caffeine derived carbene **4** calculated at B3LYP 6-311++g(d,p) level. See SI for details.

quantification of the frontier orbitals of NHCs derived from Xanthines.[15–25]

We have also evaluated the steric effect of the Xanthine NHC ligands derived from **1–3** by calculating the percent buried volume (%V_{bur}) for the linear [Cu(NHC)Cl] complexes at the B3LYP 6-311++g(d,p) level (Figure 5 and Table 5). It is now well accepted that the accurate determination of %V_{bur} of NHC ligands should be made for the linear geometry of NHC–metal complexes.[9] To eliminate packing effects from the crystallographic studies, optimum results are obtained by comparing a series of ligands calculated at the same level of theory. For this study, we selected Cu(I)–NHC complexes to facilitate computations.

Thus, Xanthine ligands **1–3** feature %V_{bur} = 27.8%, %V_{bur} = 32.3%, and %V_{bur} = 31.2%, respectively, which can be compared with **IMe**, **^{Me}IMe** and **^{Cl}IMe** of 27.2%, 27.3% and 27.3% as well as [Cu(IMes)Cl], %V_{bur} =36.4%, determined at the same level of theory. Interestingly, ligand derived from **1** features symmetrical quadrant distribution (28.0%, 28.0%, 27.5%, 27.5%), while ligands **2** and **3** feature differentiated steric impact with 27.8%, 28.3%, 27.3%, 45.8% and 28.2%, 28.2%, 39.2%, 29.2% for each quadrant. Thus, in terms of sterics ligands **2** and **3** feature unsymmetrical quadrant distribution, while Xanthine ligand **1** is similar to the smallest **IMe** and **^{Me}IMe** imidazol-2-ylidene ligands, which have found numerous applications in transition-metal-catalysis.[1–3,36]



[Cu(**1**)Cl] %V_{bur} = 27.8

[Cu(**2**)Cl] %V_{bur} = 32.3

[Cu(**3**)Cl] %V_{bur} = 31.2

[Cu(**IMe**)Cl] %V_{bur} = 27.2

Figure 5. (A-D) Topographical steric maps of [Cu(NHC)Cl] (**4–6** and **IMe**) showing % V_{bur} per quadrant calculated at B3LYP 6-311++g(d,p) level.

Table 5. %V_{bur} of Xanthine Derived NHCs in [Cu(NHC)Cl] Complexes Calculated at the B3LYP 6-311++g(d,p) Level[a]

entry	NHC	%V_{bur}
1	**1**	27.8
2	**2**	32.3
3	**3**	31.2
4	**IMe**	27.2
5	**^{Me}IMe**	27.3
6	**^{Cl}IMe**	27.3
7	**IMes**	36.4

[a] See SI for details.

3. Conclusions

In summary, there is a major economic and societal drive to use renewable resources for sustainable chemical synthesis. In this respect, it is particularly attractive to merge the abundance of 3d transition metals and bio-renewable sources of ligands. In this study, we have reported the first nickel–N-heterocyclic carbene complexes derived from Xanthines. We demonstrated the synthesis of well-defined, air- and moisture-stable, half-sandwich, cyclopentadienyl nickel–NHC complexes from the natural products caffeine and theophylline. Complex **4** has been characterized by x-ray crystallography. The high activity in Suzuki–Miyaura cross-coupling has been demonstrated. The use of phosphine additive enabled to engage aryl chlorides, including late-stage derivatization of pharmaceuticals. Finally, full evaluation of steric, electron-donating and π-accepting properties of this class of ligands has been presented. We anticipate that Xanthine derived N-heterocyclic carbenes offer a plethora of exciting applications as a sustainable alternative to the classical imidazol-2-ylidenes.

ASSOCIATED CONTENT

Supporting Information

Procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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