

Analysis of key steps in the catalytic cross-coupling of alkyl electrophiles under Negishi-like conditions†

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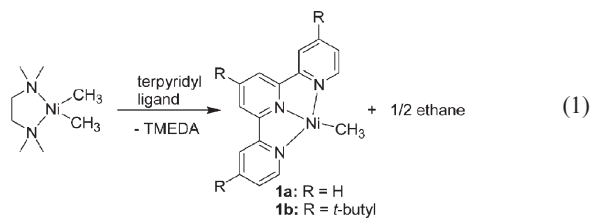
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The use of tpy' (tpy' = 4,4',4''-tri-*tert*-butyl-terpyridine) as a ligand for nickel allows for the isolation of a Ni(I)-alkyl complex and a Ni(II)-alkyl halide complex, both of which can be used as mechanistic probes of key steps in alkyl cross-coupling reactions.

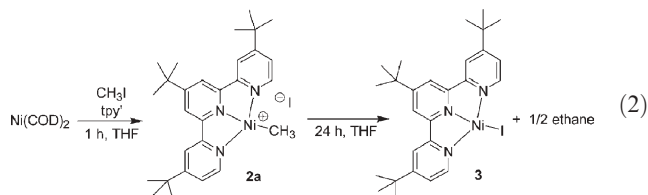
The catalytic cross-coupling of alkyl groups has historically been a difficult reaction to catalyze due to the presence of reactive β -hydrogens in both the alkyl electrophiles and the alkyl nucleophiles.^{1–4} Nickel mediated Negishi-like reactions, in which an alkyl halide is coupled with an alkylzinc halide, have been among the more successful methods recently developed that, depending on the ligand employed, are amenable to substrates containing β -hydrogens.^{5–11} We recently showed that nickel complexes containing the terpyridyl (tpy) ligand are capable of catalyzing such alkyl cross-coupling reactions.⁷ We now report a ligand modification which unexpectedly permitted the isolation of key plausible intermediates of a catalytic cycle, and determine the viability of each of these intermediates in alkane product formation.



Ni(I)-methyl complexes containing the terpyridyl ligand architectures are synthesized according to the general procedure described in eqn. (1). Isotope studies show that upon addition of terpyridyl ligand, ethane is released *via* a non-radical pathway.¹² Substitution of tpy with tpy' (tpy' = 4,4',4''-tri-*tert*-butyl-terpyridine) was found to make a number of interesting differences in the electronic and solid-state structures of the Ni(I)-alkyl complexes and in the general reactivity of the nickel complexes towards alkyl halides (see below). When the reaction in eqn. (1) is performed in ether solvent, both **1a** and **1b** can be isolated in analytically pure form by mere filtration. Unlike **1a**, which packs as head-to-head dimers in the solid-state with a short Ni...Ni separation of 3.18 Å,⁷ **1b** favors a head-to-tail stacking arrangement with a much larger intermolecular spacing of 3.72 Å and no

Ni...Ni interactions (Fig. 1, left). Electrochemical analysis of the Ni(I)-alkyl complexes reveals that **1b** ($E = -1.44$ V, vs. Ag/Ag⁺ in THF solution) is also slightly more reducing than **1a** ($E = -1.32$ V).

Surprisingly, the steric and electronic properties afforded by the *t*-butyl groups, which are far removed from the metal center, were found to make a big difference in reactivity towards alkyl halides. While reaction of Ni(COD)₂ with tpy and methyl iodide led to precipitation of (tpy)NiI from THF in nearly quantitative yield in 4 h,⁷ reaction with tpy' takes 24 h to convert to the analogous green iodo-compound **3** (eqn. (2)). Stopping the reaction at earlier reaction times permitted isolation of a new red compound, which was determined by X-ray crystallography to be the Ni(II)-alkyl halide complex **2a** (eqn. (2)). To our knowledge, this is only the second instance where both a σ -bonded C(alkyl) complex of Ni(I) and its one-electron oxidation counterpart have been structurally characterized.¹³ Remarkably, both **1b** and **2a** are relatively stable at room temperature despite the fact that the axial sites are sterically accessible. A procedure for preparing [(tpy')NiMe]PF₆ (**2b**) has also been developed (see Supporting Information†) to explore the role of counter-ions in cross-coupling reactions.



The partial packing diagram of the cationic core-unit of **2a** is shown in Fig. 1. Perhaps the most unusual feature of the solid-state structure of **2a** is the short Ni...Ni contacts of 3.32 Å, which requires that the *t*-butyl groups of two independent molecules lie in close proximity to one another.

Importantly, the isolation of the stable Ni(I)-alkyl complex **1b** and the Ni(II)-alkyl halide complex **2a** permitted a unique opportunity to study the possible involvement of both species in the catalytic cross-coupling of alkyl electrophiles and nucleophiles under Negishi-like conditions. Addition of **2a** to a five-fold excess of heptylzinc bromide in THF led to cross-coupled product in only 8% yield (eqn. (3)), indicating that product formation under catalytic conditions is not likely to be proceeding through a simple transmetalation of a Ni(II)-alkyl halide complex by an alkylzinc bromide reagent. The only other observed organic product for eqn. (3) was tetradecane (30%). The low yields of cross-coupled product do not appear to be due to iodide inhibition, as repeating the reaction described in eqn. (3) with complex **2b** as the nickel source did not produce octane in yields greater than 5%. High yields of cross-coupled product were attainable, however, when a

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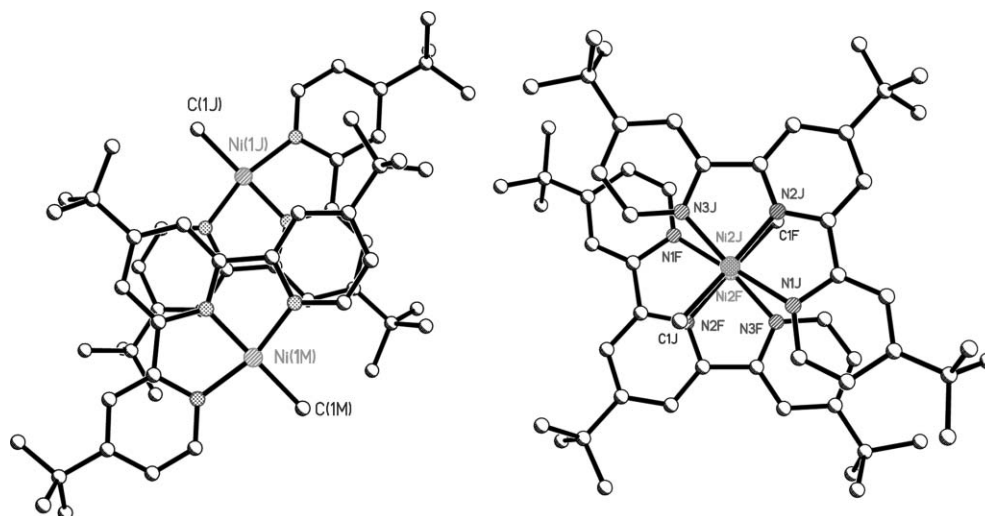
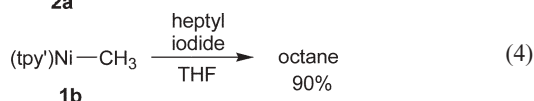
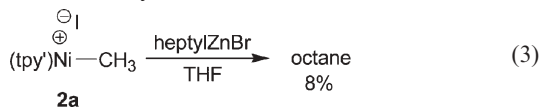


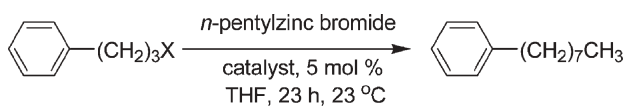
Fig. 1 Left: Partial packing diagram of **1b**. Intermolecular spacing 3.72 Å. Right: Partial packing diagram of the cationic core of **2a**. Ni...Ni spacing 3.32 Å.†

similar stoichiometric reaction was performed with the Ni(I)-alkyl complex **1b** (eqn. (4)). Reaction of **1b** with a five-fold excess of alkyl halide indeed led to formation of octane in 90% yield relative to the nickel starting material. Further stoichiometric experiments show that addition of 5 equivalents of heptylzinc bromide to **1b** in THF led to the formation of tetradecane as the only observed organic product in 36% yield relative to nickel.



The results presented above argue against a transmetallation reaction affording a Ni(II)-dialkyl complex in the catalytic chemistry involving terpyridyl ligands and are at least consistent with a possible Ni(I) to Ni(III) redox pathway to yield alkane. Catalytic runs with the newly derivatized terpyridyl ligand are described in Table 1. The simple substitution of tpy with tpy' was found to dramatically increase the yields of product for both alkyl bromide and alkyl iodide substrates (entry 1 vs. 2, and entry 3 vs. 4). We argue that the major reason for the difference in reactivity

Table 1 Catalytic C(sp³)-C(sp³) cross-coupling reactions



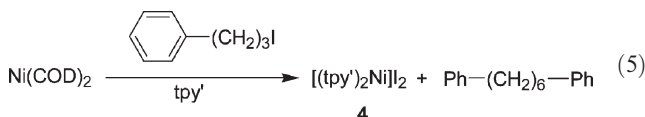
Entry	Halide	Catalyst	Yield (%) ^a
1	Br	Ni(COD) ₂ , tpy	13
2	Br	Ni(COD) ₂ , tpy'	46
3	I	Ni(COD) ₂ , tpy	60
4	I	Ni(COD) ₂ , tpy'	98
5	I	1a	60
6	I	1b	65
7	I	2a	58
8	I	3	76

^a Yields based on GC relative to a calibrated internal standard.

between the tpy and tpy' metal complexes is the improved solubility of the *t*-butyl substituted derivative. The effect of changing ligand/catalyst loading from 0.05% to 5% was investigated, and it was found that at concentrations ≤0.5% the yields of cross-coupled products were comparable (albeit lower) between tpy and tpy' (see Supporting Information†). Kickelbick and Matyjaszewski noted similar solubility effects in the ability of substituted terpyridines to better control copper mediated atom transfer radical polymerization reactions over the unsubstituted ones.¹⁴ Interestingly, complex **2a** is a moderately effective catalyst for the cross-coupling of alkyl iodides (entry 7), signifying the conversion of **2a** to a catalytically active species under the reaction conditions. More mechanistic studies are needed to unravel the true details of the catalysis, and access to the well-defined organometallic terpyridyl complexes reported herein should further aid in these endeavors.

Finally, we were curious to see if we could prepare a Ni(II)-alkyl halide complex containing β-hydrogens using the tpy' ligand. Reaction of 1-iodo-3-phenylpropane with Ni(COD)₂ and tpy' did not lead to precipitation of a stable Ni(II)-alkyl halide complex, but instead led to a decomposition reaction affording the bis-tpy' complex **4** as the only identifiable nickel species, together with formation of Ph(CH₂)₆Ph in 70% yield, respectively (eqn. (5)). Although no nickel-alkyl complex could be isolated, this result points out a possible decomposition pathway available for catalysts employing terpyridyl ligands.

In conclusion, the isolation of Ni(I)-alkyl and Ni(II)-alkyl halide complexes facilitated the study of plausible pathways involved in cross-coupling reactions involving both alkyl electrophiles and alkyl nucleophiles. While transmetallation of a terpyridyl Ni(II)-alkyl halide complex with R_{alkyl}-ZnBr was found to be unproductive, the formation of alkane in a catalytic cycle from addition of an alkyl halide to a Ni(I)-alkyl species still cannot be ruled out.



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Notes and references

‡ Crystal data for **1b** (C₂₈H₃₈N₃Ni): $M = 475.32 \text{ g mol}^{-1}$, monoclinic, space group $P2_1/c$, $a = 11.890(10)$, $b = 10.947(17)$, $c = 20.178(19) \text{ \AA}$, $\beta = 105.977(6)^\circ$, $V = 2525(5) \text{ \AA}^3$, $Z = 4$, $\mu = 0.788 \text{ mm}^{-1}$, Reflections collected/unique 12750/5826, $R_{\text{int}} = 0.0330$, $R_1 = 0.0597$, $wR_2 = 0.1377$ for $[I > 2\sigma(I)]$, $R_1 = 0.0775$, $wR_2 = 0.1482$ for all data. CCDC 268665. Crystal data for **2a**·(toluene)·(CH₂Cl₂)₂ (C₃₇H₅₀Cl₄IN₃Ni): $M = 864.21 \text{ g mol}^{-1}$, monoclinic, space group $P2_1/c$, $a = 12.78(2)$, $b = 17.04(2)$, $c = 19.13(5) \text{ \AA}$, $\beta = 104.82(2)^\circ$, $V = 4028(14) \text{ \AA}^3$, $Z = 4$, $\mu = 1.542 \text{ mm}^{-1}$, Reflections collected/unique 38471/9669, $R_{\text{int}} = 0.0767$, $R_1 = 0.1158$, $wR_2 = 0.2857$ for $[I > 2\sigma(I)]$, $R_1 = 0.1414$, $wR_2 = 0.3030$ for all data. CCDC 268664. See <http://dx.doi.org/10.1039/b504996b> for crystallographic data in CIF or other electronic format.

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